Genomic Report

Patient	Lorenzo Weiss	**Primary referrer**	Dr Oliver Baggio
Address	10 Queen St Woodside NSW 2000	**Address**	12b High St Woodside NSW 2000
Sex	MALE	**Provider No.**	918243MF
DOB	26-Dec-2010		

Family ID:	9273	**Request date:**	01-Nov-2017
DNA tube ID:	CI38772	**Collection date:**	01-Nov-2017
Unique lab ID:	SYD12345678	**Received date:**	03-Nov-2017
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:	Trio (proband, mother, father)
Indication for testing:	Severe intellectual disability, microcephaly, slender hands and feet, coarse face

RESULT SUMMARY

Primary analysis: A pathogenic variant has been identified in the TCF4 gene.

PRIMARY ANALYSIS

Variant detected (1 of 1)

Gene name	TCF4
Genomic change	Chr18(GRCh37):g.412006C>T
cDNA change	NM_001083962.1:c.1726C>T
Predicted protein change	p.Arg580Trp
Zygosity	Heterozygous
OMIM disorder(s)	Pitt-Hopkins Syndrome (Phenotype MIM 610954)
Variant classification	Pathogenic (class 5)
Inheritance	*De novo*
Orthogonal confirmation	Yes, by Sanger sequencing

Interpretation:
A de novo, heterozygous missense variant has been identified in the TCF4 gene.

This is a pathogenic variant 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.

This result would support a clinical diagnosis of Pitt-Hopkins syndrome.

Recommendations:

- Correlation of this result with the clinical phenotype
- Genetic counselling as appropriate

VARIANT ANALYSIS

Gene name	TCF4
Genomic change	Chr18(GRCh37):g.412006C>T
cDNA change	NM_001083962.1:c.1726C>T
Predicted protein change	p.Arg580Trp
Zygosity	Heterozygous
OMIM disorder(s)	Pitt-Hopkins Syndrome (Phenotype MIM 610954)
Variant classification	Pathogenic (class 5)
Inheritance	*De novo*
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.
Physicochemical difference	This change is from an Arginine (hydrophilic, polar, positively charged) amino acid to a Tryptophan (hydrophobic, non-polar, non-charged) amino acid. The Grantham distance is 101 (range 0-215).
Conservation	This amino acid residue is highly conserved in other vertebrate species
In silico predictions	Align GVGD classifies as Class C55 (range C0-C65, with C65 most likely to be deleterious). SIFT classifies as deleterious. PolyPhen-2 classifies as probably deleterious. Scaled CADD score is 28 (variants with scores > 15 are considered potentially deleterious). PROVEAN score is 1.0 (scores < -2.5 are predicted to be deleterious).
Evidence of pathogenicity	[PS1] Variant is the same amino acid change as a previously established pathogenic variant [PS2] Variant is de novo, with both maternity and paternity confirmed [PS4] The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [PS4, downgraded to moderate] This variant has been observed in multiple unrelated patients with the same phenotype (and absent in controls) [PM1] Variant is located in a critical and well-established functional domain without benign variation [PM2] Variant is absent from controls in population databases [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.

OTHER FAMILY MEMBERS TESTED

Name:	An… We…
Relationship to patient:	Mother
Phenotype:	Unaffected
DOB:	06-Jul-1979
Sex:	Female
DNA tube ID:	CI38987
Unique lab ID:	SYD12345678

Name:	Pe… We…
Relationship to patient:	Father
Phenotype:	Unaffected
DOB:	03-Sep-1980
Sex:	Male
DNA tube ID:	CI38943
Unique lab ID:	SYD12345678

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.