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An autosomal recessive limb girdle muscular dystrophy (LGMD2) with mild mental retardation is allelic to Walker–Warburg syndrome (WWS) caused by a mutation in the *POMT1* gene

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Abstract

Mutations of the protein *O-mannosyltransferase* (*POMT1*) gene affect glycosylation of α-dystroglycan, leading to Walker–Warburg syndrome, a lethal disorder in early life with severe congenital muscular dystrophy, and brain and eye malformations. Recently, we described a novel form of recessive limb girdle muscular dystrophy with mild mental retardation, associated with an abnormal α-dystroglycan pattern in the muscle, suggesting a glycosylation defect. Here, we present evidence that this distinct phenotype results from a common mutation (A200P) in the *POMT1* gene. Our findings further expand the phenotype of glycosylation disorders linked to *POMT1* mutations. Furthermore, the A200P mutation is part of a conserved core haplotype, indicating an ancestral founder mutation.

Keywords: *POMT1* gene; LGMD2; WWS; Hypoglycosylation of α-dystroglycan; A200P mutation

1. Introduction

Congenital muscular dystrophies (CMD) with central nervous system involvement are a heterogeneous group of autosomal recessive muscular dystrophies with structural eye abnormalities and severe brain malformations. The well-defined ones are the Walker–Warburg syndrome (WWS-OMIM#236670), the muscle–eye–brain disease (MEB-OMIM#253280), and the Fukuyama congenital muscular dystrophy (FCMD-OMIM#252800) [1,2]. Hypoglycosylation of α-dystroglycan (α-DG) from muscle is a common feature of these disorders, whereas the brain shows a neuronal migration defect leading to cobblestone lissencephaly (lissencephaly type II) [3,4]. Recently, the underlying genetic defects could be elucidated: mutations of the *POMT1* gene are associated with WWS [5], mutations of the protein *O-mannose β-1,2-N-acetylglucosaminyltransferase* (*POMGnT1*) gene with MEB [6], and mutations of the *Fukutin* gene with FCMD [7], respectively.

WWS is phenotypically characterized by severe cerebral malformations (regularly more severe than in FCMD and MEB) leading to lissencephaly type II, cerebellar and pontine hypoplasia as well as hydrocephalus. Patients with WWS do not survive beyond the first few years of life. Mutations in the *POMT1* gene were recently reported in 20% of patients with WWS. Furthermore, WWS is

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a genetically heterogeneous disorder and likely to be associated with mutations in additional genes [5]. Since a nonsense mutation in the *Fukutin* gene was shown to cause a severe phenotype in a non-Japanese boy, it was hypothesized that loss of function mutations in the *Fukutin* gene could also lead to a WWS phenotype [8].

α-DG is a crucial component of the dystrophin–glycoprotein complex, a group of associated proteins that play a critical role in a variety of muscular dystrophies, and has been identified as one of the possible targets for *POMT1*. *O*-Mannosyl glycan chains are transferred onto α-DG by a heteromeric enzyme complex comprising the *POMT1* and *POMT2* gene products [9,10]. These sugar moieties are not only important for the binding of laminin and other components of the extracellular matrix, but also for the maturation and proper targeting of α-DG [11]. Very recently targeted disruption of the *Pomt1* gene in mice was shown to be early embryonic lethal [12].

Here, we report a cohort of Turkish patients characterized by a moderate limb girdle muscular dystrophy and mild mental retardation without any obvious structural brain abnormality caused by a unique *POMT1* mutation.

2. Patients and methods

2.1. Patients

The present cohort consists of five patients in part previously described with a distinct clinical phenotype of limb girdle muscular dystrophy, mild microcephaly and mental retardation [13]. Fig. 1(a) shows a typical patient (patient #1). The severe reduction of the VIA4-1 glycoepitope on α-DG in the immunohistochemistry was a common finding in their muscle biopsies. Since the onset of muscular weakness started after achieving certain motor milestones such as walking a congenital muscular dystrophy (CMD) is excluded by definition. All patients presented with difficulty in climbing stairs and being slower than their peers. Four patients were characterized by a mild muscle hypertrophy and a slow disease progression summarized in Table 1 (patients #1–4). The most severely affected patient is shown in Fig. 1(b) (patient #5) with a very prominent muscle hypertrophy of the trunk and extremities. IQs of the cohort ranged between 50 and 65. Serum CK levels were increased more than 20-fold. Four patients had normal

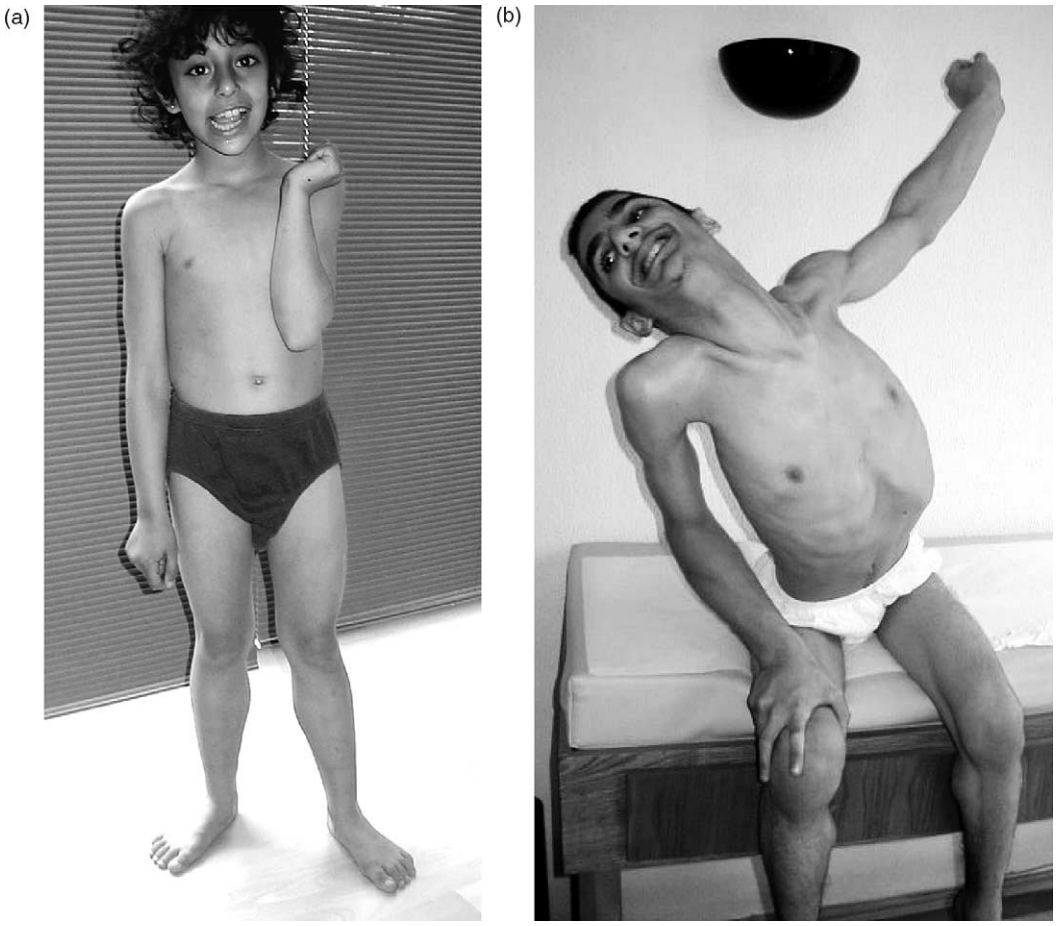

Fig. 1. (a) Case 1. Eight-year-old girl, mild muscle hypertrophy of thighs and calves. Walks alone long distances. (b) Case 5. Nineteen-year-old man, prominent hypertrophy of the trunk, arms and legs. Stopped walking at age 18.