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PARTNERS HEALTHCARE | **CENTER FOR PERSONALIZED GENETIC MEDICINE**

A teaching affiliate of: **HARVARD MEDICAL SCHOOL**

*******EXAMPLE REPORT*******

Name: DOE, JOHN
DOB: 01/23/1900 **MRN: 0123456789**
Sex: Female **Specimen: Blood, Peripheral**
Race: Caucasian **Received: 05/03/2013**
Indication for testing: MedSeq, Primary Care

Accession ID: PMXX-12345
Family #: F1234657
Referring physician: Dr. Med Seq
Referring facility: Brigham and Women's
Test: WGS-pnlA, SeqConV2, WGS-GGR

GENOME REPORT

RESULT SUMMARY

Sequencing of this individual's genome was performed and covered 95.3% of all positions at 8X coverage or higher, resulting in over 5.2 million variants compared to a reference genome. These data were analyzed to identify previously reported variants of potential clinical relevance as well as novel variants that could reasonably be assumed to cause disease (see methodology below). All results are summarized on page 1 with further details on subsequent pages.

A. MONOGENIC DISEASE RISK: 0 VARIANTS IDENTIFIED

This test did NOT identify genetic variants that may be responsible for existing disease or the development of disease in this individual's lifetime.

B. CARRIER STATUS: 3 VARIANTS IDENTIFIED

This test identified carrier status for 3 autosomal recessive disorders.

Disease Inheritance	Gene Transcript	Zygosity Variant	Classification	Carrier Phenotype*
B1. Congenital myasthenic syndrome Autosomal recessive	RAPSN NM_005055.4	Heterozygous c.264C>A p.Asn88Lys	Pathogenic	None reported
B2. Cutis laxa, type IC Autosomal recessive	LTBP4 NM_003573.2	Heterozygous c.254delT p.Leu85ArgfsX15	Pathogenic	None reported
B3. Usher syndrome type II Autosomal recessive	USH2A NM_206933	Heterozygous c.609_610insC p.Gly204ArgfsX12	Pathogenic	None reported

As a carrier for recessive genetic variants, this individual is at higher risk for having a child with one or more of these highly penetrant disorders. To determine the risk for this individual's future children to be affected, the partner of this individual would also need to be tested for variants in these genes. Other biologically related family members may also be carriers of these variants. *Carriers for some recessive disorders may be at risk for certain phenotypes. Please see variant descriptions for more information.

C. PHARMACOGENOMIC ASSOCIATIONS

This test identified the following pharmacogenomic associations. Additional pharmacogenomic results may be requested, but will require additional molecular confirmation prior to disclosure.

Drug	Risk and Dosing Information
C1. Warfarin	Increased dose requirement
C2. Clopidogrel	Increased response to clopidogrel
C3. Digoxin	Typical metabolism and serum concentration of digoxin
C4. Metformin	Increased glycemic response to metformin
C5. Simvastatin	Increased risk of simvastatin-related myopathy

D. RED BLOOD CELL AND PLATELET ANTIGENS

This test identified the ABO Rh blood type as A Positive. Additional blood group information is available at the end of the report.

It should be noted that the disease risk section of this report is limited only to variants with strong evidence for causing highly penetrant disease, or contributing to highly penetrant disease in a recessive manner. Not all variants identified have been analyzed, and not all regions of the genome have been adequately sequenced. These results should be interpreted in the context of the patient's medical evaluation, family history, and racial/ethnic background. Please note that variant classification and/or interpretation may change over time if more information becomes available. For questions about this report, please contact the Genome Resource Center at GRC@partners.org.

DETAILED VARIANT INFORMATION

A. MONOGENIC DISEASE RISK

This test did NOT identify genetic variants that may be responsible for existing disease or the development of disease in this individual's lifetime.

B. CARRIER RISK

Disease Inheritance	Gene Transcript	Zygosity Variant Classification	Variant Frequency	Disease Prevalence (Carrier Freq.)	References	Carrier Phenotype
B1. Congenital myasthenic syndrome Autosomal recessive	RAPSN NM_005055.4	heterozygous c.264C>A p.Asn88Lys Pathogenic	13/8596 (0.01%) European American	1-9/1,000,000 (Unknown)	Ohno 2002, Dunne 2003, Richard 2003, Muller 2003, Banwell 2004, Yasaki 2004, Muller 2004, Ioos 2004, Cossins 2006, Skeie 2006, Milone 2009, Brugoni 2010, Bell 2011, Alseth 2011	N/A

VARIANT INTERPRETATION: The Asn88Lys variant in RAPSN has been previously identified in many individuals with congenital myasthenic syndrome and has been shown to segregate with disease in several affected family members (Ohno 2002, Dunne 2003, Richard 2003, Muller 2003, Banwell 2004, Yasaki 2004, Muller 2004, Ioos 2004, Cossins 2006, Skeie 2006, Milone 2009, Brugoni 2010, Bell 2011, Alseth 2011). This variant has been identified in 0.01% (13/8596) of European American chromosomes by the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/; dbSNP rs104894299). Although this variant has been seen in the general population, its frequency is low enough to be consistent with a recessive carrier frequency. Functional studies indicate the Asn88Lys variant results in reduced co-localization with the acetylcholine receptor (AChR) (Cossins 2006). In summary, this variant meets our criteria to be classified as pathogenic (http://pcpgm.partners.org/LMM) based upon segregation studies and functional evidence.

DISEASE INFORMATION: Congenital myasthenic syndromes (CMSs) are characterized by fatigable weakness of skeletal muscle (e.g., ocular, bulbar, limb muscles) with onset at or shortly after birth or in early childhood; rarely, symptoms may not manifest until later in childhood. Cardiac and smooth muscle tissues are not involved. Severity and course of disease are highly variable, ranging from minor symptoms to progressive disabling weakness. In some subtypes of CMS, myasthenic symptoms may be mild, but sudden severe exacerbations of weakness or even sudden episodes of respiratory insufficiency may be precipitated by fever, infections, or excitement. Major findings of the neonatal onset subtype include: feeding difficulties; poor suck and cry; choking spells; eyelid ptosis; facial, bulbar, and generalized weakness. In addition arthrogryposis multiplex congenital may be present; respiratory insufficiency with sudden apnea and cyanosis may occur. Later childhood onset subtypes show abnormal muscle fatigability with difficulty in activities such as running or climbing stairs; motor milestones may be delayed; fluctuating eyelid ptosis and fixed or fluctuating extraocular muscle weakness are common presentations. From GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1168/

FAMILIAL RISK: CMS is inherited in an autosomal recessive manner. A carrier of CMS has a 50% chance of passing on this variant to any children. The risk of this patient's child having CMS is dependent on the carrier status of the patient's partner. Two carriers have a 25% risk for having a child with CMS. This patient likely inherited this variant from a parent. Other biologically related family members may also be carriers of this variant.

Disease Inheritance	Gene Transcript	Zygosity Variant Classification	Variant Frequency	Disease Prevalence (Carrier Freq.)	References	Carrier Phenotype
B2. Cutis laxa, type IC Autosomal recessive	LTBP4 NM_003573.4	heterozygous c.254delT p.Leu85ArgfsX15 Pathogenic	1/5840 (0.01%) European American	Unknown (Unknown)	Urban 2009, Callewaert 2013	N/A

VARIANT INTERPRETATION: The Leu85ArgfsX15 variant in LTBP4 has not been previously reported in individuals with autosomal recessive cutis laxa type I, but has been identified in 1/5840 of European American chromosomes by the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/). Although this variant has been seen in the general population, its frequency is low enough to be consistent with a recessive carrier frequency. This frameshift variant is predicted to alter the protein's amino acid sequence beginning at position 85 and lead to a premature termination codon 15 amino acids downstream. This alteration is then predicted to lead to a truncated or absent protein. Loss of LTBP4 function has previously been desribed in homozygous and compound heterozygous individuals with autosomal recessive cutis laxa type IC (Urban 2009, Callewaert 2013). In summary, this variant meets our criteria to be classified as pathogenic for autosomal recessive cutis laxa type IC (http://pcpgm.partners.org/LMM).

DISEASE INFORMATION: Cutis laxa, autosomal recessive, type IC is a form of cutis laxa with pulmonary manifestations. A characteristic of this subtype is the severity of associated malformations, including major congenital heart disease, severe pulmonary hypertension, thought to be the consequence of pulmonary artery stenosis, diaphragmatic hernia and multiple bladder diverticulae with vesicoureteral reflux were causative of life-threatening complications and short life span. Adapted from GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK5200/

FAMILIAL RISK: Cutis laxa, autosomal recessive, type IC is inherited in an autosomal recessive manner. A carrier of cutis laxa has a

50% chance of passing on this variant to any children. The risk of this patient's child having Cutis laxa is dependent on the carrier status of the patient's partner. Two carriers have a 25% risk for having a child with Cutis laxa. This patient likely inherited this variant from a parent. Other biologically related family members may also be carriers of this variant.

Disease Inheritance	Gene Transcript	Zygosity Variant Classification	Variant Frequency	Disease Prevalence (Carrier Freq.)	References	Carrier Phenotype
B3. Usher syndrome (Autosomal Recessive)	USH2A NM_206933	c.609_610insC p.Gly204ArgfsX12 Heterozygous Pathogenic	Not previously reported	4.4/100,000 (1/70)	Dreyer 2000, Weston 2000, Seyedahmadi 2004	N/A

VARIANT INTERPRETATION: The Gly204ArgfsX12 variant in USH2A has not been previously reported. This frameshift variant is predicted to lead to a truncated or absent protein, resulting in a loss-of-function. Biallelic loss-of-function variants in the USH2A gene are causative for Usher syndrome, and certain mutations can cause isolated retinitis pigmentosa (Dreyer 2000, Weston 2000, Seyedahmadi 2004).

DISEASE INFORMATION: Usher syndrome type II is characterized by congenital (i.e., prelingual) bilateral sensorineural hearing loss that is mild to moderate in the low frequencies and severe to profound in the higher frequencies, intact vestibular responses, and retinitis pigmentosa (RP). Adapted from GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1341/

FAMILIAL RISK: Usher syndrome type II is inherited in an autosomal recessive manner. A carrier of Usher syndrome type II has a 50% chance of passing on this variant to any children. The risk of this patient's child having Usher syndrome type II is dependent on the carrier status of the patient's partner. Two carriers have a 25% risk for having a child with Usher syndrome type II. This patient likely inherited this variant from a parent. Other biologically related family members may also be carriers of this variant.

PHARMACOGENOMIC ASSOCIATIONS AND BLOOD GROUPS

C. PHARMACOGENOMIC ASSOCIATIONS

Drug (Indication)	Summary	Variants Evaluated and Genotypes Identified	Interpretation	References (PMID)
C1. Warfarin (Anti-coagulation)	**Increased dose requirement**	*CYP2C9* rs1799853 rs1057910 Genotype: *1/*1 c.[430C;1075A]; c.[430C;1075A] *VKORC1* rs9923231 Genotype: GG	Patients with the CYP2C9*1/*1 genotype may require a higher dose of warfarin as compared to patients with other CYP2C9 genotypes. Patients with the VKORC1 GG genotype may require a higher dose of warfarin as compared to patients with the VKORC1 GA or AA genotypes. Patients with the combination of the CYP2C9*1/*1 genotype and VKORC1 GG genotype are predicted to require higher doses of warfarin compared to other patients. Refer to warfarindosing.org for dosing based on genotype and other clinical factors.	Johnson 2011

VKORC1/CYP2C9 genotype combination frequencies

Dosing Group	VKORC1 rs9923231	CYP2C9 Genotypes	Approximate Frequency
Lower	AA	*1/*3, *2/*2, *2/*3, *3/*3	6%
	GA	*2/*3, *3/*3	3%
Standard	AA	*1/*1, *1/*2	37%
	GA	*1/*2, *1/*3, *2/*2	14%
	GG	*1/*3, *2/*2, *2/*3	<1%
Higher	GA	*1/*1	28%
	GG	*1/*1, *1/*2	13%

C2. Clopidogrel (Anti-coagulation)	**Increased response to clopidogrel**	*CYP2C19* rs4244285 rs4986893 rs12248560 Genotype: *1/*17 c.[-806C(;)681G(;)636G]; c.[806C>T(;)681G(;)636G]	Patients with the CYP2C19 *1/*17 genotype may have ultrarapid metabolism of clopidogrel and increased response to clopidogrel as compared to patients with a *1/*1 genotype. Additional information and dosing recommendations for this result can be found at: http://www.pharmgkb.org/drug/PA449053.	Scott 2013

CYP2C19 genotype frequencies

Metabolism	Genotypes	Frequency
Ultrarapid	*1/*17, *17/*17	5-30%
Extensive	*1/*1	35-50%
Intermediate	*1/*2, *1/*3, *2/17, *3/*17	18-35%
Poor	*2/*2, *2/*3, *3/*3	2-15%

C3. Digoxin (Dysrhythmias, heart failure)	**Typical metabolism and serum concentration of digoxin**	*ABCB1* rs1045642 Genotype: CT *Genotype frequencies:* CC: 22% **CT: 51%** TT:27%	Patients with the CT genotype who take oral digoxin may have typical metabolism and serum concentrations of digoxin as compared to patients with the CC and TT genotypes.	Aarnoudse 2008, Kurata 2002, Hoffmeyer 2000
C4. Metformin (Type 2 diabetes mellitus)	**Increased glycemic response to metformin**	*C11orf65* rs11212617 Genotype: GG *Genotype frequencies:* TT:37% TG:48% **GG:15%**	Patients with the GG genotype who have Type 2 Diabetes Mellitus and are treated with metformin may have an increased glycemic response as compared to patients with the TT genotype. An association with increased or decreased glycemic response to metformin was not seen in people diagnosed with impaired glucose tolerance in the absence of Type 2 Diabetes Mellitus.	Florez 2012, GoDARTS and UKPDS Diabetes Pharmacogenetics Study Group 2011
C5. Simvastatin (Hyperlipidemia)	**Increased risk of simvastatin-related myopathy**	*SLCO1B1* rs4149056 Genotype: CT *Genotype frequencies*: TT:68% **CT:30%** CC:2%	Patients with the CT genotype may have a higher risk of simvastatin-related myopathy as compared to patients with the TT genotype, and a lower risk as compared to individuals with the CC genotype.	Wilke 2012

D. RED BLOOD CELL AND PLATELET ANTIGENS

D1. SUMMARY

ABO Rh Blood type: A Positive

Rare RBC Antigens

No rare presence or absence of RBC antigens were identified.

Rare Platelet Antigens

No rare presence or absence of platelet antigens were identified.

D2. DISCUSSION

These red blood cell (RBC) and human platelet antigen (HPA) predictions are based on published genotype to phenotype correlations for the alleles present. Some antigens have also been serologically determined using traditional blood typing methods.

During pregnancy or transfusion alloantibodies to blood group antigens and platelet antigens can form against foreign RBCs that contain immunogenic blood group and platelet antigens that the recipient is missing. These alloantibodies can cause clinically important complications during future transfusions and pregnancy.

Blood Production Transfusion

This individual does NOT have an increased risk of forming unusual RBC or platelet alloantibodies, since this test revealed a normal absence of low frequency antigens, normal presence of high frequency antigens, and no antigen gene rearrangements.

Blood Production Donation

Although this individual's results indicate that they do not have a rare donor antigen profile, they would still be a valuable RBC donor given the following uncommon changes (<40% of the population): c−, Fy(b−), and Jk(b−). If interested in becoming a RBC and/or platelet donor, this individual may contact the BWH donor recruitment supervisor (Malissa Lichtenwalter 617-632-3206, MLichtenwalter@partners.org) and mention that our testing found them to be ABO Rh Blood Type A Positive and RBC antigen c−, Fy(b−), and Jk(b−).

D3. RED BLOOD CELL ANTIGENS

A	B	H	D	C	c	E	e	K	k	Jk(a)	Jk(b)	Fy(a)	Fy(b)
+	-	+	+	+	-	-	+	-	+	+	-	+	-

M	N	S	S	Lu(a)	Lu(b)	Au(a)	Au(b)	Kp(a)	Kp(b)	Kp(c)	Di(a)	Di(b)
+	-	-	+	[-]	[+]	[+]	[+]	[-]	[+]	[-]	[-]	[+]

Wr(a)	Wr(b)	Yt(a)	Yt(b)	Sc1	Sc2	Do(a)	Do(b)	Jo(a)	Hy	Co(a)	Co(b)	LW(a)	LW(b)
[-]	[+]	[+]	[-]	[+]	[-]	[-]	[+]	[+]	[+]	[+]	[-]	[+]	[-]

Cr(a)	Kn(a)	Kn(b)	Sl(a)	Vil	Yk(a)	KCAM	McC(a)	McC(b)	In(a)	In(b)
[+]	[+]	[-]	[+]	[-]	[+]	[+]	[+]	[-]	[-]	[+]

Ok(a)	MER2	JMHK	JMHL	FORS
[+]	[+]	[+]	[+]	[-]

D4. PLATELET ANTIGENS

1a	1b	2a	2b	3a	3b	4a	4b	5a	5b	6bw	7bw	8bw	9bw
[+]	[-]	[+]	[-]	[+]	[+]	[+]	[-]	[+]	[+]	[-]	[-]	[-]	[-]

10bw	11bw	12bw	13bw	14bw	15a	15b	16bw	17bw	18bw	19bw	20bw	21bw	22bw
[-]	[-]	[-]	[-]	[-]	[+]	[+]	[-]	[-]	[-]	[-]	[-]	[-]	[-]

23bw	24bw	25bw	26bw	27bw
[-]	[-]	[-]	[-]	[-]

Key: [+] presence of antigen predicted by genotyping; + presence of antigen predicted by genotyping and confirmed by serology; +* presence of antigen detected by serology, genotype prediction not available; [+w] weak presence of antigen predicted by genotyping; +w weak presence of antigen predicted by genotyping and confirmed by serology; +w* weak presence of antigen detected by serology, genotype prediction not available; [−] absence of antigen predicted by genotyping; - absence of antigen predicted by genotyping and confirmed by serology, -* absence of antigen detected by serology, genotype prediction not available; NC indicates no sequencing coverage, Dis indicates discordant. Rare (less than 5% population frequency) presence or absence of antigen is indicated in **red**.

METHODOLOGY

Genomic sequencing is performed using next generation sequencing on the Illumina HiSeq platform. Genomes are sequenced to at least 30X mean coverage and a minimum of 95% of bases are sequenced to at least 8X coverage. Paired-end 100bp reads are aligned to the NCBI reference sequence (GRCh37) using the Burrows-Wheeler Aligner (BWA), and variant calls are made using the Genomic Analysis Tool Kit (GATK). Variants are subsequently filtered to identify: (1) variants classified as disease causing in public databases; (2) nonsense, frameshift, and +/-1,2 splice-site variants that are novel or have a minor allele frequency <1% in European American or African American chromosomes from the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/); and (3) rs11212617 (C11orf65; metformin), rs12248560 (CYP2C19; clopidogrel), rs4244285 (CYP2C19; clopidogrel), rs4986893 (CYP2C19; clopidogrel), rs28399504 (CYP2C19; clopidogrel), rs41291556 (CYP2C19; clopidogrel), rs72552267 (CYP2C19; clopidogrel), rs72558186 (CYP2C19; clopidogrel), rs56337013 (CYP2C19; clopidogrel), rs1057910 (CYP2C9; warfarin), rs1799853 (CYP2C9; warfarin), rs7900194 (CYP2C9; warfarin), rs9332131 (CYP2C9; warfarin), rs28371685 (CYP2C9; warfarin), rs28371686 (CYP2C9; warfarin), rs9923231 (VKORC1; warfarin), rs4149056 (VKORC1; simvastatin), and rs1045642 (ABCB1; digoxin). The evidence for phenotype-causality is then evaluated for each variant resulting from the filtering strategies above and variants are classified according to LMM criteria (http://pcpgm.partners.org/LMM). Only those variants with evidence for causing highly penetrant disease or contributing to disease in a recessive manner are reported. Before reporting, all variants are confirmed via Sanger sequencing or another orthogonal technology. The initial sequencing component of this test was performed by the Illumina Clinical Services Laboratory (San Diego, CA CLIA# 05D1092911) and the alignment, variant calling, data filtering, Sanger confirmation and interpretation were performed by the Laboratory for Molecular Medicine at the Partners Healthcare Center for Personalized Genetic Medicine (Cambridge, MA CLIA#22D1005307). This test has not been cleared or approved U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

LIMITATIONS

It should be noted that this test does not sequence all bases in a human genome and not all variants have been identified or interpreted. Triplet repeat expansions, translocations and large copy number events are currently not reliably detected by genome sequencing. Furthermore, not all disease-associated genes have been identified and the clinical significance of variation in many genes is not well understood. It is recommended that genomic sequencing data is periodically reinterpreted, especially when new symptoms arise.

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