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THE RARE DISEASE COMPANY

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Order no.: 63143799
Order received: 18 Sept. 2023
Sample type / Sample collection date:
blood, CentoCard® / 07 Sept. 2023
Report date: 16 Oct. 2023
Report type: Additional report

Patient no.: **1842635**, First Name: **Chris**, Last Name: **El Kik**
DOB: **22 Jul. 2019**, Sex: **male**, Your ref.: **OUT2350574**

Test(s) requested: deletion/duplication analysis in the *DMD* gene

CLINICAL INFORMATION

Difficulty climbing stairs; Difficulty standing; Gait disturbance; Highly elevated creatine kinase
(Clinical information indicated above follows HPO nomenclature.)

Family history: Yes.
Maternal cousin 1: Delayed speech and language development, Difficulty walking, Intellectual disability; Maternal cousin 2: Abnormal heart morphology
Consanguineous parents: No.

Clinician suspects: muscular dystrophy, Becker type, muscular dystrophy, Duchenne type. Rule out request(s): muscular dystrophy, sarcoglycanopathy.
Reason for this additional report: by this additional report we are providing result of deletion/duplication analysis in the *DMD* gene.

POSITIVE RESULT
Pathogenic variant identified

INTERPRETATION

A pathogenic hemizygous deletion encompassing exons 45-52 was identified in the *DMD* gene. The genetic diagnosis of X-linked dystrophinopathy is confirmed.

RECOMMENDATIONS

- Assessing the eligibility for novel genetic therapies is recommended.
- If possible, maternal targeted testing is recommended to establish whether the detected variant is inherited or *de novo*. If inherited, targeted testing for all affected, if any, and at-risk family members is recommended.
- Genetic counselling, including reproductive counselling (discussing prenatal and preimplantation diagnoses, if relevant), is recommended.

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RESULT SUMMARY

GENE (TRANSCRIPT, METHOD)	OUTCOME
DMD (NM_004006.2, MLPA)	hemizygous deletion encompassing exons 45-52

VARIANT INTERPRETATION

By MLPA analysis a hemizygous deletion encompassing exons 45-52 of the *DMD* gene was identified. According to HGMD Professional 2022.4 the detected CNV has been described as disease-causing for muscular dystrophy, Duchenne/Becker by Den Dunnen et al., 1989 (PMID: 2573997), Ling et al., 2020 (PMID:31705731), and more. According to LOVD reading-frame checker, deletion of exons 45-52 is predicted to lead to an OUT-OF-FRAME deletion. It is classified as pathogenic (class 1) according to the recommendations of CENTOGENE and ACMG (please, see additional information below).

The dystrophinopathies cover a spectrum of X-linked muscle disease ranging from mild to severe that includes Duchenne muscular dystrophy, Becker muscular dystrophy, and *DMD*-associated dilated cardiomyopathy (DCM). The mild end of the spectrum includes the phenotypes of asymptomatic increase in serum concentration of creatine phosphokinase (CK) and muscle cramps with myoglobinuria. The severe end of the spectrum includes progressive muscle diseases that are classified as Duchenne/Becker muscular dystrophy when skeletal muscle is primarily affected and as *DMD*-associated DCM when the heart is primarily affected.

Duchenne muscular dystrophy (DMD) usually presents in early childhood with delayed motor milestones including delays in walking independently and standing up from a supine position. Proximal weakness causes a waddling gait and difficulty climbing stairs, running, jumping, and standing up from a squatting position. DMD is rapidly progressive, with affected children being wheelchair dependent by age 12 years. Cardiomyopathy occurs in almost all individuals with DMD after age 18 years. Few survive beyond the third decade, with respiratory complications and progressive cardiomyopathy being common causes of death.

Becker muscular dystrophy (BMD) is characterized by later-onset skeletal muscle weakness. With improved diagnostic techniques, it has been recognized that the mild end of the spectrum includes men with onset of symptoms after age 30 years who remain ambulatory even into their 60s. Despite the milder skeletal muscle involvement, heart failure from DCM is a common cause of morbidity and the most common cause of death in BMD. Mean age of death is in the mid-40s (GeneReviews, PMID: 20301298).

CENTOGENE VARIANT CLASSIFICATION (BASED ON ACMG RECOMMENDATIONS)

Class 1 – Pathogenic
Class 2 – Likely pathogenic
Class 3 – Variant of uncertain significance (VUS)
Class 4 – Likely benign
Class 5 – Benign

Additionally, other types of clinically relevant variants can be identified (e.g. risk factors, modifiers).

METHODS

MLPA (multiplex ligation-dependent probe amplification) analyses were performed using SALSA MLPA probemix P034-B2/P035-B1 provided by MRC-Holland to test for deletions or duplications within or including the DMD gene(s).

LIMITATIONS

The genetic results are interpreted in the context of the provided clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the provided genetic data or patient information is inaccurate and/or incomplete. If the obtained genetic results are not compatible with the clinical findings, additional testing should be considered.

ADDITIONAL INFORMATION

This test was developed, and its performance was validated, by CENTOGENE. The US Food and Drug Administration (FDA) has determined that clearance or approval of this method is not necessary and thus neither have been obtained. This test has been developed for clinical purposes. All test results are reviewed, interpreted and reported by our scientific and medical experts.

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To exclude mistaken identity in your clinic, several guidelines recommend testing a second sample that is independently obtained from the proband. Please note that any further analysis will result in additional costs.

The classification of variants can change over the time. Please feel free to contact CENTOGENE (customer.support@centogene.com) in the future to determine if there have been any changes in classification of any reported variants.

DISCLAIMER

Any preparation and processing of a sample from patient material provided to CENTOGENE by a physician, clinical institute or a laboratory (by a "Partner") and the requested genetic and/or biochemical testing itself is based on the highest and most current scientific and analytical standards. However, in very few cases genetic or biochemical tests may not show the correct result, e.g. because of the quality of the material provided by a Partner to CENTOGENE or in cases where any test provided by CENTOGENE fails for unforeseeable or unknown reasons that cannot be influenced by CENTOGENE in advance. In such cases, CENTOGENE shall not be responsible and/or liable for the incomplete, potentially misleading or even wrong result of any testing if such issue could not be recognized by CENTOGENE in advance.

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