HEALTH SCIENCE INQUIRY

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Advancing Human Genetics into Health Action

Volume 6 / 2015

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Cover Design

The Rorschach Paradox *Sahil Kumar*

Description of Cover Design: Deciphering a Rorschach inkblot can rather encapsulate scientific research: looking at an incomprehensible smudge and trying to decide how it can show something significant. Either decoding the image of a Rorschach inkblot or the result of scientific research depends on the perception and interpretation of what is ambiguously presented before you; every person will see a slightly different image and form a separate narrative based on experiences, bias, and opinion. As an undergraduate laboratory assistant, I would observe Nissl stained murine brain slices with as much conviction as understanding a metaphorical inkblot. The symmetrical lobes and ventricles would create a different image depending on the location of the slice. Research to define genetic biomarkers for neurodegenerative diseases is of current interest for early detection, but often scavenging the brain for answers devises more mystery than it uncovers. Perhaps there will never be one correct answer, but the continual research will allow for the possibility of uncovering unerring biomarkers for their use in health action.

About the Artist: Sahil has a Bachelor of Science and is currently a Master's candidate in Experimental Medicine at McGill University. Hailing from Mississauga, Ontario, Sahil was trained in the Regional Arts Program at Cawthra Park SS. As a bridge between his visual arts and scientific training, Sahil incorporates medical imagery and paradigms into his works. His work mainly comprises of graphic design, painting, drawing, and smaller installation work.

Personalized Medicine and Gene Therapy

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SPECIAL THANKS TO OUR 2015 PARTNERING JOURNALS

LETTER FROM THE CO-EDITORS-IN-CHIEF

Dear Readers

It is with great pleasure that we present the 6th annual issue of the Health Science Inquiry on Advancing Human Genetics into Health Action.

Ever since the discovery of the structure of DNA in 1953, the promise of personalized medicine has inspired scientists and medical practitioners alike. In the past few decades, our discoveries in human genetics have grown exponentially. Genetics have led to a greater understanding of the underlying causes of human disease, enabled early diagnosis, and allowed patients to make decisions regarding disease inheritance. While many genetic disorders are still not treatable, we only need to look as far as the current clinical trials on genetic therapies for cystic fibrosis, hemophilia, and many others to glimpse the promises of future treatments. Despite the power advances in human genetics has on the future of medicine, this field is plagued with moral and ethical considerations. In our 6th publication of HSI, we explore these advances and considerations focusing on the themes: (1) Personalized medicine and gene therapy: advances in the treatment of genetic diseases, (2) Ethical challenges and social issues surrounding human genomics, and (3) The impact of the environment on the human genome: the role of epigenomics.

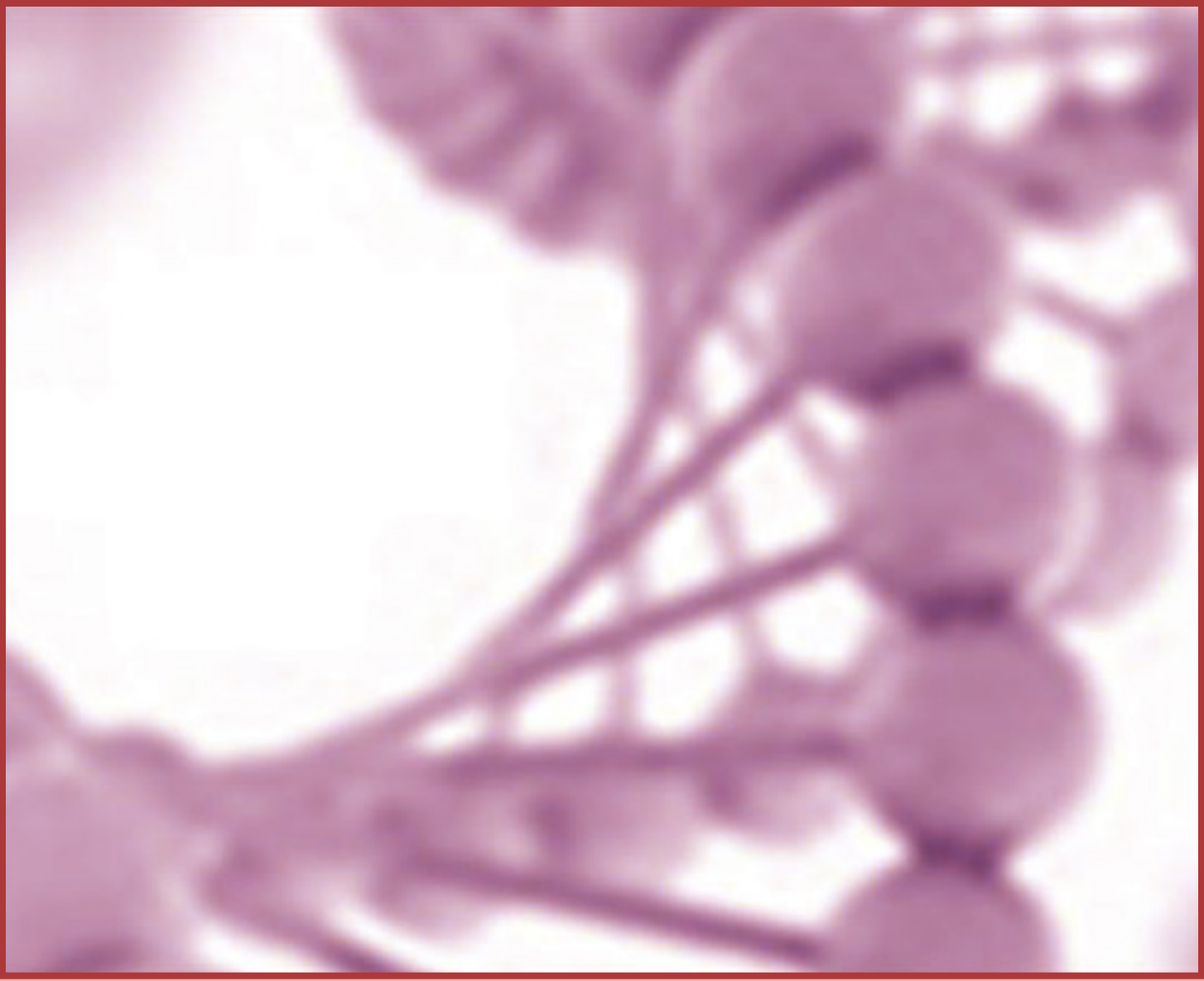
With submissions from across the country, HSI continues to serve as a national platform for student involvement and discussion. We continue to be impressed by and grateful for the excellent submissions we receive from Canadian graduate and medical students. We are equally thankful to this year's partnering journals, Epigenomics and Journal of Genomics, for their commitment to student development.

In addition to our Main Submissions, HSI also features News Articles and expert testimony on topics related to Human Genetics. We additionally publish career information and blog on all topics related to science, discovery and student life which you can find on our website (www.healthscienceinquiry.ca).

We would like to thank our dedicated 2014-2015 HSI team consisting of over 50 Canadian graduate students from across the country for their valuable contributions to provide a forum and a voice for Canadian graduate students. We hope that this publication incites discussion among readers, peers and colleagues.

Sincerely,

WooJin Kim and Suzanne Osborne
Co-Editor-in-Chief



NEWS ARTICLES

News Reporters from HSI's Editorial Team investigated various issues in **Advancing Human Genetics into Health Action.**

News Article

Ghosts of Gene Therapies Past: Lessons Learned From Jesse Gelsinger

Kevin Gorsky
News Reporter (HSI 2014-2015)

Prior to the complete sequencing of the human genome, the development of induced pluripotent stem cells and the fanfare surrounding Clustered Regularly Interspaced Short Palendromic Sequences (CRISPR) genetic editing systems, the biomedical sciences had an even bigger preeminent heavyweight: gene therapy. The development of techniques to sequence, clone, and directionally insert DNA in vitro collided at the inevitable junction of this revolutionary new science. However, bringing gene therapy applications to clinical trials revealed dangers and pitfalls that still hinder the field today. The tragic death of Jesse Gelsinger continues to highlight the multitude of hazards that have been linked to gene therapy for over 20 years, as well as the ethical considerations regarding the conflicts of interest present in clinical science.

Jesse Gelsinger did not die because he was sick. Jesse Gelsinger was born with Ornithine Transcobomylase (OTC) deficiency, a rare and often fatal X-linked genetic metabolic disorder. However, Jesse did not inherit the disease from a mutated maternal allele. Rather, his mutated X chromosome occurred de novo, and because of the spontaneity of the mutation, did not affect the entirety of his liver cells. Jesse struggled through a childhood plagued by comas and near-death spikes in his ammonia levels. However, with a strict low protein diet and a daily regimen of 32 pills, the young Mr. Gelsinger finally had his disease under control[11]. Jesse Gelsinger selflessly volunteered to be part of what he and his family believed was a low-risk trial, in hopes of someday helping children afflicted with OTC deficiency.

The clinical trial in question, the first of its kind, was conducted at the University of Pennsylvania (Penn) and headed by the renowned Dr. James Wilson. Dr. Wilson, in an effort to secure financial stability for the project, worked with Penn to further develop their technology transfer infrastructure, or as he puts it, to "establish a translational capability internal to the academic program at Penn[11]." He also cofounded Genovo, a gene therapy-centric biotechnology company with vested financial interests in the outcome of his experimentation and clinical trials involving OTC deficiency[4]. These conflicts of interest, real or perceived, must be considered when analyzing the events surrounding the death of the young Jesse Gelsinger.

Dr. Wilson's OTC deficiency gene therapy trial involved the direct administration of an engineered attenuated adenovirus to the liver of enrolled subjects[6]. The adenoviral vector would bind to hepatocytes, inject its genome into the cells, and remain as a histone-associated, stable extra-chromosomal DNA aggregate in the nucleus[6]. Cellular transcription machinery could then transcribe the engineered OTC gene. Thus, infected hepatocytes would express a functional, though transient, OTC enzyme.

Seventeen patients had undergone treatment before Gelsinger, who was in the final cohort—the one receiving the highest titer of vector[6]. Jesse was administered the treatment on September 13th 1993, and experienced a drastically different response than previous trial subjects[7]. This response led to systemic inflammation and multi-organ failure, ultimately resulting in his death. This fulminate acute inflammatory response to vector was far more drastic than the adverse events observed in the other human candidates and the preclinical studies[7], most of which presented in fever and flu-like symptoms

Disregarding all other complicating factors, the death of a healthy adolescent in a phase 1 clinical trial would be sufficient controversy and cause to examine the underlying ethical factors and regulatory oversight involved in the experiment. Prior to enrolling patients in the trial, Dr. Wilson's team had consulted a panel of bioethicists and specialists regarding whether to conduct the trial in older, less affected young adults, or symptomatic, possibly terminal newborns[2,8,11]. The choice to reject the involvement of severely ill newborns was based on issues of informed consent, which would have to be given by guardians under enormously traumatic and coercive circumstances[8]. Protocol had been "meticulously" constructed, and it had received approval from the Food and Drug Administration

(FDA) and the Institutional Review Board at the Hospital of the University of Pennsylvania[3].

But the scenario was far from simple; several instances of foul play on Penn's behalf were dotted throughout the progression of the trial. Following Jesse's death and the suspension of the trial, questions were raised concerning non-compliance in many areas including adherence to eligibility and cessation criteria, completeness and content of the consent process, monitoring of subjects following vector dosing, timely notification to the FDA regarding animal toxicity data, and timeliness and accuracy of reports to the IRB and FDA[4,9,11].

In an effort to sort out the lessons to be learned from Jesse Gelsinger's death, ethical concerns regarding gene therapy and clinical trials, importance of gene therapy over the past two decades, and appropriate relationship between academia and industry, I sat down with McGill University's Dr. Robert Murgita.

Dr. Murgita, whose accolades and experience read like a phonebook, is the founder and former director of the Sheldon Biotechnology Centre, former chairman and chief scientific officer at both IMMTEK and Atlantic Biopharmaceuticals INC., and has spent a decade as the chairman of the department of microbiology and immunology at McGill University. He has immense experience with technology transfer between academia and industry, and has been teaching a course for many years called the Business of Science, where he uses the story of Jesse Gelsinger as a case study.

The Gelsinger family and the University of Pennsylvania reached an out-of-court settlement over the negligence involved in Jesse's death. Dr. Wilson was publicly shamed and stripped of his ability to conduct clinical trials. As Dr. Murgita highlights, "The entire case was settled out of court in under four weeks. Because the case was settled in a matter of weeks, the files were frozen, and nobody knows the extent of the charges."

Dr. Murgita encourages his students to approach the case with an open mind and come to their own conclusions, but he did share some of his own inferences:

"One of the parties to be blame was the FDA. When Gelsinger was admitted to hospital prior to the procedure, his ammonia levels were high. They were higher than had been specified as the upper limit in the experimental protocol. Researchers at Penn then contacted the FDA and informed them that they would treat him to bring down his ammonia levels. That's a breach of the clinical trial rules right there. In the initial stage at least, the FDA is partially complicit." The trial team's adherence to the protocol has since been reevaluated by Wilson, who now admits that, "the protocol was not written in a way in which there was enough clarity to know when the ammonia had to be what [level], and that was a significant shortcoming[9]."

Dr. Murgita's opinion is that the implication of the FDA is what allowed the case to be settled as quickly as it was: "otherwise, no one has heard of cases like this being settled that fast. Penn didn't even have time to write their answers back to the lawsuit."

When I asked Dr. Murgita about the academic climate regarding gene therapy during the time of the clinical trial, he responded, "Very high. It's like other scientific waves, [gene therapy] was the next greatest thing. In fact Dr. Francis Collins of human genome project fame used gene therapy as one of his examples of why we needed to spend 3 billion to sequence the human genome: to help gene therapy advance." Understanding the hype and potential profit surrounding gene therapy and genetic technologies is important for appreciating the context of the Gelsinger case. Hundreds of millions of dollars from pharmaceutical corporations, biotech companies, and universities were funneled into gene therapy research during this time[9,10]. However, this incredible boom in research funding was not spurred out of a sudden coordinated generosity of "big pharma" to rid the world of rare orphan diseases, but rather due to the billions that stood to be made in gene therapy applications to cancer and degenerative disorders [3,4,9].

How far has gene therapy come since the Gelsinger case sent reverberations through the field, shutting down labs and suspending research trials across the country? Dr. Murgita notes that "there are some successes today. Macular degenerative eye disease is one. Certain kinds of diseases appear to show some benefit, perhaps in some cancers." And of course he is correct, but that's not all. Severe Combined Immune Deficiency (SCID), famously known as the 'bubble-boy' disease, is another terrible genetic affliction that renders an individual's immune system completely ineffective[1]. Late 90's gene therapy trials in SCID patients showed early success, but were quickly derailed by the development of retroviral-vector-induced-leukemia in a significant cohort of patients[1]. However, Donald Kohn, MD, from UCLA recently concluded following the October

2009 NEJM publication of his research, that "more than 50 patients have been treated by gene therapy between trials in Italy, the UK and... the US in the past decade and a half. None have had complications from the gene transfer and most have successful immune reconstitution"[1]. Though some triumphs have been reported, the initial fanfare surrounding gene therapy has markedly dissipated. Though the Gelsinger case may have nucleated this downfall, the illusiveness of gene therapy applications continue to be characterized by the difficulty of the safe and stable introduction of target genes into patient DNA[5].

Was the criticism leveled against him warranted? "Yeah, he made mistakes, as any scientist would do. I don't think he did anything malicious though. That runs counter to the conflict of interest charge leveled against him, because if something like this happens, you're finished."

Dr. Murgita can certainly relate to the circumstance. "I did the same thing with McGill in 1994. Since I was a post-doc I was studying a molecule that had potential therapeutic value and we started a company."

The gene therapy trials at Penn broach another pertinent question to the relationship between business and academia. Technology transfer and licensing fees are a huge source of revenue for universities such as Northwestern and Stanford. This may be an effective business model for an academic institution, but where is the line then drawn? "Of course you need to have protective devices, because it can be abused." In reference to McGill Dr. Murgita notes, "Professors all have contracts dictating that you can't do anything without the consent of the university over 20% of the time. Already there's oversight, you can't go running around doing what you want."

However, Murgita still thinks that technology transfer should play a significant role in sustaining a successful research oriented university. He is an advocate of the business model employed by large American institutions such as Stanford and Northwestern, whereby an entrepreneurial translational research environment is highly encouraged. Murgita: "There certainly needs to be guidelines against conflict of interest, but that should not stop entrepreneurial activity in universities. Further, universities will never have the resources that 'big pharma' have for developing drugs, and that's really not our role. We are discovery units. We are the initial source of discovery, and I don't believe we should be involved in the other end of development. Though clinical trials do go on in universities, the money to conduct these trials most often comes from some other source." At Stanford, one of the models of successful technology transfer, the office of technology licensing helps turn scientific progress into tangible products while returning income to the inventor and the university to support further research.

When money comes in from outside investors and mergers with biotechnology firms, financial incentives become part of the picture. Does this outside pressure to turn research into marketable compounds affect attention to patient safety? When asked Murgita replied, "I have a totally different perspective on this, maybe it's because I came from the states. I think we have a moral obligation to make research translational. My personal philosophy is that we should always be cognizant of the fact that we should be doing things that can be translated to the benefit of general society. That's what science ultimately is all about. It shouldn't be a matter of having outside pressure; the pressure should come from within towards translational applications."

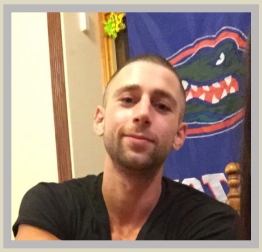
As a final thought, Dr. Murgita reflected on the future of gene therapy applications. "The newest hottest thing is CRISPR. CRISPR was discovered in bacteria as a gene editing system to allow bacteria to destroy phages that infect them. Now everyone is using CRISPR, it's said to be the replacement for classical gene therapy, because it can knock in and knock out genes in a very effective way. Everyone's using CRISPR now and CRISPR kits are becoming prevalent." Does he consider this technology to represent the resurgence of gene therapy? "Absolutely. They claim it's much more effective. This technology doesn't need viral vectors. In the scientific journal Science and Nature it was the most written about topic in 2014."

Gene therapy has yet to live up to the promises associated with the technology from its inception, and perhaps never will. However, the scientific community cannot afford to forget Jesse Gelsinger, and the successes and missteps that have become synonymous with his story as well as the evolving history of gene therapy. The intersection between research and financial incentives are nowhere more evident than in his case, and as such must be evaluated in order to maximize progress while prioritizing patient safety. As Dr. Murgita summarized, "I think that with the proper guidelines university-industrial relationships can flourish. However, there's always the possibility of a conflict of interest. These conflicts must be identified and corrected immediately, and they can be, but you have to have the

resources." ■

References

1. Rozenblum R, Jang Y, Zimlichman E, Salzberg C, Tamblyn M, Buckeridge D, et al. A qualitative study of Canada's experience with the implementation of electronic health information technology. CMAJ. 2011 Mar 22;183(5):E281-8.
2. Cavazzana-Calvo M, Fischer A. Gene therapy for severe combined immunodeficiency: are we there yet? J Clin Invest. 2007;117:1456–65.
3. Deakin CT, Alexander IE, Kerridge I. Accepting Risk in Clinical Research: Is the Gene Therapy Field Becoming Too Risk-averse? Mol Ther. 2009;17(11):1842–48. doi:10.1038/mt.2009.223
4. Hayden EC. Gene therapy researcher warns stem-cell scientists not to repeat his field's mistakes. Nature doi:10.1038/news.2009.455
5. Jenks S. Gene Therapy Death — "Everyone Has to Share in the Guilt". J Natl Cancer Inst. 2000;92(2):98-100.
6. Lewis R (2014) SCID-X1 Gene Therapy, Take 2. PLOS Blog. http://blogs.plos.org/dnascience/2014/10/09/good-guy-virus-scid-x1-gene-therapy-take-2/
7. Raper SE, Yudkoff M, Chirmule N, Gao GP, Nunes F, Haskal ZJ, Furth EE, Propert KJ, Robinson MB, Magosin S, Simoes H, Speicher L, Hughes J, Tazelaar J, Wivel NA, Wilson JM, Batshaw ML. A pilot study of in vivo liver directed gene transfer with an adenoviral vector in partial ornithine transcarbamylase deficiency. Hum Gene Ther. 2002;13:163–175.
8. Raper SE, Chirmule N, Lee FS, Wivel NA, Bagg A, Gao GP, Wilson JM, Batshaw ML. Fatal systemic inflammatory response syndrome in a ornithine transcarbamylase deficient patient following adenoviral gene transfer. Mol Gen Metab. 2003;80:148–58.
9. Shalala D. Protecting research subjects–what must be done. N Engl J Med. 2000;343:808–10.
10. Wenner M. (2009) Gene therapy: An Interview with an Unfortunate Pioneer. Web: http://www.scientificamerican.com/article/gene-therapy-an-interview/
11. Wilson JM. Medicine. A history lesson for stem cells. Science 2009;324(5928):727-728.
12. Wilson JM. Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency. Mol Gen Metab. 2009; 96: 151–57.



Kevin Gorsky

Kevin Gorsky is a medical student at McGill University with a BSc in microbiology and immunology. An avid athlete and amateur bodybuilder, Kevin also embraces outdoorsmanship and travel. Kevin's research acumen includes experiences in both fundamental and clinical research including HCV lnRNA quantification and coronary artery bypass grafting (CABG) patency studies. Kevin is currently receiving training in rheumatology at Mt. Sinai Hospital in Toronto, where he is involved with quality improvement research.

News Article

Still Assembling Parts - The barriers to personalized genetics for pain management

Isabella Albanese
News Reporter (HSI 2014-2015)

Personalized medicine is an emerging concept in the practice of medicine that involves taking a patient-centered approach to disease prevention, diagnosis and therapeutic optimization using knowledge obtained from a patient's genetic profile. Pharmacogenomics, the specific practice of using genetic information to better predict individual patient variability to treatments is becoming increasingly relevant in the field of chronic pain management[1]. Chronic pain is characterized as pain lasting longer than 12 weeks, and is one of the most common reasons for patients to seek medical care[2]. Despite its prevalence, in Canada, the management of both acute and chronic pain is considered inadequate. With an increasing number of pain medication-related deaths in Ontario[3], long wait times at pain clinics across the country[4], insufficient pain curricula taught in Canadian medical schools[5] and underfunded research relative to the severity of the issue[6], there are several aspects of pain management in the Canadian healthcare system that need improvement[7]. In addition, chronic pain has been estimated to cost Canadians approximately 6 billion dollars per year in direct costs, and this does not take into account the indirect costs such as decreased work productivity and a reduced quality of life[8]. Thus, the potential benefits on both an individual patient and societal level of approaching pain therapy and prevention in a personalized way are numerous. However, pain is a complex trait that is not only subjective and difficult to measure but also is influenced by many factors including, but not limited to, numerous environmental exposures, genetic variants, neuronal circuits, and physiological status such as inflammation and stress response. These factors present just some of the potential barriers to both personalized pain medicine, and pain management in general.

Dr. Jeffrey Mogil, a prominent pain genetics researcher at McGill University, focuses his research specifically on individual differences in pain sensitivity and susceptibility, analyzing both genetic and environmental aspects of this, as well as their interaction. Dr. Mogil says, "research in the field has shifted to becoming more and more translational". While he has had success implementing this in the behavioural study of pain differences, his most recent work on the capacity for mice to experience empathy for pain amongst familiar mice, and the reproducibility of this phenomenon among human subjects[9], Dr. Mogil cites many barriers to pain genetics research becoming translational. When asked what the main barrier is to making pain genetics research translate to the bedside, Dr. Mogil answers with one word, "Complexity".

"It [pain genetics] could have turned out to be simple like with the BRCA1/2 genes (breast cancer 1 and 2, early onset) in breast cancer or the CFTR gene (cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7) in cystic fibrosis, where there is one predominate gene responsible for the condition. But, there are a lot of other conditions like diabetes and increasingly, pain falls under this second camp of disorders that are vastly multigenic with hundreds of relevant genes."

Dr. Mogil brought up an excellent point about the complexity of pain genetics as there have been hundreds of genes associated with pain phenotypes and nociception, and the list continues to grow[10]. In fact, Dr. Mogil's research group recently published a study in which they examined the effects of pharmacologically targeting a 6-transmembrane splice variant of the μ-opioid receptor gene in mice, and found that it produced potent analgesic effects[11]. The μ-opioid receptor (MOR) is arguably the most important target in pain treatment, however despite the efficacy and widespread use of this target in treatment (e.g. morphine), there is a high rate of adverse events. In addition to having potent analgesic effects, Dr. Mogil's study found that specifically targeting 6-TM splice variants of the μ-opioid receptor gene with synthetic compound iodobenzoylnaltrexamide (IBNtxA) also resulted in a vast improvement in side effects. It is postulated that 6-TM MOR's function is mediated through completely different cellular pathways than conventional MOR hence the wide variation in side effect profiles[12]. A major contributing factor to the adverse events associated with opioid use is

individual variability, some of which may be explained by variations in the μ-opioid receptor gene[13]. There have been single nucleotide polymorphisms (SNPs) associated with the 6TM and 7TM MOR variants. This is of potential clinical significance as clinical evaluation of functional genetic variants of μ-opioid receptor gene locus may provide a clearer picture of inter-patient variability to opioid therapy, and may lead to the development of new pharmacological targets[13]. In addition to opioid receptor variants, there are several other categories of genes that have been implicated in pain genetics including, but not limited to serotonin receptors and transporters, pro-opiomelanocortin (POMC), cannabinoid receptors, adrenergic receptors, monoamine oxidase (MAO), interleukins as well as several growth factors and transporters[14].

The analogy Dr. Mogil uses is as follows: "If you want to explain how a car works, one of the first things that you need to do is get the parts list of the car. The problem is that even when you have the parts list of the car, you still don't know how the car works. That is where we are in pain genetics. We are assembling the parts list, which needs to be done but is not going to explain the other things after that which are hard for me to even envisage at this point."

Despite the complexity and the many unanswered questions regarding pain genetics, there have been advances in the use of pharmacogenetics and personalized medicine in chronic pain management. A recent study by Linares et al. presents a clinical framework for assessing a patient's CYP2D6 phenotype[15]. Categorizing patients as CYP2D6 ultra-rapid metabolizer, extensive metabolizer, or poor metabolizer phenotypes using pharmacokinetic profiling allows for a safer and more efficient method of determining oxycodone dose thus decreasing the likelihood of adverse side effects [15]. This is an important first step in the integration of the use of individual genetic variations to pain and corresponding adjustments to clinical practice. There is still a long way to go in the classification of the genetic factors contributing to pain susceptibility and response to treatment. Despite this, it is essential that we move forward and continue to support research that aims to classify genetic explanations for pain variation and the potential clinical benefits of manipulating these targets.

Dr. Mogil is also a member of the Alan Edwards Center for Research on Pain (AECRP), an organization that brings together McGill University researchers from the Faculties of Medicine, Dentistry and Science as well as members from across the province, clinicians and clinical pain researchers for the united purpose of sharing new advances in pain research and fostering discussions on clinically relevant applications of this work. In the spirit of promoting translational research and the integration of basic research science and clinical practice, the AECRP's many initiatives include providing research grants and graduate scholarships, hosting bimonthly Journal Clubs, hosting Pain Day, which is an annual research conference on the study and treatment of pain, as well as weekly pain rounds in the Alan Edwards Pain Management Unit of the McGill University Health Centre. While there is undoubtedly a great deal of progress still to be made in the field of pain genetics, it is collaborative efforts like this that encourage the continued pursuit of basic science research with the potential to have measurable impacts on clinical care and patients living with chronic pain. ■

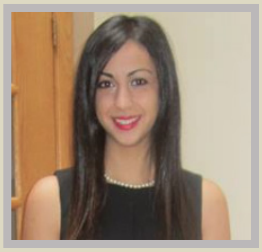
We would like to extend special thanks to Dr. Jeffrey Mogil for his time and effort in contributing to this article.

References

1. Chianta M, Guevara M. Pharmacogenetics and pain management: an opportunity to advance personalized patient care. MLO Med Lab Obs. 2014 Feb;46(2):9, 11.
2. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. JAMA. 1998 Jul 8;280(2):147-51.
3. Dhalla IA, Mamdani MM, Sivilotti ML, Kopp A, Qureshi O, Juurlink DN. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. CMAJ. 2009 Dec 8;181(12):891-6.
4. Peng P, Choiniere M, Dion D, Intrater H, Lefort S, Lynch M, et al. Challenges in accessing multidisciplinary pain treatment facilities in Canada. Can J Anaesth. 2007 Dec;54(12):977-84.
5. Watt-Watson J, McGillion M, Hunter J, Choiniere M, Clark AJ, Dewar A, et al. A survey of prelicensure pain curricula in health science faculties in Canadian universities. Pain Res Manag. 2009 Nov-Dec;14(6):439-44.
6. Lynch ME, Schopflocher D, Taenzer P, Sinclair C. Research funding for pain in Canada. Pain Res Manag. 2009 Mar-Apr;14(2):113-5.
7. Lynch ME. The need for a Canadian pain strategy. Pain Res Manag. 2011 Mar-Apr;16(2):77-80.
8. Phillips CJ, Schopflocher D. Chronic Pain: A Health Policy Perspective (eds S. Rashiq, D. Schopflocher, P. Taenzer and E. Jonsson). Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KgaA; 2008. Chapter 4, The Economics of Chronic Pain; p. 41-50.
9. Martin LJ, Hathaway G, Isbester K, Mirali S, Acland EL, Niederstrasser N, et al. Reducing Social Stress Elicits Emotional Contagion of Pain in Mouse and Human Strangers. Curr Biol. 2015 Feb 2;25(3):326-32.
10. Perkins JR, Lees J, Antunes-Martins A, Diboun I, McMahon SB, Bennett DL, et al. PainNetworks: a web-based resource for the visualisation of pain-related genes in the context of their network associations. Pain. 2013 Dec;154(12):2586 e1-12.
11. Wieskopf JS, Pan YX, Marcovitz J, Tuttle AH, Majumdar S, Pidakala J, et al. Broad-spectrum analgesic efficacy of IBNtxA is mediated by exon 11-associated splice variants of the mu-opioid receptor gene. Pain. 2014 Oct;155(10):2063-70.
12. Convertino M, Samoshkin A, Gauthier J, Gold MS, Maixner W, Dokholyan NV, et al. mu-Opioid receptor 6-transmembrane isoform: A potential therapeutic target for new effective opioids. Prog Neuropsychopharmacol

Biol Psychiatry. 2014 Dec 6. pii: S0278-5846(14)00235-8.

13. Diatchenko L, Robinson JE, Maixner W. Elucidation of mu-Opioid Gene Structure: How Genetics Can Help Predict Responses to Opioids. Eur J Pain Suppl. 2011 Nov 11;5(2):433-8.
14. Fillingim RB, Wallace MR, Herbstman DM, Ribeiro-Dasilva M, Staud R. Genetic contributions to pain: a review of findings in humans. Oral Dis. 2008 Nov;14(8):673-82.
15. Linares OA, Daly D, Linares AD, Stefanovski D, Boston RC. Personalized oxycodone dosing: using pharmacogenetic testing and clinical pharmacokinetics to reduce toxicity risk and increase effectiveness. Pain Med. 2014 May;15(5):791-806.



Isabella Albanese

Isabella is a first year medical student at McGill University. She completed her Master's degree in Experimental Medicine at McGill, studying the role of Wnt signaling pathways in atherosclerotic vascular calcification. She aims to incorporate science journalism into her career as a physician and hopes to contribute to remedying the spread of scientific misinformation to the public in our current society.

News Article

In the age of epigenetics, how do we define a gene?

Alexandra Fletcher
News Reporter (HSI 2014-2015)

Before Darwin, there was Lamarck. Lamarck believed in the inheritance of acquired characteristics; a theory that explored non-random phenotypic changes, but fell out of fashion with Darwin's Origin of Species[1]. The story that epitomizes Lamarckian evolution is that of the giraffe neck. In this instance, the giraffe was originally a short-necked creature that strengthened and lengthened its neck through consistent use, passing a longer, stronger neck down to its offspring. In contrast, Darwin believed in random mutations that may or may not increase an animal's likelihood of survival and reproduction. These mutations were more likely to be passed on if the animal survived and reproduced, but did not develop because of their inherent worth. It was cases of deviation from expected Mendelian inheritance patterns that hinted to scientists that epigenetic mechanisms must exist[2].

This immutability of genetics, the idea of an inheritable set of laws embedded within our DNA, is gaining increasing acceptance[3]. Expressions such as "it's in your genes" have become commonplace in daily conversation. Despite this, epigenetics – the study of modifiable traits that are the result of environmental modifications –transforms this point of view and thereby gives a new outlook on the nature versus nurture debate. According to Dr. Guillaume Bourque, the Bioinformatics Director at McGill University and Génome Québec Innovation Centre, one way in which epigenetics can be comprehended that does not contradict public understanding of genetics is that every cell in the body contains the same genetic message, but not all cells have the same size, shape, or function. Cellular differentiation is therefore not due to different genes, but the microenvironment surrounding each cell, which results in some parts of the genome being activated while other parts are silenced. Epigenetics functions through a variety of chemical mechanisms, such as methylation and the addition of histone markers. To add a layer of complexity, these markers can be stable enough to be 'inherited' from one cell division to the next, but these changes are not permanently encoded into the genome. In the case of methylation, a methyl group (CH3) is covalently bound to the nucleotide cytosine[4]. This methylation is conserved during DNA replication because of the action of the enzyme DNA methyltransferase, which is capable of recognizing a hemi-methylated DNA strand formed from the methylated parent strand and methylating an un-methylated daughter strand[4]. In the case of histone modification, several chemical processes (including methylation) act on the histone protein responsible for binding DNA in its heterochromatic state, although the mechanism for maintaining modification during DNA replication is less clearly understood[4]. To further complicate the genetics/epigenetics paradigm, some of these chemical modifications can be passed on to offspring, though these effects are not as strong as those seen in genetic inheritance. Originally, epigenetic marks were thought of as being 'erased' either prior to or during meiosis, thereby limiting epigenetic changes to the individual who experienced them[2]. However, the evidence is now showing that 'soft inheritance' of epigenetic modifications is possible; in rat models, the treatment of gestational females with industrial chemicals leads to male infertility in subsequent generations[5]. And yet these two processes are distinct, as one is much more permanent than the other. One final subtlety within the description of epigenetics is that these modifications to the genome might also regulate higher-level interactions between distant DNA regions within or between chromosomes, rather than simply regulating individual genes[2].

Another aspect of epigenetics that differs from genetics is that these changes occur over the course of someone's lifetime, and are therefore dependent upon the type of exposures an individual has had. The external factors capable of affecting which configuration of genes are turned on or off are still an active area of research. The field of epigenetics is still in its infancy, which means researchers such as Bourque still have many fundamental questions to answer. In his research, Dr. Bourque is working toward identifying what constitutes

a 'normal' or 'baseline' state of a given cell. Only upon understanding this is it possible to begin asking what factors have the capacity to impact these baseline states. Identifying a baseline state is more complex than it may appear, given that the moment a cell begins to interact with its environment, it can be considered 'modified' by its surroundings. One way around this is to isolate a specific factor that can be studied across many individuals, and provide empirical evidence to substantiate the assumptions being made about the cell. The types of cohort studies to conduct this kind of research include natural experiments, longitudinal birth cohorts, longitudinal twin studies, prenatal cohorts, and in-vitro fertilization conception cohorts[6]. These cohorts all aim to examine the effect of the environment and the genome at different points in time and space to see how epigenetic markers vary within and between individuals across time. The information derived from these types of studies can provide complementary evidence of the role of epigenetics (See Figure 1 for a graphical representation of study types). Much of the research in this field is also generated from studies using animal models or individual cell lines. Within this research, while it is much easier to precisely regulate the environment, the data generated are limited in their real-life applicability.

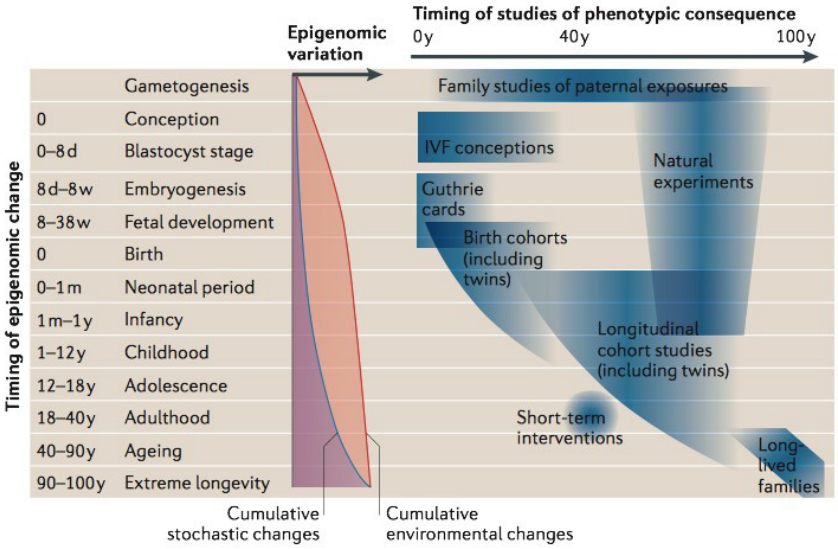


Figure 1. Description of study designs used in epigenetics and the information they provide. Taken from Mill, J. & Heijmans, B.T. From promises to practical strategies in epigenetic epidemiology. Nat. Rev. Genet. 14, 585–594

One of the features drug developers can take advantage of with respect to epigenetics is that it is not as definitive as genetics, which opens up the possibility of temporary and reversible modifications of the genome. Currently, there are drugs available that can modify one's epigenetic profile. This will become an important way to counteract disease states that alter the baseline profile of a cell, including some types of cancers. The first documented example of this was in colorectal cancer, where hypomethylated strands of DNA led to the over expression of oncogenes[4]. Currently, the research into therapeutic benefits has focused on globally inhibiting the mechanism of epigenetics by using methylation or histone acetylation inhibitors, which has the downfall of unintended effects of non-target genes.[4] The alternative would be to target treatments toward the biochemical pathways that are selectively activated or silenced by epigenetic modifications[3]. The fact that it has been recognized that there are some diseases caused by epigenetic rather than genetic mutations suggests that potential therapies provide an exciting opportunity to have an significant impact on the course of disease. ■

References

1. Bird A. Genome Biology: Not Drowning but Waving. Cell 2013;154(5):951–52.
2. Richards EJ. Inherited epigenetic variation — revisiting soft inheritance. Nat Rev Gen. 2006;7:395-401.
3. Koonin EV, Wolf YI. Is evolution Darwinian or/and Lamarckian? Biol Direct. 2009;4:42.
4. Feinberg A. Epigenetics at the Epicenter of Modern Medicine. J Am Med Assoc. 2008; 299(11):1345-50.
5. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 2005;308:1466-69.
6. Mill J, Heijmans BT. From promises to practical strategies in epigenetic epidemiology. Nat Rev Genet. 2013;14:585-94.

Alexandra Fletcher

Alexandra Fletcher is starting her second year as a medical student at McGill University. She holds a master's degree in Family Medicine from McGill. Her research interests include knowledge translation and curriculum development. She is currently working to implement a course on organ donation into the McGill medical curriculum.

News Article

Integrating Genetic Services into Primary Care: Barriers and Benefits

Safina Adatia
News Reporter (HSI 2014-2015)

Developments in genetic research are increasing at an alarming rate, and access to genetic information and testing are now more readily available than ever before[1]. In addition, genetic testing has received a significant amount of media attention resulting in greater public awareness[2]. Advances in medical genetics means that patients who are at risk for genetic conditions can be more readily identified, making disease prevention a priority[3]. Such increases in demand for genetic testing have raised concerns regarding specialist availability[4]. A potential solution to this 'supply and demand' problem is the integration of genomic testing into primary care. Family physicians are often the first point of contact, and patients seek out their primary care providers (PCPs) for information and guidance with regard to genetic testing results.

Primary care is largely focused on prevention and health promotion and is an integral part of maintaining a successful healthcare system[5]. Countries with strong systems see patients with improved health outcomes, reduced all-cause mortality and health disparities, and lower health services costs[5]. Moreover, countries with healthcare systems that are strongly oriented towards primary care tend to offer more equitable and accessible care[6]. Finally, it is estimated that almost 50% of all visits to physicians are to PCPs[7], indicating that they have the greatest accessibility in terms of the patient population.

Since PCPs typically have the largest patient contact, incorporating the use of genetic testing and service provision into primary care could be the ideal solution for the increased awareness and demand for genetic services. For some genetic conditions, such as familial cancers (e.g. breast cancer), preventative genetic testing performed by PCPs can decrease the burden faced by genetic counselors and geneticists[8]. Furthermore, family physicians that have knowledge of a patients' genetic profiles can administer medications more effectively[9], and have a greater impact on treatment plans[8]. Dr. Gillian Bartlett, Associate Professor at McGill University, focuses her research on the positive impact of implementing genetic services into primary care and works to make this integration possible. According to Dr. Bartlett, a potential area where PCPs can play a critical role is in targeted screening or therapeutics for patients. "Family physicians are already seeing patients who have results from direct-to-consumer genetic testing and are looking for more information. The same thing is also now happening with breast cancer risk and will soon spill over into other chronic diseases and their treatments," says Bartlett.

However, integration of genomic services into primary care settings also presents some significant challenges. While many agree that family physicians are in a unique position to offer genetic services to their patients, quite a few barriers exist. A systematic review conducted by Mikat-Stevens et al. (2014) reviewed the literature associated with family physicians' perceived barriers regarding genetic service provision[3]. According to the review, a lack of general genetic knowledge has been cited as the most common barrier that exists for PCPs[3]. This may include a lack of confidence in their general knowledge of genetics[10], and a lack of confidence in being able to take an accurate and detailed family history[11,12].

As the results of genetic testing are quite specific, a further challenge that needs to be considered is the clinical utility of the results. Vasiliki Rahimzadeh, a PhD student in Family Medicine at McGill University, says this barrier exists because of "the nature of what primary care aspires to do and what genomic testing promises to do." According to Rahimzadeh, "primary care is a generalist practice while genomic testing can be very specific, and the links between some genetic determinants of disease are unknown, particularly for chronic diseases." For example, genetic testing that screens for diseases such as cystic fibrosis or chromosomal disorders such as Down's syndrome are relevant to primary care practice; however, testing for genetic markers for Alzheimer's disease is not recommended, as treatment plans do not currently exist and interpretation of results are still uncertain[13].

Dr. June Carroll, a family physician based at Toronto's Mount Sinai Hospital and an Associate Professor at the University of Toronto, is an example of a physician whose goal is to increase genetic literacy among PCP's. She is Co-Director of Genetics Education Canada-Knowledge Organization (GEC-KO), which has developed a website (www.geneticseducation.ca) geared towards PCP's to provide a wealth of tools that PCP's can access. Specifically, these tools aim to guide PCPs in helping their patients navigate genetic testing and determine when it is appropriate to refer their patients for genetic counseling and/or testing. All products featured on the website are primary care-friendly and evidence-based. Based on her research, Dr. Carroll has determined that PCPs see the value of genetic testing, and its foreseeable integration into primary care, however recognizes that "they want a credible source of information and would love to have risk assessment and clinical support tools in genomic medicine integrated into the electronic medical record."

It is inevitable that genetic testing and consultation will enter the realm of primary care. In fact, it already has. PCPs will therefore need to improve their genetic literacy and skills associated with genetic screening. PCPs can help their patients navigate appropriate genetic testing, interpret results from both direct-to-consumer and hospital-based testing, and identify genetic risk factors for certain diseases. However, incorporating genomic services into primary care is not without its challenges. There is a need to identify the most effective ways of integrating genetic services into primary care in order to provide optimal patient-centred care. ■

References

1. Carroll JC, Rideout AL, Wilson BJ, Allanson JM, Blaine SM, Esplen MJ, et al. Genetic education for primary care providers: improving attitudes, knowledge, and confidence. Can Fam Physician. 2009;55(12):e92-9.
2. Etchegary H, Cappelli M, Potter B, Vloet M, Graham I, Walker M, et al. Attitude and knowledge about genetics and genetic testing. Public Health Genom. 2010;13(2):80-8.
3. Mikat-Stevens NA, Larson IA, Tarini BA. Primary-care providers perceived barriers to integration of genetics services: a systematic review of the literature. Genet Med. 2015;17:169-76.
4. Touchette N, Holtzman N, JG. D, S. F. Toward the 21st century - incorporating genetics into primary health care. New York, NY: Cold Spring Harbor Laboratory Press; 1997.
5. Starfield B, Shi L, Macinko J. Contribution of primary care to health systems and health. Milbank Q. 2005;83(3):457-502.
6. Atun N. What are the advantages and disadvantages of restructuring a health care system to be more focused on primary care services? Copenhagen: WHO Regional Office for Europe 2004.
7. Petterson SM, Liaw WR, Phillips RL, Rabin DL, Meyers DS, Bazemore AW. Projecting US Primary Care Physician Workforce Needs: 2010-2025. Annals Fam Med. 2012; 10(6):503-9.
8. Bartlett G, Rahimzadeh V, Longo C, Orlando LA, Dawes M, Lachaine J, et al. The future of genomic testing in primary care: the changing face of personalized medicine. Pers Med. 2014; 11(5):477-86.
9. Pulley JM, Denny JC, Peterson JF, Bernard GR, Vnencak-Jones CL, Ramirez AH, et al. Operational implementation of prospective genotyping for personalized medicine: the design of the Vanderbilt PREDICT project. Clin Pharmacol Ther. 2012;92(1):87-95.
10. Fuller M, Myers M, Webb T, Tabangin M, Prows C. Primary care providers' responses to patient-generated family history. J Genet Couns. 2010;19(1):84-96.
11. Carroll JC, Cappelli M, Miller F, Wilson BJ, Grunfeld E, Peeters C, et al. Genetic services for hereditary breast/ovarian and colorectal cancers - physicians' awareness, use and satisfaction. Community Genet. 2008;11(1):43-51.
12. Al-Habsi H, Lim JN, Chu CE, Hewison J. Factors influencing the referrals in primary care of asymptomatic patients with a family history of cancer. Genet Med. 2008;10(10):751-7.
13. Emery J, Hayflick S. The challenge of integrating genetic medicine into primary care. Brit Med J. 2001;322(7293):1027-30.

Safina Adatia

Safina is in the final year of the Master's program in Family Medicine at McGill University. Her research includes a mixed methods evaluation of the environment (noise levels, number of interruptions, patient experience) on a maternity ward at a Montreal hospital. She is interested in health services and policy research particularly within primary care. She is also passionate about scientific communication, specifically through the use of social media.

MAIN SUBMISSIONS

Call for Submissions

Back in October 2014, graduate students across Canadian Institutions were asked to submit commentaries on various aspects of **Advancing Human Genetics into Health Action**. The commentaries were 700-800 words in length (maximum of 10 references) and focused on one of three specified topics of interest:

- Personalized medicine and gene therapy: advances in the treatment of genetic diseases
- Ethical challenges and social issues surrounding human genomics
- The impact of the environment on the human genome: the role of epigenomics

Review / Revisions

Starting in March 2015, each submission was reviewed by three blinded Reviewers from HSI. Reviewers provided feedback to the authors by critically assessing the content and writing of each commentary. After receiving feedback from Reviewers, authors were given three weeks to revise their submission and resubmit their manuscript to the journal. Our team of Senior Editors went through each commentary, providing a decision on publication and any final comments.

Judging Process

Nine Faculty members from Canadian Institutions (see Page 22) were recruited as expert advisors, playing an instrumental role in the judging process of the journal's submissions. For each of the above categories, four faculty advisors were assigned to rank each of the submissions according to pre-defined criteria. Scores within each category were then summed as a collective rank of the individual faculty member's selections:

Example: Rank #1: Paper 1C = 5 Points
Rank #2: Paper 1A = 4 Points
Rank #3: Paper 1D = 3 Points

Section 3: Main Submissions

Winners

After processing the rankings from all our faculty advisors, a combined score was tabulated for each submission. The authors of the highest scoring paper for each category were granted expedited review for possible publication in our two partner journals: *Epigenomics and Journal of Genomics*.

The quality and creativeness of all the submissions were outstanding, and both the editorial team and faculty advisors highly commend the authors for their achievement and hard work! After tabulating the results, we are pleased to announce the winning submissions for the 2015 issue of *Health Science Inquiry*.

2015 Winners

The Impact of the Environment on The Human Genome: The Role of Epigenomics

Yichi (Tony) Zhang

Envrionmental responses mediated by histone deacetylation - biological and clinical implications *(Page 43)*

Selected for submission to Epigenomics

Personalized Medicine and Gene Therapy: Advances in the Treatment of Genetic Diseases

Jennifer Kramer

Mitochondrial replacement therapy: Modifying genes to prevent inherited mitochondrial disease *(Page 43)*

Selected for submission to Journal of Genomics

Past Winners

Chelsea Himsworth's paper was published as a 'Reflection and Reaction' piece in a 2010 issue of **The Lancet**: **http://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2810%2970148-1/fulltext**

Timothy W. Buckland's paper was published as a 'Salon' piece in a 2011 issue of **The Canadian Medical Association Journal**: **http://www.cmaj.ca/content/early/2011/10/11/cmaj.111419.long**

Marc Bomhof, Jane Polsky, and Denise Darmawikarta's paper was showcased on the 'News' section in 2012 of the **International Journal of Obesity** website: **http://www.nature.com/ijo/index.html**

Leigh M. Vanderloo and Gillian Mandich's paper was published in a 2013 issue of the **Canadian Journal of Community Mental Health**: **http://www.cjcmh.com/doi/abs/10.7870/cjcmh-2013-032**

Section 3: Main Submissions

JUDGING PANEL

We are very fortunate to have the involvement of **3 distinguished faculty members and researchers** from all across Canada for this issue of Health Science Inquiry. Each faculty advisor was assigned to one of the three categories students were asked to write commentaries on, and their main responsibilities were to judge and comment on the

Ekaterina Olkhov-Mitsel, PhD

Post-doctoral Fellow; Dr. Bharati Bapat's lab, the Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, Toronto.

Ekaterina Olkhov-Mitsel has recently completed her PhD in the Department of Laboratory medicine and pathobiology at the University of Toronto in 2015 and is currently a post-doctoral fellow in Dr. Bharati Bapat's lab at the Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, Toronto. Her research is focused on investigating prostate cancer epigenetic biomarkers for implementation in the clinical setting.

Jacques P. Tremblay, PhD

Professor; Department of Molecular Medicine, Laval University.

Dr. Tremblay has obtained a PhD in Neurosciences from the University of California in San Diego in 1974. He has been at Laval University in Québec since, as a post-doctoral fellow, a professor and a department chairman. He is currently a full professor in the Department of Molecular Medicine. He has published over 250 scientific articles.

Stephen Scherer, PhD

Director of The Centre for Applied Genomics, The Hospital for Sick Children; Director, McLaughlin Centre, Univeristy of Toronto. Professor of Department of Medicine, University of Toronto,

Known for contributions to discovering the phenomena of global copy number variation (CNVs) of DNA and genes as the most abundant type of genetic variation in the human genome, Dr. Scherer leads one of Canada's busiest laboratories. His group has discovered numerous disease susceptibility genes and most recently has defined CNV and other genetic factors underlying autism. He collaborated with Craig Venter's team to decode human chromosome 7 and to generate the first genome sequence of an individual. Some 300 scientific papers document his work (cited >20,000 times).

Main Submission

Gene Therapy: A Strategy for the Treatment of Alzheimer's Disease

Danielle Weber-Adrian

University of Toronto

In 2010, an estimated 35.6 million people worldwide were suffering from dementia[1]. This number is expected to increase, resulting in a global disease burden of 115[4]. million people by 2050[1]. Alzheimer's disease (AD) is the most common form of dementia, and is characterized by memory loss[2], gross atrophy of the brain, and the accumulation of both intraneuronal tau protein aggregates and extracellular amyloid-β protein[3]. Gene therapy allows for therapeutic treatment through the continuous expression of a transgene, and is currently under clinical investigation for a variety of neurological diseases including AD[4]. Gene therapy has two main delivery conduits: viral vectors and nonviral vectors[5]. However, a challenge in AD treatment with gene therapy is the delivery of the therapeutic vector into the brain. Systemic delivery from the blood is hindered by the presence of the blood brain barrier (BBB), which prevents passive diffusion of ~98% of small molecule drugs and limits the passage of gene therapy vectors[6]. This short review will cover current delivery strategies for overcoming the BBB along with a sample of genes that have been investigated as AD therapeutics.

Invasive delivery requires surgical administration of a therapeutic into the brain through trans-cranial injection, either into the parenchyma or intracerebroventricular space[6]. Intracerebroventricular injection allows for delivery to the entire central nervous system through circulation in the cerebrospinal fluid (CSF); however, this limits delivery in areas of the brain with less CSF exposure, and cannot target delivery to specific brain regions. Additionally, the rate of efflux from the brain into the CSF is much higher than the diffusion rate from the CSF into the brain[6]. Parenchymal injections mediate targeted delivery to specific brain regions, but this technique is associated with risks of surgical complications[6].

Despite these limitations, direct injection provides the only AD-related gene therapy clinical experience to date. As most cases of AD are attributed to idiopathic causes, as opposed to genetic predisposition, gene-mediated therapeutic strategies typically focus on neuroprotection and repair.[7] Thus far, there have been two clinical trials investigating gene therapy for the treatment of AD[8]. Both trials have investigated delivery of neurotrophic growth factor (NGF), which has been shown to prevent cholinergic neuron degeneration[8]. This is of relevance to AD since memory impairment has been directly correlated with degeneration of cholinergic neurons[9]. The phase I results of a clinical trial using intracranial delivery of NGF-expressing fibroblasts showed a reduction in the rate of cognitive decline[8]. A phase II trial using a viral vector to deliver NGF to the basal forebrain is currently underway[8]. Other gene-mediated targets for the treatment of AD in preclinical models have included brain-derived neurotrophic factor (BDNF), fibroblast growth factor 2 (FGF2), and anti-inflammatory cytokine interleukin-4 (IL-4)[7,8]. BDNF gene therapy has been shown to restore spatial memory performance in AD model rodents, partially rescue age-associated changes in gene expression, and prevent neuronal cell death when delivered prior to surgically-induced brain lesions[8]. FGF2 gene therapy directed to the hippocampus has also shown improvement in spatial learning, enhanced clearance of amyloid-β fibrils, and increased neurogenesis in an AD mouse model[8]. Lastly, IL-4 gene delivery to the hippocampus improved spatial learning and increased neurogenesis, while decreasing hypertrophy, nonspecific activation of glial cells, and amyloid β deposition[8]. Although these therapeutics show potential for the treatment of AD, the safety of gene delivery to the brain could be enhanced by a non-surgical distribution method.

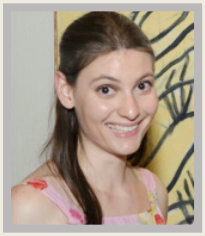
Non-invasive techniques for delivery to the brain, which do not require transporter-mediated delivery across the BBB, include intranasal delivery, chemical disruption of the BBB, and localized permeabilization of the BBB with

focused ultrasound[6,10]. Intranasal delivery bypasses the BBB by delivering the drug through the submucus space of the nose directly into the CSF. However, this technique is restricted in volume (≤100 µL) and associated with the same limitations as intracerebroventricular delivery[6]. Chemical mediated BBB disruption causes global permeabilization of the BBB, but is largely associated with leakage of toxic plasma proteins into the central nervous system[6]. Lastly, MRI-guided focused ultrasound treatment allows for transient and localized BBB permeabilization, and has been shown to mediate targeted gene delivery to the brain in a mouse model[10]. While promising, this technique has yet to be used in a clinical context. Additionally, non-invasive methods for gene delivery to the brain face the challenge of curtailing gene expression in non-target organs after systemic delivery, which could result in side effects.

In conclusion, preclinical and clinical investigations in gene therapy for AD show promise, and suggest that gene therapy could surpass the limitations of traditional pharmacology by providing treatment in a sustained manner. Future studies will hopefully lead to success in clinical trials, as well as progress in developing safer methods for therapeutic delivery. ■

References

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement [Internet]. Elsevier Ltd; 2013 Jan [cited 2014 Jul 10];9(1):63–75.e2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23305823
2. Ye X, Tai W, Zhang D. The early events of Alzheimer's disease pathology: from mitochondrial dysfunction to BDNF axonal transport deficits. Neurobiol Aging [Internet]. 2012 Jun [cited 2014 Dec 22];33(6):1122.e1–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22212405
3. Allen SJ, Watson JJ, Dawbarn D. The Neurotrophins and Their Role in Alzheimer's Disease. Curr Neuropharmacol. 2011;9:559–73.
4. Ginn SL, Alexander IE, Edelstein M l, Abedi MR, Wixon J. Gene therapy clinical trials worldwide to 2012 - an update. J Gene Med. 2013;15:65–77.
5. Lentz TB, Gray SJ, Samulski RJ. Viral vectors for gene delivery to the central nervous system. Neurobiol Dis [Internet]. Elsevier Inc.; 2011 Oct 7 [cited 2012 Aug 1];48(2):179–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22001604
6. Pardridge WM. Blood-brain barrier delivery. Drug Discov Today [Internet]. 2007 Jan [cited 2014 Mar 25];12(1-2):54–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17198973
7. Simonato M, Bennett J, Boulis NM, Castro MG, Fink DJ, Goins WF, et al. Progress in gene therapy for neurological disorders. Nat Rev Neurol [Internet]. Nature Publishing Group; 2013;9(5):277–91. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3908892&tool=pmcentrez&rendertype=abstract
8. Woodbury M, Kiyota T, Ikezu T. Gene Delivery and Gene Therapy for Alzheimer's Disease. In: Bo X, Verhaagen J, editors. Gene Delivery and Therapy for Neurological Disorders [Internet]. New York, NY: Springer Science+Business Media; 2015. p. 85–119. Available from: http://link.springer.com/10.1007/978-1-4939-2306-9
9. Tuszynski MH. Nerve growth factor gene therapy in Alzheimer disease. Alzheimer Dis Assoc Disord [Internet]. 2007;21(2):179–89. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17545746
10. Thévenot E, Jordão JF, O'Reilly MA, Markham K, Ying-Qi L, Foust K, et al. Targeted delivery of scAAV9 to the brain using MRI-guided focused ultrasound. Hum Gene Ther [Internet]. 2012 Jul 27 [cited 2012 Sep 7];23:1–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22838844



Danielle Weber-Adrian

Danielle Weber-Adrian completed her B.Sc. in Biochemistry at the University of Waterloo, and is currently a PhD candidate in the Department of Laboratory Medicine and Pathobiology at the University of Toronto. Danielle's academic passion is neurodegenerative disease research, and her PhD thesis focuses on gene therapy-based strategies for the treatment of Alzheimer's disease. Her research is conducted at the Sunnybrook Research Institute (http://sunnybrook.ca/research/content/?page=sri-groups-brain-home).

Main Submission

Cystic fibrosis drugs: One size does not fit all

Steven Molinski and Saumel Ahmadi

University of Toronto

Cystic Fibrosis (CF) is the most common autosomal recessive disease, and is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene[1]. CF is a multi-system disease primarily affecting epithelial tissues (e.g. lungs, intestine, pancreas), and the main cause of morbidity and mortality is decreased lung function with age[1]. Pathophysiology of CF is caused by disruption of folding and/or function of the CFTR chloride channel, a membrane protein necessary for maintaining epithelial surface hydration[1]. Importantly, the accepted treatment paradigm involves management of symptoms, while CFTR-targeted therapies are a recent development. However, these drugs are useful in only a small subset of patients.

To date, approximately 2000 CFTR mutations have been identified, and this list continues to grow[2]. F508del is the major mutation, present on at least one allele in 90% of CF patients (nearly 3600 Canadians), while G551D is second most common (5% of patients, ~200 Canadians)[3]. Although significant achievements have been made in CF research since the discovery of the CFTR gene at the Hospital for Sick Children in Toronto in 1989, there are still many unanswered questions, and that is why CF remains fatal[4]. However, a major success over the past 50 years in Canada is that the average lifespan of CF patients has increased from 4 to about 50 years (highest in the world)[3]. This is largely attributed to improved clinical care and disease management, although novel CFTR-targeted, drug-based therapies are showing great promise for further enhancement of lifespan and improvement of quality of life in certain patients.

The CF drug Ivacaftor and the G551D mutation: one size fits one size

The first (and only) CFTR mutation-specific drug-based therapy (approved in 2012) repairs the defect of the second most common mutation: G551D. It is a severe gating mutation, which means that it prevents the CFTR chloride channel from opening properly, thereby causing disease[5]. This CFTR-specific therapy, Ivacaftor (also called KalydecoTM or VX-770), acts directly on G551D-CFTR protein to open it and restore normal channel activity[5]. This is only possible because defective G551D-CFTR is in the right place (i.e. properly folded at the cell membrane). Conversely, F508del-CFTR has two defects: a gating defect which can be compared to G551D, as well as a significant folding defect (unlike G551D), so severe that it renders the mutant protein incapable of processing forward to the cell membrane (Figure 1)[6]. Thus, in order to repair F508del-CFTR, the trafficking defect must first be overcome. It now becomes clear why Ivacaftor alone showed minimal efficacy in clinical trials on F508del patients :Ivacaftor does not improve processing. Therefore, at least two drugs are needed to repair F508del-CFTR – a corrector that fixes the trafficking defect, and a channel potentiator with properties similar to that of Ivacaftor (Figure 1).

F508del patients do not benefit from Ivacaftor

Ivacaftor did not improve the health of CF patients with F508del, and for this reason, current research efforts aim to discover novel drugs that improve F508del-CFTR processing. Major leaps forward have been achieved by Vertex Pharmaceuticals in the past decade, where two drug 'hits' from high-throughput screens have proceeded to clinical trials. These compounds, Lumacaftor (VX-809) and VX-661, partially repair F508del-CFTR processing in vitro; however, they do not provide clinical benefit in the presence or absence of Ivacaftor[7]. This can be partly explained by recent evidence suggesting that disease variability between CF patients with the same CFTR mutation (as well as therapeutic responses) is due to the contribution of several modifier genes[8]. Further, it has recently been suggested that Ivacaftor could be detrimental to F508del patients, since it may reduce the quantity and

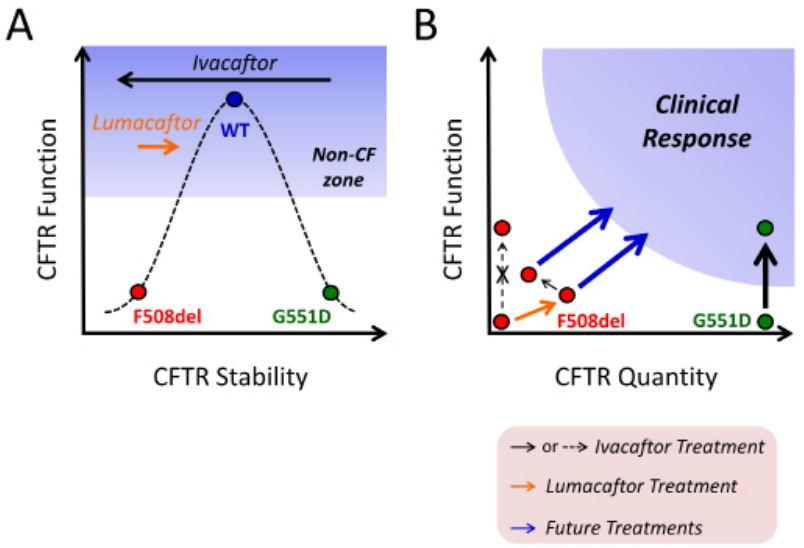


Figure 1. Comparing F508del- and G551D-CFTR function, stability and drug responses. (A) Relationship between CFTR function and stability. Wild-type (WT) CFTR has an intermediate stability, allowing for optixmal function, whereas F508del lacks stability (and therefore processing) and G551D is hyper-stable (lacks gating activity). Ivacaftor shifts G551D stability toward WT and destabilizes F508del, whereas Lumacaftor increases the stability of F508del, partially rescuing the processing defect. Modified from Cholon et al., 2014.8 (B) CF treatments and their clinical effects on patients with either the F508del or G551D mutation. Lumacaftor partially enhances F508del quantity and function, but Ivacaftor impedes this effect. Therefore, future treatments are required to achieve a clinical response. However, Ivacaftor alone provides a significant clinical response in CF patients with G551D. Modified from Cutting, 2015[1].

quality of F508del-CFTR through destabilization (Figure 1)[9]. Therefore, novel F508del-CFTR-specific drugs must be identified. This may also be the case for other mutations, requiring identification of novel compounds on a case-by-case basis. Unfortunately, it seems that repurposing current drugs is not as simple as initially thought, and previous drug discovery efforts for F508del-CFTR may not be readily translated into therapies for other CFTR mutations.

Path to successful therapies for patients with F508del or more rare mutations

Understanding drug responses for each CFTR mutation will help elucidate mechanism of action, and assist in the design of mutation-specific therapies (i.e. personalized CF medicine). Ivacaftor and Lumacaftor taught us that repurposing compounds is not straightforward – that one size does not fit all. It is clear that there are future challenges for CF drug discovery. However, there is hope for repurposing certain CF drugs towards mutations within the same dysfunctional class; for example, Ivacaftor is being approved to treat 9 additional CFTR gating mutations[10]. Therefore, by building on this innovation via future clinical testing, it may still be possible to further expand the number of mutations (population size) in which Ivacaftor and Lumacaftor have therapeutic benefits, or in other words, enhance the size in which these drugs fit CF patients.

■

References

1. Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. Nat Rev Genet. 2015; 16(1):45-56.
2. Sosnay PR, Siklosi KR, Van Goor F, Kaniecki K, Yu H, Sharma N, Ramalho AS, Amaral MD, Dorfman R, Zielenski J, Masica DL, Karchin R, Millen L, Thomas PJ, Patrinos GP, Corey M, Lewis MH, Rommens JM, Castellani C, Penland CM, Cutting GR. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. Nat Genet. 2013; 45(10):1160-7.
3. Cystic Fibrosis Canada. 2013 Annual Report [internet]. 2013 [updated 2014 April; cited 2015 February 1]. Available from: http://www.cysticfibrosis.ca/wp-content/uploads/2014/06/CFC_AnnualReport_2013_ENGLISH_FINAL.pdf.
4. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou JL, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science. 1989; 245(4922):1066-73.
5. Van Goor F, Hadida S, Grootenhuis PD, Burton B, Cao D, Neuberger T, Turnbull A, Singh A, Joubran J, Hazlewood A, Zhou J, McCartney J, Arumugam V,Decker C, Yang J, Young C, Olson ER, Wine JJ, Frizzell RA, Ashlock M, Negulescu P. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. PNAS. 2009; 106(44):18825-30.
6. Molinski S, Eckford PD, Pasyk S, Ahmadi S, Chin S, Bear CE. Functional Rescue of F508del-CFTR Using Small Molecule Correctors. Front Pharmacol. 2012; 3:160.
7. Okiyoneda T, Veit G, Dekkers JF, Bagdany M, Soya N, Xu H, Roldan A, Verkman AS, Kurth M, Simon A, Hegedus T, Beekman JM, Lukacs GL. Mechanism-based corrector combination restores ΔF508-CFTR folding and function. Nat Chem Biol. 2013; 9(7):444-54.
8. Cholon DM, Quinney NL, Fulcher ML, Esther CR Jr, Das J, Dokholyan NV, Randell SH, Boucher RC, Gentzsch M. Potentiator ivacaftor abrogates pharmacological correction of ΔF508 CFTR in cystic fibrosis. Sci Transl Med. 2014; 6(246):246ra96.
9. Veit G, Avramescu RG, Perdomo D, Phuan PW, Bagdany M, Apaja PM, Borot F, Szollosi D, Wu YS, Finkbeiner WE, Hegedus T, Verkman AS, Lukacs GL. Some gating potentiators, including VX-770, diminish ΔF508-CFTR functional expression. Sci Transl Med. 2014; 6(246):246ra97.
10. Cystic Fibrosis Canada. Patient Group Input to the Common Drug Review at CADTH [internet]. 2014 [updated 2014 July 22; cited 2015 February 1]. Available from: http://www.cysticfibrosis.ca/wp-content/uploads/2014/07/Patient-Group-Input-Kalydeco-Gating-Mutations-22July2014-Final-Version.pdf

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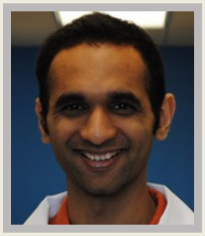

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Saumel Ahmadi received his MD from Saurashtra University in India. He is currently a PhD candidate (Physiology) at the University of Toronto, and works in Dr. Christine Bear's lab group in the Programme of Molecular Structure & Function, as well as Dr. Johanna Rommens' lab group in the Programme of Genetics & Genome Biology at The Hospital for Sick Children. Saumel is interested in the study of modifier genes and developing novel high-throughput assays for the discovery of Cystic Fibrosis drugs for F508del and other CFTR mutations.

Main Submission

Genetic screening: A cautionary tale for the public and a need for greater public education

Anita Acai and Naythrah Thevathasan

McMaster University & Queen's University

In a 2013 article written for The New York Times, American actress Angelina Jolie announced that she had chosen to undergo a double mastectomy after learning that she was a carrier of the BRCA1 mutation[1]. Her story led to unprecedented media coverage and an increased public awareness of genetic screening globally. However, according to a survey of the American general public, while 75 percent of respondents were aware of Angelina's story, fewer than 10 percent had an appropriate understanding of how to interpret her screening results and her relative risk of cancer[2]. Recent advances in our knowledge of genetics and increased media coverage of stories like Angelina's have increased public awareness of genetic screening. Unfortunately, this awareness has not necessarily translated into an improved understanding of its purpose and implications.

A direct result of the recent publicity of genetic screening has been an increased consumer demand for this health service. Research on the "Angelina Jolie effect" in the UK has shown that referrals for genetic screening more than doubled in the months after Angelina's announcement, and remained at that level for nearly five additional months[2]. While it has historically been physicians and genetic counselors ordering tests and explaining results to patients, genetic information is now readily available at an individual's fingertips. With the introduction of self-screening kits into the Canadian market, individuals can now order a kit from 23andMe Inc. for only $199. With the provision of a saliva sample, they receive information on genealogical and health information based on more than 200 genetic markers[3].

The problem with these screening kits – and genetic screening in general – is that they have limited clinical utility[4]. Simply taking a test and getting the results does not guarantee improved health outcomes. Therefore, in deciding whether or not to undergo genetic screening, one must carefully evaluate whether the information obtained from the test is likely to be useful in directing clinical care and if the value gained from the information outweighs the costs of obtaining it. This is also true in policy decisions where it is necessary to evaluate the full clinical utility of genetic tests when making decisions related to subsidizing costs in a public healthcare system.

Another problem with the widespread availability of genetic testing is that the general public may not have an adequate level of knowledge to interpret their screening results. For example, a study in 2004 found that while most respondents had conversational familiarity with genetic terminology, they became increasingly frustrated and hesitant when they were asked to specifically define these terms or to discuss the location of genes in the human body[5]. Study responses showed a poor understanding of basic scientific concepts, a result that has considerable implications for public health. Another study, which assessed individual responses to genomic risk information for Type 2 diabetes mellitus, showed that respondents were less informed about the social consequences of genetic testing (e.g., genetic discrimination by health insurers and employers) than about its medical uses[6]. Understanding of genetic concepts appears to be influenced by certain demographic variables such as race, education level, and age[6-8]. These variables have been shown to affect both an individual's understanding of genetic screens and the level of determinism with which they interpret their results.

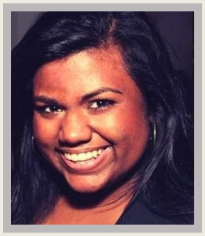
A poor understanding of genetic concepts coupled with an increased public interest in genetic screening means that consumers may be opting for genetic screens without understanding the full emotional, ethical, financial, and physical implications of doing so. An issue of primary concern is the confidentiality of results. How should the information obtained during screening be communicated, and whom should this information be shared with? For

example, the introduction of self-screening kits in Canada have led to questions about the legislation governing the privacy of results[3]. Unlike the United States, there are no similar genetic privacy or discrimination laws in Canada [9]. Thus, there is little keeping insurance companies or employers from asking about screening results and then using these results to the disadvantage of the consumer.

Given major scientific advances in genetics, there has been a significant push toward incorporating genetics into our healthcare practices. Media attention has also piqued public interest in how genetics could be used to reduce the burden of disease in society. While public awareness has translated into greater consumer demand for genetic screening, this has not been accompanied by an adequate public understanding of screening and its implications. Therefore, it is imperative that health care providers and policymakers consider the implications of mainstream genetic screening and invest in education efforts surrounding this topic. Although understanding the genetic determinants of disease is a promising field of study, its social implications deserve much greater attention than they have been given so far. ■

References

1. Jolie A. My medical choice [Internet]. The New York Times; 2013 May 14 [cited 2014 Dec 17]. Available from: http://www.nytimes.com/2013/05/14/opinion/my-medical-choice.html
2. Evans DG, Barwell J, Eccles DM, Collins A, Izatt L, Jacobs C, et al. The Angelina Jolie effect: how high celebrity profile can have a major impact on provision of cancer related services. Breast Cancer Res. 2014 Sep 19;16(5):442.
3. 23andMe - Genetic testing for ancestry [Internet]. 2015 [cited 2015 Mar 10]. Available from: https://www.23andme.com/en-ca/
4. Burgess MM. Beyond consent: ethical and social issues in genetic testing. Nat Rev Genet. 2001 Feb;2(2):147–51.
5. Lanie AD, Jayaratne TE, Sheldon JP, Kardia SLR, Anderson ES, Feldbaum M, et al. Exploring the public understanding of basic genetic concepts. J Genet Couns. 2004 Aug;13(4):305–20.
6. Haga SB, Barry WT, Mills R, Ginsburg GS, Svetkey L, Sullivan J, et al. Public knowledge of and attitudes toward genetics and genetic testing. Genet Test Mol Biomark. 2013 Apr;17(4):327–35.
7. Kaphingst KA, McBride CM, Wade C, Alford SH, Reid R, Larson E, et al. Patient understanding of and responses to multiplex genetic susceptibility test results. Genet Med Off J Am Coll Med Genet. 2012 Jul;14(7):681–7.
8. Saukko PM, Ellard S, Richards SH, Shepherd MH, Campbell JL. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res. 2007 Jun 12;7(1):82.
9. Lippman A. Why genetic self-test kits should not be allowed into Canada [Internet]. The Globe and Mail; 2014 Oct 16 [updated 2014 Oct 17; cited 2014 Dec 16]. Available from: http://www.theglobeandmail.com/globe-debate/why-genetic-self-test-kits-should-not-be-allowed-into-canada/article21124570/



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Naythrah is currently pursuing her MPH (Master of Public Health) at Queen's University. Her passion for public health stems from her interest in health and education, and how the two can come together to keep the population healthy. After completing an internship with the World Health Organization in Sri Lanka, she has further developed a particular interest in health equity issues among marginalized populations. Naythrah holds a BSc in Bio-medical Sciences from the University of Guelph. She is a 3M National Student Fellow and a two-time Young Woman of Distinction Nominee.

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Main Submission

Distinction without difference? Some considerations for 'race' in health genomics

Bianca Dreyer[1] & Eric Oosenbrug[2]

1. Wilfrid Laurier University; 2. York University

On September 20th 2008, Brian Sinclair, a 45-year-old double-amputee, died of a treatable bladder infection while waiting for care in the Emergency Room at Winnipeg's Health Sciences Centre. In their testimony, staff revealed that many had assumed the aboriginal man was drunk, homeless, or simply waiting for a ride – not someone in need of immediate medical attention[1]. The racial stereotype of the "drunken Aboriginal" was apparent in the staff's testimony. This case and many others demonstrate that race and racism are important determinants of health and health disparities within Canadian society[1-3].

As medicine advances, new technologies offer opportunities to study health disparities between populations. To understand these populations, appropriate descriptors are necessary. The concept of race is one such readily available descriptor. While the study of genetic differences in health disparity across populations might provide important insight into disease prevention for minority populations, it also poses a number of challenges. Questions such as how to label the populations being studied – and how to make meaningful comparisons without propagating differences that could lead to further discrimination – are among the most difficult to answer. The emerging opportunities for health genomics, we argue, must be accompanied by efforts to critically examine how these developments and their use of race might inadvertently perpetuate or contribute to scientific racism. We will conclude with three recommendations for best practices.

Health genomics focuses on uncovering genetic differences in the incidence and prevalence of health conditions that exist among populations. It thereby provides new opportunities for understanding the interactions between individuals and environments[4]. With increasing ease of access to genetic information it is only a matter of time before this data will be used to directly inform clinical decision-making[5]. In 2005, BiDil became the first race-specific drug approved by the FDA, laying the groundwork for more targeted medicines to come[6].

However, a topic rarely acknowledged or discussed among health genomics researchers are considerations of the merit and ethical consequence of the use of racial categories and conceptions of racial difference. Scientists have long affirmed the concept of race as being biologically meaningless[7], yet improper and/or imprecise terminology remains a potent source for racial prejudice. Labels such as 'European,' 'African' or 'Asian' derived from necessarily limited samples, disregard significant diversity within continental regions and are therefore unlikely to have useful scientific meaning – particularly from the perspective of genetics at the global level[8]. Ironically, by constructing race as a meaningful variable in genetics research, scientists interested in addressing health disparities might inadvertently contribute to the patterns of injustice they seek to eliminate[9].

It is not the association of groups to certain genetically linked diseases that is problematic, but the legitimization of clear, self-evident, natural (or genetic) boundaries between these groups[9]. Ascribing genetic susceptibility or predispositions to broad racial categories or continental groups can easily be misinterpreted as inherent (genetic) inferiority of one race compared to another. Thus, genetic findings may lead to the discrimination against constructed categories of people, while failing to acknowledge the variability within these group[8]. Given that findings from genomic research often support rather than contradict widely held assumptions about race, these findings not only spread rapidly in the general public, but they also tend to do so without notice[9].

To help prevent the perpetuation of racial difference reified by genomics we propose the following three recommendations for scientists working in public health

genomics:

1.) Avoid generalizations: Researchers need to clearly define their sample populations. Group differences should not be interpreted as legitimating clear and self-evident divisions between groups of people. Discussions of appropriate generalizability of results should also be considered.

2.) Avoid simplifications: Researchers need to anticipate how their research will be used by health care professionals and the media, and advocate for a correct translation of their findings.

3.) Avoid problematization: Researchers need to practice caution when ascribing value to group differences to avoid forming a discourse of inferiority and superiority between groups.

Central to our recommendations is a commitment to scientific accuracy and an acknowledgement that racial labels have consequences for which we, as researchers and producers of knowledge, are responsible. Further, it should be a primary concern to consider how the public may perceive and respond to the descriptors that appear in research papers and media articles[8].

Although we cannot predict if and how health genomics will contribute to scientific racism, there is a need to anticipate the various potential social and ethical problems that arise from population descriptors. As we learned from the case of Mr. Sinclair, racial stereotypes can have disastrous consequences. While examining health disparities between populations is an important endeavour for genomics, the distinction of populations based on race might perpetuate rather than mitigate poor health – legitimizing distinction with questionable differences. ■

References

1. Brian Sinclair inquest: aboriginals face racism in ERs, expert says. Global News [Internet]. 2014 June 10 [cited 2015 Mar 22]. Available from: http://globalnews.ca/news/1385222/bring-sinclair-inquest-aboriginals-face-racism-in-ers-expert-says/
2. Racism against aboriginal people in health-care system 'pervasive': study. CBC News [Internet]. 2015 February 3 [cited 2015 Mar 22] Available from: http://www.cbc.ca/news/aboriginal/racism-against-aboriginal-people-in-health-care-system-pervasive-study-1.2942644.
3. Krieger N. Stormy weather: race, gene expression, and the science of health disparities, Am J Public Health. 2005;95(12):2155-60.
4. Zusevics, KL. Public health genomics: a new space for a dialogue on racism through Community Based Participatory Research. Public Health. 2013;127:981-983.
5. Hamburg MA and Collins FS. The Path to Personalized Medicine. N Engl J Med 2010; 363:301-304
6. Kahn J. Misreading race and genomics after BiDil, Correspondence. Nature Genetics. 2005;37:655-656.
7. Morning A. The Nature of Race: How Scientists Think and Teach About Human Difference. Berkeley and Los Angeles: University of California Press; 2011.

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Main Submission

Life insurance and genetic testing: Is genetic information an exception?

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University of Western Ontario

Many believe genetics may help us to personalize medicine and prevent negative health outcomes through earlier detection and prophylactic treatment. Advances in genetic technology have reduced the cost of genetic testing and Canadians are rapidly gaining greater access to their genetic information. However, as genetic testing becomes more prevalent, so does the call for specific policy to regulate the use of genetic data. In particular, the debate in Canada has centred on the use of genetic information by life insurance companies and has led some to ask:is genetic information exceptional? And should it be treated differently than other medical information?[1]

The case study below illustrates both the potential benefit and harm of genetic testing:

A young man with no symptoms underwent genetic testing for hemochromatosis, a disorder that causes the body to absorb too much iron. His result was positive but through early detection and prophylactic treatment he prevented the iron overload that can cause life threatening organ damage. Despite his good health and testimony from his doctor, he was denied life insurance. "Even though I have proven that I prevented health problems…they condemn me to the same category as a lost cause."[2]

Genetic discrimination (GD) is defined as discrimination arising from "the real or perceived genetic status of that individual."[2] Fifty-two percent of Canadians fear their genetic information will be misused by third-parties[3], including discrimination by insurers to increase premiums or deny coverage[4]. Seventy-one percent of those expressing significant concerns said their concerns "would likely effect their willingness to get genetic testing done."[3] In Ontario, 39% of participants from the general population (n = 7173) agreed with the statement "Genetic testing is not a good idea because you might have trouble getting or keeping your insurance."[4]

Policymakers in many countries have been compelled by their constituents to enact laws that limit or ban the use of genetic information by third parties[5,6]. These laws serve two purposes[6]:

1) To protect individuals from misuse of their genetic information.

2) To benefit society by promoting use of genetic testing in healthcare and research.

Currently, Canada is the only G7 country that does not have laws in place to protect citizens from misuse of their genetic information. In 2008, the United States (U.S.) enacted Genetic Information Nondiscrimination Act (GINA) to protect individuals from GD by health insurance companies and employers[5]. While it may be tempting to follow the example set by U.S. legislation, GINA does not address life insurance or barriers to research participation[5,7]. Canadians require legislation that is tailored to our own healthcare system and insurance products.

Life insurance applicants are not required to undergo genetic testing in Canada[8]. However, insurance companies may "request that existing genetic test results be made available", including results that are disclosed to research participants[8]. An insurance policy is a contract made between an insurance company and the insured[8] with the purpose of providing financial security to surviving family members in the event of an unexpected death[7]. The Canadian Life and Health Insurance Association believes an insurance contract must be made in "good faith" and requires both parties to enter the agreement with equal knowledge[8]. Insurers feel that genetic information should be treated the same as other medical information (family history, lifestyle factors, health conditions) used for underwriting, which refers to assigning an individual to a risk group[9].

The process of underwriting is inherently discriminative; for example, men often pay higher premiums than women. Since individuals with higher risk usually pay a higher premium, it is not uncommon for applicants to try to hide information and purchase larger policies[7]. This can lead to the insurance company charging the insured less for the policy and paying out more when the insured dies: a situation known as adverse selection that can lead insurance companies to become unsustainable or to increase premiums. Recent studies have suggested that Canadian insurance companies are not likely to experience significant negative impact if genetic information use was banned[9,10]. However, it is recommended that policymakers reassess the economic impact of any laws enacted to ensure that insurance remains affordable for all Canadians[9,10].

Although from a legal perspective genetic information may not be truly exceptional, Canadians feel their genetic information should be treated differently. The perceived risk of GD affects health choices and deters participation in research that may improve healthcare for the future. This suggests laws are needed to relieve the "fear" of GD. Ideally, Canadian legislation should aim to reduce fear of GD, promote the use of genetics, and prevent significant adverse selection. This might be achieved by only granting insurers access to genetic information for policies over a threshold value. ■

References

1. Hellman D. What makes genetic discrimination exceptional? Am J law Med. 2003;29:77–116.
2. Billings PR, Kohn MA, de Cuevas M, Beckwith J, Alper JS, Natowicz MR. Discrimination as a consequence of genetic testing. Am J Hum Genet. 1992;50(3):476–82.
3. Canada. Phoenix Strategic Perspectives. Survey of Canadians on Privacy-Related Issues. Ottawa; 2013.
4. Hall MA, McEwen JE, Barton JC, Walker AP, Howe EG, Reiss JA, et al. Concerns in a primary care population about genetic discrimination by insurers. Genet Med. 2005;7(5):311–6.
5. Joly Y, Ngueng Feze I, Simard J. Genetic discrimination and life insurance: a systematic review of the evidence. BMC Med. 2013;11:25.
6. Hall MA, Rich SS. Genetic privacy laws and patients' fear of discrimination by health insurers: the view from genetic counselors. J Law Med Ethics. 2000;28:245–57.
7. Knoppers BM, Lemmens T, Godard B, Joly Y, Avard D, Clark T, et al. Genetics and life insurance in Canada: Points to consider. Can Med Assoc J. 2004;170(9):1–3.
8. Canadian Life and Health Insurance Association. Industry code : genetic testing information for insurance underwriting. 2014.
9. Macdonald A. The actuarial relevance of genetic information in the life and health insurance context. Ottawa; 2011.
10. Hoy M, Durnin M. The potential economic impact of a ban on the use of genetic information for life and health insurance. 2012.

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Main Submission

Home-based genetic testing: a risky business?

Kristen Reilly & Shawn Slade

University of Western Ontario

Introduction

Genetic tests are powerful medical tools that appraise the probability of disease[1]. *Presymptomatic* tests identify gene mutations that lead to inevitable hereditary conditions such as Huntington's disease, while *predispositional* tests locate gene expressions that are risk factors assisting in the early identification of diseases such as cancer, heart disease, and Alzheimer's disease[1,2]. Best practice guidelines for the medical provision of genetic testing state that genetic tests must be accompanied by patient education and support or counselling[1-3]. Education prior to genetic testing ensures that the patient is aware of the risks and benefits and can subsequently provide informed consent[1-4]. Genetic counselling is the process through which health professionals help and support patients as they cope with and adapt to having, or being at risk of developing, a genetic condition[3]. Genetic education and counselling are critical to minimize negative effects of, and help patients cope with, test results.

Psychosocial Impact of Genetic Testing

A positive DNA test result can cause prolonged feelings of anxiety and worrying as well as worsened psychological functioning[5]. It may also influence an individual's reproductive choices, particularly when it is determined that they are carriers of incurable hereditary diseases such as Huntington's disease or cystic fibrosis[3,6]. The risks of genetic tests extend beyond the individual, affecting their social environments. For example, results of genetic testing can lead to disruption of familial relationships and other social consequences including loss of life insurance or employment[1,2]. Despite these serious implications, scientific and technological advances in the field of genetics are making genetic testing increasingly accessible to the general public[2]. Today, Canadians can purchase simple home-based genetic tests (HBGTs) online for the price of $199. Once purchased, consumers submit a small sample of saliva to identify over 200 genetic markers which provide genealogical health information on more than 100 health conditions that the customer can interpret however they see fit without the guidance of a healthcare professional[7]. Therefore, the authors of this paper explore the potential repercussions of widespread merchandizing of HBGTs and offer recommendations to ameliorate current practices and develop policies that protect consumer health.

Current Practice of HBGT

Alarmingly, Health Canada currently has no policies in place to regulate quality, reliability, or validity of HBGTs and without government regulation and standardization of these measures, the likelihood of erroneous tests results increases[1]. Both positive and negative genetic test results can precipitate monumental life changes; therefore, inaccurate results from HBGTs may cause individuals to make fallacious and irreversible decisions about their lifestyle, relationships, and employment[4,6]. For example, false negative HBGT results may lead people to avoid necessary medical advice or treatment[1]. In contrast, if a HBGT overstates the genetic basis of a disease or provides inconclusive results, an individual may overestimate their risk of disease and subsequently seek unwarranted screening services and clinical examinations[1,8]. This increased demand for medical attention congests doctors' offices, squanders health care dollars, and increases the burden on an already strained health care system[8].

Furthermore, unlike medically administered genetic testing, businesses selling HBGTs are not obligated to obtain informed consent, provide education or offer counselling for genetic tests.[1] Without adequate education and informed consent, individuals may not be aware of the implications of their HBGT results, which may increase the risk and severity of confusion, anxiety, and psychological distress

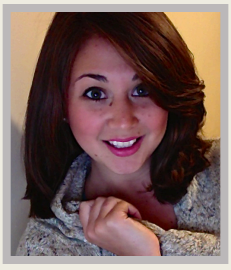
over test results. Therefore, lack of government regulation and medical oversight of HBGTs can exacerbate the existing risks of genetic testing, causing greater implications for individuals and society as a whole[1,2,9].

Recommendations and Conclusions

In accordance with the Canadian College of Medical Geneticist position on HBGT, it is recommended that only scientifically valid tests be offered, and the technical and clinical limitations of the testing including sensitivity, specificity, and utility in assessing health must be clearly stated in a manor understandable to the target market.[10] Furthermore, the authors of this paper strongly recommend the implementation of obligatory policies that require HBGT services to: 1) provide information about the psychosocial risks of genetic testing, 2) disclose who has access and ownership to genetic sample and test results, and 3) obtain informed consent from consumers. Finally, since HBGTs are already marketed and distributed in Canada, the authors call for further research to be conducted in order to establish quality standards that ensure the accuracy of these tests. The Canadian health care system has best practices in place including patient education and counselling to mitigate negative consequences and protect the health and well being of patients that undergo genetic testing. Home-based genetic tests blur the line between patient and consumer. In light of this, private companies selling HBGTs for profit must also be held accountable for the implications of their products. ■

References

1. Williams J, Skirton H, Masny A. Ethics, policy, and educational issues in genetic testing. J Nurs Scholarsh. 2006;38(2):119-25.
2. Marteau T, Croyle R. Psychological responses to genetic testing. BMJ. 1998;316(7132):693–6.
3. Aatre R, Day S. Psychological issues in genetic testing for inherited cardiovascular diseases. Circ Cardiovasc Genet. 2011;4:81-90.
4. Sandor J. Genetic testing, genetic screening and privacy. In: Chadwick R, Shickle D, Ten Have H, Wiesing U. The Ethics of Genetic Screening. Netherlands:Springer;1999. 181-190.
5. Van Dijk S, Otten W, Tollenaar R, Van Asperen C, Tibben A. Putting it all behind: Long-term psychological impact of an inconclusive DNA test result for breast cancer. Genet Med. 2008;10(10):745–50.
6. Myers R. Huntington's disease genetics. NeuroRx. 2004;1(2):255–62.
7. Gayomali C. 23 and Me Expands into Canada [Internet]. Fast Company: Healthware; 2014 October 1 [cited 2015 March 23]. Available from http://www.fastcompany.com/3036513/ healthware/23andme-expands-into-canada
8. Meiser B. "Psychological impact of genetic testing for cancer susceptibility: an update of the literature." Psycho-Oncology 2005;14(12):1060-74.
9. French M, Moore J. Harnessing genetics to prevent disease and improve health: A state policy guide. Washington, DC: The Partnership for Prevention; 2003. Available from: https://genes-r-us.uthscsa.edu/sites/genes-r-us/files/resources/genetics/GeneticsGuide.pdf
10. Nelson N, Armstrong L, Richer J, Evans J, Lauzon J, McGillivray B, Bruyère H, Dougan S. CCMG Statement on Direct-to-Consumer Genetic Testing [Internet]. Ottawa: Canadian College of Medical Geneticists; 2011 Jan 20 [cited 2015 March 23]. Available from http://www.ccmg-ccgm.org/documents/Policies_etc/Pos_Statements/PosStmt_EPP_DTC _FINAL_20Jan2011.pdf



Kristen Reilly

Kristen Reilly obtained her Master of Public Health (MPH) from the University of Guelph and is currently a Ph.D. student in the Department of Health and Rehabilitation Sciences at Western University. Kristen is passionate about health promotion, health policy, and advocacy. The primary objective of her doctoral research is to develop and implement a parent-focused advocacy network (C.H.A.M.P. Families) to engage, inform, and unite parents in London, Ontario. She hopes that this network will empower parents to advocate for the health of their families and communities by providing them with the necessary tools and resources to do so. Kristen is a recipient of the Canadian Institutes for Health Research Frederick Banting and Charles Best Canada Graduate Scholarships Doctoral Award.

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Shawn Slade is PhD student in Health Promotion at Western University in London, Ontario. His Master's thesis examined the perceived barriers, facilitators, and health benefits of sustaining a fitness facility membership amongst active and inactive adult women. Shawn's area of research for his dissertation will focus on family physicians and physical activity counselling/prescription in the primary care setting. Shawn is returning to graduate education after years as a certified exercise professional to be a professor within the health sciences. He is eager to continue developing his knowledge on the use of theory in qualitative health promotion research.

Main Submission

A three-ring circus: discussing the ethical issues of three-parent embryos

Ljiljana Nikolajev & Sahil Kumar

McGill University

As research of human genetics progresses, there appears to be a wavering boundary between ethical and unethical scientific investigation. However, as discoveries are made, current ordinance may not condone the use of such controversial techniques in practice. In February 2015, the United Kingdom Members of Parliament passed an amendment to the Human Fertilisation and Embryology Act, leading to the first policy reform for oocyte modification[1]. This contentious amendment to the in-vitro fertilisation (IVF) technique will permit the exchange of defective mitochondrial DNA (mtDNA), the cause of mitochondrial disease, for healthy mtDNA from a donor's egg, effectively creating a "three-parent zygote."[1] In the United States, the Dickey-Wicker Amendment prohibits funding of "the creation of human embryos for research purposes or research in which a human embryo is harmed or destroyed"[2]; however, the Food and Drug Administration has discussed the matter of oocyte modification at a hearing in the court of public opinion in 2014[4]. In Canada, the Assisted Human Reproduction Act restricts "[creating] an embryo from a cell or part of a cell taken from an embryo or fetus or transplant an embryo so created into a human being."[5] This new policy reform in the UK may change the tides in favour of approving mitochondrial replacement technologies in Canada and the United States.

Mitochondrial disease can occur due to DNA mutations in energy-producing mitochondria or mutations in nuclear DNA, compromising overall mitochondrial function[2]. Mitochondrial disease primarily affects tissues that require high levels of adenosine triphosphate, such as the brain, muscles, heart, and kidneys[2]. It is estimated to affect 1 in 4000 children born in the United States at a single or multiple-organ level, resulting in deafness, blindness, muscle weakness, cognitive impairments, organ failure, and death[2]. The rationale for replacement therapy (RT) would be to improve the prospect of survival of an individual highly susceptible to mitochondrial disease[6].

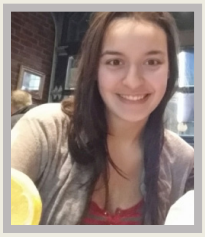
During reproduction, 37 genes from mtDNA are transmitted to the offspring through maternal cytoplasm (compared to the 20,000+ genes from parental chromosomal DNA)[2]. Individuals with mitochondrial disease often have a mixture of normal and mutant mtDNA – a threshold of 60%-90% mutant mtDNA dictates the abnormal phenotype[2]. Currently, two approaches of IVF are employed for mitochondrial replacement therapy: pronuclear transfer or maternal spindle transfer (see Figure 1). Pronuclear transfer involves the removal of the pronuclei from a fertilised zygote with abnormal mitochondria and transfer into an enucleated donor zygote with normal mitochondria[2]. Alternatively, maternal spindle transfer is a newer technique that involves the exchange of the spindle and associated chromosomes from an unfertilised egg with abnormal mitochondria with a donated, unfertilised egg possessing normal mitochondria, which is subsequently fertilised with spermatozoa via intracytoplasmic sperm injection (ICSI)[2]. Under the Assisted Human Reproduction Act, maternal spindle transfer could be considered a legal practice, as the biological material used is removed from an unfertilised egg as opposed to an embryo; hence, this could permit the induction of replacement therapy under current ruling. While RT has shown safety and efficacy in animal models,[6] controversy as to whether this technique is ethical and legal for humans remains. Although mtDNA encodes 0.1% of the total transmitted DNA and does not contribute to physical traits or personality,[7] the legal implication of three biological parents is present – namely the role of the donor and their implication in the child's life. The UK Nuffield Council on Bioethics, which scrutinized all ethical concerns regarding this therapy, arrived to the conclusion that the mtDNA donor could not be considered as a "third" parent, as only part of the egg is used and no nuclear DNA from the third-party is transferred[8]. Moreover, adversaries

express worries as to whether allowing such therapies would lead to a slippery slope of eugenics and "designer" babies; conversely, the mtDNA genes function to regulate energy homeostasis and would only improve survival of the individual highly susceptible to a mitochondrial disease, but not alter traits encoded by nuclear chromosomes[6]. Current options for women at risk of passing the disease are to adopt, choose to not conceive, or take the risk of sequential stillborn babies[9]. Should parents express the desire to conceive healthy, genetically related children, the Nuffield Report stipulates that it would be ethical to allow couples to have access to a reproductive therapy that is adequate for their needs[8].

The UK has made the first step towards advancement of mtDNA RT and evaluating this technique for humans. However, many important questions remain to be addressed, such as the implication of "foreign" gene germline transmission to future generations, incompatibilities between the haplotypes of the donor's mtDNA and the mother's nuclear DNA, or the possible epigenetic abnormalities prompting further diseased states[2,10]. The benefits of the therapy are mainly for couples wishing to conceive a child without transmission of the disease, but will not cure those currently living with mitochondrial disease. Although the opposition to the technology may bring about the hiatus of advancing three-parent babies into health action, clinical trials can greatly determine the safety and efficacy of the technique in humans for use in the imminent future[10]. ■

References

1. Knapton S. Three-parent babies to be born in Britain as MPs say yes to law change. Telegraph [Internet]. 2015 Feb 3. Available from: http://www.telegraph.co.uk/news/science/science-news/11387179/Three-parent-babies-to-be-born-in-Britain-as-MPs-say-yes-to-law-change.html
2. Amato P, Tachibana M, Sparman M, Mitalipov S. Three-parent in vitro fertilization: gene replacement for the prevention of inherited mitochondrial diseases. Fertility and Sterility. 2015 Jan;101(1):31-35.
3. Chinnery PF. Mitochondrial Disorders Overview. GeneReviews; 2000 Jun 8 [updated 2014 Aug 14].
4. Maron DF. Making Babies with 3 Genetic Parents Gets FDA Hearing. Scientific American. 2014 Feb 25.
5. Justice Laws Website. Government of Canada; 2004 Mar 29. Available from: http://laws-lois.justice.gc.ca/eng/annualstatutes/2004_2/page-2.html
6. Callaway E. Reproductive medicine: The power of three. Nature News; 2014 May 21. Available from: http://www.nature.com/news/reproductive-medicine-the-power-of-three-1.15253
7. Baylis F. The ethics of creating children with three genetic parents. Reproductive Biomedicine Online, 2013 Jun;26(6):531-534.
8. Hallowell N. Nuffield Council on Bioethics Report: Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review London: Nuffield Council of Bioethics 2012. Life Sciences Society and Policy. 2012 Sept 15;8(2):29.
9. Griggs J. Mitochondrial replacement vote: What you need to know. NewScientist; 2015 Feb 3. Available from: http://www.newscientist.com/article/dn26900-mitochondrial-replacement-vote-what-you-need-to-know.html#.VNvF6VbGwty
10. Mitalipov S, Wolf DP. Clinical and ethical implications of mitochondrial gene transfer. Trends in Endocrinology & Metabolism, 2014 Jan;25(1):5-7.



Ljiljana Nikolajev

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Sahil Kumar

Sahil Kumar completed his B.Sc. at McGill University and has recently commenced his M.Sc. in Experimental Medicine at McGill. Sahil is in the Laporte lab studying the biased signalling and allosteric modulation of the Angiotensin II type 1 Receptor, a member of the family of G-Protein Coupled Receptors. When not in the lab, Sahil is either binge-watching Netflix, dabbling in student politics, or mastering the art of the perfect French macaron.

Main Submission

The Parent Trap: An Inquiry Regarding Eugenics and Three-Parent Babies

Rebecca R. Fried & Rebecca H. Liu

University of Western Ontario

Among health professionals, 'biology and genetic endowment' is known to be one of the twelve key determinants of health.[1] This determinant is, often jokingly, described as picking your parents, referencing the fact that many determinants of health can be altered to more favourable and healthful conditions, whereas genetics cannot. Individuals do not pick their parents and therefore, do not pick their genetic temperament. But, what if the reverse were possible, in that parents could pick their children?

Designer Genes: A Discussion About Eugenics

Often discussed in science fiction novels and films (e.g. Brave New World and GATTACA), the notion of parents 'picking' their children and altering genetics is anything but new. This topic, known as eugenics, is the process of manipulating genes to conceive children that possess specific, desirable traits[2]. Eugenics has had a long and controversial history. Eugenics became greatly scrutinized during World War II, whereby the Nazis employed eugenics to justify the annihilation of millions of people[2]. Additionally, controversy surrounds the subject regarding beliefs of manipulation of nature (often deemed as 'playing God'). However, principles of eugenics have assisted with genetic screening and counseling, as well as fetal gene manipulation; and gene therapy for adults suffering from hereditary disorders[2]. The aforementioned examples highlight eugenics utility, in that adults with debilitating genetic illnesses have the ability to improve their health and to potentially lead normal lives[2]. As well, couples considering conceiving children are able to know what to expect with their children and prepare for the appropriate care.

Three-Parents and A Little Baby

The study of eugenics has acted as the catalyst for a new concept, 'Three-parent babies' (TPBS). The procedure, referred to as three-person in vitro fertilization or mitochondrial replacement therapy (hereafter referred to as TPIVF/MRT), occurs when one female wishing to conceive carries mutated mitochondria in their egg cell. Thus, TPIVF/MRT involves transferring nuclear DNA from an egg with mutated mitochondrial DNA, to a donor egg containing healthy mitochondrial DNA[3,4]. Once the donor egg is fertilized by a male sperm cell, it is argued that the resulting embryo has three parents, in a biological sense, due to the addition of the healthy mitochondrial DNA from the donor egg, which is passed down along with the mother and father's nuclear DNA[3,4].

It's All Down Hill: Negatives of TPIVF/MRT

There are notable downsides to TPBS, the first being that the science is very new, and the efficacy of TPIVF/MRT is unknown. Evolutionary biologist Klaus Reinhardt posits that issues could arise if DNA from different women proved to be incompatible[3,4]. Reinhardt cited several experiments in mice, fruit flies, and other animals in which combining nuclear and mitochondrial DNA from individuals from different genetic backgrounds sometimes led to early death, reduced reproductive ability, rapid ageing, or reduced growth[3,4]. However, this point was countered by another scientist, Shoukhrat Mitalipov, arguing that those experiments were mainly completed by combining strains of inbred animals; and in reality, species such as humans from different genetic backgrounds interbreed freely without ramifications[3,4]. Additionally, there are debates on whether or not the genetic make-up of children born as a result of TPIVF/MRT will affect their emotional well-being when they realize they differ from children conceived from two parents[5]. These arguments among scientists, as well as the ethical issues raised, evince the fact that the science is too new to fully understand the full effects.

Up We Go: Benefits of TPIVF/MRT

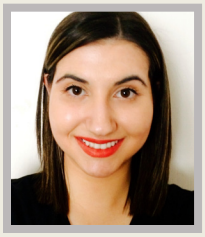
TPIVF/MRT has the potential to help hundreds of parents. Mitochondrial diseases affect one in 5,000 to 10,000 live births, suggesting that in the United States alone, between 1,000 and 4,000 children are born every year with mitochondrial diseases[6,7,8]. Although there is much controversy surrounding the use and efficacy of TPIVF/MRT, it is important to recognize that the entire premise is to prevent mitochondrial disorders such as: diabetes mellitus and deafness, muscular dystrophy, and Leigh syndrome[7,8].

According to psychiatry professor Robert Klitzman, TPIVF/MRT will save lives, not rewrite biology[9]. Klitzman argues that the media misleadingly portrays TPIVF/MRT as producing children with three parents; and a more accurate parallel would be to organ transplantation: "If I receive a kidney from a donor, no one says that I then consist of two people. One kidney, weighing perhaps 1-pound, now rests in my 185-pound body and allows me to live. Similarly, to replace less than one out of every 100,000 bits of DNA in an individual with DNA from someone else makes no major difference to the recipient's identity other than to allow him or her to survive" (paragraph 9).

Although many determinants of health can be indirectly altered to more favourable and healthful conditions, there is no direct control over genetics, which is why the notion of parents picking their children raises a variety of contentious scientific and ethical concerns. However, when the science of eugenics is strictly used to resolve debilitating genetic diseases, and to improve upon individuals' quality of life, TPIVF/MRT can be a valuable method in – at the very least – aiding in the development of a healthy child. ■

References

1. Public Health Agency of Canada. What determines health? [Internet]. Canada: Public Health Agency of Canada; 2011 [updated 2011 Oct 21; cited 2015 Feb 6]. Available from: http://www.phac-aspc.gc.ca/ph-sp/determinants/index-eng.php
2. Wilson PK, Meloni S. Eugenics. In: Chauhan Y, Rogers K, Singh S, Tikkanen A, Young G, editors. Encyclopaedia Britannica Online Academic Edition [e-book]. United States: Encyclopaedia Britannica, Inc. 2015 [updated 2015 Feb 10; cited 2015 Feb 3rd]. Available from: http://www.britannica.com/EBchecked/topic/195069/eugenics
3. Hayden EC. Regulators weigh benefits of 'three-parent' fertilization: But critics say mitochondrial replacement carries safety and ethical concerns. Nature. 2013; 502(7471):284-285.
4. Callaway E. The power of three: Techniques that transfer DNA from diseased human eggs to healthy ones – creating offspring with three biological parents – are on the verge of clinical use. Nature. 2014;502(7501):414-17.
5. Center For Genetics and Society. Inheritable genetic modification: 3-person IVF [Internet]. California: Center For Genetics and Society; 2015 [updated 2015 Feb 4; cited 2015 Feb 4]. Available from: http://www.geneticsandsociety.org/article.php?id=6527#3
6. Tachibana M, Amato P, Sparman M, Woodward J, Sanchis DM, Ma H et al. Towards germline gene therapy of inherited mitochondrial diseases. Nature. 2013;493(7434):627-631.
7. Haas RH, Parikh S, Falk MJ, Saneto RP, Wolf NI, Darin N, et al. Mitochondrial disease: A practical approach for primary care physicians. Pediatrics. 2007;120(6):1326-1333.
8. Schaefer AM, McFarland R, Blakely EL, He L, Whittaker RG, Taylor RW, et al. Prevalence of mitochondrial DNA disease in adults. Ann. Neurol. 2008;63(1):35-39.
9. Klitzman R. Three parents, one baby? Not at all: Replacing mitochondria in an unfertilized egg will save many infants' lives, not rewrite biology. The Wall Street Journal [Internet]. 2015 Feb 9 [cited 2015 Feb 9] Available from: http://www.wsj.com/articles/robert-klitzman-three-parents-one-baby-not-at-all-1423528082



Rebecca R. Fried

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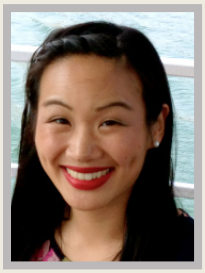


Rebecca H. Liu

Rebecca H. Liu is a second-year PhD candidate in Health & Rehabilitation Sciences (Health Promotion) at the University of Western Ontario. Her research focuses on using Co-Active Life Coaching (CALC) as a health behavioural intervention to reduce cardiometabolic risk among racial/ethnic minority groups struggling with obesity. She is also interested on investigating the impact of CALC as a psychosocial support before and after weight reduction surgery among bariatric surgical patients.

Mitochondrial Replacement Therapy: Modifying Genes to Prevent Inherited Mitochondrial Disease

Jennifer Kramer

University of Saskatchewan

Mitochondrial replacement therapy (MRT) is a novel reproductive technique with the potential to help families have genetically related children born free of devastating mitochondrial DNA (mtDNA) disease that would otherwise be inherited. While the bulk of genetic material lies inside the nuclei of cells, a small amount exists in tiny structures called mitochondria that are only passed to the child from the mother. The genes here do not affect characteristics such as appearance, height, or intelligence. Rather they support the function of mitochondria, to use oxygen to turn the body's food into energy. Cells need energy to survive so without healthy mitochondria a broad spectrum of progressive and debilitating diseases of the brain, muscles, liver, heart, and kidneys can result[1]. A national charity estimates that at least one in 5000 Canadians have some form of mtDNA disease[2]. There is no cure but today there is hope. Exciting evidence from American and British scientists suggests that replacing mitochondrial mutations with healthy genes can prevent the transmission of mtDNA disease[3,4]. After intense debate, the United Kingdom is set to begin clinical trials of MRT later this year[5]. The aims of this article are to present the arguments and implications surrounding this cutting-edge technology.

MRT

MRT is an innovative in-vitro fertilization (IVF) technique where an embryo is created with the nucleus DNA from its parents but the mitochondrial DNA from a donor woman. Proposed methods include repairing the embryo (figure 1) and repairing the egg (figure 2)[3,4]. Both result in a permanent change that would be passed on throughout the generations.

Safety, Risk, and Ethical concerns

Because science has yet to understand how nuclear and mitochondrial genomes interact with one another, the benefits and risks of MRT are unclear. Like all new technologies, these questions cannot be answered until human trials are conducted and several generations are followed. How much evidence is needed before moving forward has been rigorously debated in the UK. The

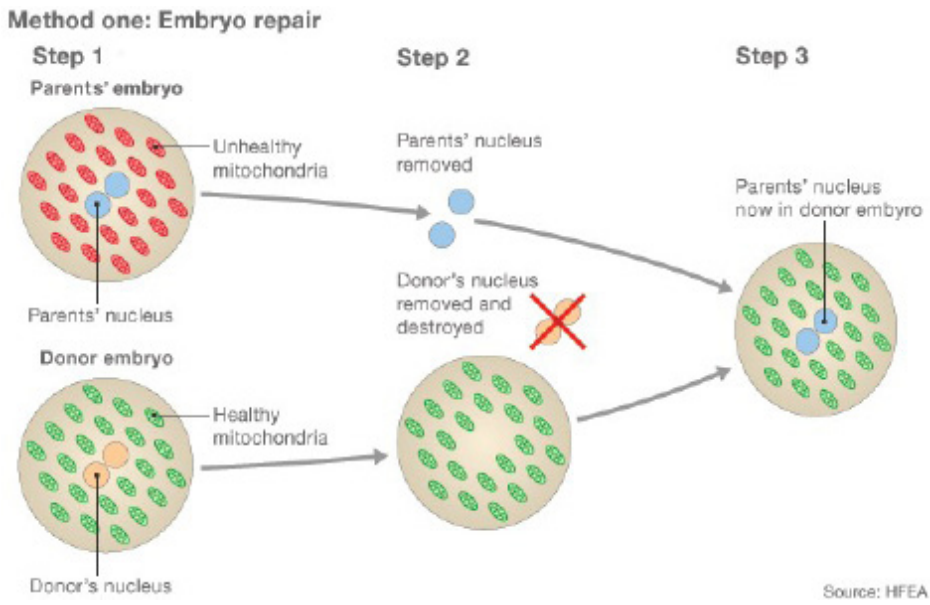


Figure 1. Step 1: Two eggs are fertilised with sperm, creating an embryo from the intended parents and another from the donors. Step 2: The pronuclei, which contain genetic information, are removed from both embryos but only the parents' are kept. Step 3: A healthy embryo is created by adding the parents' pronuclei to the donor embryo, which is finally implanted into the womb[3].

third scientific review by the Human Fertilisation and Embryology Authority (HFEA) concludes that nothing indicates MRT is unsafe[6], but the unknown carries a degree of risk. A degree that supporters of MRT argue that, with informed consent, is outweighed by the need for the procedure in preventing cruel and life-shortening inherited diseases.

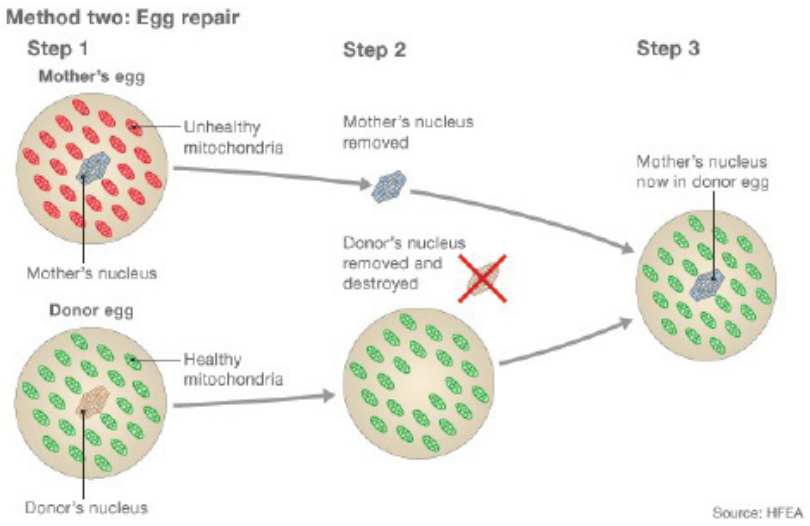


Figure 2. Step 1: Eggs from a mother with damaged mitochondria and a donor with healthy mitochondria are collected. Step 2: The majority of the genetic material is removed from both eggs. Step 3: The mother's genetic material is inserted into the donor egg, which can be fertilised by sperm[3].

Mitochondrial replacement therapy raises several ethical questions. Religious opinions vary depending on affiliation, ranging from strong objections on the claim that embryos and adults have equal moral status, to acceptance since the purpose of MRT is to ease human suffering. Fears similar to the IVF debate in the 1970s exist surrounding the potential for the technology to be used to enhance and create babies with desirable traits. A review by the London-based Nuffield Council on Bioethics asserts that MRT is ethical[7] and clear guidelines and regulations have been drafted to calm "designer baby" concerns, explicitly stating that mtDNA disease is the only indication for oocyte modification[8]. The potential for MRT is huge and ideas are circulating on how the technique may be useful in other treatments, such as age-related infertility. What about heritable diseases affecting the nuclear genome? Current draft regulations do not consider these possibilities. The need for ethical debate concerning the bounds and regulation of MRT must continue.

Social concerns

The reference to MRT in the media as three-person babies or three-parent babies does not accurately reflect the resulting offspring's genes and stimulates legal fears over parenting. A more accurate description would be 2.001-person IVF since the DNA from the donor egg amounts to less than one-tenth of one percent of the resulting embryo's genes[5]. Draft regulations in the UK recommend considering the mitochondrial donor akin to an organ donor and not legally a parent[8]. Just like sperm and egg regulations, the parents are the people raising the child and the donor woman would remain anonymous.

MRT in Canada

In Canada human trials of MRT are illegal and there is little, if any, discussion on the matter. Developed to discourage misuse of reproductive technology, the Assisted Human Reproduction Act of 2004 prohibits any gene altercations in a cell or embryo that may be transmitted to descendants[9]. How this legislation has influenced the lack of debate is unclear but Canada will likely be forced into the discussion once data returns on the safety and efficacy of the UK trials.

Conclusion

Genetic intervention studies will soon be a reality in the UK. The vertical transmission of donor mtDNA has sparked heated debate concerning heritable genetic modification and requires close monitoring of human trials. Canada appears to be waiting on the results of these trials before initiating any ethical or regulatory discussion, an approach that may hinder rapid access to modern advances that may prevent progressive and often brutal inherited mtDNA disease in Canadian children. ■

References

1. Mattman A, Sirrs S, Mezei MM, Salvarinova-Zivkovic R, Alfadhel M, Lillquist Y. Mitochondrial disease clinical manifestations: an overview. BCMJ. 2011 May; 53(4): 183-187.
2. MitoCanada. Annual report 2012: a TransCanada journey [Internet]. Brantford, Ontario: MitoCanada Foundation; June 2012 [cited 2015 March 27]. Available from: http://www.mitocanada.org/wp-content/uploads/2012/08/Annual-Report-2012-for-MITO-June-9th-FINAL.pdf
3. Craven L, Tuppen HA, Greggains GD, Harbottle S, Murphy JL, Cree LM, Murdoch AP, Chinnery PF, Taylor RW, Lightowlers RN, Herbert M, Turnbull DM. Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. Nature. 2010 May; 465(7294): 82-85.

4. Tachibaba M, Sparman M, Sritanaudomchai H, Ma H, Clepper L, Woodward J, Li Y, Ramsey C, Kolotushkina O, Shoukhrat M. Mitochondrial gene replacement in primate offspring and embryonic stem cells. Nature. 2009 Sept; 461(7262): 367-372.
5. Gallagher J. MPs say yes to three-person babies. BBC News [Internet]. 2015 February 3 [cited 2015 Feb 7]. Available from: http://www.bbc.com/news/health-31069173
6. Human Fertilisation and Embryology Authority (HFEA). Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update [Internet]. 2014 June 2 [cited 2015 Feb 7]. Available from: http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf
7. Nuffield Council on Bioethics. Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review [Internet]. 2012 June [cited 2015 Feb 7]. Available from: http://nuffieldbioethics.org/project/mitochondrial-dna-disorders/
8. Department of Health, UK. Mitochondrial donation: a consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child [Internet]. 2014 February [cited 2015 March 27]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/285251/mitochondrial_donation_consultation_document_24_02_14_Accessible_V0.4.pdf.
9. Canada, Department of Justice Canada. Assisted Human Reproduction Act, S.C. 2004, c2 [Internet]. 2004 [updated 2015 March 24; cited 2015 March 27]. Available from: http://laws-lois.justice.gc.ca/PDF/A-13.4.pdf
10. Bredenoord A, Braude P. Ethics of mitochondrial gene replacement: from bench to bedside. BMJ. 2010 Nov; 341:c6021.

Jennifer Kramer

Jennifer Kramer is currently pursing a PhD (Nursing) at the University of Saskatchewan, the institution where she also obtained her BSN and MN degrees. Her research examines the relation between the severity of nausea and vomiting in pregnancy and maternal mental health, as well as the effects of these experiences on the mother and child postpartum at one, three, and five-year intervals. This research stems from her experience as a registered nurse (RN) in the areas of labour and birth and adult psychiatry.

Environmental responses mediated by histone deacetylation - biological and clinical implications

Yichi (Tony) Zhang

Carleton University

Introduction

The term epigenetics refers to processes that lead to heritable changes in the expression of genes without changes in the sequence of DNA1. These alterations in gene expression are a result of modifications made to chromatin and non-chromatin proteins (e.g. transcription factors). Hence, not only do epigenetic modifications play a role in many, if not all, biological processes, such as cell cycle control[2] and disease[3] (Figure 1), they also add a layer of complexity to gene expression above what is already known at the genomic level.

Epigenetic modification of chromatin proteins alters the ability of the transcriptional apparatus to bind and transcribe DNA, this altering gene expression. In the case of the chromatin protein histone[3], acetylation has been shown to lead to transcriptional activation, whereas deacetylation has been shown to result in transcriptional repression. Therefore, numerous studies have been conducted on histone deacetylases (HDACs) in association with transcriptional silencing[4,5,6]. Upon further observation, HDACs have also been shown to modulate the activities of various transcription factors and non-histone proteins, thus allowing for even greater precision in the regulation of gene expression[3] (Figure 1). The present review will discuss the affect of environmental conditions on histone deacetylation, its implications for disease, and the use of HDAC inhibitors as a potential therapeutic for a multitude of diseases.

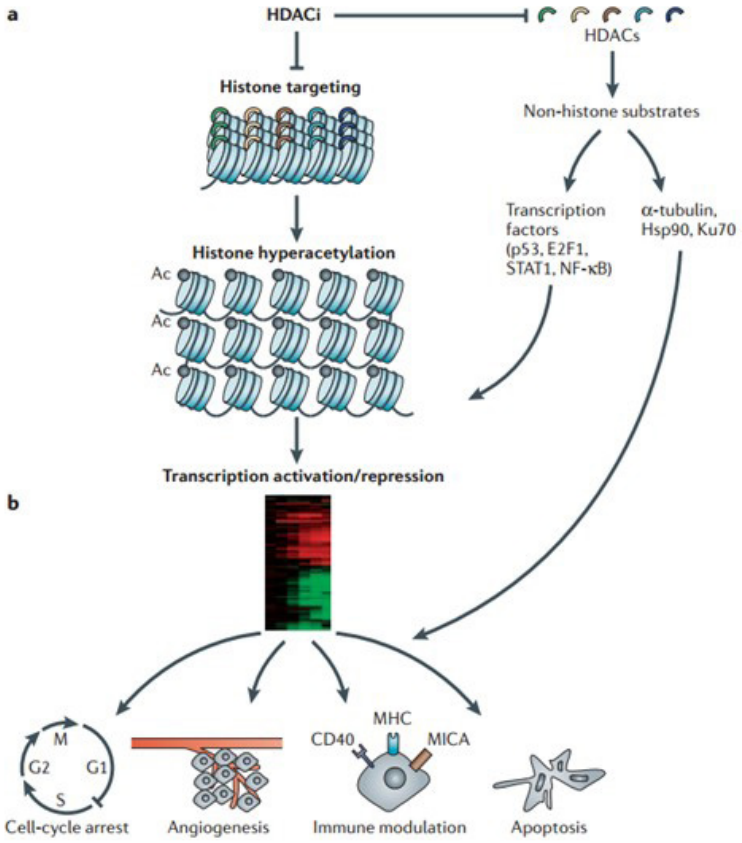


Figure 1. This diagram illustrates the mechanism by which HDACs regulate the acetylation state of histone and non-histone proteins to regulate gene expression. The effect of HDAC inhibitors on many biological processes is also shown. Figure Adapted from Bolden *et al*.[3]

Histone Deacetylation and Environmental Response

Any organism is subject to environmental and physiological stresses that puts them at risk. With regard to environmental factors (e.g. temperature, oxygen availability, water, food), histone deacetylation plays an important role. In mammals, hibernation is a hypometabolic process in response to temperature, food and other environmental changes. During hibernation, it was shown that histone H3 acetylation and RNA polymerase II transcriptional activity decreases with an accompanying increase in HDAC I and IV

protein levels[6].

Although many of the environmental stresses listed above do not apply to humans, food is a common environmental stress in our society given the prevalence of eating disorders. Therefore, caloric restriction experiments have been conducted to investigate the epigenetic basis of metabolism. A specific class of HDACs (sirtuins) have been identified to play a significant role in regulating glucose and lipid metabolism during caloric restriction[7]. The changes to histone deacetylation in response to environmental stress have formed the basis of our understanding of transcriptional silencing due to HDACs. This knowledge is paving the way for more clinically-relevant studies of histone deacetylation.

HDACs and Disease

Given the widespread and profound impact of epigenetic modifications to affect most, if not all physiological processes, HDACs have been studied in relation to a multitude of diseases[3,8,9]. For the onset and progression of cancer, research has shown that HDACs can inhibit the transcription of tumour-suppressor and apoptotic genes, thereby promoting tumour development[3] (Figure 1). Similarly during cardiac hypertrophy and heart disease, the expression of a large number of genes is altered, and HDACs were shown to be involved regulating the expression of these genes[8].

One disease that is being studied in relation to HDACs with increasing frequency is Spinal Muscular Atrophy (SMA). This life-threatening disease is a neuromuscular disorder characterized by motor neuron loss due to reduced survival of motor neuron (SMN) protein levels, and an increase in muscle atrophy. Thus children with the disease have significant impairments in mobility, leading to death in severe cases. HDACs have been shown to reduce SMN levels and promote muscle atrophy[9]. Therefore, the dual role that HDACs play in SMA pathology makes HDAC inhibitors a promising therapeutic.

Clinical Implications of Histone Deacetylation - HDAC Inhibitors as a Therapeutic

As mentioned previously, HDAC inhibitors are being studied extensively as a potential therapeutic for SMA, with Trichostatin A (an HDAC inhibitor) having been shown to ameliorate motor neuron and muscle growth[9,10].

With respect to cancer, HDAC inhibitors are highly effective in selectively targeting tumour cells, and while these drugs have potent effects when administered alone, their combination with other anticancer agents (e.g. retinoic acid, UV irradiation) have produced even greater results[3].

Presently, Vorinostat and romidepsin are two HDAC inhibitors that have already went through clinical trials and are Food and Drug Administration (FDA) approved for anticancer treatments with many others currently undergoing clinical trials for various diseases[3,8]. Therefore, the clinical applications of epigenetics-based therapeutics are very promising.

Conclusion

In contrast with changes in the genome, epigenetic changes such as histone deacetylation occur much more frequently in response to changes in the environment[6,7], thus adding further complexity to the expression of genes. The clinical implications of epigenetic modifications have already been studied extensively in relation to HDAC, with promising results that have lead to FDA approval on two HDAC inhibitors[8]. Current HDAC inhibitors either inhibit specific classes of HDACs or are global inhibitors[3]. Therefore, understanding the differential modification of specific histone and non-histone residues in disease, and the development of therapeutics to target these specific modifications will bring us closer to providing personalized gene therapies. ■

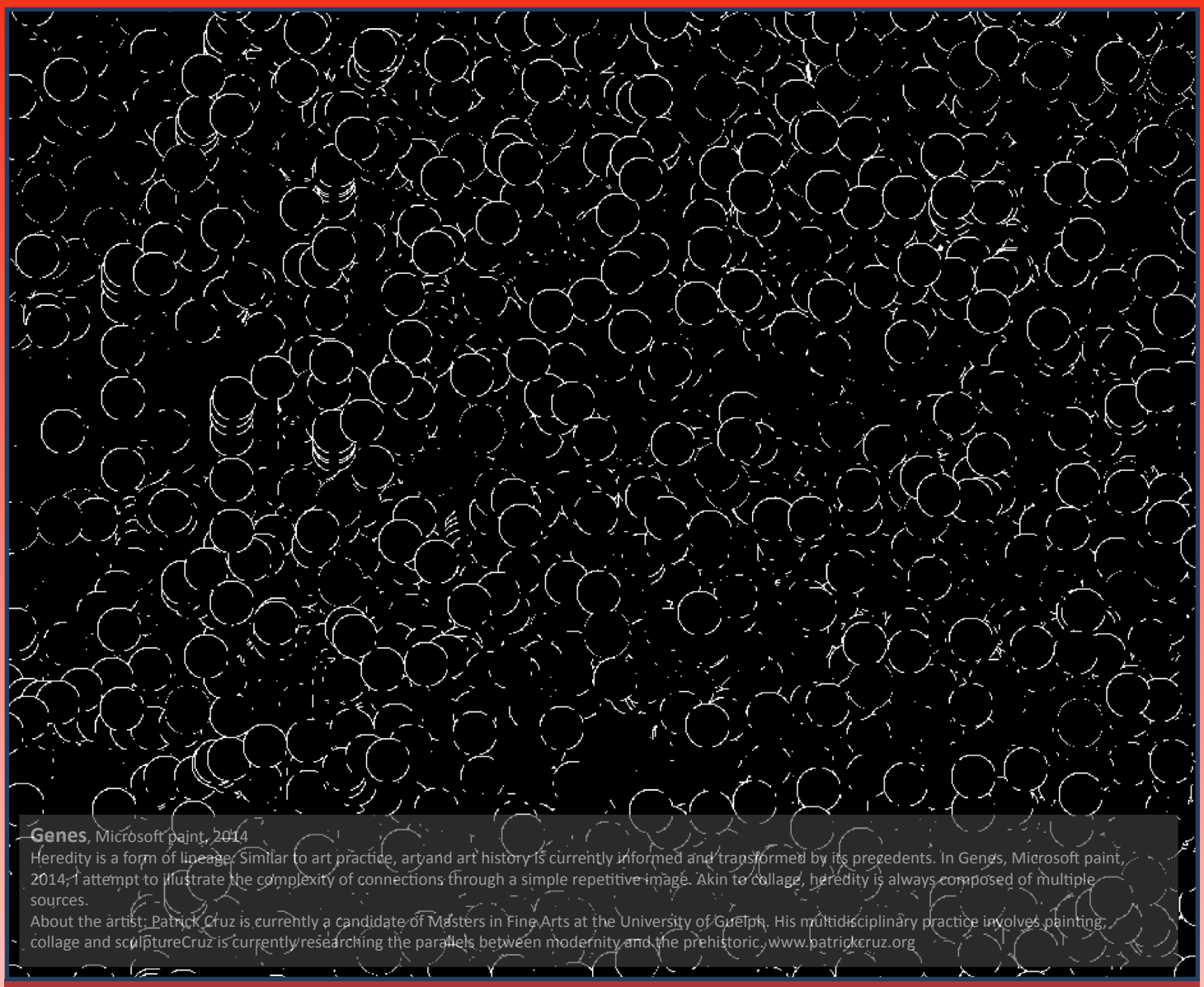
References

1. Wolffe AP, Matzke MA. Epigenetics: regulation through repression. Science 1999 Oct 15;286(5439):481-486.
2. Macaluso M, Montanari M, Cinti C, Giordano A. Modulation of cell cycle components by epigenetic and genetic events. Semin Oncol 2005 Oct;32(5):452-457.
3. Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov 2006 Sep;5(9):769-784.
4. Spange S, Wagner T, Heinzel T, Kramer OH. Acetylation of non-histone proteins modulates cellular signalling at multiple levels. Int J Biochem Cell Biol 2009 Jan;41(1):185-198.
5. Ellis DJ, Lawman ZK, Bonham K. Histone acetylation is not an accurate predictor of gene expression following treatment with histone deacetylase inhibitors. Biochem Biophys Res Commun 2008 Mar 14;367(3):656-662.
6. Morin P,Jr, Storey KB. Evidence for a reduced transcriptional state during hibernation in ground squirrels. Cryobiology 2006 Dec;53(3):310-318.
7. Auwerx J, Houtkooper RH, Pirinen E. Sirtuins as regulators of metabolism and healthspan. Nature Reviews Molecular Cell Biology 2012 04; 2015/1;13:225+.
8. Abend A, Kehat I. Histone deacetylases as therapeutic targets - From cancer to cardiac disease. Pharmacol Ther 2014 Nov 6.
9. Bricceno KV, Sampognaro PJ, Van Meerbeke JP, Sumner CJ, Fischbeck KH, Burnett BG. Histone deacetylase inhibition suppresses myogenin-dependent atrogene activation in spinal muscular atrophy mice. Hum Mol Genet 2012 Oct 15;21(20):4448-4459.

10. Liu H, Yazdani A, Murray LM, Beauvais A, Kothary R. The Smn-independent beneficial effects of trichostatin A on an intermediate mouse model of spinal muscular atrophy. PLoS One 2014 Jul 1;9(7):e101225.

Yichi (Tony) Zhang

Tony Zhang completed his B.Sc. in Kinesiology at Queen's University and is currently entering the final year of his M.Sc. at Carleton University in the Department of Biology. His research focuses on a comparison between skeletal and cardiac muscle in thirteen-lined ground squirrels. These animals hibernate during winter months, where they demonstrate a remarkable capability to preserve their muscle mass despite prolonged periods of inactivity. They also undergo reversible cardiac hypertrophy during hibernation. Understanding these physiological adaptations to stress in ground squirrels has clinical implications in developing new treatments for muscle-wasting diseases as well as heart failure. Aside from research, Tony is involved in various aspects of athletics, from officiating basketball to rowing for the Ottawa Rowing Club and Carleton University.



Genes, Microsoft paint, 2014
Heredity is a form of lineage. Similar to art practice, art and art history is currently informed and transformed by its precedents. In Genes, Microsoft paint, 2014, I attempt to illustrate the complexity of connections through a simple repetitive image. Akin to collage, heredity is always composed of multiple sources.
About the artist: Patrick Cruz is currently a candidate of Masters in Fine Arts at the University of Guelph. His multidisciplinary practice involves painting, collage and sculptureCruz is currently researching the parallels between modernity and the prehistoric. www.patrickcruz.org

ASK AN EXPERT

Canadian experts in the field of medical genetics were asked to answer and give their opinion about genetic breakthroughs with considerable importance in healthcare management and medicine. The Ask an Expert section presents the thoughts and opinions of those specialists who spend their lives studying these issues from different perspectives, whether on the fundamental level, applied, clinical or translational research.

Ask an Expert

Why is gene therapy so attractive and so controversial?

Jacques P. Tremblay, Ph.D.

Professor of Molecular Medicine, University of Laval

All the characteristics of the human body are encoded in DNA molecules; long double stranded helixes. These DNA molecules are made of only 4 nucleotides: adenosine, cytosine, guanine, and thymidine. It is a sequence of these nucleotides that constitutes a gene that determines, for example, the colour of our eyes or of our hairs. The human genome (i.e., all our genes) contains about 3 billion nucleotides received from our father and 3 billion nucleotides received from our mother. The complete sequence of all these nucleotides has been initially obtained by the collaborative work of hundreds of laboratories over several years and has cost several billion dollars. It is now possible to obtain the complete genome sequence of one individual in one laboratory in one week for less than $1,000. All hereditary diseases are due to modifications of the sequence of nucleotides of a gene and the progress in the rapidity of genome sequencing has permitted to identify modifications (i.e., mutations) responsible for 7000 different hereditary diseases.

Now that the modifications responsible for so many hereditary diseases are known, the next logical step is to develop therapies for them. Since these diseases are due to gene modifications, a therapeutic approach that would apply to all of them would be to replace or correct the defective gene – this is gene therapy.

During the last 25 years, gene therapy has been aiming to compensate for a defective gene by introducing a complete copy of the normal gene. This normal gene can be inserted in the patient cells in culture. The genetically corrected cells are then proliferated and transplanted in the appropriate organ of the patient with a genetic disease. This approach can work for some tissues like the muscles, where muscle precursor cells (i.e., myoblasts) can be injected in the muscles and fuse with the existing muscle fibers. However, such a therapeutic approach requiring cell transplantation does not work for complex tissues such as the brain. Thus, an alternative approach is to deliver the normal gene directly to the cells in the human body. This delivery can be achieved via viral vector (i.e., a virus in which the viral genes have been removed and replaced by a therapeutic gene). This gene therapy approach has already been used successfully to treat some diseases, such as Leber amaurosis (an hereditary blindness) and Hemophilia type B (a coagulation problem).

However in the last 5 years, new techniques now permit to correct specifically the defective gene (i.e., replacing the few nucleotides that are missing or incorrect) instead of introducing a complete replacement gene. This new approach is very advantageous when the gene is very big, like for example, the dystrophin gene mutated in Duchenne muscular dystrophy is more than 10 million nucleotides long and thus impossible to include in most viral vectors.

For some persons (usually not those affected by an hereditary disease), gene therapy is controversial because it touches a very fundamental aspect of life. Indeed for these persons, this is as controversial as saying that the universe was not made in 7 days, that the earth is not the centre of the universe, or permitting to transplant a human heart. The capacity to modify genes opens the possibility of curing most, if not all, hereditary diseases. However, as any knowledge, this could also eventually be used to modify other human characteristics not for a medical treatment. Currently, gene therapy is closely supervised by regulatory agencies such as the Food and Drug Administration (FDA) to make sure that the aims are scientifically and ethically correct. ■

Dr. Tremblay has obtained a PhD in Neurosciences from the University of California in San Diego in 1974. He has been at Laval University in Québec since, as a post-doctoral fellow, a professor and a department chairman. He is currently a full professor in the Department of Molecular Medicine. He has published over 250 scientific articles.

Ask an Expert

How will the knowledge gained from epigenetics be translated to patient care in the following decade? How does this compare to traditional genetics?

Ekaterina Olkhov-Mitsel, Ph.D.[1] & Bharati Bapat, Ph.D.[2]

1. Post-doctoral Fellow, Bapat Lab, Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, 2. Professor, Department of Laboratory Medicine and Pathobiology, University of Toronto

Progress in epigenetic research in the past two decades has led to the discovery of novel exciting avenues to improve patient care. It is a rapidly expanding and versatile field that has translational implications for a diverse range of healthcare modalities including regenerative medicine, aging, nutrition, drug dependency, mental health, infertility as well as prevention, screening, diagnosis and treatment of numerous chronic diseases. Additionally, advancements in epigenetic research drive the development of novel technology platforms and consequently improved medical procedures.

Epigenetics and genetics represent two sides of the same coin, with the former referring to heritable phenotypic variation which is potentially reversible and is distinct from genetic variation. Key epigenetic mechanisms include DNA methylation and its oxidation derivatives, histone modifications and non-coding RNAs. These diverse modifications are reversible and are regulated by epigenetic enzymes, also known as writers, readers and erasers, which allow for dynamic fine-tuning of gene expression. Thus, epigenetics serves as an interface between the dynamic environment and the largely static genome. Epigenetic mechanisms are essential for normal development and maintenance of tissue-specific gene expression patterns in mammals. Accordingly, disruption of epigenetic processes is associated with disease initiation and progression. Knowledge of epigenetic alterations during disease development can lead to the discovery of novel biomarkers and therapeutic targets. In this regard, a major focus of current epigenetic biomedical research is in the area of oncology. Given that DNA methylation changes tend to be tumor cell-specific, this unique feature has been further exploited in the discovery of epigenetic cancer biomarkers. The list of genes reported to be methylated in cancer in association with clinical parameters, response to treatment and survival is extensive. The challenge in the following decade will be to identify the most robust markers among the plethora of such promising biomarkers and translate these findings into clinically usable tests. Clinical tests based on epigenetic biomarkers will either replace or improve current gene-based tests in terms of efficiency, accuracy and cost. Proof-of-principle examples of cancer epigenetic biomarkers already used in clinical practice include detection of hypermethylation of *MGMT* gene for prediction of temozolomide treatment response in glioblastoma, *SEPT9* methylation for blood-based colon cancer diagnosis and a test for the detection of *GSTP1*, *APC* and *RASSF1A* methylation for prostate cancer diagnosis on biopsy. An emerging focus is also on additional promising epigenetic changes such as key histone modifications and non-coding RNAs and their significance as diagnostic, prognostic or predictive markers in cancer and other diseases.

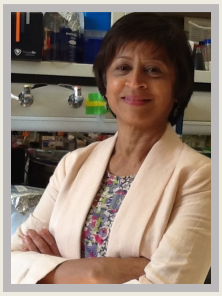
One of the most attractive characteristics of epigenetic abnormalities is their reversible nature, making them emerging as both therapeutic agents and targets for personalized therapy. At present, epigenetic therapy has been established as a successful treatment approach for hematological malignancies and research is underway for epigenetic therapy in solid tumors. In the following decade, the major goal for the use of epigenetic agents in solid tumors will be to reverse resistance and/or sensitize cancers to chemotherapy, hormonal therapies and/or immunomodulatory therapies that will provide meaningful benefits to patients. Additional future research of epi-drugs that can reprogram the epigenome of cancer cells and promote their self-renewal will be translated into new and more effective cancer treatments.

Our knowledge of epigenetics continues to expand through initiatives such as the International Human Epigenome Consortium and the NIH Roadmap Epigenomics Mapping Consortium, which will pave the road to a comprehensive epigenome encyclopaedia for all cell types and disease

states. Discoveries from these and other initiatives may then be translated to the development of an epigenotyping chip that will allow for highly sensitive analysis of disease-related epigenomic changes that will be simultaneously tested in a variety of minimally invasive samples. This will complement gene chips to guide patient care in the era of personalized medicine. ■

Ekaterina Olkhov-Mitsel

Ekaterina Olkhov-Mitsel has recently completed her PhD in the Department of Laboratory medicine and pathobiology at the University of Toronto in 2015 and is currently a post-doctoral fellow in Dr. Bharati Bapat's lab at the Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, Toronto. Her research is focused on investigating prostate cancer epigenetic biomarkers for implementation in the clinical setting.



Bharati Bapat

Dr. Bharati Bapat is Professor in the Department of Laboratory Medicine and Pathobiology at the University of Toronto, Staff Scientist at the Department of Laboratory Medicine and Pathology, University Health Network, and Associate Member at the Lunenfeld-Tannenbaum Research Institute, Mount Sinai Hospital. Dr. Bapat has authored over 100 peer-reviewed publications. Her research program focuses on translational (epi)genomics, discovery of biomarkers and their applications to improve patient care in a clinical setting.

Ask an Expert

Are we responsible for the epigenetic changes we pass on to our offspring?

Marc-André Sirard, Ph.D.

Chaire de Recherche du Canada en Génomique, Département des Sciences Animales, Université Laval, Québec, Canada, G1V 0A6
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Darwin was the father of genetic determinism as he demonstrated the effect of the environment on the selection of individuals to be able to transmit their genes to the next generation. The natural selection takes thousands of years to change a character in a whole population while Lamarck was rather under the impression that the environment could have an immediate impact on the traits of the next generation and ended up being ridiculed when genetic experiments supported Darwin's views. As predicted by his daughter and inscribed on his tomb: "La postérité vous admirera, elle vous vengera, mon père" (time will bring revenge and admiration) Lamarck could well be avenged by recent discoveries. Indeed, it is now increasingly recognized that the environment of the parent has an impact on the next generation through a mechanism called epigenetics. Epigenetics modifies the labelling of the DNA without changing the genetic sequence and can be transmitted through the eggs and sperm. Epigenetics is also the mechanism by which all of our cells have the same genome but different functions. Most of the epigenetic programming occurs during embryonic and fetal development, however aberrant alterations also occur in many diseases including cancers.

The recent review in Science by Sarah Robertson's research group[1] provides a long list of evidence that parents, mothers and fathers alike, in all mammals tested, influence the future phenotype(health) of their children with more than the genes they transmit. It has been observed that both over- and under-nutrition in parents create a propensity for accumulating fat in the offspring. While it might seem bizarre that two opposite conditions cause the same phenotype, indeed excess weight gain and weight loss can indeed lead to the same consequence: a release of fatty acids/triglyceride in the blood caused by excess eating in one case or by their release of fatty acids from fat reserves during starvation. The result is a tendency for the next generation to store more calories. This phenomenon would represent rapid adaptation to variable calories availability between seasons and some types of sugar associated with fall harvest such as fructose, would be a signal for energy storage. In our modern society where food is abundant all year round, such programmed responses generate insulin resistance and rapid fat uptake for storage, leading to obesity, diabetes and cardio-metabolic diseases.

If parental environment and lifestyle affect their unborn offspring, this begs the question: "who is responsible? Our ancestors, our parents, society, big companies adding fructose and/or fat in our food or scientific ignorance? Admittedly, individual freedom allows everyone to eat what they want, even if some may die more rapidly because of their unhealthy diet. But what about the harm we cause others such as our children? I would argue, our knowledge of epigenetics necessitates the introduction of a new regulatory framework for society which must protect the innocent and in this case future generations against harm caused by the parents' lifestyle. To implement such a framework involves explaining the scientific basis of the phenomenon and informing future parents through proper communication programs and better food labelling. Who is responsible? We as scientists and we as parents! ■

References

1. Lane M, Robker RL, Robertson SA. Parenting from before conception. Science. 2014 Aug 15;345(6198):756-60.

Dr. Sirard holds a Canadian Research Chair in genomics applied to reproduction since 2001. He has spent most of his carrier in the field of animal and human reproduction, especially in vitro fertilization before developing an expertise in genomics and more recently epigenomics. Through the Embryogene network his team have develop transcriptomic and epigenomic platforms to study minute samples as gametes and embryos.

Ask an Expert

The impact of the environment on the human (epi)genome: Are we responsible for the epigenetic changes we pass on to our offspring?

Luigi Bouchard, Ph.D. M.B.A.

Associate professor of Department of Biochemistry, Faculty of Medicine and Health Sciences, Université de Sherbrooke and Head of the Department of Molecular Biology and Medical Genetics, Chicoutimi Hospital

Many human traits including metabolic diseases are transmitted, at least partially, from parents to their offspring. By definition, these traits are complex, with the combined interactions of genetics and the environment writing an intricate scenario. Resolving this complexity is far from simple.

The era of human genetic epidemiology – the science studying the role of genetic factors in health and disease in families and populations – started in the '80s and culminated with the resolution of the human genome in 2003 and the concordant development of technologies capable of genotyping hundred of thousands of genetic polymorphisms at a relatively low cost. Many large genome-wide epidemiological studies have been conducted so far. These studies have been useful, allowing the identification of new genes and metabolic pathways involved in human diseases such as diabetes[1]. However, the gene polymorphisms that have been identified so far, even all together, only contribute marginally to explain the variance of complex traits attributed to genetic factors. This evidence suggests that other molecular mechanisms are involved. This is where epigenetic mechanisms make their entrance.

Epigenetics refers to the regulation of DNA transcription without changing the DNA sequence[2]. Epigenetic marks are partially inherited with profound phenotypic effects. The epigenetic regulation of cellular functions is a normal and essential process in cell development and differentiation. Epigenetic marks are transmitted end enduring through cell divisions, producing long-term changes in gene expression, but they are also malleable[3]. Indeed, they can be subjected to reprogramming by both stochastic and environmental stimuli, but more determinedly by factors influencing the in utero environment[4].

A wide range of epidemiological studies and animal models have provided strong evidence for a link between an exposure to metabolically challenging environmental conditions in the first months of in utero development and the development of diseases such as obesity and diabetes[5]. This phenomenon is called foetal metabolic programming. Interestingly, the offspring of mothers exposed to metabolic insults in utero have an increased risk of obesity-related metabolic perturbations and diabetes even if they were not themselves exposed to this adverse foetal environment[6]. Both foetal metabolic programming and its transgenerational effects might be supported by epigenetic adaptations.

Our group has provided some of the first evidence supporting the role of epigenetics in foetal metabolic programming using gestational diabetes mellitus (GDM) as a human model. GDM is a carbohydrate intolerance first diagnosed during pregnancy (the most common metabolic complication in pregnancy). GDM is of interest in foetal metabolic programming because it is associated with a higher risk of developing obesity and diabetes[7], but the mechanisms involved remain largely unknown. In addition to the identification of specific epigenetic alterations, we have shown that the epigenetic changes associated with GDM exposure are not randomly distributed throughout the genome but primarily affect genes involved in diabetes and glucose metabolism pathways[8]. These results provided the first evidence linking GDM exposure and epigenetic dysregulation of genes regulating metabolic pathways.

Human studies are still limited because only few other designs besides GDM can address the role of epigenetics in foetal metabolic programming in human. The Dutch Hunger Winter Cohort provided such a framework. Very briefly, the authors showed using candidate gene and genome-wide approaches that foetal exposure to maternal malnutrition could have effects lasting over 50 years on the epigenomic profile[11-13]. Nevertheless, neither our nor other groups

have yet provided evidence that the epigenetic variations inherited at birth through foetal metabolic programming are predictive of obesity and diabetes later in life. This objective is challenging, but is nevertheless needed to prove that epigenetics is involved in foetal metabolic programming in humans.

Contrary to the more "traditional" genetic mechanisms, epigenetics offer the possibility for rapid (at the generation level) genomic adaptations to changing environmental conditions. However, this adaptive strategy may have maladaptive consequences, such as obesity and diabetes, when mismatches between intrauterine and extrauterine conditions exist. This situation is more likely to occur considering the current obesity and diabetes epidemics. Therefore, unhealthy environmental conditions will be to blame for epigenetic changes the parents might pass on to their offspring. Improved prevention programs during and after pregnancy are needed and must clearly be part of the solution. The stigmatization of parents and their offspring would at best be counterproductive. ■

References

1. Berndt SI, Gustafsson S, Magi R, Ganna A, Wheeler E, Feitosa MF, et al. Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. Nat Genet 2013; 45:501-12.
2. Bird A. DNA methylation patterns and epigenetic memory. Genes Dev 2002; 16:6-21.
3. Kangaspeska S, Stride B, Metivier R, Polycarpou-Schwarz M, Ibberson D, Carmouche RP, et al. Transient cyclical methylation of promoter DNA. Nature 2008; 452:112-5.
4. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet 2003; 33 Suppl:245-54.
5. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med 2008; 359:61-73.
6. Margetts BM, Mohd Yusof S, Al Dallal Z, Jackson AA. Persistence of lower birth weight in second generation South Asian babies born in the United Kingdom. J Epidemiol Community Health 2002; 56:684-7.
7. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 1992; 35:595-601.
8. Ruchat SM, Houde AA, Voisin G, St-Pierre J, Perron P, Baillargeon JP, et al. Gestational diabetes mellitus epigenetically affects genes predominantly involved in metabolic diseases. Epigenetics 2013; 8:935-43.
9. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A 2008; 105:17046-9.
10. Tobi EW, Goeman JJ, Monajemi R, Gu H, Putter H, Zhang Y, et al. DNA methylation signatures link prenatal famine exposure to growth and metabolism. Nature communications 2014; 5:5592.
11. Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, Stein AD, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. Hum Mol Genet 2009; 18:4046-53.

Luigi Bouchard, Ph.D. M.B.A

Dr. Bouchard is associate professor of genetics and epigenetics at the Department of Biochemistry, Faculty of Medicine and Health Sciences, Université de Sherbrooke and head of the Department of Molecular Biology and Medical Genetics at the university-affiliated Chicoutimi Hospital. He is leading a research group dedicated to understand how epigenetic mechanisms are involved in the development of obesity, diabetes and cardiovascular disease, and identifying epigenetically-modified genes that play a causal role in fetal metabolic programming. He pioneered the field in which he has published numerous papers.

Ask an Expert

Should whole genome sequencing be performed in all newborns?

Michael Shevell MD CM, FRCP, FCHAS

Chair of Department of Pediatrics and Professor of Departments of Pediatrics and Neurology/ Neurosurgery, McGill University
Pediatrician-in-Chief, Montreal Children's Hospital-McGill University Health Centre

Circa 2015, the answer to this question in my opinion is an emphatic no. We are simply not ready for prime-time on this matter yet due to a multitude of reasons. Recent technological advances have enabled whole genome sequencing (WGS), and rapidly declining costs (the fabled $1000 genome) have made it potentially feasible on a population-wide basis. Theoretically, WGS in newborns offers the possibility of achieving population-health gains as a byproduct of advances in genetic understanding and technology[1]. However, that something is doable does not necessarily entail that we should do so. There are enormous technical, ethical, legal and policy challenges which must be addressed prior to implementing universal neonatal WGS.

Newborn screening has been available for an ever-expanding group of pre-symptomatically diagnosable and treatable genetically determined disorders for slightly more than 50 years[2]. It has been formulated and implemented as a public-health measure, applied universally on a population-wide basis without the needed consent of participants. There is no doubt that it has saved many lives and reduced morbidity, making possible for thousands of individuals a life of 'normality' as opposed to often frequent devastating neurodevelopmental disability that renders an individual dependent rather than autonomous. Wilson and Jungner in 1968[3] elaborated in a seminal and highly influential publication the criteria for population screening for a disorder (Table 1). These have stood the test of time and remain the gold-standard for evaluation as new disorders are added to those screened in newborns. Special emphasis should be placed on criteria #2 and #3.

The mechanics of testing is but one aspect of newborn screening. An enormous network of infrastructure and human resources are additionally necessary for education, counselling, treatment (where possible) and programmatic follow up (criteria #3)[4]. WGS will offer the possibility of diagnosing more than

Table 1: Wilson and Jungner Screening Criteria (Adapted from Andermann *et al.*[1]

1.	The condition sought should be an important health problem
2.	There should be an accepted treatment for patients with recognized disease
3.	Facilities for diagnosis and treatment should be available
4.	There should be a recognizable latent or early symptomatic phase
5.	There should be a suitable test or examination
6.	The test should be acceptable to the population
7.	The natural history of the condition, including development from latent to declared disease, should be adequately understood
8.	There should be an agreed policy on whom to test as patients
9.	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
10.	Case-finding should be a continuing process and not a "once and for all" project

3000 genetic disorders and elucidating variants in an ever-expanding multitude of other genes that confer not disease, but an increased risk for a disorder. Less than 100 of these disorders are treatable presently in a manner analogous to the substantial treatment effects conferred by interventions for those disorders now screened for (criteria #2). Furthermore, many of these disorders have an onset decades removed from infancy. Thus for the vast majority of diseases to be diagnosed by WGS, only the time of diagnosis will be advanced leaving health outcome ultimately unaffected. Thus no measurable population-health gain is achieved. Rather what is created is an enormous additional demand on an already over-burdened public health care system as individuals and families seek counselling, education and risk management information for which we have little in the way of present objective evidence or help to offer[5].

Newborn WGS would result in the generation of substantial

amounts of data, which would need to be stored while respecting privacy concerns and incorporated into the individual's health record. The potential impact of incidental findings (for example mistaken paternity assumptions) and their use in future employment and insurance matters are enormous and have yet to be carefully considered by society[6]. What is desperately needed is a careful, detailed, wide-ranging and objective assessment of the impacts foreseen for newborn WGS. Fortunately, the American National Institutes of Health in 2013 has directed $25 million for prospective studies in WGS best practices under their Genomic Sequencing and Newborn Screening Disorders program[2]. To provide a Canadian context to the discussion, the Canadian Institute for Health Research (CIHR) and CIHR and Social Sciences and Humanities Research Council (SSHRC) granting agencies should undertake a similar commitment. This will then need to be followed by a broad public discussion of these matters holding at its pinnacle the following key question: What is in the best interests of the screened newborn?[4]

Only once this data becomes available and an ensuing informed public discussion has taken place, may we be ready for 'prime-time' with reference to newborn WGS. ■

References

1. Andermann A, Blancquaert I, Beauchamp S, Dery V. Revisiting Wilson and Jungner in the genomic era: A review of screening criteria over the past 40 years. Bull WHO 86: 2008.
2. Meade C , Bonhomme NF. Newborn screening: Adapting to advancements in whole-genome sequencing. Genetic Test Mol Biomark 18:597-598, 2014.
3. Wilson JMG, Jungner J. Principles and Practice of Screening for Disease. WHO (Geneva): 1968.
4. Knoppers BM, Senecal K, Borry P, Avard D. Whole-genome sequencing in newborn screening programs. Sci Trans Med 26:229, 2014
5. Ulm E, Feero WG, Dineen R, Charrow J, Wicklund C. Genetics'professionals' opinions of whole-genome sequencing in the newborn period. J Genet Couns [Epub ahead of print] Oct 28, 2014.
6. ACMG. Incidental findings in clinical genomics:A clarification. Gent Med 8:664-666, 2013.

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Ask an Expert

Newborn screening by whole genome sequencing? Not quite yet.

Stephen Scherer, Ph.D.[1], Ronald Cohn, MD, FACMG[2], Christian Marshall, Ph.D.[3] & Michael Szego, Ph.D.[4]

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Advances in sequencing technology and informatics have made it possible to elucidate the genomes of individuals[1,2]. With falling sequencing costs, and improving accuracy and speed of the technology, application of whole genome sequencing (WGS) is increasing in clinical research, and will likely soon be a clinical test. Here we propose that, while WGS holds great promise, it is premature to employ it as a newborn screening tool. We will suggest a tiered screening model that could be employed in the future.

Newborn screening programs provide accurate tests with high clinical utility to identify treatable conditions before symptoms are evident[3]. WGS is a relatively new test whose clinical validity and utility are still being established. The Centre for Genetic Medicine at the Hospital for Sick Children in Toronto (SickKids) has launched the "genome clinic", a five-year cohort study to compare the efficacy of WGS to conventional genetic testing[4]. This study is being performed because WGS shows great promise as a diagnostic tool that will better guide treatment. First, individuals metabolize drugs at different rates, and WGS can help clinicians to prescribe the most effective medication and dose for each patient[5]. Second, the use of WGS can expedite diagnosis compared to conventional -- often sequential -- genetic testing, particularly in cases of unclear clinical diagnoses or atypical disease manifestations[6]. Third, WGS can lead to individualized treatment. For example, a boy with life-threatening inflammatory bowel disease had not responded to standard therapies, but whole exome sequencing identified a mutation in a gene associated with a blood disorder; as a consequence clinicians performed a hematopoetic stem cell transplant and the boy's symptoms improved[7].

WGS is a promising technology, but there are some barriers before its clinical utility can be established. First, the methodology is highly, but not perfectly accurate, for a variety of technical reasons[8]. Given the large data set, even a small false positive rate translates into many errors[3]. Second, the interpretation of genomic variants is challenging, and can be a source of error and uncertainty. In silico prediction tools are imperfect for detecting pathogenic variants, and even the most up-to-date lists of pathogenic variants from large-scale databases are incomplete and sometimes inaccurate[3,9]. Third, genome analysis is still time-consuming, usually including manual curation[10]. As technology and analysis tool improve, these issues will likely be addressed.

Current newborn screening programs are efficient at informing a child's parents of positive screen results for the selected tests, typically chosen due to immediate health implications for the child. In contrast, WGS is a sweeping collection of all genomic data, both massive and complex to interpret, and has the potential to reveal unwanted or harmful information. There is controversy about what results should be returned to patients/parents from such analyses[11,12]. Should most data be masked, and only the genes revealed that have immediate relevance to the newborn? Or should we take the opportunity for more information? For example, should pathogenic mutations in BRCA1 be assayed for in newborn screening given the health implications for the biological parents and the future health implications for the child? With prior consent, the SickKids genome clinic will inform parents about variants associated with treatable adult onset disorders found in their child if the child is unable to consent for herself. Such findings may have health implications for the parents, with

considerations in the best interests of their children[13]. Our position is consistent with American College of Medical Genetics (ACMG) guidelines[14] which suggest that medically actionable conditions (most of which are adult-onset) should be tested for at any age, provided there is consent. This position on testing for adult-onset conditions in young children (or any child not capable of consenting to the test) is controversial[15, 16].

Given the technical efficiency of a single full genomic scan, we foresee that eventually every individual will have such data as part of his medical record, and probably it will take place at birth (if not before). In the short term, however, WGS is not appropriate as a newborn screening tool, but plans are needed in anticipation of its eventuality. For now, WGS is best employed for targeted diagnostic investigations, and we propose a tiered approach to future applications in screening. With fully automated interpretation, WGS could be performed for all newborns, with a series of different informatics filters to be applied to the data as the child ages. In addition, whenever a patient interacts with a healthcare provider and genetic testing is recommended, the WGS data could be probed selectively for diagnosis and/or treatment. We anticipate that WGS, used as a screening tool in a tiered manner, could positively contribute to the health of Canadians from birth until adulthood. Not yet – but coming. ■

Acknowledgements

The authors thank Dr. Janet Buchanan for helpful commentary.

References

1. Levy S, Sutton G, Ng PC, Feuk L, Halpern AL, Walenz BP, et al. The diploid genome sequence of an individual human. PLoS biology. 2007;5(10):e254. Epub 2007/09/07.
2. Wheeler DA, Srinivasan M, Egholm M, Shen Y, Chen L, McGuire A, et al. The complete genome of an individual by massively parallel DNA sequencing. Nature. 2008;452(7189):872-6. Epub 2008/04/19.
3. Canadian Agency for Drugs and Technologies in Health. Newborn Screening for Disorders and Abnormalities in Canada. 2015 [cited 2015 March 9]; Available from: http://www.cadth.ca/products/environmental-scanning/environmental-scans/newborn-screening.
4. Bowdin S, Ray PN, Cohn RD, Meyn MS. The genome clinic: a multidisciplinary approach to assessing the opportunities and challenges of integrating genomic analysis into clinical care. Human mutation. 2014;35(5):513-9. Epub 2014/03/07.
5. Harper AR, Topol EJ. Pharmacogenomics in clinical practice and drug development. Nature biotechnology. 2012;30(11):1117-24. Epub 2012/11/10.
6. Johansen Taber KA, Dickinson BD, Wilson M. The promise and challenges of next-generation genome sequencing for clinical care. JAMA internal medicine. 2014;174(2):275-80. Epub 2013/11/13.
7. Worthey EA, Mayer AN, Syverson GD, Helbling D, Bonacci BB, Decker B, et al. Making a definitive diagnosis: successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. Genetics in medicine : official journal of the American College of Medical Genetics. 2011;13(3):255-62. Epub 2010/12/22.
8. Pang AW, Macdonald JR, Yuen RK, Hayes VM, Scherer SW. Performance of high-throughput sequencing for the discovery of genetic variation across the complete size spectrum. G3. 2014;4(1):63-5. Epub 2013/11/07.
9. Xue Y, Chen Y, Ayub Q, Huang N, Ball EV, Mort M, et al. Deleterious- and disease-allele prevalence in healthy individuals: insights from current predictions, mutation databases, and population-scale resequencing. American journal of human genetics. 2012;91(6):1022-32. Epub 2012/12/12.
10. Bell CJ, Dinwiddie DL, Miller NA, Hateley SL, Ganusova EE, Mudge J, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. Science translational medicine. 2011;3(65):65ra4. Epub 2011/01/14.
11. Anderson JA, Hayeems RZ, Shuman C, Szego MJ, Monfared N, Bowdin S, et al. Predictive genetic testing for adult-onset disorders in minors: a critical analysis of the arguments for and against the 2013 ACMG guidelines. Clinical genetics. 2014. Epub 2014/07/22.
12. Clayton EW, McCullough LB, Biesecker LG, Joffe S, Ross LF, Wolf SM, et al. Addressing the ethical challenges in genetic testing and sequencing of children. The American journal of bioethics : AJOB. 2014;14(3):3-9. Epub 2014/03/07.
13. Szego MJ, Meyn MS, Anderson JA, Hayeems R, Shuman C, Monfared N, et al. Predictive genomic testing of children for adult onset disorders: a Canadian perspective. The American journal of bioethics : AJOB. 2014;14(3):19-21. Epub 2014/03/07.
14. Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genetics in medicine : official journal of the American College of Medical Genetics. 2013;15(7):565-74. Epub 2013/06/22.
15. Knoppers BM, Senecal K, Borry P, Avard D. Whole-genome sequencing in newborn screening programs. Science translational medicine. 2014;6(229):229cm2. Epub 2014/03/29.

16. Zawati MH, Parry D, Thorogood A, Nguyen MT, Boycott KM, Rosenblatt D, et al. Reporting results from whole-genome and whole-exome sequencing in clinical practice: a proposal for Canada? Journal of medical genetics. 2014;51(1):68-70. Epub 2013/10/01.

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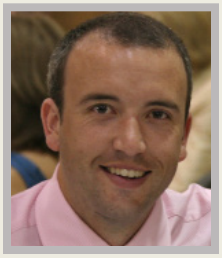

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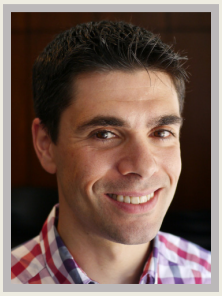

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SPOTLIGHT ON CAREERS

Industrial postdoc: choosing a different path

Aida Sivro, Ph.D.

While the number of Ph.D. graduates has been on a steady increase throughout the world, the number of academic positions has been continuously declining. An article in The Economist in 2010 reported that USA produced 100,000 doctoral degrees between 2005 and 2009, while in the same period there were only 16,000 new professorships. Moreover, according to the National Institute of Health (NIH), only 26% of Ph.D. graduates from biomedical sciences obtained tenured track positions in 2012. With the lack of academic positions, an increasing number of Ph.D. graduates are choosing industry over academia. A 2006 article in Science estimated that in 2001 industry employed 35% of life science Ph.D.s, an increase from 15% in 1981. For Ph.D.s who would like to experience working in the industry setting but keep the academia dream alive, there is a new option on the table: industrial postdoc. Undertaking an industry postdoc is likely the best way to get introduced to the culture of research and development in the private sector. It is a unique opportunity to design and perform research in a pharmaceutical setting with guidance and support from industry-based investigators.

From the perspective of a Ph.D. graduate, an obvious benefit to industry is increased salaries and benefits. Most postdoctoral placements in Canada and the USA pay their postdocs approximately $40,000 per year. Annual starting salary at Genentech is $63,000 with a promise of increase each year based on satisfactory performance. In addition, postdocs are eligible for the following benefits: medical, dental, and vision; life and disability insurance; 401(k); 12 paid holidays; and 3 weeks of vacation time.

Another benefit to working in industry is the access to state-of-theart equipment and facilities, as well as a wide variety of expertise ranging from bioinformatics to chemistry, and biology. A large advantage to doing research in industry is that there is usually more funding allocated for each project, leaving you able to pursue your scientific questions without worrying about funding or grant writing. This access to resources can significantly speed up your scientific research and discoveries while making you more competitive for both academia and industry jobs.

Things to consider

Will an industrial postdoc cut you off from a career in academia? It is commonly believed that working in industry makes it difficult to return to academia, which is the reason why most Ph.D. graduates take a postdoc position. However: is this truly the case? Two things are likely to be most important if you are looking for a career in academia: networking, and the quantity and quality of one's publications. The lines between academia and industry are becoming increasingly blurred, and partnerships between the two are on the rise. Through your industrial postdoc you are likely to come into contact with scientists from various disciplines, from both the industrial and academic sector. Becoming an 'industry-academia' hybrid could provide you with valuable contacts on both sides and significantly increase your market value.

Since publications are crucial for obtaining an academic position, postdoc experience should more than anything become the time to build a strong publication record and improve your CV. Several pharmaceutical companies (e.g. Novartis and AstraZeneca) specifically state on their postdoctoral job advertisements that they encourage publishing and conference presentations. However, as with any academic placement, your publication record will ultimately depend on the project, supervisor, and quality of your results. Before committing to an industrial placement you need to discuss this with a prospective employer. For instance, Genentech postdocs are kept away from any research that involves development of a product.

This allows the fellows to openly present and discuss their research at conferences and continue working on their projects once they leave the company. Similarly, Novartis Institutes for Biomedical Research (NIBR) do not place restrictions on postdoctoral publications, and projects are designed with this in mind. For postdoctoral fellows looking to pursue a career in academia, the NIBR program offers the opportunity to apply for a NIBR Young Investigator Development Award, a grant to continue research for an additional year at NIBR as well as three years as a tenure track faculty member at an accredited academic institution. Some postdoctoral fellows may wilfully choose to work on a project that cannot be published, considering the potential benefit of being an inventor on a patent and choose a different career path to the one in academia.

Will the industrial postdoc position guarantee you a job in the company later on? Postdoctoral appointments typically lead to permanent positions at some companies, but this is not a rule. Certain companies like AstraZeneca aim to retain their fellows as permanent employees. This is not the case with companies such as Genentech, where only about 10% of postdocs end up being hired by the company as scientists.

How to apply?

Industrial postdoctoral appointments vary in scope, length and application process depending on the company. As with any research placement, it is important to select a position that excites you; the salary alone will not be enough to motivate your work if you find the work and science uninteresting. Industry will have a list of opened projects and proposed supervisors. It is important to contact other postdoctoral fellows in the laboratory and determine the work and supervision style of the research group. Some companies like NIBR and Genentech have a formal application process managed through a centralized office. In other companies such as AstraZeneca, prospective postdocs apply to the human resource department in response to a specific position listed on the company's websites. In some cases it may be possible to obtain a position by contacting a researcher of interest directly.

Some of the pharmaceutical companies with industrial post-doc opportunities include:

- **Roche** (http://www.roche.com/careers/workplaces/wp_research/postdoc_fellowship_rpf_program.htm)
- **Genentech** (http://www.gene.com/careers/academic-programs/postdocs)
- **NOVARTIS** Institutes for Biomedical Research (http://postdoc.nibr.com)
- **MERCK** (http://www.merck.com/research/fellow/home.html)
- **GlaxoSmithKline** (http://www.gsk.com/en-gb/careers/postgraduates/randd-postdoctoral-global-training-programme/)
- **AstraZeneca** (http://www.astrazenecacareers.com/students/programmes/postdoc/)
- **Pfizer** (http://pfizercareers.com/university-relations/postdoc) ■

Aida Sivro, Ph.D.

Aida Sivro is a postdoctoral fellow at Centre for AIDS Programme of Research in South Africa (CAPRISA) and department of Medical MIcrobiology, University of Manitoba. Her current research interests include studying the predictors of HIV acquistion and pathogenesis.

Interview with Dr. Ruby Nadler

Rebecca Liu

Dr. Ruby Nadler is a Postdoctoral Research Fellow at Research Psychologists Press Inc through the MITACS Elevate program. MITACS is a Canadian not-for-profit organization that provides internships and training programs combining scientific and business skills in partnership with industry, government and academia.

Dr. Nadler received her PhD in Cognitive Psychology from Western University in 2013. When I first spoke with Dr. Nadler at a Graduate Career Day event, she was very kind and thoughtful in sharing her career path following the completion of her PhD. In my interview with Dr. Nadler, she shares in depth her steps and experiences working in an industry setting as a postdoctoral fellow.

What is your position, what does the MITACS fellowship entail?

The MITACS Elevate Postdoctoral Fellowship program was created to provide a bridge between academia and industry. Postdoctoral scholars spend roughly equal amounts of time at the headquarters of their industrial sponsor, and at their academic institution. Scholars work on a research problem that is of interest to their industrial partner and to their academic supervisor.

I have a Ph.D. from the Psychology department's Cognition and Perception area, and am leveraging my cognitive psychology expertise to explore more applied research questions.

Can you briefly describe one of the projects you are currently working on?

My primary project uses eye-tracking technology to investigate faking behavior on personality assessments used for employee selection. My industrial partner, Research Psychologists Press, creates and administers personality assessments for employee selection purposes so the topic of faking is of significant interest to them.

What steps did you take to find or acquire this position? In particular, what educational background and extracurricular involvement helped prepare you for this position?

As I was completing my Ph.D., I knew I wanted to stay in London, ON if possible so that constraint influenced my job search quite a bit. I learned about the MITACS postdoctoral fellowship through my graduate department, and was aware that Research Psychologists Press had previously hired people with Ph.D.'s in psychology so I contacted them to see if they were interested in working on a research project together through the Elevate program.

Giving presentations and talks at meetings and conferences helped me to develop strong communication and public speaking skills which are very helpful for job interviews and working with others. When I interviewed at Research Psychologists Press, I was able to clearly communicate what I had done while I was in graduate school and what skills I particularly enjoyed using or felt were my strongest assets. I spent a lot of time during graduate school working on identifying my transferrable skills, and polishing my interviewing skills through my university career centre. I think that helped me to sell myself during the interview stage.

What are the benefits and drawbacks of your current position?

The primary benefit is that I'm gaining experience in industry while still being affiliated with an academic institution. Having a foot in each door has provided me with a lot of useful experience I wouldn't have gained if I were solely associated with either my industrial partner or with the university. I'm still participating in academic life, publishing in academic journals and building my CV, but I'm also gaining "real world" work experience. The drawback is the flipside of that, which is that my time and attention are split to an extent, but overall it's been a great opportunity.

Can you describe a typical day in your position?

When I'm working at the university I'm usually collecting the behavioral data for my research study and working on data analyses or preparing results for publication. When I'm working at my industrial sponsor's headquarters, I'm consulting with the research team about the study, presenting results, and preparing for the next steps. It's similar to being in graduate school when you're working on a research-based dissertation, but I'm getting the perspective from industry in addition to the input of academic supervisors.

What unique non-academic skills do you believe are most valuable in your current position?

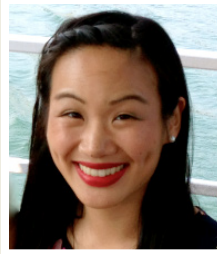
I'm not sure that it's a unique or non-academic skill, but being able to adapt to changing circumstances and priorities is always beneficial. There are always competing priorities and unknowns that make flexibility essential so that you can stay on track, but also be open to new possibilities or adapt to constraints.

If you were graduating this year, what career path would you pursue that is not your current one and why?

I'm not sure I can give a good answer to that, but to give graduate students an idea of what other people with similar backgrounds in psychology from my cohort (graduating in 2013-2014) are doing: some are in Tri-Council-funded postdoctoral positions at universities, and others are working as research coordinators, grant writers, research analysts, and lecturers (adjunct professors). Some have switched entirely out of academia and are leveraging programming and computational skills that they gained during their studies in the private sector. There are obviously a lot of different possibilities. I think spending time figuring out what your strengths and transferrable skills are, updating and converting CV's into resumes (often several different ones so that they're tailored to each specific job or type of job), doing mock interviews, and applying for different jobs is time well spent. Versatilephd.com has stories of academics that switched successfully from academia to other industries (along with their CV's and resumes) and it's a resource that helped me a lot. Many universities have access to it now, so it's worth looking into.

Can you give any advice to graduate students looking to pursue a career in your field?

There are so many different paths graduate students can take. I think it's important to start thinking about next steps as early as possible, and to be open to different possibilities because the job market changes so quickly. Don't be afraid to reach out to alumni and people who might be able to connect you to potential employers or people who have valuable information, and don't be afraid of taking a direction that you hadn't anticipated: you might end up loving it! ■



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