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Expanded Clinical and Genetic Characterization of Autosomal Recessive *HMGCR*-Related Limb-Girdle Muscular Dystrophy

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INTRODUCTION

Autosomal recessive limb-girdle muscular dystrophy type R28 (LGMDR28; OMIM #620375) is a recently identified subtype of limb-girdle muscular dystrophy with 15 individuals from six unrelated families carrying biallelic variants in the *HMGCR* gene reported to date [a, b]. Here we describe 10 individuals from five unrelated Middle Eastern families diagnosed with LGMDR28, all carrying homozygous *HMGCR* variants.

RESULTS

Five unrelated families presenting with a variety of clinical indications were aggregated from three different centers by direct communication or via GeneMatcher.

Family 1: Three siblings with initial symptoms, including proximal and axial muscle weakness and fatigue, appeared between the ages of 13 and 14 years.

Family 2: One child, soon after achieving independent ambulation, parents noticed muscular weakness and the child tired very quickly.

Family 3: One child with limb myopathy at birth, at age 3, muscle biopsy findings showed myopathic atrophy with multiple dispersed degenerative/regenerative fibers, and EMG findings revealed myopathic process involving mostly proximal muscles of lower limbs.

Family 4: Index at 1 month of age exhibited diminished deep tendon reflexes and mild muscle atrophy. He was admitted to the hospital due to significant hypotonia, severe congenital myopathy, and respiratory distress, which necessitated his reliance on a ventilator for adequate breathing support.

Family 5: The proband was a 6-year-old male who showed neuromotor retardation, hypotonia, and decreased muscle strength. He had a history of sucking difficulties.

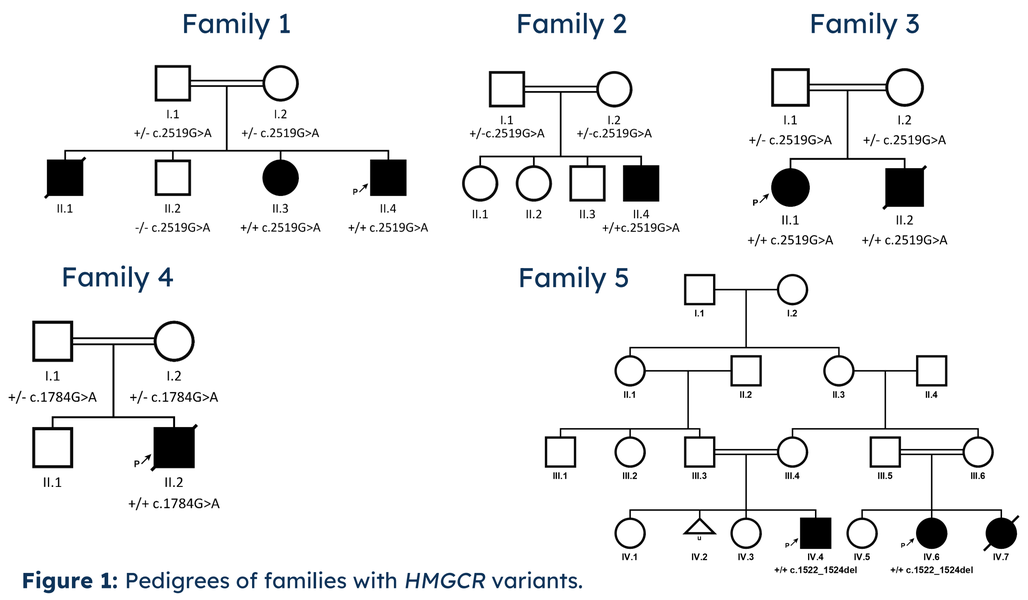

Figure 1: Pedigrees of families with *HMGCR* variants.

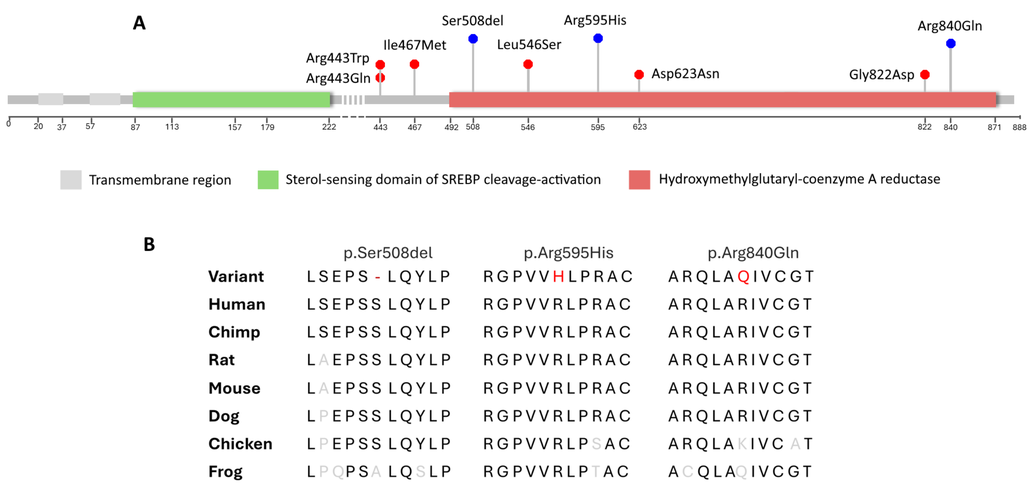

Figure 2: The positions of all reported causal variations in *HMGCR*. Blue circles represent variants reported in this study; B: Cross-species comparison of *HMGCR* sequences, showing the conserved nature of the variant residues.

Table 1. Clinical features of patients and genetic findings in our cohort

	Family 1			Family 2	Family 3		Family 4	Family 5	
Features	F1-11:4	F1-II:3	F1-II:1	F2-II:4	F3-II:1	F3-II:2	F4-II:2	F5-IV:4	F5-IV:6
Country of Origin	Lebanon	Lebanon	Lebanon	Lebanon	Iran	Iran	Iran	Turkey	Turkey
Family History	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Gender	Male	Female	Male; deceased (respiratory failure)	Male	Female	Male; deceased (respiratory and liver failure)	Male, deceased (respiratory failure)	Male	Female
Age at onset (Years)	14	13-14	14	2,5	At birth	At birth	1 month	N/A	N/A
Age at molecular diagnosis (Years)	28	34	N/A	15	13	9	3 months	6	9
Consanguinity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gower's sign	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	yes
Muscle atrophy	Severe	Severe	Severe	Severe	No	No	Mild	Yes	Yes
Calf Hypertrophy	No	No	N/A	Yes, mild	No	No	N/A	Yes	Yes
Proximal Weakness	Yes	Yes	Yes	Yes	Yes, mild	Yes, mild	No	Yes	Yes
Axial Weakness	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Lumbar Lordosis	Yes	Yes	N/A	Yes	No	No	No	No	No
Scoliosis	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
DTR	No	No	N/A	No	No	No	Diminished	No	Diminished
Gait Disturbance	Severe	Severe	Severe	Severe	Severe	Severe	N/A	No, tip toe walking	Yes and tip toe walking
Age of loss of ambulation	25 years	27 years	25 years	N/A	N/A	9 years	N/A	No	No
Wheelchair use	Yes	Yes (from age 20)	Yes	No	No	Yes	No	No	No
Myalgias	Yes	Yes	N/A	No	Yes	Yes	N/A	No	Yes
Respiratory involvement	Yes, rigid chest, vital capacity <50%, tracheotomized	Yes, tracheotomized	Yes, respiratory failure	No	Yes, mild	Yes, respiratory failure	Yes, respiratory failure	No	No
CK levels	1200 U/L	N/A	N/A	6000 U/L	2700 U/L	7000 U/L	N/A	9000 U/L	3022 U/L
Disease progression	Fast progressive	Fast progressive	Fast progressive	Moderate progressive	Stable	Fast progressive	Fast progressive	Slow, stable	Slow
HMGCR variant cDNA (NM_000859.2)	c.2519G>A	c.2519G>A	N/A	c.2519G>A	c.2519G>A	c.2519G>A	c.1784G>A	c.1522_1524del	c.1522_1524del
Protein (NP_00850.1)	p.(Arg840Gln)	p.(Arg840Gln)	N/A	p.(Arg840Gln)	p.(Arg840Gln)	p.(Arg840Gln)	p.(Arg595His)	p.Ser508del	p.Ser508del
Zygosity	Hom	Hom	Hom	Hom	Hom	Hom	Hom	Hom	Hom

METHOD

Patient recruitment: Biological samples from five unrelated families were collected after obtaining informed consent from the patients or their parents. Index patients were analysed by Genome Sequencing (GS) (families 1&2) or Exome Sequencing (ES) (families 3-5). Sanger sequencing was used for segregation analyses in all available family members.

GS: DNA libraries were prepared using TruSeq Nano DNA High Throughput Library Prep Kit (Illumina®). Libraries were 150nt paired-end sequenced on an Illumina platform to yield a mean coverage depth of 30x for the nuclear genome and at least 1000x for the mitochondrial genome.

ES: Exome libraries were generated using Agilent SureSelect V7 and sequenced on the NovaSeqX Plus with a 150nt paired-end configuration, resulting in an average coverage depth of 100x. Raw reads were aligned to reference genome.

CONCLUSION

This study consolidates the disease-causing role of *HMGCR* in LGMDR28, illustrates a wide range of symptom onset from birth to the fourth decade, and suggests the value of liver function monitoring in patients diagnosed with LGMDR28.

CONFLICT OF INTEREST STATEMENT: AR, MA and GO are current employees of Arcensus GmbH.

Acknowledgement: This work was made possible by all patients who participated in this study.

References:
[a] Yogev *et al*, Proc Natl Acad Sci U S A .2023
[b] Morales-Rosado *et al*, Am J Hum Genet. 2023

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