

Patient Details

Name	:	Sex / Age	:	Case ID	:
Ref By	:	PT. ID	:	Test Name	: ORION (WES-Whole Exome Sequencing)
Bill. Loc.	:				

Sample Details

Registration Date & Time	:	2024-05-10 05:01:29 PM	Sample Type	:	Whole Blood EDTA	Sample Date & Time	:	2024-05-12 09:58:00 AM
Ref ID 1.	:	-	Report Date & Time	:	2024-06-11 04:23:28 PM			

Clinical History

Clinical symptoms: Unexplained cardiac arrest at day 30 of life
Antenatal and birth history: 30 week delivery, BW- 1.33kg
Clinical suspicion: Arrhythmia

Test Results and Interpretation

HETEROZYGOUS VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS) RELATED TO PHENOTYPE DETECTED.

Summary of Variants

Gene and Transcript	Exon/Intron Number	Variant Nomenclature [Variant depth/ Total depth]	Zygosity	Classification	OMIM Phenotype	Inheritance
ANK2 (NM_001148.6)	Exon 13	c.1355A>G p.Gln452Arg [Depth - 38X/97X]	Heterozygous	Uncertain significance	Cardiac arrhythmia, ankyrin-B-related	Autosomal dominant
DSP (NM_004415.4)	Exon 24	c.8608G>A p.Gly2870Arg [Depth - 38X/62X]	Heterozygous	Uncertain significance	Arrhythmogenic right ventricular dysplasia 8	Autosomal dominant

Variant Details

ANK2

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Variant Details

Variant Nomenclature	c.1355A>G (p.Gln452Arg)
Genomic Nomenclature	chr4:g.114179536A>G
Zygosity	Heterozygous

Type of variant	gnomAD frequency	Computational evidences	Amino acids conserved by	ClinVar	Previously reported	Variant references
Missense	Absent	SIFT: Damaging Polyphen: Benign REVEL: 0.42 MutationTaster: Disease causing CADD Phred: 23.80	GERP++ PhyloP	Not submitted	No	NA

Disease

CARDIAC ARRHYTHMIA, ANKYRIN-B-RELATED

Primary arrhythmogenic disorders of the heart are a major cause of sudden cardiac death in otherwise healthy, and frequently young individuals. Variants in ANK2 gene are associated with a wide range of electrical and structural heart disease. Reported cardiac phenotypes include **arrhythmia**, corrected QT interval prolongation (sometimes referred to as long QT type 4), and sudden cardiac death. A prolonged QT interval on an electrocardiogram corrected for heart rate (QTc) is a predictor of ventricular arrhythmias and sudden cardiac death (York *et al.*, 2022).

References

1.York NS, *et al.* Mechanisms underlying the role of ankyrin-B in cardiac and neurological health and disease. Front Cardiovasc Med. 2022 Aug 4;9:964675.

DSP

Variant Nomenclature	c.8608G>A (p.Gly2870Arg)
Genomic Nomenclature	chr6:g.7586103G>A
Zygosity	Heterozygous

Type of variant	gnomAD frequency	Computational evidences	Amino acids conserved by	ClinVar	Previously reported	Variant references

Variant Details

Disease

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 8

Arrhythmogenic right ventricular cardiomyopathy is a genetic cardiomyopathy, characterized histologically by fibrofatty replacement of the myocardium which causes frequent electrical instability, **ventricular arrhythmia** and an increased risk of **sudden cardiac death** (van Lint *et al.*, 2019). **Variants of DSP gene are also associated with autosomal recessive Cardiomyopathy, dilated, with woolly hair and keratoderma; Epidermolysis bullosa, lethal acantholytic and autosomal dominant Dilated cardiomyopathy with woolly hair, keratoderma, and tooth agenesis, Keratosis palmoplantaris striata II.**

References

1. van Lint FHM, *et al.* Arrhythmogenic Right Ventricular Cardiomyopathy-Associated Desmosomal Variants Are Rarely De Novo. *Circ Genom Precis Med.* 2019 Aug;12(8):e002467.

Recommendations

1. Please correlate clinically.
2. Variant depth/Total depth has been mentioned in summary of the variants.
3. Genetic counseling for accurate interpretation of test results is recommended.
4. The reported findings are based on NGS analysis.
5. Parental/Maternal testing as applicable is recommended for variants when detected and/or to confirm if variants are in trans (if applicable).
6. Segregation analysis (testing of multiple affected as well as unaffected members) of detected variants (if any) is recommended. Variant classification is subject to change after segregation.
7. CNV confirmation via MLPA or Exon array is recommended for copy number variants involving a single gene as well as for CNV <400kb. Only large constitutional CNV can be tested via other array platforms.
8. If the above results do not correlate completely with patient phenotype, additional testing is advised based on clinician's discretion.

Technical Notes

Methodology - Massively Parallel Sequencing (Next Generation Sequencing): Genomic DNA from the submitted specimen was enriched for the complete coding regions and splice site junctions of genes listed below using a custom bait- capture system. Paired End Sequencing was performed with 2x100/2x150 chemistry. Reads were assembled and were aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. Data was filtered and analyzed to identify variants of interest and interpreted in the context of a single most damaging, clinically relevant transcript for the purpose of the report, indicated as a part of variant details. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 5-10bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Deletion and duplication analysis is performed in cases when indicated but detected variations need to be confirmed by an alternate methodology. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS).

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Technical Notes

Laboratory reporting protocol: The analysis is based on the provided phenotype: relevant HPO terms, curated gene panels and relevant literature is assessed for phenotype based analysis. Variant reporting is limited to exon regions and upto 10 basepairs within exon intron boundaries. Previously reported deep intronic and non coding variants will be included when detected at a depth more than 10X . Variant reporting is performed at a minimum depth of 10X.

For Mitochondrial Genome Sequencing (if requested): Only phenotype-related Pathogenic and Likely Pathogenic variations reported in the MitoMap database as well as literature are reported. Haplogroups are not analyzed. A list of variants other than the above are available on request. Analyzed genes include:MT-ND1, MT-ND2, MT-ND3, MT-ND4L, MT-ND4, MT-ND5, MT-ND6, MT-CYB, MT-CO1, MT-CO2, MT-CO3, MT-ATP6, MT-ATP8, MT-RNR2, MT-RNR1, MT-RNR2, MT-TA, MT-TR, MT-TN, MT-TD, MT-TC, MT-TE, MT-TQ, MT-TG, MT-TH, MT-TI, MT-TL1, MT-TL2, MT-TK, MT-TM, MT-TF, MT-TP, MT-TS1, MT-TS2, MT-TT, MT-TW, MT-TY, MT-TV.

Tools and Databases employed for analysis: Clinvar, OMIM, HGMD, UCSC genome browser, Uniprot, Ensembl, dbSNP, gnomAD, ExAC, Pubmed, Dgap, icgc, Kaviar, various bioinformatics analysis, predictive tools and disease specific databases used as available and appropriate. Such tools/databases would be mentioned wherever used.

Bioinformatics pipeline version: 13.0.1.

Gene Coverage

Indication Based Analysis:

Gene	Coverage	Gene	Coverage	Gene	Coverage	Gene	Coverage
A2ML1	100%	ABCA1	99.6%	ABCC6	100%	ABCC9	100%
ABCG5	100%	ABCG8	100%	ABL1	100%	ACE	100%
ACTA1	100%	ACTA2	100%	ACTB	100%	ACTC1	100%
ACTG1	100%	ACTN2	99.3%	ADAMTS10	100%	ADAMTS17	99.9%
ADAMTS2	100%	ADAMTSL4	100%	AKAP9	100%	ALDH18A1	100%
ALMS1	100%	ALPK3	100%	ANGPTL3	100%	ANK2	100%
ANKRD1	100%	APOA1	100%	APOA2	100%	APOA5	100%
APOB	100%	APOC2	100%	APOC3	100%	APOE	100%
ARIH1	100%	ATP7A	100%	B3GAT3	100%	BAG3	100%
BCL11B	100%	BGN	100%	BRAF	99.9%	CACNA1C	100%
CACNA2D1	98.5%	CACNB1	100%	CACNB2	98.4%	CACNB3	100%
CACNB4	100%	CALM1	100%	CALM2	100%	CALM3	100%
CALR3	100%	CASQ2	100%	CAV3	100%	CAVIN4	100%
CBL	99.2%	CBS	100%	CDH2	100%	CEL	88.6%
CELSR2	100%	CETP	100%	CHRM2	100%	COL1A1	99.2%
COL1A2	99.7%	COL2A1	100%	COL3A1	100%	COL4A5	100%

Gene Coverage

Gene	Coverage	Gene	Coverage	Gene	Coverage	Gene	Coverage
COL5A1	100%	COL5A2	100%	COLGALT1	100%	CPT1A	100%
CREB3L3	100%	CRYAB	100%	CSRP3	100%	CTF1	99.7%
CTNNA3	100%	CYP27A1	100%	DEPDC5	100%	DES	100%
DMD	99.7%	DOLK	100%	DPP6	100%	DSC2	98.3%
DSC3	100%	DSG2	100%	DSP	100%	DSPP	100%
DTNA	100%	EFEMP2	100%	ELN	100%	EMD	100%
ENPP1	99.9%	EPHX2	100%	ESR1	100%	EYA4	100%
F13A1	100%	F7	100%	FBLN5	100%	FBN1	100%
FBN2	100%	FHL2	100%	FKBP14	100%	FLNA	99.6%
FLNC	100%	FOXE3	100%	FXN	100%	GAA	100%
GATA5	100%	GATAD1	100%	GCLC	100%	GCLM	100%
GHR	100%	GJA5	100%	GLA	100%	GPD1	100%
GPD1L	100%	GPIHBP1	100%	GYG1	100%	HCN4	100%
HFE	100%	HRAS	100%	ILK	100%	ITGB3	100%
JPH2	100%	JUP	100%	KAT6B	100%	KCNA5	100%
KCND3	100%	KCNE1	100%	KCNE2	100%	KCNE3	100%
KCNE5	100%	KCNH2	100%	KCNJ2	97.9%	KCNJ5	100%
KCNJ8	100%	KCNK3	100%	KCNQ1	100%	KCNQ2	100%
KCNQ3	99.5%	KCNT1	100%	KLF10	100%	KRAS	94.5%
LAMA4	100%	LAMP2	100%	LCAT	100%	LCP1	100%
LDB3	98.8%	LDLR	99.9%	LDLRAP1	100%	LIPA	100%
LIPC	100%	LMF1	100%	LMNA	100%	LOX	100%
LPL	100%	LRP6	100%	LRRIC10	100%	LTBP1	100%
LTBP2	100%	LTBP3	100%	LZTR1	100%	MAP2K1	99.9%
MAP2K2	100%	MAT2A	100%	MED12	99.7%	MFAP5	100%
MGA	100%	MGAM	100%	MIB1	100%	MRAS	100%

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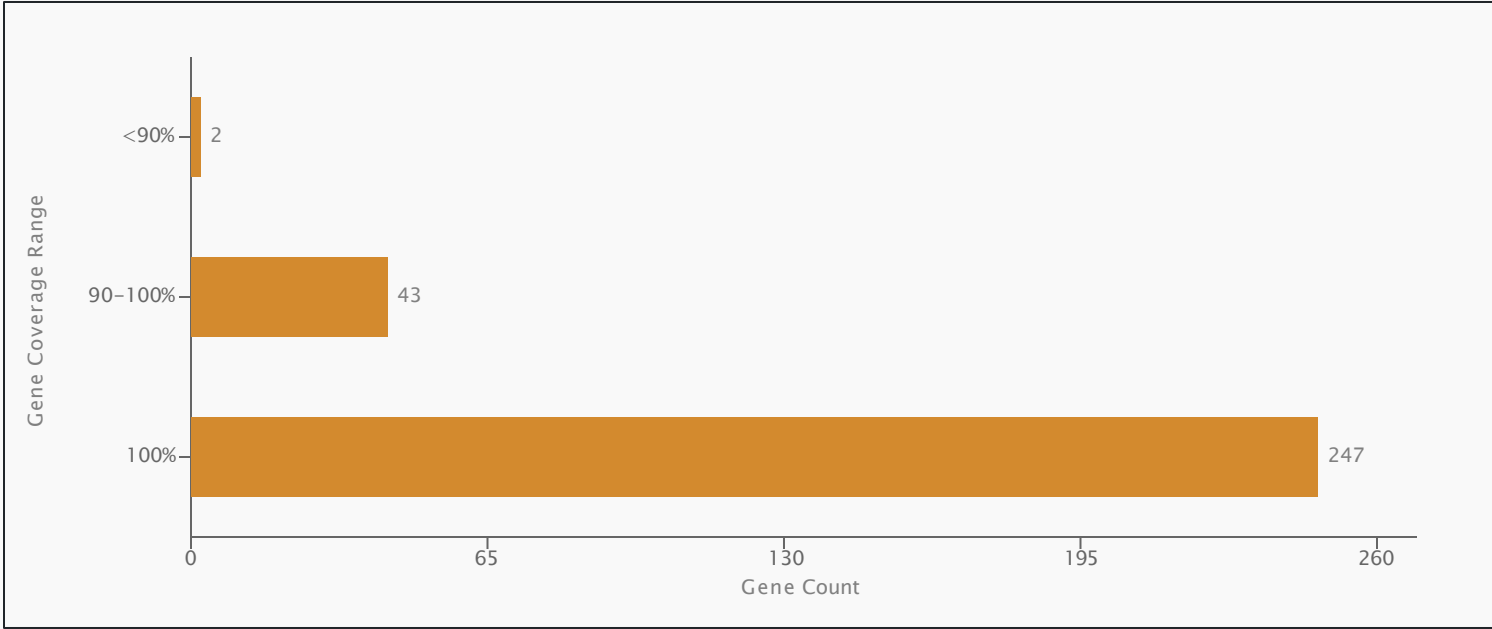
Gene Coverage

Gene	Coverage	Gene	Coverage	Gene	Coverage	Gene	Coverage
MTTP	100%	MYBPC3	100%	MYH11	100%	MYH6	100%
MYH7	100%	MYL2	100%	MYL3	100%	MYL4	100%
MYLIP	100%	MYLK	100%	MYLK2	100%	MYOM1	100%
MYOZ2	100%	MYPN	100%	NAT8	100%	NEBL	100%
NEXN	100%	NF1	99.3%	NKX2-5	100%	NNT	100%
NOTCH1	100%	NPPA	100%	NRAS	99.9%	NYNRIN	100%
OBSCN	100%	PCDH10	100%	PCDH19	100%	PCSK9	100%
PDLIM3	100%	PKP2	100%	PLEKHM2	100%	PLN	89%
PLOD1	100%	PLOD3	100%	POTEF	100%	PPP1CB	100%
PPP1R13L	100%	PRDM16	100%	PRKAG2	96.1%	PRKG1	100%
PRRT2	100%	PSEN1	100%	PSEN2	100%	PTPN11	100%
RAF1	99.8%	RANGRF	100%	RASA1	100%	RASA2	100%
RBM20	100%	RIT1	100%	RNASE3	100%	ROBO4	100%
RRAS	100%	RRAS2	100%	RYR2	99.6%	SAR1B	100%
SCARB1	100%	SCGB1D1	100%	SCN10A	100%	SCN1A	100%
SCN1B	99.1%	SCN2B	100%	SCN3B	98.7%	SCN4B	100%
SCN5A	100%	SCN8A	100%	SCN9A	98.4%	SGCD	99.3%
SHOC2	100%	SKI	100%	SLC12A3	100%	SLC22A1	99.9%
SLC22A5	100%	SLC25A20	100%	SLC25A4	100%	SLC2A1	100%
SLC2A10	100%	SLC39A13	100%	SLC4A3	100%	SLMAP	100%
SMAD2	100%	SMAD3	99.7%	SMAD4	99.9%	SMAD6	100%
SMIM6	100%	SNTA1	100%	SOS1	99.2%	SOS2	100%
SPRED1	93.9%	SREBF2	100%	ST3GAL4	100%	STAP1	100%
SYNGAP1	98.1%	TAB2	100%	TBX20	100%	TBX5	100%
TCAP	100%	TECRL	100%	TGFB2	99.4%	TGFB3	100%
TGFBR1	100%	TGFBR2	99%	TIMP1	98.9%	TJP1	100%

Gene Coverage

Gene	Coverage	Gene	Coverage	Gene	Coverage	Gene	Coverage
TMEM43	100%	TMPO	100%	TNNC1	100%	TNNC2	100%
TNNI3	100%	TNNI3K	100%	TNNT2	100%	TOX4	100%
TPM1	100%	TRDN	91.8%	TRIM63	100%	TRNP1	100%
TRPM4	100%	TTN	100%	TTR	100%	UXT	100%
VCL	100%	WWTR1	100%	YWHAZ	100%	ZDHHC9	100%

Gene Coverage Distribution



QC Metrics

Total Aligned Reads	99.96 %
Total Reads	42.01 (M)
Total data generated	6.18 (Gb)
Total reads which passed mapping quality cut-off	5.48 (Gb)

Test Limitations

Testing has been performed assuming that the sample received belongs to the above named individual(s) and any stated relationships between individuals are accepted as true. It is also assumed that consent for the same was provided after pre-test counseling at the point of collection/referral.

The current results are based on analysis of coding regions (exons) as well as certain intron padding regions on patient's genomic DNA with respect to patient phenotype as defined in the target regions (link available below). However, due to inherent technology limitations, coverage is not uniform across all regions. Hence pathogenic variants present in areas of insufficient coverage as well as those variants which currently do not co-relate with the provided phenotype may not be analyzed/ reported. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity.

The reported findings are based on NGS analysis.

The test methodology currently does not detect large deletions/duplications, triplet repeat expansions and epigenetic changes.

The test also does not include analysis of predictors for multifactorial, polygenic and/or complex diseases. Novel synonymous changes as well as intronic mutations (excluding those affecting invariant splice nucleotides) are not routinely reported.

Phenotype variability may be due to modifying genetic/non-genetic factors and is not a part of the current analysis.

The classification and interpretation of all the variants in this assay reflects the current state of scientific understanding at the time this report was issued. In some instances, the classification and interpretation of such variants may change as new scientific information comes to light. We recommend re-analysis of this report yearly, in order to take advantage of any new scientific data that may become available. Please contact laboratory in case re-analysis of the report is desired. It is the lab's policy to perform re-analysis once on a complimentary basis. However, this re-analysis is performed only when requested.