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dante labs

Provider Information
Institution 12121212
Patient Id
Case Id 212121212

Sample Information

Sample Type
Saliva
Collection Method
DNA Genotek - DNA saliva collection Oragene OGD-500
Panel Coverage
WGS: Full DNA(introns and exons)

Avg. Read Depth
WGS: 30X

Report Date
6/21/2018

Results

Positive: Variants with established pathogenicity detected in genes surveyed. Variants with uncertain significance detected in genes surveyed.

Affected Genes

ACADVL (0)	*ADAMTS2* (0)	*AGRN* (0)	*ALG14* (0)	*AMPD1* (0)	*APOPT1* (0)	*B3GALT6* (0)	*B4GALT7* (0)	*C12ORF62* (0)	*C1R* (0)	*C1S* (0)
CACNA1A **(1)**	*CAV3* (0)	*CHAT* (0)	*CHRNA1* (0)	*CHRNB1* (0)	*CHRND* (0)	***CHRNE*** **(1)**	*CHST14* (0)	*CLCN1* (0)	*CLCN1* (0)	*CMTX1* (0)
CNBP (0)	*COA3* (0)	*COA5* (0)	*COA6* (0)	*COL12A1* (0)	*COL13A1* (0)	*COL1A1* (0)	*COL1A1* (0)	*COL1A2* (0)	*COL3A1* (0)	*COL5A1* (0)
COL5A1 (0)	*COL5A2* (0)	*COL5A2* (0)	*COLQ* (0)	*COX10* (0)	*COX14* (0)	*COX15* (0)	*COX20* (0)	*COX6B1* (0)	*CPT2* (0)	*CYP11B1* (0)
CYP11B2 (0)	*DOK7* (0)	*DPAGT1* (0)	*DSE* (0)	*ENO3* (0)	*FARS2* (0)	*FASTKD2* (0)	*FKBP14* (0)	*FMR1* (0)	*GAA* (0)	***GFPT1*** **(1)**
KCNE3 (0)	*KCNJ18* (0)	*KCNJ5* (0)	*LDHA* (0)	*LRP4* (0)	*LRPPRC* (0)	*MT-ATP6* (0)	*MT-ATP8* (0)	*MTCO1* (0)	*MTCO2* (0)	*MTCO3* (0)

MTTL1 MTTS1 (0)	***MUSK*** **(1)**	*NOD2* (0)	*PET100* (0)	*PFKM* (0)	*PGAM2* (0)	*PGM1* (0)	*PLEC* (0)	*PLOD1* (0)	*PMP22* (0)	*POLG* (0)
PPPT2 (0)	*PRDM5* (0)	*PREPL* (0)	***PYGM*** **(1)**	*RAPSN* (0)	*RYR1* (0)	*SCN1A* (0)	*SCN4A* (0)	*SCO1* (0)	*SCO2* (0)	*SLC12A3* (0)
SLC16A1 (0)	*SLC39A13* (0)	*SNAP25* (0)	*SPR* (0)	*SPR* (0)	*SYT2* (0)	*TACO1* (0)	*TNFRSF1A* (0)	*TNXB* (0)	*TNXB* (0)	*ZNF469* (0)

Primary Findings

Gene	Zygosity	Variant	Exon	Pathogenicity
GFPT1	Heterozygous	NM_002056.3:c.1828G>A(NP_002047.2:p.Val610Ile)	17	Uncertain Significance
MUSK	Heterozygous	NM_005592.3:c.-82T>C(?)	1	Uncertain Significance
PYGM	Heterozygous	NM_005609.3:c.645G>A(NP_005600.1:p.Lys215=)	5	Uncertain Significance
C17orf107,CHRNE	Heterozygous	NM_001145536.1:c.*1434G>A(?)	3,5	Uncertain Significance
CACNA1A	Heterozygous	NM_001127221.1:c.*185_*187delCAG(?)	47	Pathogenic

Recommendations

Dante Labs suggests you to discuss your results with a doctor/geneticist or Genetic Counselor in other to correctly interpret the relevance of the variants

Individual Variant Interpretations

NP_002047.2:p.Val610Ile in Exon 17 of *GFPT1* (NM_002056.3:c.1828G>A) Uncertain Significance

This is a Missense Variant located in the GFPT1 gene.

The GFPT1 gene encodes an isoform of glutamine:fructose-6-phosphate amidotransferase (GFAT), which catalyzes the transfer of an amino group from glutamine onto fructose-6-phosphate, yielding glucosamine 6-phosphate and glutamate. It is the first and rate-limiting enzyme of the hexosamine biosynthetic pathway. Hexosamine is the obligatory source of essential amino sugars for the synthesis of glycoproteins, glycolipids, and proteoglycans. GFPT1 is a homodimeric cytoplasmic enzyme (summary by Senderek et al., 2011).

See also GFPT2 (603865).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Myasthenia congenital 12 with tubular aggregates.

5 Prime UTR Variant in *MUSK* (NM_005592.3:c.-82T>C) Uncertain Significance

This is a 5 Prime UTR Variant located in the MUSK gene.

Intercellular communication is often mediated by receptors on the surface of one cell that recognize and are activated by specific protein ligands released by other cells. Members of one class of cell surface receptors, receptor tyrosine kinases (RTKs), are characterized by having a cytoplasmic domain containing intrinsic tyrosine kinase activity. This kinase activity is regulated by the binding of a cognate ligand to the extracellular portion of the receptor. RTKs, known to be expressed in cell type-specific fashions, play a role critical for the growth and differentiation of those cell types. The MUSK gene is a muscle-specific kinase required for neuromuscular junction formation (summary by DeChiara et al., 1996).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with Fetal akinesia deformation sequence and Myasthenic syndrome congenital 9 associated with acetylcholine receptor deficiency.

NP_005600.1:p.Lys215= in Exon 5 of *PYGM* (NM_005609.3:c.645G>A) Uncertain Significance

This is a Synonymous Variant located in the PYGM gene.

The PYGM gene encodes the muscle isoform of glycogen phosphorylase ({EC 2.4.1.1}), which catalyzes and regulates the breakdown of glycogen to glucose-1-phosphate during glycogenolysis. This metabolic pathway is necessary for the generation of ATP during physical activity (Gautron et al., 1987).

This gene has been observed to exhibit Autosomal recessive inheritance pattern.

It has been associated with McArdle disease.

3 Prime UTR Variant in *C17orf107* (NM_001145536.1:c.*1434G>A) Uncertain Significance

NP_000071.1:p.Phe155= in Exon 5 of *CHRNE* (NM_000080.3:c.465C>T) Uncertain Significance

This is a 3 Prime UTR Variant (NM_001145536.1) and Synonymous Variant (NM_000080.3). It is located in the *C17orf107 and CHRNE* genes.

Acetylcholine receptors (AChRs) at mature mammalian neuromuscular junctions (NMJs) are pentameric protein complexes composed of 4 subunits in the ratio of 2 alpha subunits (CHRNA1; 100690) to 1 beta (CHRNB1; 100710), 1 epsilon, and 1 delta subunit (CHRND; 100720). Most, if not all, embryonic AChRs contain a different subunit, gamma (CHRNG; 100730), in place of the epsilon subunit. It is likely that this change in subunit composition, which occurs during the first 2 weeks after birth, accounts for the switch in properties of ACh-activated channels from low-conductance, long open time to high-conductance, brief open time that occurs over approximately the same time course. In neonatal mouse and rat myotubes, epsilon-subunit mRNA is present at low levels, whereas gamma-subunit mRNA is present at relatively high levels. During the first 2 weeks after birth, the amount of epsilon-subunit mRNA rises 10-fold and gamma-subunit mRNA falls to undetectable levels. The increase in epsilon-subunit mRNA appears to be confined to the developing motor endplate. The switch to the epsilon subunit is mediated by ARIA (acetylcholine receptor-inducing activity; 142445).

This gene has been observed to exhibit Autosomal recessive and Autosomal dominant inheritance pattern.

It has been associated with Myasthenic syndrome congenital 4A slow-channel, Myasthenic syndrome congenital 4B fast-channel, and Myasthenic syndrome congenital 4C associated with acetylcholine receptor deficiency.

3 Prime UTR Variant in *CACNA1A* (NM_001127221.1:c.*185_*187delCAG) Pathogenic

This is a 3 Prime UTR Variant located in the CACNA1A gene.

The CACNA1A gene encodes the transmembrane pore-forming subunit of the P/Q-type or CaV2.1 voltage-gated calcium channel (VGCC) (Kordasiewicz et al., 2006). Voltage-dependent Ca(2+) channels not only mediate the entry of Ca(2+) ions into excitable cells but are also involved in a variety of Ca(2+)-dependent processes, including muscle contraction, hormone or neurotransmitter release, and gene expression. Diriong et al. (1995) noted that calcium channels are multisubunit complexes and that the channel activity is directed by a pore-forming alpha-1 subunit, which is often sufficient to generate voltage-sensitive Ca(2+) channel activity. There are at least 6 classes of alpha-1 subunits: alpha-1A, B, C, D, E, and S, which are derived from 6 genes representing members of a gene family. The auxiliary subunits beta (e.g., 114207), alpha-2/delta, and gamma (e.g., 114209) regulate channel activity.

In addition to full-length CACNA1A, use of an internal ribosomal entry site in the CACNA1A transcript generates the CACNA1A C-terminal polypeptide, or alpha-1ACT, which functions as a transcription factor that mediates cerebellar development (Du et al., 2013).

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Epileptic encephalopathy early infantile 42, Episodic ataxia type 2, Migraine familial hemiplegic 1, Migraine familial hemiplegic 1 with progressive cerebellar ataxia, and Spinocerebellar ataxia 6.

References

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Gautron S. Daegelen D. Mennecier F. Dubocq D. Kahn A. Dreyfus J.-C. Molecular mechanisms of McArdle's disease (muscle glycogen phosphorylase deficiency). J. Clin. Invest. 79: 275-281 1987. [PubMed: 3466902] [Full Text]

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Senderek J. Muller J. S. Dusl M. Strom T. M. Guergueltcheva V. Diepolder I. Laval S. H. Maxwell S. Cossins J. Krause S. Muelas N. Vilchez J. J. {and 27 others} Hexosamine biosynthetic pathway mutations cause neuromuscular transmission defect. Am. J. Hum. Genet. 88: 162-172 2011. [PubMed: 21310273] [Full Text]

Additional Information

Test

Periodic Paralysis 2 - Expanded Panel Dante Labs

Indication

Data produced by tertiary bioinformatic analysis on WGS 30X

Background

WGS was performed using Next-Generation-Sequencing Technology.Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen) and ACMG Guidelines (https://www.acmg.net/)

Method

Whole genome sequencing

The qualified genomic DNA sample was randomly fragmented by Covaris technology and the fragment of 350bp was obtained after fragment selection. The end repair of DNA fragments was performed and an "A" base was added at the 3'-end of each strand. Adapters were then ligated to both ends of the end repaired/dA tailed DNA fragments, then amplification by ligation-mediated PCR (LM-PCR), then single strand separation and cyclization. The rolling circle amplification (RCA) was performed to produce DNA Nanoballs (DNBs). The qualified DNBs were loaded into the patterned nanoarrays and pair-end read were read through on the BGISEQ-500 platform and high-throughput sequencing are performed for each library to ensure that each sample meet the average sequencing coverage requirement. Sequencing-derived raw image files were processed by BGISEQ-500 basecalling Software for base-calling with default parameters and the sequence data of each individual is generated as paired-end reads, which is defined as "raw data" and stored in FASTQ format.

Sequencing of this individual's genome was performed and covered an average of 30X. 99.66% on average of the whole genome excluding gap regions were covered by at least 1X coverage, 99.27% had at least 4X coverage and 98.28% had at least 10X coverage.

Bioinformatic analysis

Reads were aligned to the human reference sequence (GRCh37) using the Burrows-Wheeler Aligner (BWA), and variant calls are made using the Genomic Analysis Tool Kit (GATK). The GATK Variant Quality Score Recalibration (VQSR) that uses machine learning algorithm was used to filter the raw variant callset. The SNPs and InDels marked PASS in the output VCF file were high-confident variation set. All the variants with pathogenic or unknown significance for causing or contributing to diseases are reported.

Data Quality Control

The strict data quality control (QC) was performed in the whole analysis pipeline for the clean data , the mapping data, the variant calling, etc. Several quality control items for each sample were checked.

Variant classification

The classification of variants is largely based on the American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al., Genet. Med., 2015, http://www.ncbi.nlm.nih.gov/pubmed/25741868, and Richards et al.,Genet. Med., 2008, http://www.ncbi.nlm.nih.gov/pubmed/18414213).

Based on the evidence available, a given variant will be classified according to the weighted classification system as set out by the ACMG (for more information about the specific criteria, see also tables 3 and 4 in

http://www.ncbi.nlm.nih.gov/pubmed/25741868). In general, variant evidence can comprise previous reports and functional data about that specific variant if available (e.g. described as pathogenic, reports about the effect of that specific variant on protein expression and function, as verified in functional in vitro or in vivo experiments), reports

and functional data about other similar variants within the same gene (e.g. information about the type of known

pathogenic and benign variants within a specific gene, known mutational hot spots or certain protein domains, are

also taken into account when classifying a variant within the same gene), phenotype data (e.g. the clinical phenotype

of the patient is taken into account when classifying a variant, the match between the phenotype in the patient and

the gene’s disease association is of relevance), population data (e.g. variant and disease population frequencies),

segregation data (e.g. whether the variant co-segregates with the disease in a family), and computational data (e.g. in

silico predictive algorithms). The combination of the above mentioned evidence categories will allow to classify a