CeGaT

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Patient	Doe, Jane
ID #	Female (*DD.MM.YYYY)
Sample receipt	xxx
Material	EDTA blood
Report date	xxx
Report-ID	R#

Genetic Report – Doe, Jane (*DD.MM.YYYY)

Indication Carrier testing for dystrophinopathies; positive family history with pathogenic deletion of exons 46-49 in gene *DMD*

Order Deletion/duplication analysis: *DMD*

Result: Report with Significant Findings

- **Detection of a heterozygous deletion of exons 46-49 within the *DMD* gene, which results in a shift of the reading frame and consequently in the loss of the dystrophin protein. Your patient is therefore a carrier for Duchenne muscular dystrophy and has an increased risk of developing a cardiomyopathy.**

Gene	Variant	Zygosity	Heredity	MAF (%)	Classification
DMD	**deletion of coding exons 46-49** **chrX:31137339-33229666 (hg19)**	**het.**	**XL**	**-**	**pathogenic**

Information for the interpretation of this table can be found in section *Additional Information*.

Recommendation

We recommend further clinical management according to the current guidelines for dystrophinopathies (Darras et al., updated 2022, PMID: 20301298, GeneReviews; Beckers et al., 2021; PMID: 33542429).

Patients with the out-of-frame deletion of exon 46-49 appear to benefit from exon skipping therapy (exon 45), hence resulting in an inframe-deletion and subsequently in partially functional dystrophin protein (Beckers et al., 2021, PMID: 33542429).

As carriers for pathogenic *DMD* variations have a higher risk for cardiomyopathies, regular cardiologic check-ups are indicated.

Testing of asymptomatic family members regarding the identified deletion in gene *DMD* may only be performed following genetic counseling.

Genetic Relevance

The patient is heterozygous for a pathogenic deletion in gene *DMD*. This may be of relevance for further family planning and at-risk family members.

This variant in gene *DMD* has a 50% probability of being passed on to each respective offspring. The risk of disease occurrence in male offspring is 50%. Female offspring have a 50% probability of being heterozygous for the identified variant and may show clinical features of disease with variable severity.

Clinical Information and Variant Interpretation

DMD, NM_004006.3

OMIM / Reference	Phenotype	Heredity
310200	Duchenne muscular dystrophy (DMD)	XL
300376	Becker muscular dystrophy (BMD)	XL
302045	Dilated cardiomyopathy 3B (CMD3B)	XL

The gene ***DMD*** encodes the cytoplasmic protein dystrophin, which is an essential part of a cytoskeletal protein complex needed for anchoring of muscle fibers to the surrounding connective tissue, and for stabilizing actin filaments. Hemizygous pathogenic alterations in males result in dystrophinopathy: Becker muscular dystrophy (BMD) and Duchenne muscular dystrophy (DMD) are characterized by progressive degeneration of muscle tissue.

DMD occurs more frequently with an earlier manifestation and typically following a more severe course. Cardiomyopathy occurs in almost all individuals with DMD after age 18 years. Pathogenic loss-of-function variants lead to a complete absence of the dystrophin protein. Common causes include deletions, duplications, as well as nonsense or splice variants that result in a frameshift (out-of-frame).

In patients with BMD, dystrophin biosynthesis is either significantly reduced, or a shortened or structurally altered protein with residual activity is being produced. In-frame deletions and duplications as well as pathogenic single nucleotide variants located outside the functional N- and C-terminal domains cause the milder Becker phenotype. In BMD, symptom progression is slower, and life expectancy is only slightly or not at all reduced.

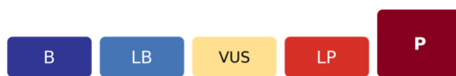
Furthermore, alterations in *DMD* affecting the muscle promoter (P_M) and exon 1 can cause dilated cardiomyopathy type 3B (CMD3B), with no skeletal myopathy. This condition is also referred to as subclinical or benign BMD (Darras et al., updated 2022, PMID: 20301298, GeneReviews).

Dystrophinopathies in males exhibit complete penetrance. Female heterozygous carriers of pathogenic variants in *DMD* have an increased risk of cardiomyopathy and may also present clinical signs of dystrophinopathies (Darras et al., updated 2022, PMID: 20301298, GeneReviews). The severity of the disease in females correlates with nonrandom X-chromosome inactivation favoring the altered *DMD* allele and is associated with a wide phenotypic spectrum.

DMD, deletion of coding exons 46-49 (het.)

Evidence
This deletion results in the loss or truncation of a protein, which coincides with the known pathomechanism for the associated disease.
A similar deletion has been reported in the literature/in DECIPHER/in ClinVar in patients with similar symptoms. Ling et al., 2020, PMID: 31705731; Nallamilli et al., 2021, PMID: 33644936
This aberration is not present in population databases or occurs at a very low allele frequency within the general population, which is consistent with reduced penetrance (gnomAD, DGV, DECIPHER).

Classification:
pathogenic



Genetic counseling should be offered with all diagnostic genetic testing, especially following the identification of the molecular cause of a genetic disease.

Medical report written by: XXX

Proofread by: XXX

Validated by: XXX

With kind regards,

Dr. med. Berit Kerner

Consultant for Human Genetics

Additional Information

Requested Regions	***DMD*** (Del/Dup)
Information for the interpretation of the tables	**Heredity:** AD – autosomal dominant, AR – autosomal recessive, XL – X-linked, mito – mitochondrial **MAF:** The ***minor allele frequency*** describes the least frequent allele at a specific locus in a given population. For mitochondrial variants, the population frequency (MAF column) is based on the homoplasmic frequency within a reference population (gnomAD). **Classification:** Variant classification is based on ACMG, ACGS-2024v1.2, and ClinGen SVI WG guidelines (Richards et al., 2015, PMID: 25741868; Durkie et al., 2024, Association for Clinical Genomic Science; https://clinicalgenome.org/working-groups/sequence-variant-interpretation/). If applicable, the following approach is used. The weighting of criteria and their modification follows the current ACGS guidelines in the strength levels *very strong* (+ 8), *strong* (+/- 4), *moderate* (+/- 2), and *supporting* (+/- 1). According to the respective category (pathogenic or benign) and criterion strength, positive or negative points are assigned as mentioned above (Tavtigian et al., 2020, PMID: 32720330). Variants of uncertain significance (VUS) are subcategorized into *hot*, *warm*, *tepid*, *cool*, *cold*, and *ice cold* VUS according to their likelihood of reaching a pathogenic classification in the future. Posterior probability decreases from 90% to 10% in this order (Durkie et al., 2024, Association for Clinical Genomic Science). If a variant reaches the classification pathogenic, after checking of all benign criteria, not necessarily all other applicable criteria are listed. The chromosomal positions of variants listed in the report refer to the human reference genome hg19.
Methods	**Copy Number Analysis:** Deletion and duplication analysis of the gene *DMD* was performed using MLPA (MRC Holland P035-B1 and P034-B2) as relative quantification in comparison to a reference sample DNA (a probemix does not necessarily contain probes for all exons of a certain gene). If pathogenic alterations are present within a gene which are not the result of copy number changes (e.g. SNVs), these cannot be detected via MLPA unless covered by variant-specific probes, and therefore cannot be ruled out. MLPA analysis cannot determine the allele configuration of copy number variants. In rare cases, the presence of an unexpected copy number distribution, e.g. a gene duplication on one allele and a deletion on the other allele, may lead to false negative results. The sample fulfilled our quality criteria upon arrival and during/after each processing step in the laboratory. The procedure described above was developed and validated in-house (Laboratory developed test; LDT).

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