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Volume 5, Number 2

Welcome to the June 2013 PreventionGenetics newsletter. In this issue, we present 58 new and updated Next-Gen and Sanger tests. We also discuss PreventionGenetics' partnership with the University of Wisconsin-Madison. In the President's corner, Dr. Jim Weber discusses sequence variant databases.

PreventionGenetics expands clinical Next-Gen sequencing

Recent additions to our Next-Gen menu include tests for Chromosomal Instability, Fanconi Anemia, Breast and Ovarian Cancer (two panels), Congenital Muscular Dystrophy and Dystroglycan-related Congenital Muscular Dystrophy. (See expanded list below.) These panels join our established Ciliopathy panels (Bardet-Biedl, Joubert, Meckel-Gruber, Nephronophthisis, Heterotaxy/Situs inversus and Primary Ciliary Dyskinesia). Panels which will be launched in the near future include Gastrointestinal Cancer, Aortopathies and Rasopathies.

Advantages of PreventionGenetics Next-Gen sequencing include:
* Three-stage manual review of all Next-Gen data. We do not rely solely on software packages to call sequence variants.
* The largest Sanger sequencing test menu of any lab in North America. In nearly all cases, we provide fully validated and lab-ready Sanger tests to confirm likely pathogenic and unknown variants, cover regions of low Next-Gen coverage and test family members and perform prenatal testing.
* Outstanding interpretation of sequence variants. Our years of experience with sequencing tests for the great majority of genes in our Next-Gen panels means that our clients receive expert and complete interpretation of variants.

New and updated Next-Gen, Sanger Sequencing and Panel Tests at PreventionGenetics

Please follow the links for full descriptions of each new test.

Next-Gen panel tests

Bardet-Biedl Syndrome Next-Gen Sequencing Panel *BBS1, BBS2, ARL6, BBS4, BBS5, MKKS, BBS7, TTC8, BBS9, BBS10, TRIM32,*

BBS12, MKS1, SDCCAG8 (Test #1053)

Chromosomal Instability Syndromes NextGen Sequencing Panel *BLM, ATM, ERCC8, MRE11A, WRN, RECQL4, ERCC6, NBN* (Test #1214)

Congenital Muscular Dystrophy Next-Gen Sequencing Panel *ITGA7, SEPN1, FKTN, FKRP, LAMA2, LARGE, POMT1, POMT2, POMGNT1, DAG1, DPM3, CHKB, COL6A2, ISPD, COL6A1, COL6A3, LMNA, GTDC2, TMEM5* (Test #1301)

Dystroglycan-Related Congenital Muscular Dystrophy Next-Gen Sequencing Panel *FKTN, FKRP, LARGE, POMT1, POMT2, POMGNT1, DAG1, DPM3, ISPD, GTDC2, TMEM5* (Test #1303)

Fanconi Anemia Next-Gen Sequencing Panel *BRIP1, FANCM, PALB2, FANCL, FANCA, FANCC, FANCG, FANCE, FANCF, FANCB, FANCI SLX4, FANCD2, RAD51C* (Test #1217)

Ciliopathy Next-Gen Sequencing Panel *NODAL, BBS1, BBS2, ARL6, BBS4, BBS5, MKKS, BBS7, TTC8, BBS9, BBS10, TRIM32, BBS12, AHI1, CEP290, TMEM67, RPGRIP1L, ARL13B, CC2D2A, INPP5E, TMEM216, OFD1, MKS1, TCTN2, IQCB1, NPHP1, INVS, NPHP3, NPHP4, GLIS2, NEK8, SDCCAG8, DNAH11, DNAI1, DNAI2, RSPH4A, RSPH9, DNAAF2, TXNDC3, CCDC39, CCDC40, DNAL1, CFTR, FOXH1, NKX2-5, DNAAF3, LEFTY2, DNAAF1, ACVR2B, RPGR, C5orf42, GDF1, DNAH5, TMEM138, B9D1, CEP41, TMEM237* (Test #1056)

Hereditary Breast and Ovarian Cancer Syndrome - HBOC SELECT Next-Gen Sequencing Panel *TP53, PTEN, CDH1, STK11,RAD51C* (Test #1305)

Hereditary Breast and Ovarian Cancer Syndrome - HBOC Expanded Next-Gen Sequencing Panel *BRIP1, PALB2, TP53, ATM, PTEN, CDH1, MRE11A, CHEK2, RAD51C, NBN, STK11* (Test #1307)

Heterotaxy/Situs Inversus and Kartagener's Syndrome NextGen Sequencing Panel *NODAL, ZIC3, INVS, DNAH5, DNAH11, DNAI1, DNAI2, DNAAF2, CCDC39, CCDC40, DNAL1, FOXH1, NKX2-5, DNAAF3, LEFTY2, DNAAF1, ACVR2B, GDF1* (Test #1060)

Joubert and Meckel-Gruber Syndromes Next-Gen Sequencing Panel *AHI1, CEP290, TMEM67, RPGRIP1L, ARL13B, CC2D2A, INPP5E, TMEM216, OFD1, MKS1, TCTN2, NPHP1, C5orf42, TMEM138, B9D1, CEP41, TMEM237* (Test #1057)

Nephronophthisis Next-Gen Sequencing Panel *CEP290, RPGRIP1L, IQCB1, NPHP1, INVS, NPHP3, NPHP4, GLIS2, NEK8, SDCCAG8* (Test #1058)

Immotile Cilia Syndrome/Primary Ciliary Dyskinesia (PCD) NextGen Sequencing Panel OFD1, INVS, DNAH5, DNAH11, DNAI1, DNAI2, RSPH4A, RSPH9, DNAAF2, TXNDC3, CCDC39, CCDC40, DNAL1, CFTR, DNAAF3, DNAAF1, RPGR (Test #1059)

New and updated Sanger sequencing tests

Blood

Von Willebrand Disease Types 1, 2, and 3 VWF (Test #449)
Familial Hypercholesterolemia APOB (Test #872)

Familial Hypercholesterolemia LDLR (Test #871)

Cancer

Hereditary Neuroblastoma KIF1B (Test #1172)

Hereditary Neuroblastoma ALK (Test #1171)
Rhabdoid Tumor Predisposition Syndrome SMARCB1 (Test #1202)
Hereditary Papillary Renal Cell Carcinoma MET (Test #1203)

Cardiovascular
Arterial tortuosity syndrome ADK (Test #938)
Ciliopathy
Joubert Syndrome Sanger Sequencing Panel AHI1, CEP290, TMEM67, RPGRIP1L, ARL13B, CC2D2A, INPP5E, TMEM216, TCTN2, C5orf42 (Test #294)

Eye
Leber Congenital Amaurosis 2 and Retinitis Pigmentosa 20 RPE65 (Test #682)
Leber congenital amaurosis 14 or Early Onset Retinal Dystrophy and Juvenile Retinitis pigmentosa LRAT (Test #688)
Leber Congenital Amaurosis 13, Retinitis Pigmentosa 53 and Early Onset Cone-Rod Dystrophy RDH12 (Test #821)
Hearing
Pendred Syndrome and DFNB4 Nonsyndromic Hearing Loss SLC26A4 (Test #849)
Kidney
Alport Syndrome COL4A4 (Test #993)

Alport Syndrome COL4A3 (Test #992)
Neurohypophyseal Diabetes Insipidus AVP (Test #983)

Metabolic
GLDC-Related Glycine Encephalopathy GLDC (Test #1261)
Glutathione Synthetase Deficiency GSS (Test #1233)
Hyperammonemia NAGS (Test #555)

Microcephaly
CENPJ-Related Disorders CENPJ (Test #1104)
Primary Microcephaly, Autosomal Recessiveaspm ASPM (Test #1101)

Primary Microcephaly, Autosomal Recessive WDR62 (Test #293)

Mitochondrial
SUCLG1-Related Encephalomyopathic Form of Mitochondrial DNA Depletion Syndrome SUCLG1 (Test #1249)
DGUOK-Related Hepatocerebral Form of Mitochondrial DNA Depletion Syndrome DGUOK (Test #1243)
TK2-Related Mitochondrial DNA Depletion Syndrome TK2 (Test #1245)
Autosomal Dominant Progressive External Ophthalmoplegia and other C10orf2-related disorders C10orf2 (Test #1255)
Autosomal Dominant Progressive External Ophthalmoplegia POLG2 (Test #1248)
MPV17-Related Hepatocerebral Form of Mitochondrial DNA Depletion Syndrome MPV17 (Test #1247)

Neurological
Tuberous Sclerosis Complex Sanger Sequencing Panel TSC1, TSC2 (Test #1010)

Neuromuscular
Walker-Warburg Syndrome TMEM5 (Test #1196)
Centronuclear Myopathy-4, Autosomal Dominant CCDC78 (Test #923)
Inclusion Body Myopathy and Autosomal Recessive, Early Onset Myopathy MYH2 (Test #361)
Sodium Channel, Voltage-Gated, Type IX, Alpha Subunit Disorders SCN9A (Test #927)
Facioscapulohumeral Muscular Dystrophy 2SMCHD1 (Test #874)

Skeletal
Ellis-van Creveld Syndrome EVC (Test #988)

Ellis-van Creveld Syndrome EVC2 (Test #989)
Ellis-van Creveld Syndrome Sanger Sequencing Panel EVC, EVC2 (Test #783)

Skin
Epidermolysis Bullosa with Pyloric Atresia *DLEC* (Test #970)
Epidermolysis Bullosa with Pyloric Atresia *ITGA6* (Test #977)
Epidermolysis Bullosa Simplex *KRT5* (Test #978)
Epidermolysis Bullosa with Pyloric Atresia ITGB4 (Test #976)
Supravalvular Aortic Stenosis and Cutis Laxa *ELN* (Test #966)
Kindler Syndrome *FERMT1* (Test #969)
Melanoma Predisposition CDK4 (Test #1169)
Dyskeratosis Congenita and Related Disorders Sanger Sequencing Panel DKC1, NHP2, NOP10, TERT, WRAP53, TINF2 (Test #1120)
Ehlers-Danlos Syndrome, Kyphoscoliotic Form PLOD1 (Test #845)

PreventionGenetics partners with UW-Madison on clinical molecular genetics fellowship

PreventionGenetics will now be part of a unique training opportunity for post-doctoral fellows at the University of Wisconsin. The training will be in collaboration with the UW's School of Medicine and Public Health Department of Pediatrics, Department of Pathology and Laboratory Medicine and the BloodCenter of Wisconsin.

"The American Board of Medical Genetics (ABMG) Molecular Genetics Fellowship is a new program at UW-Madison that rounds out the clinical genetics laboratory training programs, which also include biochemical genetics and cytogenetics," said Jennifer Laffin, Ph.D., FACMG, director, UW Cytogenetic Services Laboratory and assistant professor at UW's Department of Pediatrics. "These post-doctoral fellowship programs are intended to prepare individuals for the ABMG board exams and become clinical laboratory directors in their respective specialty."

The training program, slated to begin July 1, will be overseen by ABMG-certified clinical molecular laboratory directors Dr. Laffin, Dr. Thomas Winder of PreventionGenetics and Dr. Dan Bellissimo of the Blood Center of Wisconsin. Trainees will come to PreventionGenetics for two, three-month blocks of time during the two-year program and will be involved in all aspects of testing patient specimens.

"PreventionGenetics performs diagnostic tests for many rare inherited disorders," said Dr. Winder. "The trainee will benefit by having the opportunity to work on cases that he or she may not experience at an academic-based laboratory. We will benefit by having a trainee help develop new technologies and interact with our staff."

"The benefits of this partnership extend beyond fellowship training to all laboratory staff by providing a continuing education environment and communication network. This will ensure that the patients these sites provide services for get the safest and highest quality health care available," added Dr. Laffin.

Jim Weber, Ph.D.

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President's corner

Sequence variant databases need careful curation by experts

Jim Weber, Ph.D.
PreventionGenetics
founder and president

Over the last 25 years, there have been several efforts to develop databases of the sequence variants found in patients.These include the Human Gene Mutation Database (HGMD), locus-specific databases championed by Richard Cotton, ClinVar at the NIH and Mutadatabase operated by Gendia in Europe. Some of these efforts are only just beginning. The only successful, genomewide effort to date has been HGMD, although many of the locus-specific databases are also quite advanced.

Recently, there has been a push by a number of prominent clinical geneticists to expand these databases, especially ClinVar, and to encourage clinical labs to contribute their data. In general, PreventionGenetics supports these efforts, and we will contribute data to ClinVar, but I think the approach that is taken will greatly affect the success of these efforts.

In particular, I do not think that large data dumps from testing labs directly into ClinVar will be especially useful. These data dumps will be loaded with errors of all sorts. They are essentially just "personal communications." I do not think they will be of sufficiently high quality to be used in patient care.

The only way I think the data will be truly useful in patient care is if the data are carefully curated by experts. Experienced, knowledgeable human geneticists need to manually weigh the evidence.

Our favorite approach to communication of such curation is peer-reviewed publication. Preparing data for peer-reviewed publication is

indeed a time-consuming and demanding task, but that is why these publications are useful. PreventionGenetics has therefore established a policy of sharing our patient data with colleagues for purposes of publication. A list of publications that has already resulted from this policy is available from our website. We welcome inquiries from those who would like to access our data for publication purposes.

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.