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01.01.2026

Dept of Clinical Genetics
University Hopital
Street
postal code, City
Country

Name: **Doe, Joanne**
Date of birth: **01.01.2010** Gender: **F**
Order number: **000000000**

Reception date: 01.01.2026 Order date: 01.01.2026
Collection date: 01.01.2026 External No.: XXX
Reference No.: XXX

Sample material: EDTA blood

Dear Sir or Madam,

Thank you for your order from 01.01.2026.

**Order:** molecular genetic analysis of the cardiomyopathy panel
**Diagnosis/ indication:** Myocarditis, high troponin levels (900-1200). Extensive subepicardial enhancement on MRI, LVEF: 35%

## Result:

Detection of a *DSP* variant that is associated with autosomal dominant arrhythmogenic cardiomyopathy.

| Gene | Variant | Zygosity | Classification |
|---|---|---|---|
| *DSP* | NM_004415.4:c.6310del p.(Thr2104Glnfs*12) | heterozygous | pathogenic |

## Interpretation:

The detection of a pathogenic variant in *DSP* indicates a genetic predisposition to desmoplakin-related arrhythmogenic cardiomyopathy, potentially associated with additional dermatological manifestations. Available data from familial cases with this variant suggest reduced and age-dependent penetrance, with significant cardiac manifestations infrequently observed before the age of 40, while by 60 years of age, cardiomyopathy could be diagnosed in approximately 50% of carriers (Heliö et al. 2020, BMC Med Genet 21:19, PMID: 32005173; Heliö et al. 2023, Front Cardiovasc Med 10:1130903, PMID: 37008330).

The *DSP* gene encodes desmoplakin, a structural protein that plays a key role in the organisation of desmosomal cadherin–plakoglobin complexes and in anchoring intermediate filaments to the desmosome. Loss-of-function variants in *DSP* are a well-established cause of arrhythmogenic cardiomyopathy (ACM), typically with predominant left ventricular involvement and episodes of myocardial injury with clinical features resembling myocarditis. Pathogenic *DSP* variants are also enriched in cohorts of patients with dilated cardiomyopathy (DCM) (Walsh et al. 2017, Genet Med 19:192), reflecting phenotypic overlap between these entities. In addition, some *DSP* variants are associated with extracardiac manifestations, most notably involving the skin and hair.

## Clinical management and further information:

It is recommended to consult the latest ESC guidelines regarding the management of hereditary cardiomyopathies and the prevention of sudden cardiac death (Zeppenfeld et al. 2022, European Heart Journal 43:3997, PMID: 36017572; Arbelo et al. 2023, European Heart Journal 44:3503, PMID: 37622657).

Genetic counselling is recommended for the patient and biological relatives. Targeted testing for the variant detected here should be offered.



Geschäftsführer
Dr. med. Hartmut Campe, Dr. med. Konstanze Hörtnagel
Dr. med. Hanns-Georg Klein, Dr. rer. nat. Stefan Mehrle

Ärztliche Leitung
Dr. med. Konstanze Hörtnagel

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| | | | | | |
|---|---|---|---|---|---|
| Name: | **Doe, Joanne** | DOB: | **01.01.2026** | Gender: | **F** |
| Order number: | **000000000** | Collection date: | **01.01.2026** | Report date: | **01.01.2026** |

## Genetic relevance:

Each direct offspring inherits the variant with a probability of 50%.

## Variant details:

pathogenic variant NM_004415.4:c.6310del p.(Thr2104Glnfs*12), *DSP*
ACMG-criteria: PVS1_Strong, PP1_Strong, PS4, PM2_Supporting

This frameshift variant is predicted to cause loss-of-function due to protein truncation and multiple truncation variants located downstream of this variant are known to cause ACM or DCM. The variant has been reported in heterozygous state in multiple individuals from several affected families (mainly Finnish), showing an arrhythmogenic phenotype, curly hair and palmoplantar keratoderma (ClinVar ID: 180343; Heliö et al. 2023, Front Cardiovasc Med 10:1130903, PMID: 37008330; Heliö et al. 2020, BMC Med Genet 21:19, PMID: 32005173). It has also been reported in compound heterozygous state with another truncating or missense variant in two individuals affected with severe cardiomyopathies and skin, hair, and/or tooth abnormalities (Mahoney et al. 2010, J Invest Dermatol 130:968, PMID: 19924139). The variant is enriched in the Finnish population (gnomAD database).

Kind regards,

**Scientific validation / inquiries**
**Dr. rer. nat. Alexandra Musterfrau**
**01.01.2026**

**Medical validation**
**Dr. med. Erika Mustermann**
**01.01.2026**

## Analysed genes:

DSP (NM_004415.4), AARS2 (NM_020745.4), ABCC9 (NM_020297.4), ACAD9 (NM_014049.5), ACADVL (NM_000018.4), ACTC1 (NM_005159.5), ACTN2 (NM_001103.4), AGK (NM_018238.4), AGL (NM_000642.3), ALMS1 (NM_015120.4), ALPK3 (NM_020778.5), ANKRD1 (NM_014391.3), ASNA1 (NM_004317.4), ATP7B (NM_000053.4), BAG3 (NM_004281.4), BAG5 (NM_001015048.3), BMP5 (NM_021073.4), BMP7 (NM_001719.3), BRAF (NM_004333.6), CACNA1C (NM_000719.7), CACNB2 (NM_201596.3), CALR3 (NM_145046.5), CASQ2 (NM_001232.4), CAV3 (NM_033337.3), CBL (NM_005188.4), CDH2 (NM_001792.5), COX15 (NM_078470.6), CPT2 (NM_000098.3), CRYAB (NM_001289808.2), CSRP3 (NM_003476.5), CTF1 (NM_001330.5), CTNNA3 (NM_013266.4), CYP2C19 (NM_000769.4), DES (NM_001927.4), DMD (NM_004006.3), DNAJB6 (NM_058246.4), DNAJC19 (NM_145261.4), DOLK (NM_014908.4), DSC2 (NM_024422.6), DSG2 (NM_001943.5), DTNA (NM_001386795.1), ELAC2 (NM_018127.7), EMD (NM_000117.3), EYA4 (NM_004100.5), FBXO32 (NM_058229.4), FHL1 (NM_001159699.2), FHL2 (NM_001318895.3), FHOD3 (NM_001281740.3), FKRP (NM_024301.5), FKTN (NM_001079802.2), FLII (NM_002018.4), FLNC (NM_001458.5), FXN (NM_000144.5), GAA (NM_000152.5), GATAD1 (NM_021167.5), GBA (NM_000157.4), GLA (NM_000169.3), HAMP (NM_021175.4), HCN4 (NM_005477.3), HFE (NM_000410.4), HJV (NM_213653.4), HRAS (NM_005343.4), IDS (NM_000202.8), IDUA (NM_000203.5), ILK (NM_004517.4), JPH2 (NM_020433.5), JUP (NM_002230.4), KCNQ1 (NM_000218.3), KLF10 (NM_005655.4), KLHL24 (NM_017644.3), KRAS (NM_004985.5), LAMA4 (NM_001105206.3), LAMP2 (NM_002294.3), LDB3 (NM_001080116.1), LMNA (NM_170707.4), LMOD2 (NM_207163.3), LZTR1 (NM_006767.4), MAP2K1 (NM_002755.4), MAP2K2 (NM_030662.4), MAP3K7 (NM_145331.3), MAPK1 (NM_002745.5), MGME1 (NM_052865.4), MIB1 (NM_020774.4), MRAS (NM_001085049.3), MT-ATP6 (ENST00000361899.2), MT-ATP8 (ENST00000361851.1), MT-CO1 (ENST00000361624.2), MT-CO2 (ENST00000361739.1), MT-CO3 (ENST00000362079.2), MT-CYB (ENST00000361789.2), MT-ND1 (ENST00000361390.2), MT-ND2 (ENST00000361453.3), MT-ND3 (ENST00000361227.2), MT-ND4 (ENST00000361381.2), MT-ND4L (ENST00000361335.1), MT-ND5 (ENST00000361567.2), MT-ND6 (ENST00000361681.2), MT-RNR1 (ENST00000389680.2), MT-RNR2 (ENST00000387347.2), MT-TA (ENST00000387392.1), MT-TC (ENST00000387405.1), MT-TD (ENST00000387419.1), MT-TE (ENST00000387459.1), MT-TF (ENST00000387314.1), MT-TG (ENST00000387429.1), MT-TH (ENST00000387441.1), MT-TI (ENST00000387365.1), MT-TK (ENST00000387421.1), MT-TL1 (ENST00000386347.1), MT-TL2 (ENST00000387456.1), MT-TM (ENST00000387377.1), MT-TN (ENST00000387400.1), MT-TP (ENST00000387461.2), MT-TQ (ENST00000387372.1), MT-TR (ENST00000387439.1), MT-TS1 (ENST00000387416.2), MT-TS2 (ENST00000387449.1), MT-TT (ENST00000387460.2), MT-TV (ENST00000387342.1), MT-TW (ENST00000387382.1), MT-TY (ENST00000387409.1), MTO1 (NM_012123.4), MYBPC3 (NM_000256.3), MYH6 (NM_002471.4), MYH7 (NM_000257.4), MYL2 (NM_000432.4), MYL3 (NM_000258.3), MYLK2 (NM_033118.4), MYLK3 (NM_182493.3), MYO6 (NM_004999.4), MYOM1 (NM_003803.4), MYOZ2 (NM_016599.5), MYPN (NM_032578.4), MYZAP (NM_001018100.5), NEBL (NM_006393.3), NEDD4L (NM_001144967.3), NEXN (NM_144573.4), NF1 (NM_000267.3), NKX2-5 (NM_004387.4), NONO (NM_007363.5), NRAP (NM_198060.4), NRAS (NM_002524.5), OBSCN (NM_001386125.1), PDLIM3 (NM_014476.6), PKP2 (NM_001005242.3), PLEKHM2 (NM_015164.4), PLN (NM_002667.5), PPA2 (NM_176869.3), PPCS (NM_024664.4),



Geschäftsführer
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PPP1CB (NM_002709.3), PPP1R13L (NM_006663.4), PRDM16 (NM_022114.4), PRKAG2 (NM_016203.4), PSEN1 (NM_000021.4), PSEN2 (NM_000447.3), PTPN11 (NM_002834.5), RAF1 (NM_002880.4), RASA1 (NM_002890.3), RASA2 (NM_006506.5), RBM20 (NM_001134363.3), RIT1 (NM_006912.6), RPL3L (NM_005061.3), RPS6KB1 (NM_003161.4), RRAS2 (NM_012250.6), RYR2 (NM_001035.3), SCN5A (NM_000335.5), SCO2 (NM_005138.3), SDHA (NM_004168.4), SGCD (NM_000337.6), SHOC2 (NM_007373.4), SLC22A5 (NM_003060.4), SLC25A3 (NM_002635.4), SLC25A4 (NM_001151.4), SLC25A5 (NM_001152.5), SLC38A6 (NM_153811.3), SLC40A1 (NM_014585.6), SOS1 (NM_005633.4), SOS2 (NM_006939.4), SPEG (NM_005876.5), SPRED1 (NM_152594.3), SSPN (NM_005086.5), TANGO2 (NM_152906.7), TAZ (NM_000116.5), TBX20 (NM_001077653.2), TBX5 (NM_000192.3), TCAP (NM_003673.4), TFR2 (NM_003227.4), TGFB3 (NM_003239.5), TJP1 (NM_001330239.4), TMEM43 (NM_024334.3), TMEM70 (NM_017866.6), TMOD1 (NM_003275.4), TMPO (NM_003276.2), TNNC1 (NM_003280.3), TNNI3 (NM_000363.5), TNNI3K (NM_015978.3), TNNT2 (NM_001276345.2), TP63 (NM_003722.5), TPM1 (NM_001018005.2), TRIM55 (NM_184085.2), TRIM63 (NM_032588.4), TTN (NM_001267550.2), TTR (NM_000371.4), VCL (NM_014000.3)

## Additional information:

| Method | | | |
|---|---|---|---|
| **Sequencing** | **Enrichment** | **SNV and CNV analyses** | **Data evaluation** |
| Next Generation Sequencing (Illumina) | Twist Exome 2.0 plus Comprehensive + Custom Spike-in (54 Mb target sequence) | Illumina Dragen Bio-IT Platform | Franklin by QIAGEN |
| **Quality criteria** | **Reference genome** | **Databases** | **In silico algorithms** |
| Quality Score >30 (accuracy >99,9%) for at least 75% of bases; sensitivity of SNV detection 99.92%; sensitivity of CNV detection 91% | hg38, NCBI GRCh38 (transcript variant from HGMD is usually used) | HGMD Professional release, ClinVar, LOVD, gnomAD (data of the population with the highest allele frequency are usually considered (prerequisite: sufficient number of alleles examined) | REVEL, Splice AI |

### Limitations

Reduced sensitivity for mosaics (<20%), deletions/insertions (>20 bp), repeat expansions, homopolymers and pseudogenes. No reporting of benign/likely benign variants. Variants (or variant constellations) of uncertain significance are only reported if, in case of autosomal dominant or X-linked inheritance, the posterior probability of pathogenicity for SNVs is ≥50% (Tavtigian et al. 2018, Genet Med 20:1054), or in the case of autosomal recessive inheritance, if at least one of two variants in a gene has a posterior probability of pathogenicity ≥67.5%, or if the score for CNVs is ≥0.5 each (Riggs et al. 2020, Genet Med 22:245)

### Variant classification

Variants within +/- 10 bp of coding exons are classified according to Richards et al. 2015, Genet Med 17:405, with modifications based on the ClinGen SVI (Sequence Variant Interpretation) general recommendations and the ClinGen expert panel specifications to the ACMG/AMP variant interpretation guidelines. CNVs are classified according to Riggs et al. 2020, Genet Med 22:245; In silico algorithms used: REVEL and SpliceAI; Databases consulted: HGMD® Professional release, LOVD, ClinVar, and gnomAD (considering data from the population with the highest allele frequency, provided a sufficient number of alleles are examined)

### Coverage

20-fold coverage of target region: 99.68%

### Note

According to § 10 GenDG, genetic counselling should be offered as part of genetic testing. In the case of a non-treatable disease, the responsible medical person must offer genetic counseling. In the case of a predictive test, genetic counseling must be offered before the test and after the result is available. This report may only be forwarded in full.



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