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Volume 8, Number 2

PGxome – DIAGNOSIS THROUGH THE POWER OF MANY

We are excited to introduce PGxome, PreventionGenetics' whole exome sequencing test. PGxome uses NextGen sequencing technology and advanced interpretation to analyze nearly all genes from the human genome. Our exome test builds upon our many years of experience with single gene and small panel sequencing tests covering approximately 2,000 genes.

Variants identified in the ~3,700 genes known to be involved in Mendelian disorders are first manually interpreted by a team of about 20 (and growing) MD and PhD geneticists. Each of our geneticists specializes in a specific disease area. Through scholarly study and through preparation of many test reports, our geneticists become expert in their disease areas. When we interpret the PGxome sequence variants, each geneticist interprets only the variants which fall within their disease areas. This approach harnesses the collective knowledge and experience of many geneticists working in collaboration. Through the power of many, we are able to generate exome reports of the highest quality.

PGxome is intended for health care providers who are looking for a genetic diagnosis when the clinical phenotype is unclear and/or when previous test results have been uninformative. This is especially important given that over 50% of patients with genetic diseases are not given a specific diagnosis even after repeated clinical examinations and tests (Shashi et al. 2014).

PGxome usually includes testing of trios (typically the patient and both biological parents) in order to provide the highest probability of identifying a genetic explanation for the patient's phenotype. Approximately 20-40% of patients will receive a diagnosis or suspected diagnosis from this testing (Atwal et al. 2014; Iglesias et al. 2014; Farwell et al. 2015). PGxome also offers multiple options to opt out of information on secondary findings. This customization allows us to provide the most appropriate results for each patient's needs.

PGxome will also soon be extended to provide carrier testing for reproductive planning in healthy

individuals.

For more details regarding PGxome, click here.

To order testing, see our PGxome Test Requisition Form and Consent Form.

Use the power of many to end your patients' diagnostic odyssey. PGxome: Put us to the test!

References:

Atwal P.S. et al. 2014. Genetics in Medicine : Official Journal of the American College of Medical Genetics. 16: 717-9. PubMed ID: 24525916

Farwell K.D. et al. 2015. Genetics in Medicine : Official Journal of the American College of Medical Genetics. 17: 578-86. PubMed ID: 25356970

Shashi V. et al. 2014. Genetics in Medicine : Official Journal of the American College of Medical Genetics. 16: 176-82. PubMed ID: 23928913

EXPANDED VISION TEST MENU NOW AVAILABLE

According to the World Health Organization (WHO) and the American Academy of ophthalmology (AAO),
~ 39 million people worldwide are blind and another 246 million people are visually impaired (WHO Visual impairment and blindness Fact Sheet 2015).

Amazingly, ~ 80% of blindness can be prevented or cured if detected at early stages (WHO and AAO). Given these statistics, the importance of early and accurate diagnosis cannot be understated.

At PreventionGenetics, we believe that in many cases, genetic testing can provide the early detection needed to prevent or cure eye disorders. We have significantly increased our portfolio of genetic tests for vision disorders. Additionally, PreventionGenetics will be giving away a free genetic test from our eye disorders test menu. For a list of new tests and more information, visit our website.

PRESIDENT'S CORNER

James L. Weber, PhD

Quantitative Interpretation of Sequence Variants, Part 2

In Issue 1 of our 2016 Newsletter, I outlined the rationale for quantitative interpretation of sequence variants and presented our quantitative definitions of the five interpretation categories (Pathogenic, Likely Pathogenic, Uncertain, Likely Benign and Benign). In this Issue, I discuss in more detail two quantitative approaches with results and with limitations and pitfalls.

Our first approach is simply the comparison of the frequency of a variant in affected individuals (cases) versus controls. This is certainly not a novel approach, but is still quite powerful and useful. An example is shown in Figure 1 for dominant*RYR1* variants responsible for Malignant Hyperthermia. For cases, we used only clearly affected probands tested at PreventionGenetics. For controls, we used ExAC allele frequencies combined for all populations. p values were calculated using Fisher's exact test. Clear differences can be seen in the p values for between Pathogenic and Benign variants (interpreted using ACMG guidelines in the absence of quantitative assistance). We have also shown that this approach works well for recessive disease.

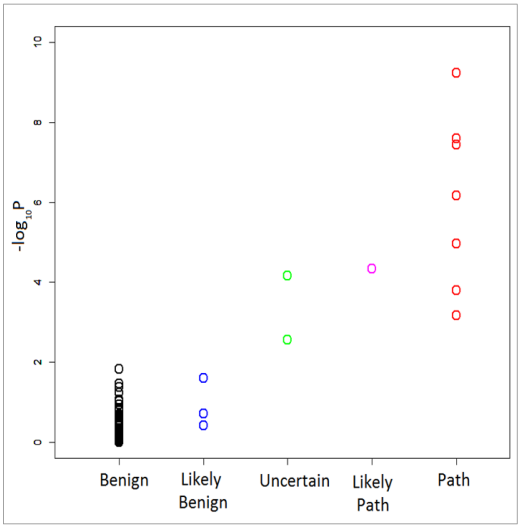

Figure 1: Dominant RYR1 Variants Responsible for Malignant Hyperthermia

All interpretation approaches have limitations and pitfalls. One significant limitation of comparison of case and control allele frequencies is that the variant of interest must be observed multiple times. A single observation is very likely insufficient. We used a minimum of two cases in our analyses, but three

or more cases should provide better discrimination and more accurate p values. Potential pitfalls of this approach include that the populations used for cases and controls need to be the same, and that errors and omissions in the control allele frequency databases (which do exist) must be avoided.

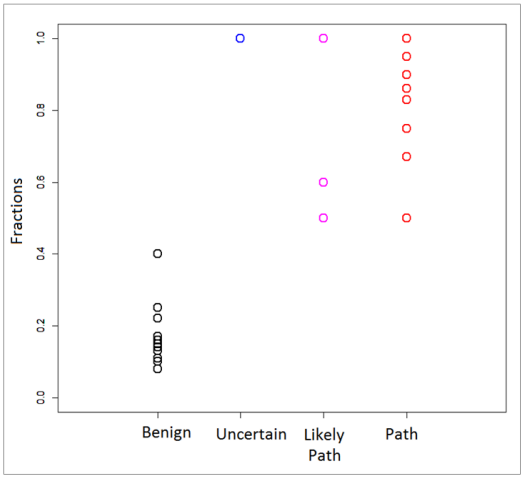

Figure 2: Times the Variant of Interest was Accompanied by a Second Pathogenic or Likely Pathogenic Variant for ARPKD

Our second quantitative approach applies only to autosomal recessive disorders. Data for the fraction of times the variant of interest was accompanied by a second pathogenic or likely pathogenic variant for Autosomal Recessive Polycystic Kidney Disease (*PKHD1* gene) are shown in the Figure 2. With this approach, there is also generally clear distinction between pathogenic and benign variants. As before, analysis was restricted to variants observed in at least two affected individuals. Some of the likely pathogenic and uncertain variants which were seen every time with second pathogenic variants are candidates for pathogenic designation. Variants with intermediate fractions may have incomplete penetrance.

Note that for most recessive disorders, the true fraction seen with second pathogenic variants will not be 100% because copy number variants and other variants not detectable by sequencing will be present. Also, less commonly, a proband may be only a heterozygous carrier for the variant of interest. Ideally therefore, known pathogenic variants should be used as controls for each disorder analyzed.

For both of the quantitative approaches described here, data can come from either testing labs or from the literature. We strongly recommend that such quantitative approaches be used as a first line approach for interpretation wherever possible. We also recommend that all non-quantitative evidence also be carefully examined for each variant.

I hope that the clinical genetics community will see a rapid move toward quantitative interpretation approaches and away from the highly subjective approaches outlined in the current ACMG Guidelines. Our work is an important step in this process, but just a first step. More powerful statistical methods very likely can be employed and additional quantitative approaches are also likely.

DR. FAN SPECIALIZES IN NEUROLOGIC DISORDERS

Li Fan, MD, PhD, M.Phil. FCCMG, FACMG, joined PreventionGenetics in July 2015 as a Clinical Molecular Geneticist. Her primary area of expertise is neurogenetics. Dr. Fan's portfolio at PreventionGenetics includes tests for Epilepsy and Intellectual Disability.

Dr. Fan received her medical degree from Zhejiang Medical University and her Ph.D. in biochemistry from The University of Queensland in Australia. Her doctoral research involved biochemistry of the human brain and neuroscience.

It was after entering a Canadian College of Medical Genetics fellow-training program at McGill University that Dr. Fan discovered her greatest passion, clinical molecular genetics. She has been working in a Clinical Molecular Diagnostic setting for over 15 years, previously at the University of Montreal.

Dr. Fan was initially interested in PreventionGenetics because of the large test menu and high level of test quality. Upon visiting the company, she was impressed with the knowledge and dedication of all the staff at PreventionGenetics as well as the care taken to provide accurate and appropriate results for patients. Happy to be a part of an organization "full of scientific spirit, humanity and responsibility towards society," she is passionate about providing diagnosis that may lead to treatment or other measures to improve the quality of patients' lives.

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