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NOVEL FUKUTIN MUTATIONS IN LIMB-GIRDLE MUSCULAR DYSTROPHY TYPE 2M WITH CHILDHOOD ONSET

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Limb-girdle muscular dystrophies (LGMDs) are a heterogeneous group of childhood- or adult-onset inherited neuromuscular disorders, which are characterized by weakness and wasting of proximal limb and axial muscles. LGMDs are divided into 8 autosomal-dominant (LGMD1)[1] and 25 autosomal-recessive (LGMD2) forms (omim.org/phenotypicSeries/PS253600). One autosomal-recessive form is the LGMD2M (new nomenclature: Muscular Dystrophy-Dystroglycanopathy, type C, 4, MDDGC4, MIM #611588), which is caused by homozygous or compound heterozygous mutations in the fukutin gene (*FKTN*; MIM #607440) on chromosome 9q31.2. The LGMD2M, as the clinical mild end of fukutin-related muscle dystrophy without mental retardation, is rare worldwide and described mostly in individuals of non-Japanese descent (table e-1 at Neurology.org/ng).[2–5]

Here, we report the second German case with an LGMD2M phenotype and describe 2 previously unreported mutations in the *FKTN* gene in a German female patient.

Clinical case presentation. A 32-year-old female patient was admitted to our Neuromuscular Center. Written consent was obtained for the use of all clinical and diagnostic data. The patient was born to healthy nonconsanguineous parents. At the age of 7 years, cramping muscle pain, especially in the thighs, started and was accompanied by creatine kinase (CK) elevation. A muscle biopsy record described a chronic myopathic pattern and marked inflammation. The patient was treated with a corticosteroid, which profoundly reduced the CK level. In the following years, the patient developed a slowly progressive muscle weakness of both legs. At the age of 16 years, problems in climbing stairs and lifting heavy objects were noted. At the time of admission, the patient started to use a wheelchair for outdoor activities.

Neurologic examination revealed normal intellectual status, cranial nerve function, and sensorium. Inspection showed scapular winging, calf muscle enlargement, toe walking, and lumbar hyperlordosis (figure, A and D). We observed muscular atrophy with accentuation of the proximal lower extremities and reduced muscle strength. Gower and Trendelenburg signs were positive. Deep tendon reflexes were diminished. The patient also suffered from mild dysphagia and respiratory distress. EMG showed myopathic changes. Muscular MRI revealed a pronounced lipodystrophy of proximal upper and lower limb and limb-girdle muscles (figure, B, C, E, G, and H).

A multigene panel for LGMDs by next-generation sequencing (NGS) on genomic DNA isolated from a blood sample of our patient was performed. Coding and flanking sequences of all relevant genes were enriched using Agilent SureSelect technology. Massively parallel sequencing was performed using the HiSeq 2500 Sequencing platform from Illumina. Sanger sequencing was used for badly covered regions and validation of potentially pathogenic mutations.

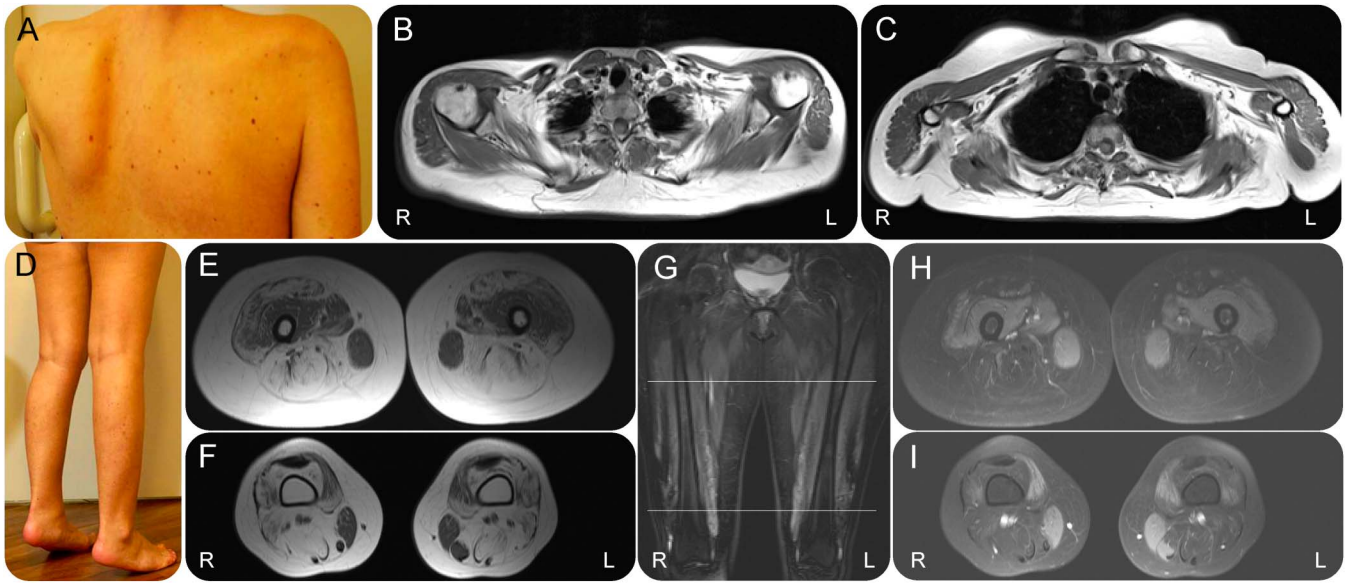
In our patient, 2 novel missense mutations c.895A>C; p.Ser299Arg and c.1325A>G; p.Asn442Ser of the *FKTN* gene (NM_001079802.1) were found by NGS analysis and confirmed by Sanger sequencing. Both mutations disturb highly conserved positions in the fukutin protein. Several in silico prediction programs (MutationTaster, PolyPhen-2, SIFT) indicated that these mutations are most likely damaging. In Exome Aggregation Consortium (ExAC) and in Exome Server Browser, the variant c.895A>C was detected in heterozygous state only in one person, whereas the variant c.1325A>G had not been observed before.

With only one mutation c.1325A>G present in the father, a compound heterozygosity of the 2 mutations in our patient is strongly implied. Based on all information, we predict these 2 mutations as causative for the patients' disease.

Discussion. Mutations in *FKTN* cause a wide clinical spectrum of myopathies: from severe congenital forms of muscular dystrophy with additional extramuscular symptoms to a milder form of LGMD2M, which is normally not associated with cognitive impairment.[2] In the phenotypical spectrum of *FKTN* mutations, the classification from congenital muscular dystrophy (CMD) to LGMD2M was defined according to the onset of weakness.[2] In practice, patients might display a phenotype well in between CMD and LGMD,[2,6]

Supplemental data at Neurology.org/ng

Figure **Clinical presentation and imaging findings in the patient**



Clinical presentation: atrophy of the proximal muscles in the upper extremities. Note the scapula alata (A) and the characteristic symmetric hypertrophy of gastrocnemius muscles (D). Imaging findings: MRI of the upper extremity demonstrates a moderate atrophy of the rotator cuff and the deltoid muscle (B and C). MRI of the lower extremity shows a severe symmetric atrophy with fatty degeneration of musculature of both tights (E and F). The less atrophied sartorius and gracilis muscles depict a pronounced edema (G) and a strong gadolinium enhancement representing acute disease activity (H and I). B, C, E, and F: transverse T1-weighted images, G: coronal STIR sequence; H and I: transverse fat-saturated T1-weighted images postcontrast.

pointing to an inherent difficulty of a strict classification. The phenotype of our patient is characterized by childhood onset, hypertrophy of calves, normal intelligence, and initial responsiveness to steroids.

The reduced ability of our patient to walk in her teens is in line with previous reports.[7] In addition, we can provide clinical data of our patient until the age of 32 years. Our patient initially responded to steroid therapy, which might be explained by the profound inflammation in the muscle biopsy, comparable with the positive effect of steroids in Duchenne muscular dystrophy.

We show a rare case of LGMD2M and provide further insight into heterogeneity of phenotypes caused by mutations in *FKTN* and underline the importance of broad genetic assessment to provide correct diagnosis and to facilitate individual treatment in the future.

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