46. Liao LM, Nesic J, Chadwick PM, Brooke-Wavell K, Prelevic GM. Exercise and body image distress in overweight and obese women with polycystic ovary syndrome: A pilot investigation. Gynecol Endocrinol. 2008 Oct;24(10):555-561.
47. Moran LJ, Brinkworth G, Noakes M, Norman RJ. Effects of lifestyle modification in polycystic ovarian syndrome. Reprod Biomed Online. 2006 May;12(5):569-578.
48. Lau D. Screening for diabetes in women with polycystic ovary syndrome. CMAJ. 2007 Mar 27;176(7):951-952.
49. Gagnon C, Baillargeon JP. Suitability of recommended limits for fasting glucose tests in women with polycystic ovary syndrome. CMAJ. 2007 Mar 27;176(7):933-938.

How Genomics is Changing Medical Practice

Ruth Thomas, MSc[a], Shelin Adam, MSc[a], Lesley Phillips, PhD[a], Marion Thomas, PhD[a]

[a]BC Clinical Genomics Network, University of British Columbia, Vancouver, BC

ABSTRACT

Exponential improvements in genomic technology allows researchers to focus on the information contained in the human genome, in the hope of applying that knowledge clinically. The field of genomics, where all of an individual's genes are considered at once, has already begun to change medical practice. For instance, chromosomal microarrays are already being utilized to diagnose autism spectrum disorder, development delay, intellectual disability, and birth defects. By recognizing duplications and deletions, which are too small to identify with traditional chromosome analysis, we are able to improve diagnostic yield for these disorders. Whole genome sequencing has been used to diagnosis genetic illnesses, even in cases when the clinical picture or diagnosis is unclear. Through pharmacogenomics, which can help explain how genetic variants affect drug metabolism, we will be able to decrease the staggering incidence of adverse drug reactions, and guide physicians in medication choice for individual patients. With a better understanding of the relationship between genomic compositions, susceptibility to illness and treatment options, physicians will be able to practice more personalized medicine, offering more effective and safer treatment. Genomics has already begun to impact medical care and will likely revolutionize how medicine is practiced in the near future.

KEYWORDS: *genomics, personalized medicine, pharmacogenomics, chromosomal microarray, whole genome sequencing*

THE FIELD OF GENOMICS IS BORN

Following the completion of the Human Genome Project (HGP) in 2001, scientists and researchers were able to spell out the sequence, or code, of the human genome.[1] Since the completion of the HGP more than 10 years ago, there have been exponential improvements in the technology.[2] For instance, sequencing is now 100,000 times less expensive, and the newer generation machines are able to read sequences 50,000 times faster. While it took 13 years to complete the human genome project, it is now possible to sequence a human genome in a day.[2] With the technology ever-improving, scientists are able to focus on the information being produced.

THE TREMENDOUS POTENTIAL IN SEQUENCING THE HUMAN GENOME: PERSONALIZED MEDICINE

Advances in genomic research have resulted in an increasing awareness of the tremendous potential in interpreting and understanding the sequence of the human genome. One of the early discoveries was its sheer complexity, as there is incredible variation amongst the genomes of even two healthy individuals.[3] In fact, each individual differs in their sequence by as much as 0.5%. For instance, when compared to the reference human genome, each individual will have between 3 and 3.5 million single nucleotide variants (SNVs), and approximately 1,000 relatively large copy number variants (CNVs).[3] SNVs involve changes to single nucleotides, such as the substitution of one base pair for another (single nucleotide polymorphisms or SNPs), or the deletion or duplication of a single nucleotide. In contrast, CNVs occur when a particular portion of the genome is either duplicated or deleted, and therefore leads to a divergence from each person having two copies of each gene, one from each parent.[3] While seemingly daunting, for scientists, these variations were seen as an opportunity to harness these sequences in order to better understand disease and treatment options.[2,3] Better understanding of the human genome will result in increasingly personalized medicine, "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease.[4] Genomics has already begun to impact medical

Correspondence
Ruth Thomas, rthomas@cfri.ca

care and will likely revolutionize how medicine is practiced in the near future.

MICROARRAYS: GENOMICS IS ALREADY IN ACTION, PROVIDING DIAGNOSES

Genomics has already entered the clinical realm to diagnose illnesses such as development delay, intellectual disability, autism spectrum disorder (ASD), and birth defects.[5] It is estimated that 3% of the population has developmental delay/intellectual disability and approximately 1 in 110 individuals have ASD.[6] Traditionally, when trying to diagnose these types of illnesses, physicians have relied on G–banding chromosomal analysis, which involves viewing chromosomes under a microscope to visualize and inspect chromosomes for missing or added segments.[5] Chromosomal microarray (CMA) represents a newer genomic technology which utilizes computer chips and fluorescently labeled DNA, and offers significant improved diagnostic yield. For instance, CMAs have significantly improved resolution and can detect gains and losses which are ten times smaller than traditional chromosomal analysis, which translates to 10% more diagnoses.[5] The American College of Medical Genetics now recommends that CMA should be the first test ordered for diagnosing patients with intellectual disability, developmental delay, autism, and multiple congenital anomalies of unknown cause.[7] With more children receiving a diagnosis for their illness, physicians are better able to provide appropriate medical care and to offer accurate recurrence risk information to their families.[5]

Case example: Genomic sequencing provides an answer to a diagnostic dilemma

The following case demonstrates how genome sequencing can not only provide a diagnosis, but also guide the appropriate treatment. Fraternal twins were diagnosed with dopamine response dystonia (DRD) at the age of 5, after it was found that L–dopa relieved symptoms of dystonia exhibited in one of the twins.[8] The twins were responding well to their treatment until the age of 14, when they started exhibiting a myriad of symptoms including tremors, dystonia, unsteady gait, bradykinesia, and difficulty breathing. Following this decline in their clinical presentation, it was clear that further intervention was needed.

In order to elucidate the cause of the new symptoms in these twins, researchers sequenced both of their genomes, and compared them to their healthy sibling and parents. It was found that the twins carried mutations in SPR, which is an enzyme involved in the molecular pathway that produces dopamine and serotonin. With a better understanding of where the defect in the pathway was, the physicians were able to prescribe 5-hydroxytryptophan (5–HTP), a serotonin precursor which these twins needed in conjunction with the L–dopa. Following the initiation of the new treatment, the twins saw improvement in their symptomatology.

While SPR mutations have been associated with DRD in the past, clinical genetic testing for mutations in this gene was not indicated, because the presentation in the twins did not fit the classical clinical presentation for individuals with SPR mutations, which includes intellectual disability and unresponsiveness to L–dopa.[8] Had it not been for the ability to sequence the entire genome, it is possible that a proper diagnosis would not have been reached. In this case, genomics was not only able provide an accurate diagnosis, but was also able guide to the appropriate treatment.

PHARMACOGENOMICS

A rapidly evolving area of genomics is pharmacogenomics which takes into account how particular genetic variants affect our ability to respond to and metabolize drugs.[2,9] Using pharmacogenomics, we hope to decrease the staggering incidence of adverse drug reactions, as well as to guide physicians on which medications are the most appropriate for individual patients.

Adverse drug reactions (ADRs) are defined by the World Health Organization as a response "to a drug which is noxious and unintended, and which occurs at doses normally used in man" for prophylaxis, diagnosis, or therapy.[10] It has been estimated that genetic factors may be responsible for up to 95% of the variability in drug response and have been shown to play a role in both incidence and severity of ADRs.[11] Previous studies have indicated that fatal ADRs represent the fourth to sixth leading cause of death in the United States.[12] It is estimated that between 5 and 7% of hospital admissions are due to ADRs, and the most commonly responsible drugs are ubiquitous medications such as aspirins, other NSAIDs, and antibiotics.[9,13] The prevalence of ADRs is not surprising when you consider that Health Canada estimates that over 50% of newly approved therapeutic health products have serious side effects that are discovered only after the product is on the market.[14]

Pharmacogenomics will likely be able to lessen the economic and health burden of ADRs because if we know how particular genetic variants, in particular SNPs, will contribute to an individual's metabolism of a drug, physicians will be better equipped to prescribe the right drug, at the right dose, for the right patient.[11,12]

Case example: An ADR resulting from codeine use

For an example of pharmacogenomics in clinical practice, consider codeine, a commonly prescribed analgesic which is metabolized into its active form, morphine, by the enzyme CYP2D6.[15] Until recently, it was common practice to prescribe codeine to new mothers for postpartum pain.[16] This was the case when codeine was prescribed to a new mother in 2005, after she delivered a healthy, full-term baby boy. The mother took her son home but after a week the infant started to exhibit difficulty with breast feeding and lethargy. At a well–baby appointment on day 11, his pediatrician noted that the baby had regained his birth weight, but then only two days later, the infant passed away suddenly. Testing revealed that he had extremely high levels of morphine in his blood which had led to an opioid overdose and central nervous system depression. Analysis of the mother's blood and breast milk indicated morphine levels that were much higher than expected from her prescription, indicating that she was metabolizing codeine into morphine at a much higher than average rate. Genetic analysis of CYP2D6 was later performed and confirmed that variants in the mother's gene that resulted in her being an ultra-rapid metabolizer.[16] The frequency of variants in this gene

differ between ethnic populations and can vary from 1% to as high as 29%, which demonstrates that testing for variants would be clinically relevant for many patients.[15] Given the possible risk that codeine poses to infants, it is now recommended that should codeine be prescribed in the postpartum period, physicians, as well as parents, should be vigilant and well-educated regarding the risks.[17]

GENOMICS IS CHANGING MEDICINE

Genomics is a rapidly evolving field that will likely change how medicine is practiced in the near future. We have evolved from just having the sequence of the human genome, to harnessing that sequence to improve clinical outcomes and diagnoses in patients.[5,15] With the continuing advances in genomic technologies, we will continue to answer more clinical questions and solve more diagnostic dilemmas.[8,16] It is important that physicians become well-educated on genomics and stay abreast of the different advances, as genomics becomes incorporated into routine medical care.[3] The BC Clinical Genomics Network (www.bccgn.ca), which is funded by the Michael Smith Foundation for Health Research, understands the importance of physician education on genomics and provides many educational opportunities through conferences, hospital rounds, educational films, and seminars.

REFERENCES

1. International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. Nature. 2001 February 15;409:860-921.
2. Lander ES. Initial impact of the sequencing of the human genome. Nature. 2011 February 10; 470 (7333): 187-197.
3. Gonzaga–Jauregui C, Lupski JR, Gibbs RA. Human genome sequencing in health and disease. Annu Rev Med. 2012;63:35-61.
4. Tran B, Dancey JE, Kamel–Reid S, McPherson JD, Bedard PL, Brown AM, et al. Cancer Genomics; technology, discovery, and translation. J Clin Oncol. 2010 April 1; 30(5): 647-660.
5. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010 May 14;86(5):749-764.
6. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2006 Principal Investigators. Prevalence of Autism Spectrum Disorders -Autism and Developmental Disabilities Monitoring Network, United States, 2006. MMWR Surveill. Summ. 2009 December 18; 58(SS10):1-20.
7. Manning M, Hudgins, L. Array–base technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. Genet Med. 2010 November; 12(11):742-745.
8. Bainbridge MN, Wiszniewski W, Murdock DR, et al. Whole genome sequencing enables optimized patient management. Sci. Translational Med. 2011 June 15; 87re3.
9. Martinez–Mir I, Garcia–Lopez M, Palop V, et al. A prospective study of adverse drug reactions in hospitalized children. Br J Clin Pharmacol 1999 June; 47(6): 681-688.
10. World Health Organization. International Drug Monitoring: The Role of the National Centres. World Health Organ Tech Rep Ser. 1972; 498:1-25
11. Carleton B, Poole R, Smith M, Leeder J, Ghannadan R, Ross C, et al. Adverse drug reaction active surveillance: developing a national network in Canada's children's hospitals. Pharmacoepidemiol Drug Saf. 2009 August;18(8):713-721.
12. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998 April 15;279(15):1200-1205.
13. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al.. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004 July 4:329(7456):15-19.
14. Health Canada. Health Professional Reporting of Adverse (Drug) Reactions: A Vital Link in the Patient Safety Chain[homepage on the Internet]. [updated 2007 March 5; cited 2012 Feb 1]. Available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/centre-learn-appren/hcp-ps_ar-ei_module-eng.php
15. Cascorbi I. Pharmacogenetics of cytochrome P4502D6: genetic background and clinical implication. Eur J Clin Invest. 2003 November;33 Suppl 2:17-22.
16. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother [case report]. Lancet 2006 August 19; 368(9536): 704.
17. Madadi P, Moretti M, Djokanovic N, Bozzo P, Nulman I, Ito S, et al. Guidelines for maternal codeine use during breastfeeding. Can Fam Physician. 2009 November; 55(11):1077-1078.