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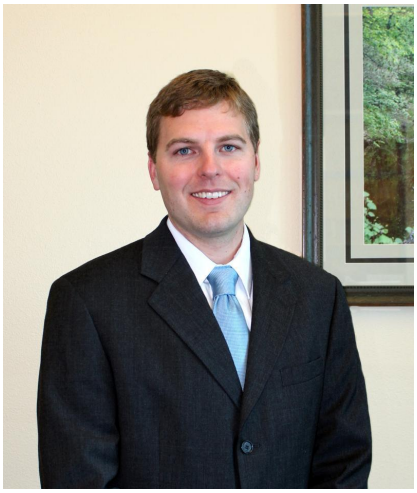
Volume 4, Number 2

Welcome to the June 2012 PreventionGenetics Newsletter. In this issue, we introduce Dr. Anthony Krentz and his Portfolio of heart disease genes. We also describe our new Florida state license and 40 new Sanger sequencing tests. In the President's corner, Dr. Jim Weber discusses the storage of patient DNA sequences in electronic medical records.

PreventionGenetics Introduces Dr. Anthony Krentz



Dr. Krentz received his PhD in Molecular, Cellular, Developmental Biology and Genetics from the University of Minnesota. As a graduate student, Dr. Krentz studied the genetics of testicular cancer, infertility and stem cell biology. Dr. Krentz joined PreventionGenetics in October 2011 and has developed a portfolio of genetic tests for heart disorders including cardiomyopathies, cardiac arrhythmias, monogenic congenital heart defects and heterotaxy. In addition to his responsibilities as a Human Molecular Geneticist, Dr. Krentz oversees the next-gen sequencing laboratory.

One of the initial next-gen sequencing panels offered at PreventionGenetics will be for genes implicated in heterotaxy. Heterotaxy syndrome or situs ambiguus results from a failure to properly establish left-right asymmetry during embryogenesis resulting in an abnormal arrangement of thoracic and/or abdominal visceral organs, including the heart, lungs, liver, spleen, intestines, and stomach. Affected patients frequently have significant morbidity and mortality due to a wide variety of cyanotic congenital heart defects. Common defects besides cardiac malformations include asplenia or polysplenia, left-sided liver, right-sided stomach, gastrointestinal malrotation, and altered lung lobation. Classic heterotaxy (cardiac malformations and visceral laterality defects) has an estimated prevalence of 1:10,000 live births (Lin et al. Genet Med 2:157-172, 2000). Heterotaxy is a heterogeneous genetic disorder. Mutations in at least 7 genes involved in NODAL signaling have been proposed to cause heterotaxy and/or congenital heart defects. PreventionGenetics has developed Sanger sequencing tests for *NODAL, ZIC3, FOXH1, LEFTY2, GDF1,* and *ACVR2B*. These genes will also be offered as part of the situs ambiguus/heterotaxy next-gen sequencing panel, which will also include genes implicated in primary ciliary dyskinesia. PreventionGenetics will continue to add new next-gen sequencing gene cluster tests throughout 2012, including tests

for hypertrophic cardiomyopathy, dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy/dysplasia.
For information on our next-gen sequencing please Click Here.

Florida License

PreventionGenetics is now licensed as a Clinical Laboratory by the State of Florida. This should make it easier for our Florida colleagues to make use of our services.

New and updated Sanger Gene Sequencing Tests at PreventionGenetics

Please follow the gene links for the corresponding test descriptions.
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Amyotrophic Lateral Sclerosis, X-Linked Dominant *UBQLN2* (Test #158)
Autosomal Dominant, Non-Syndromic Holoprosencephaly *GAS1* (Test #587)
Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay *SACS* (Test #917)
Autosomal Recessive Spinocerebellar Ataxia-10 *ANO10* (Test #916)
Catecholaminergic Polymorphic Ventricular Tachycardia *CASQ2* (Test #941)
Catecholaminergic Polymorphic Ventricular Tachycardia *CPVT Panel* (Test #940)
Congenital Muscular Dystrophy, Megaconial Type *CHKB* (Test #912)
Congenital Myasthenic Syndrome *CMS PANEL* (Test # 412)
Dystroglycanopathy *ADG PANEL* (Test #340)
Early-Onset Myopathy, Areflexia, Respiratory Distress and Dysphagia *MEGF10* (Test #922)
Ehlers-Danlos Syndrome, Type III *TNXB* (Test #843)
Ehlers-Danlos Syndrome, Kyphoscoliotic Form *PLOD1* (Test #845)
Fanconi Anemia *FANCP/SLX4* (Test # 881)
Fanconi Anemia-like Disorder *RAD51C* (Test #882)
Heterotaxy and Conotruncal Heart Defects *GDF1* (Test #937)
Heterotaxy *LEFTY2* (Test #936)
Hereditary Lymphedema *GJC2* (Test #285)
Isolated Nonsyndromic Congenital Heart Defects *GATA4* (Test #943)
Isolated Nonsyndromic Congenital Heart Defects *NKX2-5* (Test #944)
Junctional Epidermolysis Bullosa *JEB Panel* (Test #975)
Junctional Epidermolysis Bullosa *LAMA3* (Test #972)
Junctional Epidermolysis Bullosa *LAMB3* (Test #973)
Junctional Epidermolysis Bullosa *LAMC2* (Test #971)
Junctional Epidermolysis Bullosa *COL17A1* (Test # 974)
Methylmalonic Acidemia *MAS Panel* (Test #310)
Methylmalonic Aciduria and Homocystinuria *MMA Panel* (Test #325)
Microform Holoprosencephaly *DISP1* (Test #588)
Nemaline Myopathy *NM Panel* (Test #350)
Neutral Lipid Storage Disease with Myopathy *PNPLA2* (Test #599)
Noonan and Leopard Syndromes *RAF1* (Test #1113)
Popliteal Pterygium Syndrome and Van der Woude Syndrome *IRF6*

(Test #896)
Sorsby Fundus Dystrophy, Autosomal Dominant *TIMP3* (Test #699)
Ventricular Septal Defects, Tetralogy of Fallot *FOXH1* (Test #933)
Type IV Voltage-Gated Sodium Channel (Alpha Subunit)-Related Disorders *SCN4A* (Test #416)
Schimke Immunoosseous Dysplasia *SMARCAL1* (Test #1031)
Hereditary Sensory Neuropathy *DNMT1* (Test #915)
Giant Axonal Neuropathy *GAN* (Test # 918)
Dynamin-2 Related Disorders *DNM2* (Test #914)
Plectinopathy *PLEC* (Test #593)
Walker-Warburg Syndrome *ISPD* (Test #913)

Jim Weber, PhD

President's Corner

Patient Sequences in Electronic Medical Records I

This is the first in a series of three editorials on the storage of patient DNA sequences in Electronic Medical Records (EMRs). In this first article I emphasize the use of patient sequences in the EMR for sequence reinterpretation and to provide health care providers with crucial medical alerts.

At PreventionGenetics we are frequently contacted by physicians and counselors to request reinterpretation of sequence variants that were previously identified in a patient. Often, especially if it has been some time since the test was originally performed, we can significantly improve the initial interpretation because new information has become available. Most commonly, a sequence variant of unknown significance is reinterpreted as benign. Less often, an unknown variant becomes pathogenic or even a variant originally interpreted as benign is now interpreted as pathogenic.

As many others have pointed out, our ability today to generate DNA sequence vastly outstrips our ability to interpret the sequence. The good news is that sequence interpretation is improving rapidly. To utilize these improvements, however, we have to create a cost-effective mechanism for reinterpretation. The key to accomplishing this is to insert the patient sequences into the EMR. Once this is completed, then it will be relatively easy to automatically reinterpret the sequences periodically (say every 6 or 12 months). Many companies will compete to produce the best software and underlying databases for reinterpretation. If such software can be applied to large numbers of patients, then the cost per patient should be quite low, perhaps ≤ $10 per patient per reinterpretation.

Another important application of patient sequences in the EMR, is the ability to make crucial medical alerts available to providers. These alerts may ultimately take many forms, but one obvious application would be warnings against severe adverse drug reactions. One of the very first tests offered at PreventionGenetics was sequencing of the *RYR1* gene to detect susceptibility to Malignant Hyperthermia. Malignant Hyperthermia is a severe, sometimes deadly, reaction to commonly used anesthetics. If a patient is known to be susceptible to Malignant Hyperthermia, then it's obvious that all health care

providers should have access to this information.
Nearly everyone is predicting rapid expansion of DNA sequencing in health care, including exome and genome sequencing. We will never be able to make effective use of this valuable information, however, until the sequences are stored in the EMRs. In our next newsletter I will address the importance of sharing sequence information electronically among family members.

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.