TEST REPORT
GENE PANEL

REPORT DETAILS

Forename:	Jane	**Hospital ID:**	121212
Surname:	Doe	**Report Date:**	01/10/2025
DOB:	01/01/1970	**Test Requested:**	Long QT syndrome – Expanded panel
Biological sex:	Female		

SAMPLE DETAILS

Sample ID:	LO-000001-1
Sample Type:	Whole Blood
Collection Date:	08/09/2025
Receipt Date:	09/09/2025

HEALTH PRACTITIONER DETAILS

Full name:	Dr Cardiology
Institution:	Hospital
Email Adress:	
Report Copy (CC):	

CLINICAL DETAILS

Referral Reason: Clinically affected with prolonged QT. No reported family history.

RESULTS

***KCNQ1* variant detected**
Heterozygous for NM_000218.3 c.1780C>T p.(Arg594Ter)

Consistent with a genetic diagnosis of familial Long QT Syndrome.

This patient is heterozygous for a likely pathogenic *KCNQ1* variant (details below).

Monoallelic pathogenic *KCNQ1* variants are associated with Long QT Syndrome. This result is consistent with the clinical phenotype provided for this patient.

Given the genetic implications of this result, it is recommended that the patient and their family be referred for genetic counselling. Offspring have a 50% risk of inheriting this variant and being at increased risk of developing the associated disorder. The reported variant may be used for predictive testing for appropriate family members, following genetic counselling.

VARIANTS WITH POSSIBLE RELEVANCE TO THE PATIENT'S CLINICAL DETAILS

Gene	HGVS Description	Exon	dbSNP	Zygosity	Classification
KCNQ1	NM_000218.3 c.1780C>T NP_000209.2 p.Arg594Ter NC_000011.10:g.2778023C>T	15	rs794728537	Heterozygous	Likely Pathogenic

Analyses performed by Clinical Scientist: *CS-2003*

Approved by Clinical Geneticist: *CG-2001*

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VARIANT INTERPRETATION

Supporting evidence for variant classification	Rule_Strength
This nonsense variant results in a truncated protein with loss of region critical to function. Loss-of-function is a known mechanism of disease for this gene.	PVS1_Moderate
This variant has been reported in at least 10 unrelated patients affected with long QT syndrome [PMID: 27479201; PMID: 32893267; PMID: 37449562].	PS4_Strong
This variant is found at very low frequency in large control databases (allele frequency of 0.001% in the gnomAD database v4.0.0)	PM2_Supporting

REFERENCES

Qureshi SF, Ali A, Venkateshwari A, Rao H, Jayakrishnan MP, Narasimhan C, Shenthar J, Thangaraj K, Nallari P. Genotype-phenotype correlation in long QT syndrome families. Indian Pacing Electrophysiol J. 2015 Dec 17;15(6):269-85. doi: 10.1016/j.ipej.2015.12.001. PMID: 27479201

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METHODS

Laboratory process: Genomic DNA was extracted from the participant's whole peripheral blood. Target enrichment was performed on the patient's genomic DNA using Twist Bioscience for Illumina Exome 2.5 Panel and the Twist Bioscience for Illumina Mitochondrial Panel. Whole Exome Sequencing (WES) was performed using a NovaSeq 6000 instrument, with on-target coverage average >100x, and with >93% of exome target being covered >= 20x.

Bioinformatics and quality control: Raw sequencing FASTQ data was aligned to the GRCh38/hg38 reference genome. Alignment and small variant calling of single nucleotide variants (SNVs), indels (+/- 20 bp from exon-intron border), copy number variants (CNVs), and mitochondrial variants were performed using the DRAGEN workflow (Illumina) within the Emedgene platform (version 35). VCFs and BAMs were analysed on the Emedgene platform (Illumina). The patient's sample was subjected to thorough quality control measures including assessment for sample quality, coverage and contamination.

Gene Panel content: *AKAP9, ANK2, CACNA1C, CALM1, CALM2, CALM3, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN4B, SCN5A, SNTA1, TRDN*

Case interpretation and reporting: The report includes Pathogenic or Likely Pathogenic variants identified on the subset of genes on the panel selected (these genes are listed on the Gene Content section above). Variants of unknown significance (VUS) are not standardly reported. A VUS identified in a clinically relevant gene may be reported as a supplemental finding, where there is a high level of evidence supporting pathogenicity, and where further family history, familial testing or phenotypic evidence may help re-classify the variant. Likely benign and benign variants are not reported. VUS may be discussed with the Requesting Health Practitioner on request within 6 months of issuing the report. Single heterozygous variants in genes associated with recessive inheritance are not standardly reported.

Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen). The predicted variant classifications are based on ACMG/AMP 2015 SNV classification guidelines (PMID: 25741868), ACMG/AMP 2020 CNV classification guidelines (PMID: 31690835), and ACMG/AMP 2020 mitochondrial classification guidelines (PMID: 32906214), including any differences in classification arising from the ClinGen rule specifications (https://www.clinicalgenome.org/working-groups/sequence-variant-interpretation/), ACGS 2024 (https://www.acgs.uk.com/media/12533/uk-practice-guidelines-for-variant-classification-v12-2024.pdf) and ClinGen Variant Curation Expert Panels (VCEPs; https://clinicalgenome.org/affiliation/vcep/#ep_table_heading).

Variant validation: Reported SNVs and Indels were validated by Sanger sequencing. Reported CNVs were not validated by Sanger sequencing due to assay limitations.

Test restrictions: Absence of a disease-causing variant does not exclude the possibility of a genetic basis for the disorder in the patient. It is possible that a particular variant may not be recognised as the underlying cause of the patient's genetic disorder because the clinical implications of this variant may not be known at the time of this report. It is also possible that the classification of variants may change in the future due to improvements in scientific understanding. Test results should always be interpreted in the context of clinical findings, family history, and other relevant laboratory data. Inaccurate, or incomplete information may lead to misinterpretation of the results.

Technical limitations: Some genetic abnormalities may not be detectable with the current technologies performed, including: variants in untargeted regions (e.g. variants in the promoter or intergenic regions), inversions, balanced translocations, repeat expansions, non-coding variants deeper than ±20 base pairs from exon-intron boundary. In addition, this test may not reliably detect some types of variants, including: low level mosaicism, low level mitochondrial heteroplasmy, variants in mononucleotide repeat regions, indels larger than 50 base pairs, deletions or duplications with size lower than 10 Kb, variants within regions with suboptimal coverage (e.g. variants within pseudogene regions, repeat elements, segmental duplications, and high GC content regions). Detection sensitivity and specificity for SNVs: 99.6% and 99.8%, and for indels: 95.6% and 95.3%, respectively. The sensitivity and specificity for CNV detection is dependent on location and size, therefore the absence of a reported CNV does not exclude the possibility of the presence of a CNV.