MedGenome Labs Pvt. Ltd.
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DNA TEST REPORT

Exome Sequencing Analysis Report			
Subject information		**Sample information**	
Patient name	**Lazhechnikov Egor**	Order ID/sample ID	**2430/9358**
Gender	**Male**	Collection date & time	**NA**
Age	**3 years**	Receipt date & time	**28th October 2014, 10.00 AM**
Father-mother	**NA**	Report date & time	**24rd January 2015, 6.00 PM**
Sample type	**DNA**	Requested by	**Dr. Korostelev Sergey, Genomed, Russia**
Clinical indication	**Syndromal form of delayed mental and motor development and hearing loss**		

The raw sequencing files (including the .vcf and variant annotation files) can be provided upon request from the referring physician.

Analysis: Exome Sequencing Analysis Report

Table 1	Germline variations previously reported for the phenotype in literature or databases and are recognized cause of clinical phenotype					
S. No	Genomic Position	Gene Strand	Sequence Depth**	cDNA position #	Amino acid change	Exon no.
NONE						

Table 2	Germline variations previously unreported for the phenotype in literature or databases and are of the type that is expected to be the cause of the clinical phenotype					
S. No	Genomic Position	Gene Strand	Sequence Depth**	cDNA position #	Amino acid change	Exon no.
NONE						

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Table 3	Germline variations previously unreported for the phenotype and are of the type which may or may not be causative of the clinical phenotype					
S. No	Genomic Position	Gene Strand	Sequence Depth**	cDNA position #	Amino acid schange	Exon no.
1	**chrX:106882652; C>T (HEMI)**	***PRPS1* (+)**	**56x**	**c.250C>T (ENST00000372435)**	**p.R84W**	**2**
2	**chr10:89720750; G>G/A (HET)**	***PTEN* (+)**	**99x**	**c.901G>G/A (ENST00000371953)**	**p.D301N**	**8**

*** Annotation is performed against GRCh37/hg19 version of human gene.**

**** sequence Depth, is the number of times the nucleotide position has been sequenced.**

 # cDNA base is reverse compliment of genomic base in case on negative strand.

Test Details & Interpretation

Background

Targeted exome sequencing involves selective capture and sequencing of the protein coding regions of the genome. Mutations identified in the exonic regions are generally actionable compared to variations that occur in non-coding regions. Targeted sequencing represents a cost-effective approach to detect variants present in multiple/large genes in an individual.

Test

DNA was used to perform exome capture using Agilent SureSelect V5 exome capture kit. The libraries were sequenced to mean>80-100X coverage on Illumina sequencing platform. The sequences obtained were aligned to human reference genome (GRCh37/hg19) using BWA program [2, 3] and analyzed using Picard and GATK-Lite toolkit [4, 5] to identify variants in the exome relevant to clinical indication. Clinically relevant mutations were annotated using published variants in literature and a set of variant databases including ClinVar, OMIM, GWAS, HGMD and SwissVar [6-10]. Only non-synonymous and splice site variants found in the coding regions were used for clinical interpretation. Silent variations that do not result in any change in amino acid in the coding region are not reported.

Total data generated	6.65 Gb
Total reads aligned (%)	98.91
Reads that passed alignment (%)	95.55
Data ≥ Q30 (%)	90.40

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Interpretation

Master Lazhechnikov Egor, born of a non-consanguineous marriage, displays clinical indications of a syndromal form of delayed mental and motor development and hearing loss. He has been evaluated for pathogenic gene variations.

An unreported hemizygous missense variation in exon 2 of the ***PRPS1*** gene **(chrX:106882652; C>T)** that results the amino acid substitution of Tryptophan for Arginine at codon 84 **(p.R84W; ENST00000372435)** was detected (Table 3). Homozygous mutations in *PRPS1* have been implicated in the following X-linked recessive disorders; Arts syndrome (OMIM#301835), X-linked recessive Charcot-Marie-Tooth disease-5 (OMIM#311070) and phosphoribosylpyrophosphate synthetase I superactivity (OMIM#300661). The R84W variant is not reported in the 1000 genomes database and is predicted to be damaging by SIFT, LRT and Mutation Taster. This region is conserved across species. Based on the above evidence, ***this PRPS1 variation is classified as a variant of unknown significance and has to be correlated carefully with the clinical symptoms.***

An unreported heterozygous missense variation in exon 8 of the ***PTEN*** gene **(chr10:89720750; G>G/A)** that results the amino acid substitution of Asparagine for Aspartic acid at codon 301 **(p.D301N; ENST00000371953)** was detected (Table 3). Heterozygous mutations in *PTEN* have been implicated in autosomal dominant Cowden syndrome 1 (OMIM#158350). The D301N variant is not reported in the 1000 genomes database and is predicted to be damaging by LRT and Mutation Taster. This region is conserved across mammals. Based on the above evidence, ***this PTEN variation is classified as a variant of unknown significance and has to be correlated carefully with the clinical symptoms.***

Sequencing these variations in parents and other affected and unaffected members in the family is recommended to confirm their significance.

No other variant that warrants to be reported were detected. Variations with high minor allele frequencies which are likely to be benign will be given upon request.

Genetic counselling is advised for interpretation on the consequences of these mutations.

Disclaimer:

- **The classification of variants of unknown significance can change over time. Please contact MedGenome at a later date for any change.**
- **Intronic variants are not assessed using this method.**
- **Large deletions of more than 10 bp or copy number variations cannot be assessed using this method.**
- **Certain genes may not be covered completely and few mutations could be missed.**

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- **The mutations have not been validated by Sanger sequencing.**

References:

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9. http://www.biobase-international.com/product/hgmd
10. http://swissvar.expasy.org/

Reported By:	Mutations Verified by:	Report Released by:
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