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PreventionGenetics

Disease prevention through genetic testing

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Volume 3, Number 2

Welcome to the August 2011 PreventionGenetics Newsletter. In this issue, we present new DNA sequencing tests for 19 disorders. In addition, we introduce one of our new geneticists, Dr. Keith Nykamp, and highlight some of his work. In the President's Corner, Dr. Jim Weber discusses selected exon sequencing at PreventionGenetics.

New Tests at PreventionGenetics

Please follow the gene links for the corresponding test description.

Dilated Cardiomyopathy ABCC9 (Test#147)
Stargardt Disease ABCA4 (Test#696)
Bloom's Syndrome BLM (Test#717)
Fructose-1,6-Bisphosphatase Deficiency FBP1 (Test#238)
Creatine Deficiency Syndrome GATM (Test#241)
Creatine Deficiency Syndrome GAMT (Test#242)
Hereditary Multiple Osteochondromas EXT1, EXT2 (Test#806, #808)
Oligodontia-Colorectal Cancer AXIN2 (Text#719)
Androgen Insensitivity Syndrome AR (Test#736)
Piebaldism and Familial Gastrointestinal Stromal Tumors KIT (Test#718)
Primary Ciliary Dyskinesia RPGR (Test#753)
Amyotrophic Lateral Sclerosis, Autosomal Dominant and Sporadic FIG4 (Test#157)
Methylmalonic Aciduria and Homocystinuria, cblC type MMACHC (Test#211)
Autosomal Dominant Severe Congenital Neutropenia and Cyclic Neutropenia ELANE (Test#414)
Autosomal Recessive Severe Congenital Neutropenia HAX1 (Test#446)
Pseudoachondroplasia and Multiple Epiphyseal Dysplasia COMP (Test#474)
Multiple Epiphyseal Dysplasia MATN3 (Test#816)
Multiple Epiphyseal Dysplasia COL9A2 (Test#817)
Multiple Epiphyseal Dysplasia COL9A3 (Test# 818)

PreventionGenetics proudly introduces Dr. Keith Nykamp.

Dr. Nykamp received his PhD in Genetics in 2003

Dr. Keith Nykamp

from the Department of Molecular Genetics and Microbiology at the University of Florida, Gainesville. As a graduate student, he explored the basic mechanisms of gene expression using the budding yeast, *Saccharomyces cerevisiae*, as a model system. After graduating, he moved to the Department of Biochemistry at the University of Wisconsin-Madison, where he studied genes responsible for sex differentiation and germline development in the free-living nematode *Caenorhabditis elegans*. Prior to graduate school, Dr. Nykamp also worked for two years at the Henry Ford Hospital Sleep Disorders Center where he supervised a number of research studies exploring the mechanisms of sleep homeostasis in normal individuals. Throughout his scientific career, Dr. Nykamp has been interested in how gene expression controls stem cell proliferation and reproductive development, and how genetic mutations can lead to tumor formation, infertility and sleep disorders.

At PreventionGenetics, he will combine his scientific expertise and clinical interests to oversee a portfolio of genetic tests for inherited cancer syndromes, male and female infertility, disorders of sexual development, and familial disorders of sleep and insomnia.

Infertility Testing at PreventionGenetics.

Over 500 million couples (~15%) worldwide suffer from infertility. In developed nations, ~1% of all live births are products of Artificial Reproductive Techniques (ART). The costs associated with ART can run from ~$15,000 for routine treatments to more than $100,000 when multiple children are born or post-natal complications arise. The overall financial burden of infertility in the US alone likely tops $3 billion per year. By comparison, the financial burden of breast cancer is estimated to be ~$14 billion per year (National Cancer Institute, NIH)

What are the causes of infertility? Infertility is defined as the inability of a couple to conceive after 1 year of regular, unprotected intercourse. The cause of infertility can be associated with female factors, male factors, or both. In females, premature loss of ovarian function is most often the cause; in males, some form of spermatogenic failure is usually the problem. A multitude of factors have been shown to affect both ovarian function and sperm production. These include lifestyle choices (smoking, excessive drug and alcohol use), recreational activities (hot tub use, cycling, competitive swimming), health concerns (obesity, viral infections, hormonal imbalances, autoimmunity), prescription drugs, pesticide exposure,

congenital abnormalities and specific genetic mutations. Some of these factors, when identified, are easily reversible, while others are not. Where possible, it is important to pinpoint the cause of infertility. Detection of conditions that are irreversible and untreatable will spare couples the physical, psychological and financial burdens associated with treatment failure. When conception is possible, identification of a specific gene mutation will facilitate genetic counseling. At PreventionGenetics, we are building a comprehensive portfolio of gene sequencing tests that will give fertility specialists and genetic counselors the tools they need to diagnose genetic causes of infertility and maximize the information communicated to patients.

Attribute a cause to the disease. Most women continue to ovulate until they are ~50 years old. However, a significant fraction (~1%) of women develop unexpected amenorrhea in their 20s or 30s due to premature cessation of ovarian function, or premature ovarian failure (POF). An autoimmune disorder, and resulting high levels of ovarian specific antibodies, has been linked to ovarian failure in many (30%) cases (Goswami & Conway, Hum Reprod Update 11:391-410, 2005). Chromosomal aberrations, such as Fragile X, and specific genetic mutations are also known to contribute to ovarian failure. We currently offer three gene tests (FSHR, Test#732; BMP15, Test#733; and FSHB, Test#734) that will help with the diagnosis of POF; 30-40% of women without an autoimmune disorder, a normal karyotype and onset of amenorrhea before the age of 40 are likely to have a mutation in one of these genes (see references in test descriptions).

Protect the health of future generations. We also offer tests for genetic mutations that may affect future generations, when assisted reproductive techniques are employed. Mutations in the DNAH5 (Test #740), DNAH11 (Test #743) and DNAI1 (Test #744) genes cause defects in sperm mobility, a condition known as Asthenozoospermia (ASZ); ~8% of patients with ASZ have a single heterozygous mutation in one of these genes (Zucarello et al. Hum Reprod 23:1957-1962, 2008). Importantly, biallelic mutations in one of these three genes cause a much more severe and debilitating respiratory disorder known as Primary Ciliary Dyskinesia (PCD; OMIM 244400). Thus, testing for these genes in patients with idiopathic ASZ can identify deleterious mutations, indicate carrier testing for the mother, and guide the use of Preimplantation Genetic Diagnosis when necessary. Mutations in the CFTR gene can also cause Azoospermia, or severe Oligozoospermia; ~9% of infertile males with one of these two conditions have been found to carry a single heterozygous mutation in CFTR (Dohle et al. Hum Reprod 17:13-16, 2002). We offer comprehensive mutation analysis of the CFTR gene (Test #150), including full gene sequencing and 5T/TG tract analysis.

Save money, stress and heartache. While artificial reproductive techniques can be a godsend for many infertile couples, it is also a very stressful and expensive course of treatment. Each in vitro fertilization (IVF) cycle

requires multiple hormone injections and painful procedures for the women, and can cost upwards of $20,000. Often times, multiple IVF cycles are required before a child is born. In some cases, likely due to specific genetic defects, IVF fails altogether. Recessive mutations in the AURKC gene (Dieterich et al. Nat Genet 39:661-665, 2007) result in an IVF/ICSI failure rate of 100% (Achard et al. J. Androl 28:600-606, 2007). For only $540, a genetic test for AURKC mutations (Test #731) could save a patient upwards of $40,000 in medical bills, as well as great stress and heartache.

In the future, we plan to add tests for additional causes of POF, the Disorders of Sex Development (DSD; OMIM 400044), and other male infertility conditions, including Globozoospermia (OMIM 102530) and Idiopathic Hypogonadotropic Hypogonadism (IHH; OMIM 146110). Please watch for these tests in future newsletters, and contact Dr. Nykamp if there are other infertility tests you would like to see developed.

PRESIDENT'S CORNER

Jim Weber, PhD

Selected Exon Sequencing at PreventionGenetics

PreventionGenetics offers single, double or triple exon Sanger sequencing (Tests #100, 200, 300 respectively) for any of the genes listed on our test menu. The two primary purposes of this selected exon sequencing are to determine carrier status in relatives of probands who are found to have clearly causative mutations, and to investigate the pathogenicity of sequence variants of unknown significance. Such testing is also carried out to confirm results originally determined in research or other non-CLIA labs.

Although only infrequently utilized today, another purpose of the single, double or triple exon sequencing is to confirm results obtained in a second CLIA lab. I first heard this idea in a talk given by Nancy Wexler. The concept is that in cases where crucial life decisions are involved, such as major surgery, long term ingestion of drugs or reproductive planning, it is worthwhile to spend a few extra dollars to make *certain* that the DNA test results are correct. Even high quality clinical labs may occasionally make mistakes. A rare specimen labeling error could occur or there could be allele dropout during PCR. By repeating the testing in a different lab using (in nearly all cases) different PCR primers, the chance of error is virtually eliminated.

The single, double and triple exon sequencing may also be used to confirm results obtained through NextGen sequencing. At this time, NextGen sequencing is considerably more error prone than Sanger sequencing. This is especially true for deletions and insertions.

The same emphasis on quality that is applied to all of our full gene sequencing tests is also applied at PreventionGenetics to our single, double and triple exon sequencing. The prices for our selected exon sequencing

($190-$390) are also lower than most other labs. PreventionGenetics now has the largest gene sequencing menu of any clinical lab in North America. We are an excellent choice for selected exon sequencing.

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.