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PREVENTION GENETICS

DISEASE PREVENTION THROUGH GENETIC TESTING

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Volume 4, Number 1

Welcome to the March 2012 PreventionGenetics Newsletter. In this issue, we introduce our first Next Generation clinical DNA sequencing tests. We also describe Sanger sequencing tests for 25 new genes. In the President's corner Dr. Jim Weber discusses some of the advantages of Next Gen Sequencing.

PreventionGenetics Introduces Clinical Next Generation Sequencing

PreventionGenetics is proud to introduce gene cluster tests using our customized approach to Next Generation Sequencing (NGS). Our methods begin with gene capture in solution using an optimized set of DNA hybridization probes provided by Roche/Nimblegen. Optimization of the probe set ensures maximum sequence coverage of all genes. NGS is performed using the MiSeq instrument from Illumina. The MiSeq gives us the most reliable results with the fastest turnaround time. Finally, because no DNA hybridization method is capable of capturing all regions of interest, we will PCR amplify and Sanger sequence all regions with low sequence coverage. All likely pathogenic mutations and undocumented variants will also be confirmed by Sanger sequencing.

Our initial offering involves six NGS gene cluster tests: Joubert/Meckel Gruber Syndrome (13 genes), Bardet-Biedl Syndrome (14 genes), Nephronophthisis (10 genes), Primary Ciliary Dyskinesia (16 genes), Situs Inversus/Heterotaxy (20 genes), and a complete Ciliopathy Panel (55 genes). The genes covered by these tests all encode proteins that make up cilia, a ubiquitous structure found on the surface of nearly every human cell. Recent evidence points to essential roles for cilia in cell motility, directing fluid flow across the cell surface, and key signal transduction pathways. Due to the ubiquitous nature of the human cilium, recessive mutations in one of the cilia genes can lead to a panoply of clinical symptoms, including retinitis pigmentosa, renal

cystic disease, polydactyly, situs inversus, mental retardation, hypoplasia of the corpus callosum, Dandy-Walker malformation, posterior encephalocele, hepatic disease, respiratory distress, and infertility (Baker and Beales, Am J Med Genet 151C:281-295, 2009). Our Ciliopathy NGS tests encompass the entire clinical spectrum, and will allow for testing flexibility depending on the patient's clinical presentation.

PreventionGenetics continues to offer the most comprehensive list of Sanger single gene sequencing tests of any lab in North America. To ensure that our NGS tests are held to the same standard as our Sanger tests, we will not rely solely on computer algorithms to detect variants but will utilize a 3-stage manual review process that has been validated against our own Sanger results. As always, our goal is to offer the highest quality results.

Throughout the remainder of 2012, we will continue to add new NGS gene cluster tests--so check our website (www.preventiongenetics.com) frequently to find out what new NGS tests are available. Importantly, the implementation of NGS at PreventionGenetics will not affect our menu of Sanger gene sequencing tests, nor our commitment to the rapid development of new Sanger gene tests. Sanger sequencing is still the "gold standard" in clinical diagnostics, and is the most appropriate approach when a definitive diagnosis points to a specific gene or when family members would like to pursue carrier testing.

New Tests at PreventionGenetics Please follow the gene links for the corresponding test descriptions.

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Sorsby Fundus Dystrophy *TIMP3* (Test #669)

Usher Syndrome *DFNB31* (Test #697)

Usher Syndrome *USH1G* (Test #649)

Usher Syndrome Type 2 *GPR98* (Test #698)

Ehlers-Danlos Syndrome *COL5A2* (Test #841)

Ehlers-Danlos Syndrome *COL5A1* & *COL5A2* (Test #842),or (Test #840)

Megalencephalic Leukoencephalopathy *MLC1* (Test #601)Megalencephalic Leukoencephalopathy *HEPACAM* (Test #602)

Aarskog-Scott Syndrome *FGD1* (Test #837)

Heterotaxy *ACVR2B* (Test #935)

Ehlers-Danlos Syndrome *COL3A1* (Test #844)

Heterotaxy *NODAL* (Test #931)

Dilated Cardiomyopathy *PLN* (Test #148)

Barth Syndrome *TAZ* (Test #149)

Small Patella Syndrome *TBX4* (Test #859)

Arrhythmogenic Right Ventricular Cardiomyopathy *TMEM43* (Test #209)

X-linked Heterotaxy *ZIC3* (Test #932)

Familial Limb-Girdle Myasthenic Syndrome *GFPT1* (Test #594)

Nemaline Myopathy *KBTBD13* (Test #598)

Valosin-Containing Protein-Related Disorders *VCP* (Test #597)

Joubert Syndrome *TCTN2* (Test #576)

Methylmalonic Aciduria *MMADHC* (Test #212)

Methylmalonic Aciduria *LMBRD1* (Test #326)

X-linked Fanconi Anemia *FANCB* (Test #883)

Jim Weber, PhD

President's Corner

The Big Picture

Most of us know the old Indian folk tale about the blind man who touched the elephant's trunk and thought he was holding a snake. We can often be misled in clinical genetics by results that come from sequencing only one or a few genes. The great improvements in sequencing technology are now beginning to allow us to view the Big Picture.

The ciliopathy genes offer a great example. The ciliopathies are nearly all caused by recessive mutations in a single gene. However, heterozygous mutations in a second ciliopathy gene have been reported to significantly increase phenotypic severity (Tory et al. J Am Soc Nephrol 18:1566-1575, 2007; Khanna et al. Nat Genet 41:739-745, 2009). This has substantial implications for reproductive planning. As part of our NGS test validation, we sequenced (on a research basis) all the ciliopathy genes in a patient with many symptoms suggestive of nephronophthisis. Surprisingly, there were no pathogenic mutations in any of the traditional nephronophthisis genes. We did however, find two documented causative muations in a Bardet-Biedel Syndrome gene (*BBS10*) and one undocumented frameshift mutation in a Joubert gene (*TMEM67*). If we had only sequenced the genes in our nephronophthisis panel, we would have found nothing at all. If by chance we had Sanger sequenced all 55 of the ciliopathy genes sequentially, we would have stopped with the mutated gene we happened to sequence first, either *BBS10* or *TMEM67*. In both cases, we would have missed key mutation(s)--and the Big Picture.

We have not yet set final prices for our NGS tests, but we will do our very best to keep your costs low, while maintaining the highest possible quality; something you have come to expect from PreventionGenetics. In cases where a definitive diagnosis can be made and the disorder is known to be caused by mutations in one or a few genes, Sanger sequencing will likely be less expensive than NGS for some time. However, when a patient's symptoms are consistant with multiple disorders, and a clinical diagnosis is difficult to reach, NGS will potentially save thousands of dollars and reduce the turnaround time from several months to several weeks.

Clearly, the ultimate genetic "Big Picture" is whole genome sequencing. PreventionGenetics will move in that direction as soon as possible, but for now, we are pleased to offer the NGS gene cluster tests as an important stepping stone between single gene Sanger sequencing and the full genome.

Interested in a test we don't currently offer?

PreventionGenetics continues to expand our gene sequencing test menu. If you are interested in a particular test that we don't currently offer, please contact us. There is an excellent chance we can develop a test to suit your needs.