Genomic Report

Patient	**Bobby Zhang**	**Primary referrer**	**Dr Amara Adebayo**
Address	1/197 King St Newport NT 8000	**Address**	87 Railway Rd Newport NT 8000
Sex	MALE	**Provider No.**	918211MF
DOB	09-Oct-1999		

Family ID:	6193	**Request date:**	01-Jun-2018
DNA tube ID:	CI81625	**Collection date:**	01-Jun-2018
Unique lab ID:	SYD12345678	**Received date:**	06-Jun-2018
External reference(s):	N/A	**Submitted specimen:**	EDTA blood

Test requested:	Whole genome sequencing
Primary analysis:	Whole genome analysis
Additional analysis:	None requested
Samples analysed:	Proband only
Indication for testing:	Intellectual disability, microcephaly, joint hypermobility

RESULT SUMMARY

Primary analysis: A variant of uncertain significance (VUS) has been identified in the TAF1 gene.

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Accreditation Number 101010

PRIMARY ANALYSIS

Variant detected (1 of 1)

Gene name	TAF1
Genomic change	ChrX(GRCh37):g.13916A>T
cDNA change	NM_004606.4c.425A>T
Predicted protein change	p.(Asp142Val)
Zygosity	Hemizygous
OMIM disorder(s)	X-Linked Syndromic Mental Retardation (Phenotype MIM 300966)
Variant classification	Uncertain significance (class 3)
Inheritance	Not known
Orthogonal confirmation	Yes, by Sanger sequencing

Interpretation:
A hemizygous missense variant has been identified in the TAF1 gene. This is predicted to result in substitution at amino acid residue 142.

This is a variant of uncertain significance by ACMG/AMP criteria (see 'Variant classification' in Methodology). The classification of this variant may change over time, with additions to the literature or new clinical information.

Recommendations:

- Correlation of this result with the clinical phenotype
- Genetic counselling as appropriate
- Further laboratory testing, imaging, or specialist referral as deemed clinically appropriate
- Testing for this variant in other affected and unaffected members of this family; demonstrating that the variant is present in affected members and absent in unaffected members would add further weight to the pathogenicity of this variant (EDTA blood samples would be required, and testing will be performed by Sanger sequencing)
- Testing for this variant in parental samples; demonstrating that this variant is absent in parents (and therefore likely de novo) would add further weight to the pathogenicity of this variant (EDTA blood samples would be required, and testing will be performed by Sanger sequencing)
- Given the uncertain clinical significance of this variant, predictive testing in other family members is not recommended at this time
- Request periodic review and re-analysis of this case in light of new clinical information or new gene-disease associations in the literature

VARIANT ANALYSIS

Gene name	TAF1
Genomic change	ChrX(GRCh37):g.13916A>T
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Variant classification	Uncertain significance (class 3)
Inheritance	Not known
Orthogonal confirmation	Yes, by Sanger sequencing
Population databases	This variant is absent in population databases
Variant databases	This variant has been reported in the ClinVar database as a variant of uncertain significance.
Physicochemical difference	This change is from an Aspartate (negatively charged, polar, hydrophilic) amino acid to a Valine (non-polar, hydrophobic) amino acid. The Grantham distance is 0 (range 0-215).
Conservation	Moderately conserved
In silico predictions	SIFT classifies as deleterious. PolyPhen-2 classifies as possibly damaging. Scaled CADD score is 34 (variants with scores > 15 are considered potentially deleterious).
In silico splicing predictions	No splicing effect is predicted.
Evidence of pathogenicity	[PM2] Variant is absent from controls in population databases [PP2] It is a missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease [PP3] Multiple lines of computational evidence support a deleterious effect on the gene or gene product

COMMENTS

All genes included in the analysis achieved ≥ 15X sequencing coverage for > 90% of coding bases and splice sites (±8 nucleotides). The exceptions have been included in the table below. Further coverage information at the exon-level can be provided on request. Note that for X-linked genes in males, only 3X coverage would be sufficient to call a hemizygous variant with 95% confidence using our bioinformatics pipeline.

Genomic analysis and report preparation by Dr Luisa Sutton PhD FRCPA.

METHODOLOGY

Laboratory accreditation	This laboratory is NATA-accredited to perform whole genome sequencing and whole exome sequencing, in accordance with the requirements of the National Pathology Accreditation Advisory Council of Australia (NPAAC) and AS ISO 15189-2013.
Test	Whole genome sequencing was performed using the KAPA Hyper PCR-free Library Preparation kit and Illumina HiSeq X instruments.
Test performance	Genomes are sequenced to a mean coverage of ≥30X, with 98% of canonical protein coding transcripts and splice sites covered at ≥15X. Over the reportable range, sensitivity is over 99% for single nucleotide variants and over 96% for small insertions or deletions. Sensitivity in specific regions will vary according to depth of coverage.
Bioinformatics	Paired-end reads are aligned to the human genome reference sequence (GRCh37) using the Burrows-Wheeler Aligner (BWA-MEM), and variant calls are made using the Genomic Analysis Tool Kit (GATK).
Variant filtering	Variants are filtered according to the patient's phenotype, suspected pattern of inheritance in the family, variant allele frequency in the general population, predicted protein consequence, in silico predictions, and published literature. Please contact the laboratory for our policy on incidental and secondary findings.
Variant classification	Variants are classified according to the joint consensus recommendations of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (PMID 25741868). Subsequent literature offering commentary on these recommendations has also been considered (PMID 27181684, 28492532). Variants are reported using HGVS nomenclature (v15.11).
Test limitations	This test does not sequence all regions of the human genome. The following are either not detected or not analysed: insertions or deletions >20 nucleotides in size, synonymous variants, most non-coding variants, oligonucleotide repeat expansions, some GC-rich regions, some pseudogenes, mosaic variants, and methylation variants. Variant analysis and classification is based on information that is current at the time of reporting. Carrier status for recessive phenotypes is not reported.