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PREVENTION GENETICS

DISEASE PREVENTION THROUGH GENETIC TESTING



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Welcome to the November 2011 PreventionGenetics Newsletter. In this issue, we present new DNA sequencing tests for 27 disorders. We also introduce senior staff member Michael Chicka and some of the disorders on which he is working. In the President's Corner, Dr. Jim Weber discusses sanger sequencing error rates at PreventionGenetics.

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

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- Cranioectodermal Dysplasia *WDR35* ([Test #292](#))
- Duane-Radial Ray Syndrome *SALL4* ([Test #832](#))
- GDF5-related Disorders *GDF5* ([Test #852](#))
- Fanconi Anemia *FANCD2* ([Test #884](#))
- Fanconi Anemia *FANCI* ([Test #885](#))
- Hereditary Hemorrhagic Telangiectasia *ENG* ([Test #861](#))
- Hereditary Hemorrhagic Telangiectasia *ACVRL1/ALK1* ([Test #862](#))
- Hereditary Hemorrhagic Telangiectasia *ENG, CVRL1/ALK1 and SMAD4* ([Test #860](#))
- Hypertrophic Cardiomyopathy *TNNC1* ([Test #194](#))
- Hypochondroplasia *FGFR3* ([Test #428](#))
- Hypophosphatasia *ALPL* ([Test #851](#))
- Leber Congenital Amaurosis *RDH12* ([Test #821](#))
- Maple Syrup Urine Disease *BCKDHA* ([Test #526](#))
- Maple Syrup Urine Disease *BCKDHB* ([Test #527](#))
- Maple Syrup Urine Disease *DBT* ([Test #528](#))
- Maple Syrup Urine Disease *DLD* ([Test #529](#))
- Microcephaly *WDR62* ([Test #293](#))
- Multiple Epiphyseal Dysplasia *MED, COMP MATN3, SLC26A2, COL9A2, COL9A* ([Test #815](#))
- Neutropenia *GF11* ([Test #447](#))
- Nephronophthisis *SDCCAGB* ([Test #659](#))
- Paget Disease *SQSTM1* ([Test #853](#))
- Paget Disease *TNFRSF11A* ([Test #854](#))
- Paget Disease *TNFRSF11B* ([Test #855](#))
- Paget Disease *SQSTM1 and TNFRSF11A* ([Test # 850](#))
- Primary Ciliary Dyskinesia *CCDC39* ([Test #754](#))

Primary Ciliary Dyskinesia *CCDC40* ([Test #755](#))
Primary Ciliary Dyskinesia (PCD) *DNAH5, HNA11, CCDC39, CCDC40, DNAI2, DNAH11, KTU, LRRC50, TXNDC3* ([Test #745](#))
Primary Ciliary Dyskinesia *DNAL1* ([Test #756](#))
Progressive Bulbar Palsy *C20orf54* ([Test #417](#))
Roberts Syndrome *ESCO2* ([Test #836](#))
Severe Congenital Neutropenia *ELANE, HAX1, G6PC3, GF11, and WAS* ([Test #445](#))
Short Stature *FGFR3* ([Test #425](#))
Short Stature *FGFR3* ([Test #426](#))
Short Stature *COL10A1* ([Test #802](#))
Stickler Syndrome *COL11A1* ([Test #831](#))
Stickler Syndrome *COL2A, COL11A1 and COL11A2* ([Test #830](#))
Stickler Syndrome *COL11A2* ([Test #829](#))
TRPV4-related Disorders *TRPV4* ([Test #833](#))
Townes-Brocks Syndrome *SALL1* ([Test #835](#))
TP63-Related Disorders *TP63* ([Test #834](#))
X-linked Retinitis Pigmentosa (XLRP) *RP2* ([Test #680](#))



Prevention Genetics proudly introduces Michael Chicka.

Dr. Chicka received his PhD in Cellular and Molecular Biology from the University of Wisconsin - Madison in 2007. As a graduate student, Dr. Chicka's focus was in neuroscience where he studied the molecular mechanisms that couple calcium ions to membrane fusion and synaptic transmission. After graduating, he moved to Kentucky where he worked in the

Department of Biochemistry at the University of Kentucky and studied the molecular machinery that drives platelet secretion. He also taught both graduate and undergraduate courses while in Kentucky. Prior to graduate school, Dr. Chicka worked as a researcher at the Mayo Clinic in Rochester, Minnesota where he studied Plasma Membrane Ca^{2+} -ATPases (PMCA) and their roles in calcium ion clearance. Dr. Chicka joined PreventionGenetics in August of 2010 and has developed a portfolio of genetic tests for Blood and Lymph disorders including thrombocytopenia, familial hemophagocytic lymphohistiocytosis (FHL), Fanconi Anemia (FA), and lymphedema. In addition, Dr. Chicka applies his extensive research and teaching experiences to his role as Clinical Laboratory Supervisor at PreventionGenetics.

Hereditary Blood and Lymph Disorders

Two distinct fluids help connect cells in the human body to the circulatory system: blood and lymph. The heart, blood vessels, and blood make up the circulatory system, and the lymphatics comprise lymph nodes and vessels, and lymph. Mutations that affect components of these systems can result in developmental and

functional abnormalities that leave the body more susceptible to illness, infection and certain malignancies.

Fanconi Anemia

Fanconi Anemia (FA) is an X-linked or autosomal recessive blood disorder characterized by a host of congenital abnormalities, bone marrow failure (aplastic anemia), and predisposition to cancers--in particular leukemia and squamous cell carcinoma. The incidence rate of FA is approximately 1 in 131,000 with the carrier frequency in the United States estimated to be around 1 in 181 (see www.fanconi.org).

Approximately 95% of FA cases are the result of mutations in one of the 15 known FA genes. Early diagnosis is essential as it permits exclusion of other diseases and expedites consideration of stem cell transplant, surgical intervention, and cancer surveillance. Currently, Western Blot analysis of the FANCD2 gene product and complementation analysis are used to identify genes of interest in FA patients, but these methods can be time consuming and do not identify specific mutation(s) present in a patient's genome. Sequencing of the FA genes is fast and precise and represents the most comprehensive technique used for identifying pathogenic mutations in FA genes.

PreventionGenetics currently offers one of the most comprehensive FA test panels available from a CAP/CLIA certified genetic testing laboratory. Currently, we offer sequence analysis for fourteen of the fifteen FA genes and deletion / duplication analysis (via aCGH) for ten FA genes. When appropriate, targeted testing is also available. Candidates for FA genetic testing include individuals with a family history of FA, individuals with symptoms of FA, and anybody who has a positive chromosomal breakage test. Genetic testing for FA has the advantages of rapid turnaround times, and provides accurate, comprehensive results that aid in clinical diagnosis.

For more information on Fanconi Anemia, see the Fanconi Anemia Research Fund website at www.fanconi.org, or visit the Fanconi Anemia Mutation Database at www.rockefeller.edu/fanconi/

Jim Weber, PhD
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President's Corner Sanger Sequencing Error Rates at PreventionGenetics

At the beginning of this year, PreventionGenetics began comparing Sanger sequences generated in our lab against NextGen sequence data generated in other labs. We used DNA template from two Nigerian individuals (NA18570 and NA19240). DNA from these individuals is readily available from the Coriell Repository (www.coriell.org). The

entire genomes of both individuals have been sequenced in house by Illumina and one of them (19240) by Complete Genomics. These same two genomes have also been independently sequenced in the 1000 Genomes Project and have been genotyped for millions of common SNPs through the HapMap Project. We therefore have the opportunity to compare our Sanger sequencing against entire different sequencing (and genotyping) methodologies. I think this is a much better approach than comparing Sanger sequencing to other Sanger sequencing.

To date we have analyzed close to 2 million nucleotides of our Sanger sequence. We found one error for an estimated error rate of 5×10^{-7} . The error was due to PCR allele drop out. Perhaps more importantly, our single error was out of about 1300 sequence variants (defined as differences between the Nigerian sequences and the reference sequences).


Although, of course, we will need to do much more sequencing to get precise estimates of our Sanger error rates, I am still encouraged by our initial low numbers. How do our error rates compare with other clinical DNA testing labs? I suspect that they compare very favorably, but we don't really know. Such numbers are not readily available. It is clear, however, that Sanger sequencing at PreventionGenetics is highly accurate. Perhaps organizations such as ACMG and CAP should begin to consider what error rates are appropriate for clinical testing.

It is also interesting to note that the error rates for the in-house Illumina and Complete Genomics NextGen sequencing were apparently much higher than our Sanger error rates. The error rates that we determined for these methodologies were roughly 50 times our Sanger error rate. Our data indicate that Sanger sequencing (at least in our hands) is considerably more accurate than recent NextGen methodologies. Perhaps, as Elaine Lyon of ARUP labs put it in the November 2011 issue of CAP Today, "Sanger sequencing will continue to be an important companion to next-gen sequencing".

On the other hand, we should also keep in mind that NextGen methodologies are improving very rapidly. Error rates will likely drop, and Sanger sequencing can't come close to NextGen methodologies in terms of cost (at least for large-scale sequencing). At PreventionGenetics, we will continue to offer Sanger sequencing tests for the genes on our menu as long as they are in demand. We will also, however, soon begin offering NextGen clinical sequencing for clusters of genes. Regardless of how quickly clinical sequencing methodologies change, it's comforting to know that at PreventionGenetics we now have a large collection of high quality Sanger sequence data available for training our NextGen variant calling algorithms and for gauging the quality of the NextGen sequences.

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.