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## Volume 6, Number 3

Welcome to the third newsletter of 2014 from PreventionGenetics. In this issue we introduce our Chromosomal Microarray test, CMA-ISCA. We present our updated test menu with 11 new NextGen Panels and 72 new single gene Sanger tests. We also introduce Dr. Luke Drury, a recent addition to our expanding team of geneticists.

In the President's corner, Dr. Jim Weber continues his discussion of obstacles to routine genome sequencing of patients.

## CHROMOSOMAL MICROARRAY TESTING AT PREVENTIONGENETICS

PreventionGenetics recently added a Chromosomal Microarray (CMA) test to our menu. CMA is often used as a first-tier test for clinical diagnosis of patients with idiopathic intellectual disability, developmental delay, autism spectrum disorders and/or multiple congenital anomalies (Miller, D.T. et al. 2010).


Our current chromosomal array test, CMA-ISCA combines a total of 180K CGH and SNP probes to allow for detection of copy number variations, as well as loss of heterozygosity (LOH) and uniparental disomy (UPD).
We will continue to offer our gene-centric array (Test #600) as a complimentary test to sequencing. In the coming months, PreventionGenetics will be releasing two additional chromosomal array tests: a higher density 400K CGH and SNP array, as well as a 850K SNP array. Copy number variations may account for up to 13% of the human genome (Stankiewicz, P. et al 2010). Our goal is to offer a comprehensive selection of array-based tests to detect as many of these variations as possible.
For more information about our Chromosomal Microarray test, CMA-ISCA, view the test description on our website: CMA-ISCA Test #2000

## NEW TESTS

**NextGen Sequencing**
Chronic Pancreatitis NextGen Sequencing Panel (#1395)

Congenital Central Hypoventilation Syndrome NextGen Sequencing Panel (#1397)
Early Infantile Epileptic Encephalopathy NextGen Sequencing Panel (#1905)
Gastrointestinal Cancer NextGen Sequencing and Del/Dup Panel (#1907)
Glycogen Storage Disease NextGen Sequencing Panel (#1381)
Isolated Polycystic Liver Disease NextGen Sequencing Panel (#1385)
Maturity Onset Diabetes of the Young NextGen Sequencing Panel (#1903)
Mitochondrial Genome Maintenance/Integrity NextGen Sequencing Panel (#1399)
Neuronal Ceroid Lipofuscinoses NextGen Sequencing Panel (#1909)
Optic Atrophy OA NextGen Sequencing Panel (#1901)
Waardenburg Syndrome NextGen Sequencing Panel (#1393)

**Autoimmune**
Chronic Pancreatitis NextGen Sequencing Panel (#1395)

**Blood and Lymph**
Alpha-Thalassemia X-linked Intellectual Disability Syndrome *ATRX* (#1695)
Autoimmune Lymphoproliferative Syndrome *FAS* (#1648)
Chronic Granulomatous Disease *CYBB* (#1651)
Common Variable Immune Deficiency | IGA Deficiency *TNFRSF13B* (#1692)
Erythropoietic Protoporphyria *FECH* (#1691)
Familial Hemophagocytic Lymphohistiocytosis, X-linked Lymphoproliferative Disease *SH2D1A* (#138)
Familial Hemophagocytic Lymphohistiocytosis, X-linked Lymphoproliferative Disease *XIAP* (#139)
Glycogen Storage Disease NextGen Sequencing Panel (#1381)
Hemochromatosis *HFE* (#1693)
Hemophilia A *F8* (#1576)
Hyper IgE Syndrome *STAT3* (#1613)
Hypomyelination and Congenital Cataract *FAM126A* (#1669)
Omenn Syndrome Sanger Panel (#1800)
Protein S Deficiency *PROS1* (#1654)
Pyruvate Kinase Deficiency *PKLR* (#1652)
Severe Combined Immunodeficiency/ Omenn syndrome *IL7R* (#189), *DCLRE1C* (#1698), *RAG1* (#1696), *RAG2* (#1697)
Thrombocytopenia *THPO* (#1647)
Warts, Hyogammaglobulinemia, Infections, and Myelokathexis Syndrome *CXCR4* (#1690)
X-Linked Agammaglobulinemia *BTK* (#1650)
X-Linked Hyper IgM Syndrome *CD40LG* (#1653)
X-Linked Severe Combined Immunodeficiency *IL2RG* (#1655)

**Cancer**
Alpha-Thalassemia X-linked Intellectual Disability Syndrome *ATRX* (#1695)
Common Variable Immune Deficiency | IGA Deficiency *TNFRSF13B* (#1692)
Gastrointestinal Cancer NextGen Sequencing and Del/Dup Panel (#1907)
Hereditary Paraganglioma-Pheochromocytoma Syndrome *SDHA* (#1137)
Infantile Myofibromatosis and Idiopathic Basal Ganglia Calcification *PDGFRB* (#1609)
Protein S Deficiency *PROS1* (#1654)

**Ciliopathies**
Primary Ciliary Dyskinesia Sanger Panel (Added *CFTR* and *INVS* #750)

**Cardiovascular**
Hemochromatosis *HFE* (#1693)

**Cognitive**
Neuronal Ceroid Lipofuscinoses NextGen Sequencing Panel (#1909)

**Developmental**
Alpha-Thalassemia X-linked Intellectual Disability Syndrome *ATRX* (#1695)
Common Variable Immune Deficiency | IGA Deficiency *TNFRSF13B* (#1692)
Cutis Laxa *PYCR1* (#1066)
Peroxisome Biogenesis Disorders, Zellweger Syndrome Spectrum *PEX14* (#1091), *PEX16* (#1092), *PEX26* (#1077), *PEX2* (#1072), *PEX3* (#1078), *PEX5* (#1079), *PEX6* (#1073), *PEX10* (#1074), *PEX12* (#1076), *PEX13* (#1090), *PEX19* (#1093)
Peroxisome Biogenesis Disorders, Zellweger Syndrome Spectrum Sanger panel (#1080)
Protein S Deficiency *PROS1* (#1654)

**Dental**
Amelogenesis Imperfecta Sanger Panel (#1790)
Ectodermal Dysplasia *EDA* (#616), *EDAR* (#617), *EDARADD* (#618)
Oculodentodigital Dysplasia *GJA1* (#1506)

**Digestive**
Chronic Pancreatitis NextGen Sequencing Panel (#1395)

**Endocrine**
Hereditary Paraganglioma-Pheochromocytoma Syndrome *SDHA* (#1137)
Hypercalcemic and Hypocalcemic Disorders *GNA11* (#1505)
Hypoparathyroidism, Sensorineural Deafness and Renal Dysplasia *GATA3* (#1616)
Maturity Onset Diabetes of the Young NextGen Sequencing Panel (#1903)

**Eye**
Cerebrotendinous Xanthomatosis *CYP27A1* (#1670)
Congenital Hereditary Endothelial Dystrophy Type 2 | Harboyan Syndrome *SLC4A11* (#1677)
Corneal Dystrophy *TGFBI* (#1680)
Keratoconus and Posterior Polymorphous Corneal Dystrophy *VSX1* (#1676)
Nance-Horan Syndrome | Congenital Cataract *NHS* (#1668)
Neuronal Ceroid Lipofuscinoses NextGen Sequencing Panel (#1909)
Oculodentodigital Dysplasia *GJA1* (#1506)
Oguchi Disease and Retinitis Pigmentosa *SAG* (#1678)
Optic Atrophy *TMEM126A* (#1729)
Optic Atrophy NextGen Sequencing Panel (#1901)
Peters Plus Syndrome *B3GALTL* (#1671)
PITX2-related Disorders *PITX2* (#1675)
Stargardt Disease *ELOVL4* (#1848)
Waardenburg Syndrome NextGen Sequencing Panel (#1393)
Wagner Syndrome *VCAN* (#523)
X-linked Megalocornea *CHRDL1* (#1679)

**Hearing**

Alport syndrome NGS Panel (#1388)
Congenital Hereditary Endothelial Dystrophy Type 2 | Harboyan Syndrome *SLC4A11* (#1677)
Hypoparathyroidism, Sensorineural Deafness and Renal Dysplasia *GATA3* (#1616)
Optic Atrophy *TMEM126A* (#1729)
PRPS1-related Disorders *PRPS1* (#1550)
Waardenburg Syndrome NextGen Sequencing Panel (#1393)

**Kidney**
Alport Syndrome NGS Panel (#1388)
Bartter Syndrome *KCNJ1* (#1266), *SLC12A1* (#1264)
Hypercalcemic and Hypocalcemic Disorders GNA11 (#1505)
Hypoparathyroidism, Sensorineural Deafness and Renal Dysplasia *GATA3* (#1616)
Renal Tubular Dysgenesis *ACE* (#1622), *AGT* (#1623), *AGTR1* (#1624), *REN* (#1625)
Renal Tubular Dysgenesis Sanger Sequencing Panel (#1840)
Xanthinuria Type I *XDH* (#1431)

**Lysosomal**
Neuronal Ceroid Lipofuscinoses NextGen Sequencing Panel (#1909)

**Liver**
Isolated Polycystic Liver Disease NextGen Sequencing Panel (#1385)

**Metabolic**
Cerebrotendinous Xanthomatosis *CYP27A1* (#1670)
Methylmalonic Aciduria and Homocystinuria *ABCD4* (#1451)
Neuronal Ceroid Lipofuscinoses NextGen Sequencing Panel (#1909)
Peroxisome Biogenesis Disorders, Zellweger Syndrome Spectrum *PEX14* (#1091), *PEX16* (#1092), *PEX26* (#1077), *PEX2* (#1072), *PEX3* (#1078), *PEX5* (#1079), *PEX6* (#1073), *PEX10* (#1074), *PEX12* (#1076), *PEX13* (#1090), *PEX19* (#1093)
Peroxisome Biogenesis Disorders, Zellweger syndrome spectrum Sanger panel (#1080)
PRPS1-related disorders *PRPS1* (#1550)
Xanthinuria Type I *XDH* (#1431)

**Mitochrondrial**
Mitochondrial Genome Maintenance/Integrity NextGen Sequencing Panel (#1399)
Nance-Horan Syndrome | Congenital Cataract *NHS* (#1668)
Optic Atrophy OA NextGen Sequencing Panel (#1901)

**Neurologic**
Alzheimer's Disease *PSEN2* (#1415)
Cerebrotendinous Xanthomatosis *CYP27A1* (#1670)
Congenital Central Hypoventilation Syndrome NextGen Sequencing Panel (#1397)
Cutis Laxa *PYCR1* (#1066)
Early Infantile Epileptic Encephalopathy NextGen Sequencing Panel (#1905)
Familial Focal Epilepsy with Variable Foci *DEPDC5* (#1423)
Infantile Myofibromatosis and Idiopathic Basal Ganglia Calcification *PDGFRB* (#1609)
Lafora Disease *EPM2A* (#1425)

Neuronal Ceroid Lipofuscinoses NextGen Sequencing Panel (#1909)
Osteopetrosis *OSTM1* (#1486)
Parkinson's disease *PARK7* (#1029)
PRPS1-related disorders *PRPS1* (#1550)
Spinocerebellar Ataxia *WWOX* (#1270)

**Neuromuscular**
Malignant Hyperthermia NextGen Sequencing Panel (#1383)

**Skeletal**
Osteogenesis Imperfecta *IFITM5* (#1657), *SP7* (#1666)
Osteopetrosis *OSTM1* (#1486), *CLCN7* (#1485)

**Skin**
Cutis Laxa *PYCR1* (#1066)
Ectodermal Dysplasia *EDA* (#616), *EDAR* (#617), *EDARADD* (#618)
Erythropoietic Protoporphyria *FECH* (#1691)
Hemochromatosis *HFE* (#1693)
Hypomyelination and Congenital Cataract *FAM126A* (#1669)
Warts, Hyogammaglobulinemia, Infections, and Myelokathexis Syndrome *CXCR4* (#1690)

**CMA**
Chromosomal Microarray CMA-ISCA (#2000)
*A High Density array and a SNP array will follow in the coming months

**Revised**:

**Blood and Lymph**
Cryopyrin-Associated Periodic Syndromes *NLRP3* (Combined 2 test descriptions, #1638)
*ABCD1* was removed from the array
Chronic Hereditary Pancreatitis *SPINK1* (Inherited gene update, #1401)
Hereditary Paraganglioma-Pheochromocytoma Syndrome Sanger Sequencing Panel
Added *SDHA* (#1135)
Hereditary Paraganglioma-Pheochromocytoma Syndrome NextGen Sequencing Panel Added SDHA (#1329)

Single-gene test descriptions were released for the following NextGen Sequencing only genes: *ACY1*, *ALDH7A1, ARFGEF2, BCKDK, C8orf37, FARS2, GOSR2, PLCB1, SPG7, ST3GAL3, ST3GAL5, SZT2* and *UNC119*.

## DR. DRURY SPECIALIZES IN BLOOD DISORDERS, CANCER, NEXTGEN

## TECHNOLOGIES

Luke Drury, Ph.D., joined PreventionGenetics in September 2013 as a human molecular geneticist. His portfolio focuses on blood disorders, cancer and NextGen technologies.

Dr. Drury received his Ph.D. in microbiology and molecular genetics from the Medical College of Wisconsin. Prior to coming to PreventionGenetics, he was a postdoctoral research scholar at the University of Iowa.

His doctoral research involved investigation of how chemokines regulate colorectal cancer metastasis. His studies led to three publications and unveiled novel chemokine-based therapeutic approaches to limit metastasis

During his postdoctoral fellowship, he sought to understand the genetic processes leading to onset of T-cell adult lymphoblastic leukemia (T-ALL). Using a transposon-based mouse model system to study T-ALL, he developed a NextGen sequencing approach to better define causative genetic events leading to disease onset. Dr. Drury used his expertise in NextGen library preparation and analysis to help other collaborators using similar mouse models study a variety of other cancer types.

A big impetus in his desire to work in the area of blood disorders and cancer was his wife, who after being seriously ill has been cancer free for more than 10 years.

A native of Littleton, Colorado, he was drawn to PreventionGenetics by the opportunity to continue in the field of genetics and work more closely with clinicians and patients, having a more direct impact on patients' lives. "In research, your goal is to discover something that will impact patients. But this process is often very long and tedious. At PreventionGenetics, I am able to make an impact on a daily basis."

Dr. Drury finds that the most exciting element of his job is when he can give resolution to a medical issue that a patient has been struggling with for years. Working together with the genetic counselor and other caring medical professionals, "it's all about team science."

Email luke.drury@preventiongenetics.com or call 715-387-0484, ext. 177.

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### President's Corner

Earlier this year in our Newsletters, I began a discussion of obstacles to routine genomic sequencing of patients. Here again is the list of what I think are the major obstacles that need to be overcome. Sequencing technology is insufficient. Patient sequences are not being stored in electronic health records.
Patient sequences are not being shared across providers and family members.
Sequence interpretation is in its infancy.
Health care providers and patients are not ready.

I previously covered the first and last items on the list. I think that virtually everyone working in human genetics knows that sequencing technology has raced far ahead of our ability to interpret the sequences. So in this issue, I'll conclude my discussion with brief coverage of what I feel to be the greatest


I previously covered the first and last items on the list. I think that virtually everyone working in human genetics knows that sequencing technology has raced far ahead of our ability to interpret the sequences. So in this issue, I'll conclude my discussion with brief coverage of what I feel to be the greatest current impediment to advancement of clinical genetics, namely the absence of storage of patient sequences in electronic health records (EHRs) and sharing of these sequences across providers and family members.

Until we achieve routine storage of sequences in EHRs we will not be able to automatically reinterpret these sequences nor use them in medical alerts. It will be difficult to share sequences across providers and among family members and reproductive partners. We also won't be able to easily use common variants to predict risk for complex disease and severity of Mendelian disease.

In all PreventionGenetics test reports, we include the statement
"PreventionGenetics recommends that DNA sequences from this test be stored in the patient's electronic medical record. This will permit automatic reinterpretation of the sequences in the future, and will best benefit the patient and family members. Upon request, we will be pleased to transfer the patient's sequences."
Unfortunately, not one of our clients has yet taken us up on our offer. To my knowledge, no health care facility is currently storing the sequences generated through clinical tests in a form that is readily amenable to analysis.

The good news is that there are no technological obstacles to storage of the sequences. We already have all the computer knowledge and hardware that we need. We only lack the will. Clearly, genetics is not a big revenue generator at hospitals and clinics. It's difficult to compete with other specialties for limited medical informatics resources. Nonetheless we need to keep hammering away at this task. Achieving the storage of patient sequences in EHRs will open the doors to routine genomic sequencing of patients. Let's all work together to achieve this vital and extremely worthwhile goal.

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