

<b>Patient name:</b> Joseph M Murphy	<b>Sample type:</b> gDNA	<b>Report date:</b> 27-MAY-2025
<b>DOB:</b> 06-MAR-1985	<b>Sample collection date:</b> 12-AUG-2022	<b>Invitae #:</b> RQ3965178-1
<b>Sex assigned at birth:</b> Male	<b>Sample accession date:</b> 25-AUG-2022	<b>Clinical team:</b> Cardiology/Obstetrics Genetics
<b>Gender:</b>		David Deyle
<b>Patient ID (MRN):</b> 13-575-491		

#### Reason for testing

Diagnostic test for both a personal and a family history of disease

#### Test performed

Sequence analysis and deletion/duplication testing of the 168 genes listed in the Genes Analyzed section.

- Invitae Arrhythmia and Cardiomyopathy Comprehensive Panel
- Add-on Preliminary-evidence Genes for Arrhythmia and Cardiomyopathy
- Add-on Sudden Unexpected Death in Epilepsy (SUDEP) Genes

### ADDENDED REPORT

This report supersedes RQ3965178 (06-SEP-2022) and updates the interpretation of the variant(s) in the table below. See bullet(s) below for a complete list of the report updates.

- The change in variant classification was made as a result of re-review of the evidence in light of new variant interpretation guidelines and/or new information. Updating variant classification may result in variant(s) being added to, removed from, or moved to a different section of the report.

#### Updated Interpretations

GENE	VARIANT	ZYGOSITY	PRIOR VARIANT CLASSIFICATION	NEW VARIANT CLASSIFICATION
NF1	c.7310G>A (p.Arg2437Lys)	heterozygous	Uncertain Significance	Likely Benign



## RESULT: NEGATIVE

#### About this test

This diagnostic test evaluates 168 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

### Clinical comments

- When a single Variant of Uncertain Significance is found in a requisitioned gene that is only associated with autosomal recessive condition(s), it may not be included in the report.



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## Next steps

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- This test did not identify any pathogenic variants known to cause disease. This result does NOT exclude a genetic diagnosis and should be discussed with a healthcare provider, such as a genetic counselor, to learn about the appropriate next steps for further evaluation. Clinical follow up may still be warranted. This result should be interpreted within the context of additional laboratory results, family history and clinical findings.
- Register your test at [www.invitae.com/patients](https://www.invitae.com/patients) to download a digital copy of your results. You can also access educational resources about how your results can help inform your health.



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## Clinical summary

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No reportable genetic variants were identified by this analysis, however, this individual may still be at risk for certain medical conditions based on other factors such as family history, genetic causes not evaluated with this test, or other environmental influences. Follow up of this individual and surveillance of their family members may still be indicated.

## Genes analyzed

This table represents a complete list of genes analyzed for this individual, including the relevant gene transcript(s). If more than one transcript is listed for a single gene, variants were reported using the first transcript listed unless otherwise indicated in the report. An asterisk (\*) indicates that this gene has a limitation. Please see the Limitations section for details. Results are negative unless otherwise indicated in the report. Benign and Likely Benign variants are not included in this report and in specific scenarios variants of uncertain significance in the requisitioned gene(s) may not be included in this report.

GENE	TRANSCRIPT	GENE	TRANSCRIPT	GENE	TRANSCRIPT
A2ML1	NM_144670.4	DOLK	NM_014908.3	KCNJ2	NM_000891.2
ABCC9	NM_005691.3	DSC2	NM_024422.4	KCNJ5	NM_000890.3
ACADVL	NM_000018.3	DSG2	NM_001943.3	KCNJ8	NM_004982.3
ACTC1	NM_005159.4	DSP	NM_004415.2	KCNK3	NM_002246.2
ACTN2	NM_001103.3	DTNA	NM_001390.4	KCNQ1	NM_000218.2
AGL	NM_000642.2	ELAC2	NM_018127.6	KCNQ2	NM_172107.2
AKAP9	NM_005751.4	EMD	NM_000117.2	KCNQ3	NM_004519.3
ALMS1	NM_015120.4	EYA4	NM_004100.4	KCNT1	NM_020822.2
ALPK3	NM_020778.4	FHL1	NM_001449.4	KIF20A	NM_005733.2
ANK2	NM_001148.4	FHL2	NM_201555.1	KLF10	NM_005655.3
ANKRD1*	NM_014391.2	FKRP	NM_024301.4	KRAS	NM_004985.4
BAG3	NM_004281.3	FKTN	NM_001079802.1	LAMA4	NM_002290.4
BRAF	NM_004333.4	FLNC*	NM_001458.4	LAMP2	NM_002294.2
CACNA1C	NM_000719.6;NM_00112984.0.1	GAA	NM_000152.3	LDB3	NM_001080116.1;NM_0011716.10.1;NM_007078.3
CACNA1D	NM_000720.3	GATA4	NM_002052.3	LMNA	NM_170707.3
CACNA2D1	NM_000722.3	GATA5	NM_080473.4	LRRIC10	NM_201550.3
CACNB2	NM_201590.2	GATA6	NM_005257.5	LZTR1	NM_006767.3
CALM1	NM_006888.4	GATAD1	NM_021167.4	MAP2K1	NM_002755.3
CALM2	NM_001743.4	GJA5	NM_005266.6	MAP2K2	NM_030662.3
CALM3	NM_005184.2	GLA	NM_000169.2	MAP3K8	NM_005204.3
CALR3	NM_145046.4	GPD1L	NM_015141.3	MED12	NM_005120.2
CASQ2	NM_001232.3	HAND1	NM_004821.2	MRAS	NM_012219.4
CAV3	NM_033337.2	HCN4	NM_005477.2	MTO1	NM_012123.3
CBL	NM_005188.3	HRAS	NM_005343.2	MYBPC3	NM_000256.3
CDH2	NM_001792.4	ILK	NM_004517.3	MYH6	NM_002471.3
CHRM2	NM_000739.2	JPH2	NM_020433.4	MYH7	NM_000257.3
CPT2	NM_000098.2	JUP	NM_002230.2	MYL2	NM_000432.3
CRYAB	NM_001885.2	KCNA1	NM_000217.2	MYL3	NM_000258.2
CSRP3	NM_003476.4	KCNA5	NM_002234.3	MYL4	NM_001002841.1
CTF1*	NM_001330.3	KCND3	NM_004980.4	MYLK2	NM_033118.3
CTNNA3	NM_013266.3	KCNE1	NM_000219.5	MYLK3	NM_182493.2
DEPDC5	NM_001242896.1	KCNE2	NM_172201.1	MYOM1	NM_003803.3
DES	NM_001927.3	KCNE3	NM_005472.4	MYOZ2	NM_016599.4
DMD	NM_004006.2	KCNE5	NM_012282.2	MYPN	NM_032578.3
DNAJC19	NM_145261.3	KCNH2	NM_000238.3		

GENE	TRANSCRIPT
NEBL	NM_006393.2
NEXN	NM_144573.3
NF1*	NM_000267.3
NKX2-5	NM_004387.3
NPPA	NM_006172.3
NRAS	NM_002524.4
PCCA	NM_000282.3
PCCB	NM_000532.4
PCDH19	NM_001184880.1
PDLIM3	NM_014476.5
PKP2	NM_004572.3
PLEKHM2	NM_015164.2
PLN	NM_002667.3
PPA2	NM_176869.2
PPCS	NM_024664.3
PPP1CB	NM_206876.1
PRDM16*	NM_022114.3
PRKAG2	NM_016203.3
PRRT2	NM_145239.2
PTPN11	NM_002834.3
RAF1	NM_002880.3
RANGRF	NM_016492.4
RASA1	NM_002890.2
RASA2	NM_006506.3
RBM20	NM_001134363.2
RIT1	NM_006912.5
RRAS	NM_006270.4
RYR2	NM_001035.2
SCN10A	NM_006514.3
SCN1A	NM_001165963.1
SCN1B	NM_199037.3;NM_001037.4
SCN2B	NM_004588.4
SCN3B	NM_018400.3
SCN4B	NM_174934.3
SCN5A	NM_198056.2
SCN8A	NM_014191.3;NM_001330260.1
SCN9A	NM_002977.3
SDHA*	NM_004168.3
SGCD	NM_000337.5

GENE	TRANSCRIPT
SHOC2	NM_007373.3
SLC22A5	NM_003060.3
SLC2A1	NM_006516.2
SLMAP	NM_007159.2
SNTA1	NM_003098.2
SOS1	NM_005633.3
SOS2	NM_006939.2
SPRED1	NM_152594.2
TAZ	NM_000116.4
TBX20	NM_001077653.2
TCAP	NM_003673.3
TMEM43	NM_024334.2
TMEM70	NM_017866.5
TMPO	NM_003276.2
TNNC1	NM_003280.2
TNNI3	NM_000363.4
TNNI3K	NM_015978.2
TNNT2	NM_001001430.2
TPM1	NM_001018005.1
TRDN	NM_006073.3
TRPM4	NM_017636.3
TTN*	NM_001267550.2
TTR	NM_000371.3
TXNRD2	NM_006440.4
VCL	NM_014000.2

## Methods

- Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. Unless otherwise indicated, all targeted regions are sequenced with  $\geq 50\times$  depth or are supplemented with additional analysis. Reads are aligned to a reference sequence (GRCh37), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, indicated below. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 20bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. For some genes only targeted loci are analyzed (indicated in the table above). Exonic deletions and duplications are called using an in-house algorithm that determines copy number at each target by comparing the read depth for each target in the proband sequence with both mean read-depth and read-depth distribution, obtained from a set of clinical samples. Markers across the X and Y chromosomes are analyzed for quality control purposes and may detect deviations from the expected sex chromosome complement. Such deviations may be included in the report in accordance with internal guidelines. Confirmation of the presence and location of reportable variants is performed based on stringent criteria established by Invitae (1400 16th Street, San Francisco, CA 94103, #05D2040778), as needed, using one of several validated orthogonal approaches (PubMed ID 30610921). The following analyses are performed if relevant to the requisition. For PMS2 exons 12-15, the reference genome has been modified to force all sequence reads derived from PMS2 and the PMS2CL pseudogene to align to PMS2, and variant calling algorithms are modified to support an expectation of 4 alleles. If a rare SNP or indel variant is identified by this method, both PMS2 and the PMS2CL pseudogene are amplified by long-range PCR and the location of the variant is determined by Pacific Biosciences (PacBio) SMRT sequencing of the relevant exon in both long-range amplicons. If a CNV is identified, MLPA or MLPA-seq is run to confirm the variant. If confirmed, both PMS2 and PMS2CL are amplified by long-range PCR, and the identity of the fixed differences between PMS2 and PMS2CL are sequenced by PacBio from the long-range amplicon to disambiguate the location of the CNV. Technical component of confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). For C9orf72 repeat expansion testing, hexanucleotide repeat units are detected by repeat-primed PCR (RP-PCR) with fluorescently labeled primers followed by capillary electrophoresis. Interpretation Reference Ranges: Benign (Normal Range):  $<25$  repeat units, Uncertain: 25-30 repeat units, Pathogenic (Full Mutation):  $\geq 31$  repeat units. A second round of RP-PCR utilizing a non-overlapping set of primers is used to confirm the initial call in the case of suspected allele sizes of 22 or more repeats. For RNA analysis of the genes indicated in the Genes Analyzed table, complementary DNA is synthesized by reverse transcription from RNA derived from a blood specimen and enriched for specific gene sequences using capture hybridization. After high-throughput sequencing using Illumina technology, the output reads are aligned to a reference sequence (genome build GRCh37; custom derivative of the RefSeq transcriptome) to identify the locations of exon junctions through the detection of split reads. The relative usage of exon junctions in a test specimen is assessed quantitatively and compared to the usage seen in control specimens. Abnormal exon junction usage is evaluated as evidence in the Sherlock variant interpretation framework. If an abnormal splicing pattern is predicted based on a DNA variant outside the typical reportable range, as described above, the presence of the variant is confirmed by targeted DNA sequencing. RNA sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2094793). Technical component of Fibroblast cell-culturing and gDNA extraction from skin punch biopsy is performed by Invitae Corporation (5 Technology Drive, Irvine CA 92618, #05D1052995).
- A PMID is a unique identifier referring to a published, scientific paper. Search by PMID at <http://www.ncbi.nlm.nih.gov/pubmed>.
- An rsID is a unique identifier referring to a single genomic position, and is used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including ExAC (<http://exac.broadinstitute.org>), gnomAD (<http://gnomad.broadinstitute.org>), and dbSNP (<http://ncbi.nlm.nih.gov/SNP>).
- A MedGen ID is a unique identifier referring to an article in MedGen, NCBI's centralized database of information about genetic disorders and phenotypes. Search by MedGen ID at <http://www.ncbi.nlm.nih.gov/medgen>. An OMIM number is a unique identifier referring to a comprehensive entry in Online Mendelian Inheritance in Man (OMIM). Search by OMIM number at <http://omim.org/>.
- Invitae uses information from individuals undergoing testing to inform variant interpretation. If "Invitae" is cited as a reference in the variant details this may refer to the individual in this requisition and/or historical internal observations.

## Limitations

Based on validation study results, this assay achieves  $>99\%$  analytical sensitivity and specificity for single nucleotide variants, insertions and deletions  $<15\text{bp}$  in length, and exon-level deletions and duplications. Invitae's methods also detect insertions and deletions larger than 15bp but smaller than a full



exon but sensitivity for these may be marginally reduced. Invitae's deletion/duplication analysis determines copy number at a single exon resolution at virtually all targeted exons. However, in rare situations, single-exon copy number events may not be analyzed due to inherent sequence properties or isolated reduction in data quality. Certain types of variants, such as structural rearrangements (e.g. inversions, gene conversion events, translocations, etc.) or variants embedded in sequence with complex architecture (e.g. short tandem repeats or segmental duplications), may not be detected. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity. Unless explicitly guaranteed, sequence changes in the promoter, non-coding exons, and other non-coding regions are not covered by this assay. Please consult the test definition on our website for details regarding regions or types of variants that are covered or excluded for this test. This report reflects the analysis of an extracted genomic DNA sample. While this test is intended to reflect the analysis of extracted genomic DNA from a referred patient, in very rare cases the analyzed DNA may not represent that individual's constitutional genome, such as in the case of a circulating hematolymphoid neoplasm, bone marrow transplant, blood transfusion, chimerism, culture artifact or maternal cell contamination. Invitae's RNA analysis is not designed for use as a stand-alone diagnostic method and cannot determine absolute RNA levels. Results from the RNA analysis may not be informative for interpreting copy number gains. TTN: Exons 45-46, 147, 149, 164, 172-201 (NM\_001267550.2) are excluded from analysis. TTN variants are included in the primary report based on functional effect and/or location. A complete list of variants of uncertain significance, likely benign and benign variants in TTN is available upon request. Variants are named relative to the NM\_001267550.2 (meta) transcript. Variants in the coding sequence and intronic boundaries of the clinically relevant NM\_133378.4 (N2A) and fetal isoforms are reported (PMID: 25589632, 29598826, 29691892, 31660661), with the exception of the PEVK tandem repeat region (172-198) (PMID: 28040389). FLNC: Deletion/duplication analysis is not offered for exon 47. Sensitivity and specificity for single nucleotide variants, insertions and deletions in exons 47-48 may be reduced due to the presence of segmental duplications overlapping the region. ANKRD1: Deletion/duplication analysis is not offered for exons 3-4. CTF1: Deletion/duplication and sequencing analysis is not offered for exon 1. NF1: Sequencing analysis for exons 2, 7, 25, 41, 48 includes only cds +/- 10 bp. PRDM16: Deletion/duplication analysis is not offered for exon 1. SDHA: Deletion/duplication analysis is not offered for this gene and sequencing analysis is not offered for exon 14. Sequencing analysis for exons 6-8 includes only cds +/- 10 bp.

For Added, Amended, Corrected and Reanalysis reports, orthogonal confirmation may not have been performed on variants that would have otherwise met criteria for confirmation at the time of the original analysis.

## Disclaimer

DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan, but it is not a diagnosis itself. This test was developed and its performance characteristics determined by Invitae. It has not been cleared or approved by the FDA. The laboratory is regulated under the Clinical Laboratory Improvement Act (CLIA) as qualified to perform high-complexity clinical tests (CLIA ID: 05D2040778). This test is used for clinical purposes. It should not be regarded as investigational or for research.



Patient name: Joseph M Murphy DOB: 06-MAR-1985

Invitae #: RQ3965178-1

### Genes analyzed

A2ML1, ABCC9, ACADVL, ACTC1, ACTN2, AGL, AKAP9, ALMS1, ALPK3, ANK2, ANKRD1\*, BAG3, BRAF, CACNA1C, CACNA1D, CACNA2D1, CACNB2, CALM1, CALM2, CALM3, CALR3, CASQ2, CAV3, CBL, CDH2, CHRM2, CPT2, CRYAB, CSRP3, CTF1\*, CTNNA3, DEPDC5, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, DTNA, ELAC2, EMD, EYA4, FHL1, FHL2, FKR, FKTN, FLNC\*, GAA, GATA4, GATA5, GATA6, GATAD1, GJA5, GLA, GPD1L, HAND1, HCN4, HRAS, ILK, JPH2, JUP, KCNA1, KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNE5, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNK3, KCNQ1, KCNQ2, KCNQ3, KCNT1, KIF20A, KLF10, KRAS, LAMA4, LAMP2, LDB3, LMNA, LRRC10, LZTR1, MAP2K1, MAP2K2, MAP3K8, MED12, MRAS, MTO1, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYL4, MYLK2, MYLK3, MYOM1, MYOZ2, MYPN, NEBL, NEXN, NF1\*, NKX2-5, NPPA, NRAS, PCCA, PCCB, PCDH19, PDLIM3, PKP2, PLEKHM2, PLN, PPA2, PPCS, PPP1CB, PRDM16\*, PRKAG2, PRRT2, PTPN11, RAF1, RANGRF, RASA1, RASA2, RBM20, RIT1, RRAS, RYR2, SCN10A, SCN1A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SCN8A, SCN9A, SDHA\*, SGCD, SHOC2, SLC22A5, SLC2A1, SLMAP, SNTA1, SOS1, SOS2, SPRED1, TAZ, TBX20, TCAP, TMEM43, TMEM70, TMPO, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TRDN, TRPM4, TTN\*, TTR, TXNRD2, VCL





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This report has been released utilizing a validated procedure approved by:



Jeana DaRe, Ph.D., FACMG  
Laboratory Director

jd\_0835\_pr

This document is not part of the Invitae® clinical report and does not represent medical advice. These are general guidelines that are not specific to your result and may not represent all relevant international recommendations. You can use this guide to talk to your healthcare provider about your test results, clinical history, and the most current guidelines. We recognize that individuals have diverse gender and sexual identities. In this guide, the terms female, male, women, and men refer to sex assigned at birth.

### What is a negative result?



A negative test result means that no significant genetic changes (“pathogenic” or “likely pathogenic” variants) were found. Risk for disease can still be influenced by a combination of personal, lifestyle, environmental, and/or unidentified genetic factors.

### Create a plan with a healthcare provider



It is important to share these results with a healthcare provider to determine appropriate next steps. The chance for an individual to develop a disease is not usually determined by genetic test results alone.

### What does this result mean for family members?



Parents, siblings, children, and other relatives have their own genetic makeup. Although these results did not find a significant genetic change, family members can discuss their own potential health and/or reproductive risks and the option of genetic testing with their own healthcare providers.

### Resources



Genetic counseling can help individuals understand their genetic test results and options for next steps. Reviewing test results with a genetic counselor or other healthcare provider is recommended. Local or telehealth genetic counselors can be identified using the Find a Genetic Counselor search tool at [nsgc.org](https://nsgc.org) (US and Canada). Individuals with an Invitae test result can also log in to their patient portal ([invitae.com](https://invitae.com)) to view their results, contact a genetic counselor, or join Invitae’s Patient Insights Network (PIN) ([pin.invitae.com](https://pin.invitae.com)), an online platform where individuals can share information about their health and experiences to help advance research and drug development.