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Clinical Observations

Sarcolemmal Alpha and Gamma Sarcoglycan Protein Deficiencies in Turkish Siblings With a Novel Missense Mutation in the Alpha Sarcoglycan Gene

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ABSTRACT

BACKGROUND: The sarcoglycan alpha gene, also known as the adhalin gene, is located on chromosome 17q21; mutations in this gene are associated with limb-girdle muscular dystrophy type 2D. We describe two Turkish siblings with findings consistent with limb-girdle muscular dystrophy type 2D. The evaluation excluded a dystrophinopathy, which is the most common form of muscular dystrophy. **PATIENTS:** Both siblings had very high levels of creatinine phosphokinase and negative molecular tests for deletions and duplications of the dystrophin gene. The older boy presented at 8 years of age with an inability to climb steps and an abnormal gait. His younger brother was 5 years old and had similar symptoms. The muscle biopsy evaluation was performed only in the older brother. **RESULTS:** The muscle biopsy showed dystrophic features as well as a deficiency in the expression of two different glycoproteins: the alpha sarcoglycan and the gamma sarcoglycan. Sarcolemmal expressions of dystrophin and other sarcoglycans (beta and delta) were diffusely present. DNA analysis demonstrated the presence of previously unknown homozygous mutations [c.226 C > T (p.L76 F)] in exon 3 in the sarcoglycan alpha genes of both siblings. Similar heterozygous point mutations at the same locus were found in both parents, but the genes of beta, delta, and gamma sarcoglycan were normal in the remaining family members. **CONCLUSIONS:** We describe two siblings with limb-girdle muscular dystrophy type 2D with a novel missense mutation. These patients illustrate that the differential diagnosis of muscular dystrophies is impossible with clinical findings alone. Therefore, a muscle biopsy and DNA analysis remain essential methods for diagnosis of muscle diseases.

Keywords: LGMD type 2D, alpha sarcoglycan, adhalin gene, novel mutation

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Introduction

The sarcoglycan alpha (SGCA) gene encodes instructions for making the alpha subunit of the sarcolemmal proteins called the sarcoglycans (SGCs). These proteins (SGC alpha, beta, delta, and gamma) help maintain the structure of muscle tissue by binding to the dystrophin-glycoprotein complex (DGC), which provides structural support to the sarcolemma and protect it from the mechanical stress of contractile activity. SGCA gene mutations may prevent the sarcoglycan complex from forming or from binding to the DGC. Defects in SGCs destroy the backbone of the sarcolemma so that the cell membrane becomes exposed to muscle contraction stresses. As a consequence, focal membrane rupture occurs, leading to a series of pathogenic events that result in the dystrophic phenotype.[1-3]

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The SGCA, as known as adhalin gene, is located on chromosome 17q21. Mutations in this gene causes limb-girdle muscular dystrophy type 2D (LGMD-2D), an autosomal recessive muscle-wasting disorder.[1,4] LGMD-2D predominantly affects the shoulders, hips, and proximal muscles of the limbs. It has a very heterogeneous clinical phenotype. The age of onset, rate of progression, and severity of disease can vary even between affected families. The most clinically severe course is generally observed when the sarcolemmal alpha sarcoglycan totally absent. On the contrary, milder phenotypes occur when residual proteins are present.[1-4] Interestingly, a mutation in any SGC gene can lead to a reduction or absence of the other SGCs.[4-7] Babameto-Laku et al.[4] also reported that the SGCA gene must be first evaluated if there is a concomitant absence of both alpha (α)-sarcoglycan and gamma (γ)-sarcoglycan proteins.

TABLE 1.
Nucleotide and Amino Acid Sequences of the SGCA Gene

1	ATG	GCT	GAG	ACA	CTC	TTC	TGG	ACT	CCT	CTC	CTC	GTG	GTT	CTC	CTG
1	Met	**Ala**	**Glu**	Thr	Leu	**Phe**	**Trp**	Thr	Pro	Leu	Leu	Val	Val	Leu	Leu
46	GCA	GGG	CTG	GGG	GAC	ACC	GAG	GCC	CAG	CAG	ACC	ACG	CTA	CAC	CCA
16	**Ala**	**Gly**	Leu	**Gly**	Asp	Thr	**Glu**	**Ala**	**Gln**	**Gln**	Thr	Thr	Leu	His	Pro
91	CTT	GTG	GGC	CGT	GTC	TTT	GTG	CAC	ACC	TTG	GAC	CAT	GAG	ACG	TTT
31	Leu	Val	**Gly**	**Arg**	Val	**Phe**	Val	His	Thr	Leu	Asp	His	**Glu**	Thr	**Phe**
136	CTG	AGC	CTT	CCT	GAG	CAT	GTC	GCT	GTC	CCA	CCC	GCT	GTC	CAC	ATC
46	Leu	**Ser**	Leu	Pro	**Glu**	His	Val	**Ala**	Val	Pro	Pro	**Ala**	Val	His	**Ile**
181	ACC	TAC	CAC	GCC	CAC	CTC	CAG	GGA	CAC	CCA	GAC	CTG	CCC	CGG	TGG
61	Thr	Tyr	His	**Ala**	His	Leu	**Gln**	**Gly**	His	Pro	Asp	Leu	Pro	**Arg**	**Trp**
226	CTC	CGC	TAC	ACC	CAG	CGC	AGC	CCC	CAC	CAC	CCT	GGC	TTC	CTC	TAC
76	Leu	**Arg**	Tyr	Thr	**Gln**	**Arg**	**Ser**	Pro	His	His	Pro	**Gly**	**Phe**	Leu	Tyr
271	GGC	TCT	GCC	ACC	CCA	GAA	GAT	CGT	GGG	CTC	CAG	GTC	ATT	GAG	GTC
91	**Gly**	**Ser**	**Ala**	Thr	Pro	**Glu**	Asp	**Arg**	**Gly**	Leu	**Gln**	Val	**Ile**	**Glu**	Val
316	ACA	GCC	TAC	AAT	CGG	GAC	AGC	TTT	GAT	ACC	ACT	CGG	CAG	AGG	CTG
106	Thr	**Ala**	Tyr	**Asn**	**Arg**	Asp	**Ser**	**Phe**	Asp	Thr	Thr	**Arg**	**Gln**	**Arg**	Leu
361	GTG	CTG	GAG	ATT	GGG	GAC	CCA	GAA	GGC	CCC	CTG	CTG	CCA	TAC	CAA
121	Val	Leu	**Glu**	**Ile**	**Gly**	Asp	Pro	**Glu**	**Gly**	Pro	Leu	Leu	Pro	Tyr	**Gln**
406	GCC	GAG	TTC	CTG	GTG	CGC	AGC	CAC	GAT	GCG	GAG	GAG	GTG	CTG	CCC
136	**Ala**	**Glu**	**Phe**	Leu	Val	**Arg**	**Ser**	His	Asp	**Ala**	**Glu**	**Glu**	Val	Leu	Pro
451	TCA	ACA	CCT	GCC	AGC	CGC	TTC	CTC	TCA	GCC	TTG	GGG	GGA	CTC	TGG
151	**Ser**	Thr	Pro	**Ala**	**Ser**	**Arg**	**Phe**	Leu	**Ser**	**Ala**	Leu	**Gly**	**Gly**	Leu	**Trp**
496	GAG	CCC	GGA	GAG	CTT	CAG	CTG	CTC	AAC	GTC	ACC	TCT	GCC	TTG	GAC
166	**Glu**	Pro	**Gly**	**Glu**	Leu	**Gln**	Leu	Leu	**Asn**	Val	Thr	**Ser**	**Ala**	Leu	Asp
541	CGT	GGG	GGC	CGT	GTC	CCC	CTT	CCC	ATT	GAG	GGC	CGA	AAA	GAA	GGG
181	**Arg**	**Gly**	**Gly**	**Arg**	Val	Pro	Leu	Pro	**Ile**	**Glu**	**Gly**	**Arg**	**Lys**	**Glu**	**Gly**
586	GTA	TAC	ATT	AAG	GTG	GGT	TCT	GCC	TCA	CCT	TTT	TCT	ACT	TGC	CTG
196	Val	Tyr	**Ile**	**Lys**	Val	**Gly**	**Ser**	**Ala**	**Ser**	**Pro**	**Phe**	**Ser**	Thr	**Cys**	Leu
631	AAG	ATG	GTG	GCA	TCC	CCC	GAT	AGC	CAC	GCC	CGC	TGT	GCC	CAG	GGC
211	**Lys**	Met	Val	**Ala**	**Ser**	Pro	Asp	**Ser**	His	**Ala**	**Arg**	**Cys**	**Ala**	**Gln**	**Gly**
676	CAG	CCT	CCA	CTT	CTG	TCT	TGC	TAC	GAC	ACC	TTG	GCA	CCC	CAC	TTC
226	**Gln**	Pro	Pro	Leu	Leu	**Ser**	**Cys**	Tyr	Asp	Thr	Leu	**Ala**	Pro	His	**Phe**
721	CGC	GTT	GAC	TGG	TGC	AAT	GTG	ACC	CTG	GTG	GAT	AAG	TCA	GTG	CCG
241	**Arg**	Val	Asp	**Trp**	**Cys**	**Asn**	Val	Thr	Leu	Val	Asp	**Lys**	**Ser**	Val	Pro
766	GAG	CCT	GCA	GAT	GAG	GTG	CCC	ACC	CCA	GGT	GAT	GGG	ATC	CTG	GAG
256	**Glu**	Pro	**Ala**	Asp	**Glu**	Val	Pro	Thr	Pro	**Gly**	Asp	**Gly**	**Ile**	Leu	**Glu**
811	CAT	GAC	CCG	TTC	TTC	TGC	CCA	CCC	ACT	GAG	GCC	CCA	GAC	CGT	GAC
271	His	Asp	Pro	**Phe**	**Phe**	**Cys**	Pro	Pro	Thr	**Glu**	**Ala**	Pro	Asp	**Arg**	Asp
856	TTC	TTG	GTG	GAT	GCT	CTG	GTC	ACC	CTC	CTG	GTG	CCC	CTG	CTG	GTG
286	**Phe**	Leu	Val	Asp	**Ala**	Leu	Val	Thr	Leu	Leu	Val	Pro	Leu	Leu	Val
901	GCC	CTG	CTT	CTC	ACC	TTG	CTG	CTG	GCC	TAT	GTC	ATG	TGC	TGC	CGG
301	**Ala**	Leu	Leu	Leu	Thr	Leu	Leu	Leu	**Ala**	Tyr	Val	Met	**Cys**	**Cys**	**Arg**
946	CGG	GAG	GGA	AGG	CTG	AAG	AGA	GAC	CTG	GCT	ACC	TCC	GAC	ATC	CAG
316	**Arg**	**Glu**	**Gly**	**Arg**	Leu	**Lys**	**Arg**	Asp	Leu	**Ala**	Thr	**Ser**	Asp	**Ile**	**Gln**
991	ATG	GTC	CAC	CAC	TGC	ACC	ATC	CAC	GGG	AAC	ACA	GAG	GAG	CTG	CGG
331	Met	Val	His	His	**Cys**	Thr	**Ile**	His	**Gly**	**Asn**	Thr	**Glu**	**Glu**	Leu	**Arg**
1036	CAG	ATG	GCG	GCC	AGC	CGC	GAG	GTG	CCC	CGG	CCA	CTC	TCC	ACC	CTG
346	**Gln**	Met	**Ala**	**Ala**	**Ser**	**Arg**	**Glu**	Val	Pro	**Arg**	Pro	Leu	**Ser**	Thr	Leu
1081	CCC	ATG	TTC	AAT	GTG	CAC	ACA	GGT	GAG	CGG	CTG	CCT	CCC	CGC	GTG
361	Pro	Met	**Phe**	**Asn**	Val	His	Thr	**Gly**	**Glu**	**Arg**	Leu	Pro	Pro	**Arg**	Val
1126	GAC	AGC	GCC	CAG	GTG	CCC	CTC	ATT	CTG	GAC	CAG	CAC	TGA		
376	Asp	**Ser**	**Ala**	**Gln**	Val	Pro	Leu	**Ile**	Leu	Asp	**Gln**	His	**Ter**		

* The previously determined missense mutations are listed in bold. The present mutation is underlined.