Genomic Report

Patient	Catarina Rennell	**Primary referrer**	Dr Meera Chaudhri
Address	123 Station St Townsville VIC 3000	**Address**	66 John Rd Townsville VIC 3000
Sex	FEMALE	**Provider No.**	837129AA
DOB	24-May-2003		

Family ID:	1438	**Request date:**	08-Mar-2018
DNA tube ID:	CJ81723	**Collection date:**	08-Mar-2018
Unique lab ID:	SYD-12345678	**Received date:**	10-Mar-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:	Syndromic intellectual disability, short stature, cleft lip/palate

RESULT SUMMARY

Primary analysis: No variants clinically significant to the patient's phenotype have been identified.

Additional analysis: A pathogenic variant in MEN1 has been incidentally identified.

PRIMARY ANALYSIS

Interpretation
NO clinically significant variants relevant to the patient's phenotype have been identified. This result does not exclude a genetic cause of disease (see 'Test limitations' in Methodology).

Recommendations

- Genetic counselling as appropriate
- Request periodic review and re-analysis of this case in light of new clinical information or new gene-disease associations in the literature

ADDITIONAL ANALYSIS

Variant detected (1 of 1)

Gene name	MEN1
Genomic change	Chr11(GRCh37):g.11792G>A
cDNA change	NM_000244.3:c.1679G>A
Predicted protein change	p.Ser555Asn
Zygosity	Heterozygous
OMIM disorder(s)	Multiple Endocrine Neoplasia (Phenotype MIM 131100)
Variant classification	Pathogenic (class 5)
Inheritance	Not known
Orthogonal confirmation	Yes, by Sanger sequencing

Interpretation:
An incidental finding of a heterozygous missense variant was identified in the MEN1 gene. This is predicted to result in substitution at amino acid residue 555.

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 multiple endocrine neoplasia type 1.

Recommendations:

- Correlation of this result with the clinical phenotype
- Genetic counselling as appropriate
- Further laboratory testing, imaging, or specialist referral as deemed clinically appropriate
- Predictive testing is available for family members; this patient's offspring will have a 50% chance of inheriting this variant

VARIANT ANALYSIS

Gene name	MEN1
Genomic change	Chr11(GRCh37):g.11792G>A
cDNA change	NM_000244.3:c.1679G>A
Predicted protein change	p.Ser555Asn
Zygosity	Heterozygous
OMIM disorder(s)	Multiple Endocrine Neoplasia (Phenotype MIM 131100)
Variant classification	Pathogenic (class 5)
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 pathogenic
Physicochemical difference	This change is from a Serine (non-charged, polar, hydrophilic) amino acid to a Asparagine (non-charged, polar, hydrophilic) amino acid. The Grantham distance is 46 (range 0-215).
Conservation	This amino acid residue is highly conserved in other vertebrate species
In silico predictions	SIFT classifies this variant as delterious. PolyPhen-2 classifies as probably-damaging. Scaled CADD score is 30 (variants with scores > 15 are considered potentially deleterious).
In silico splicing predictions	No splicing effect is predicted.
Evidence of pathogenicity	[PS1] Variant is the same amino acid change as a previously established pathogenic variant [PS4] The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [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.