Research Report

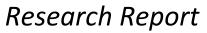


Whole Exome Sequencing Diagnostic Panel

Subject ID: Specimen Type: Date Specimen Obtained:

Peripheral Blood 2012-09-12 Date Test Started: Date of Report:

TEST PERFORMED	Whole exome sequencing (WES) with Focused Diagnostic Panel(s): Neuropathy, Leukodystrophy, Myopathy See below for a complete list of genes analyzed.				
RESULTS	1 sequence variant with potential clinical relevance was identified in disease-related genes.				
	These sequence variants were submitted for confirmation in the CLIA-approved UNC Molecular Diagnostic Laboratory. See separate report for interpretation and recommendations.				
INTERPRETIVE NOTES	This report details findings from WES and targeted informatics analysis performed on a research basis. <i>Absence of a definitive disease-causing variant does not exclude the possibility of a genetic basis for the subject's medical condition.</i> Only variants in genes associated with the medical condition, or thought to be potentially clinically relevant to the medical condition, were analyzed. The clinical implications of most genomic variations are not known at the time of this report. Specific limitations of the WES technique are as follows:				
	 Some types of genetic abnormalities may not be detectable with the technologies used in this test. For example, this assay is not designed to detect large chromosomal aberrations, such as larger deletions and duplications (larger than ~20bp) or rearrangements. This assay also cannot detect repeat expansions. 				
	 It is possible that the disease causing mutation(s): exists in a region of the genome that was not included by the exome capture reagents, exists in a gene that was not included in the diagnostic panel analyzed due to incomplete scientific knowledge about the genes that cause human diseases, is not recognized as a type of genetic variant that causes genetic disorders due to incomplete scientific knowledge about the causation of human diseases, or exists in an exon that had low coverage or base quality in the assay performed in this subject, such that a mutation exists but was not detected. 				
	The exome data generated here will be reanalyzed on an annual basis during the course of the NCGENES research study. The data will be reassessed if newly characterized genes and/or disorders identified since the date of this report have been added to the diagnostic panel, or new algorithms are developed for more accurate base calling.				
	This exome data will also be used for research analyses intended to examine potentially novel causes of human disease. The likelihood of success is small, but it is possible that this report would be revised if a genetic variant were found in a gene that was subsequently determined to be implicated in a disorder consistent with the subject's presenting symptoms.				



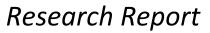


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SUMMARY	SUMMARY The overall results of the WES analysis are as follows:							
	Total reads: 65084795	Total reads: 65084795						
	- mapped: 98.75 %							
	- paired: 97.92 %							
	Average coverage: 56.87							
		Tatal Number of Veriants Datastad, 02005						
	Total Number of Variants Detect	By location By type By effect						
	Coding: 18390	Substitution: 73572	Intergenic: 4396					
	Non-Coding: 61109	Small indel: 9033	Intronic: 50595					
	Transcript-dependent: 3106	Smail maei. 5055	Untranslated: 6024					
			Synonymous: 11547					
			Missense: 9348					
			Non-frameshifting indel: 243					
			Frameshifting indel: 226					
			Splice site: 112					
			Nonsense: 81					
			Stoploss: 11					
			Other: 22					
	 Reported mutations: 3 Novel/rare truncating variants: Novel/rare missense variants: 5 Uncommon protein-coding or r 	 Novel/rare truncating variants: 1 Novel/rare missense variants: 5 Uncommon protein-coding or rare intronic variants: 328 Common protein-coding or uncommon intronic variants: 106 						
METHODS	kit was used to capture the prote of the exome was sequenced usi system with 100bp paired-end re human reference genome seque Genome Analysis Toolkit. Variant variant calling pipeline. The targeted coding exons and s were assessed for the average de	Genomic DNA was extracted from the submitted specimen and the Agilent SureSelect v4 kit was used to capture the protein-coding regions of the genome. The enriched fraction of the exome was sequenced using the Illumina HiSeq 2000 or HiSeq 2500 sequencing system with 100bp paired-end reads. Raw DNA sequence reads were mapped to the human reference genome sequence NCBI 37.1 (hg19) using bwa and aligned using the Genome Analysis Toolkit. Variants were identified using version 13 of the NCGENES variant calling pipeline. The targeted coding exons and splice junctions of the known protein-coding RefSeq genes were assessed for the average depth of coverage and data quality threshold values. The following values represent metrics from this subject's WES analysis:						





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Quality Metrics Average number of sequence reads across the entire region targeted for enrichment:		
At least 8x coverage	97.99	
	At least 20x coverage	92.89

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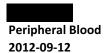
DIAGNOSTIC PANEL AND COVERAGE DETAILS	analyzed using	the Neuropath	is of the WES va iy, Leukodystro ally implicated i	phy, Myopathy	diagnostic pan	el(s) consisting
	AAAS	AARS	ABAT	ABCD1*	ABHD12*	ACADM
	ACADS	ACADVL	ACOX1	ACP5	ACTA1	AFG3L2
	AGL	AIFM1	AIMP1	AMPD1	ARHGEF10	ARSA
	ASPA	ATL1	ATP2A1	ATP7A	ATXN1	ATXN2*
	ATXN3	BAG3	BIN1	BSCL2	C10orf2	CACNA1A
	CAV3	CCT5	CFL2	CNBP	CNTN1	COX14
	CPT1B	CPT2	CRYAB	CTC1	CTDP1	DCTN1
	DDC	DES	DHH	DMD	DMPK	DNM2
	DNMT1	DST	DYNC1H1	EGR2	EIF2B1	EIF2B2
	EIF2B3	EIF2B4	EIF2B5	ENO3	ETFA	ETFB
	ETFDH	ETHE1	FA2H*	FAM126A	FAM134B	FASTKD2
	FBLN5	FGD4	FGF14	FHL1	FIG4	FLVCR1
	FOLR1	FOXRED1	GAA	GALC	GAN	GARS
	GBE1	GDAP1	GFAP	GFER*	GJB1	GJC2*
	GNE	GYG1	GYS1	HADHA	HADHB	HEPACAM*
	HOXD10	HRAS	HSPB1	HSPB3	HSPB8	HSPD1*
	HSPG2	ΙΚΒΚΑΡ	ISCU	KARS	KBTBD13*	KIF1A
	KIF1B	KLHL9	LAMP2	LDHA*	LITAF	LMNA
	LMNB1	LPIN1	MATR3	MCCC1	MED25	MFN2
	MLC1	MPV17	MPZ	MRPS22	MSTN	MTM1
	MTMR2	MYH2	MYH7	МҮОТ	NDRG1	NDUFA1
	NDUFA11	NDUFAF1	NDUFAF2	NDUFAF3	NDUFAF4	NDUFS1
	NDUFS2	NDUFS4	NDUFS6	NDUFV1	NDUFV2	NEFL
	NGF	NTRK1	NUBPL	OPA1	OPA3	PABPN1*
	PEX16	PEX7	PFKM	PGAM2	PGK1*	PGM1
	РНКА1	РНҮН	PLEKHG4	PLEKHG5	PLP1	PMP22
	PNPLA2	POLG	POLG2	POLR3A	POLR3B	PPP2R2B

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PRKCG	PRNP	PRPS1	PRX	PSAP	PUS1
PYGM	RAB7A	RNASEH2A	RNASEH2B	RNASEH2C	RNF170
RRM2B	RYR1	SAMHD1	SBF2	SCN9A	SCO2
SDHA*	SEPN1*	SEPT9	SH3TC2	SLC12A6	SLC16A2
SLC22A5	SLC25A20	SLC25A3	SLC25A4	SOX10	SPTLC1
SUCLA2	SUCLG1	SUMF1	TDP1	TK1	TK2
TMEM70	TNNT1	TPM3	TREX1	TRIM32	TSFM
TTN	TTR	TUFM	TYMP*	WNK1	YARS
YARS2					
Genes labeled nucleotides.	with an asteris	< did not achiev	e at least 8x co	verage for 90%	of coding