WE HEALTH

Report for Scientific Research Service

We-health in Shanghai CO.,LTD

Consignor：Beijing Institute of Technology

Contractor: Shanghai We-health Biomedical Technology Co.,Ltd

Project：WES detection and analysis

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Basic information:

Project: WES detection and analysis Sale manager: Jing-min Yang

Consignor: Beijing Institute of Technology Client:

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Description: Trio WES analysis for a Pakistani pedigree. The index(son) suffers astatia phenotype. This test is designed to find candidate variants to explain index's phenotype.

Results:

This test analyzed whole exons and adjacent splicing area, the result found a variant could explain index's phenotype.

List of candidate variants:

Gene	hg19 location	dbSNP ID	HGVS	gnomAD EAS AF	Inheritance	Zygosity	Father	Mother
SMS	ChrX:22003301	/	SMS:NM_004595:exon9:c.905C>T:p.S302L	/	XLR	hemi	/	het

The abnormality of *SMS* gene could induce X chromosome linked Snyder-Robinson mental retardation syndrome(Mental retardation, X-linked, Snyder-Robinson type, SRS [MIM:309583]). Loss of spermine synthase enzymatic activity causes SRS. Decreased SMS enzyme activity confirms the pathogenicity of an SMS sequence variant. SRS shows variable phenotypes and female carriers are normal[1,2]. The characteristic features of SRS include asthenic build, facial dysmorphism with a prominent lower lip, kyphoscoliosis, osteoporosis, and speech abnormalities[3,4]. Developmental delay usually presents as failure to meet early developmental milestones and then evolves to moderate to profound intellectual disability(which appears to remain stable over time) and variable motor disability[5]. Asthenic habitus and low muscle mass usually develop during the first year, even in males who are ambulatory. During the first decade, males with SRS develop osteoporosis, resulting in fractures in the absence of trauma[3]. The phenotypes of the index match the disease characteristics well. The variant (NM_004595:exon9:c.905C>T:p.S302L) has not been reported in published papers or crowd frequency database (gnomAD). Multiple lines of computational evidence support

a deleterious effect of this variant on the *SMS* gene(We use 12 softwares to detect the effect of this variant, 8 show deleterious results).This result is only used for research.

Description and recommendations:

Pedigree description：

This is a pedigree with 5 generation， index(VI:1), father(V:1) and mother(V:2). The parents are consanguinity. Index suffered intellectual disability, skeletal deformity, bone fragility, pectus excavatum, astatia or non ambulate. Two brothers of the index share te same phenotypes, while two sisters and parents are normal. The other members in the 5 generations are all normal.

Inheritance pattern analysis：

This a consanguineous pedigree, 3 brothers suffer the same phenotype，the 2 sisters and parents are normal. The onset model indicating that the inheritance pattern of the disease could be autosomal recessive or X chromosome linked recessive (XLR).

Recommendations for further analysis：

According to analysis of WES sequencing data, a missense variant NM_004595:c.905C>T: p.S302L was found in the 9th exon of *SMS* gene. The phenotypes of index match the abnormity of SRS causing by pathogenic variant in *SMS* gene. The inheritance pattern of SRS is XLR which is in line with the probable inheritance pattern in this pedigree (The variant is inherited from the mother(V:2)).

Clinical examination is recommended for the uncle of the index(maternal side) and the brothers of the index's grandmother (maternal side) showed the same phenotype. Sanger test is recommended for other family members (VI:2, VI:3, VI:4, VI:5 and III:2) to testify the source of variant.

QC parameter

QC for sequencing data

Relationship	No.	Raw data	Avg.depth	>=4 X	>=20 X
Index	QW-22654	13.63 Gb	147.4 X	99.85%	99.51%
Father	QW-22657	12.14 Gb	132.78 X	99.84%	99.56%
Mother	QW-22658	13.06 Gb	147.01 X	99.7%	99.54%

>=4X：Depth>=4X Target area ratio；

>=20X：Depth>=20X Target area ratio；

Reference

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