A Novel Founder Mutation in the SGCB Gene Causes Severe Form Of Limb Girdle Muscular Dystrophy (LGMD) 2E in Sathwara Community of India

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Abstract

- Autosomal recessive limb girdle muscular dystrophy (LGMD2) is characterized by progressive skeletal muscle weakness.
- It's onset, advancement and severity of the weakness may vary depending on the genetic subtypes like LGMD2C, LGMD2D, LGMD2E, LGMD2F.
- Among these the most common subtype in Indian population is LGMD2C. Although, LGMD2E is relatively rare subtype, in present study we report clinical and genetic data of 6 children diagnosed as LGMD2E with same novel mutation (Chr 4:52894204C>T; c.683G>A; p.Gly228Glu) in SGCB gene from three different families of Sathwara community of Gujarat, India.
- The identified novel missense mutation present on extracellular domain of SGCB protein resulting in its conformational change may leads to modification of sarcoglycan complex assembly results in sarcoglycanopathy.
- This novel mutation was found in three different unrelated families of sathwara community suggesting its high prevalence with founder effect.

Objective

To Evaluate identified novel mutation (Chr 4:52894204C>T; c.683G>A; p.Gly228Glu) in SGCB gene in disease severity in LGMD patient and its penetrance and founder effect in Sathwara community of Gujarat, India.

Materials and Methods

Next Genetation Sequencing Analysis : Target specific probes used to pull down the region of interest.Sequencing performed using a standard kit on illumine MiSeq with the expected data output of ~3 GB per sample. The trimmed FASTQ files were generated using MiSeq reporter from Illumina. The variant is predicted to be damaging by 6 (SIFT, LRT, Mutation Taster, PolyPhen-r, Mutation Assessor and FATHMM) out of 6 in silico missense prediction tools. **Sanger Sequencing:** The identified variant in SGCB gene then validated using the mutation specific test, a bidirectional Sanger sequencing was performed in parents and other family members including suspected asymptomatic carriers. **Bioinformatics analysis:** Moreover, we did the protein homology modeling and evaluated the bioinformatics of the proteins as shown in figure 3. In this study we discuss the result of structure predicted by YASARA software.

	Family-1			Family-2		Family-3
	Case-1 (III-1)	Case-2 (III-4)	Case-3 (III-5)	Case-4 (III-1)	Case-5 (III-2)	Case-6 (III-1)
Present Age / Gender	11yrs / Female	12 yrs / Male	13yrs / Male	11 yrs / Female	5yrs / Female	12 yrs / Female
Serum CPK levels (IU/mL)	1841	6937	10517	2144	3687	7340
Age when first symptom appear	8 yrs Walking difficulties	1.5 Year delayed motor milestones	6 Years Difficulty in walking	8 years difficulty in walking	2 years slight difficulty in walking	2.5 Mths Dev. Delay and walking difficulties
Lower limb Involvement	Yes	Yes	Yes	Yes	Yes	Yes
Upper limb Involvement	No	Yes (Mild)	No	Yes (Asymmetrical shoulder weakness)	No	Yes (bilateral shoulder weakness)
Motor Abilities	Walking with frequent falls and unable to get up without support since the age 10 years 6 months	Unable to walk unsupported at the age of 12 years	Walking with frequent falls and unable to get up from the floor at the age of 11 years	Walking with frequent falls and unable to get up from the floor at the age of 10 years	Able to walk unsupported but mild difficulty in standing up from the floor	Unable to get up from the floor and difficulty in climbing stairs at the age of 10 years.
Cardiac or respiratory involvement	No	No	No	No	No	No
Swallowing difficulties	No	No	No	No	No	No

Results

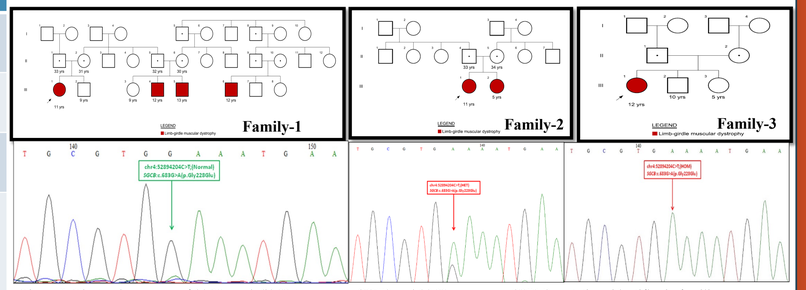

Figure 2: Electropherograms of (a) Normal, (b) Heterozygous (HET) and (c) Homozygous (HOM) mutations identifies in families

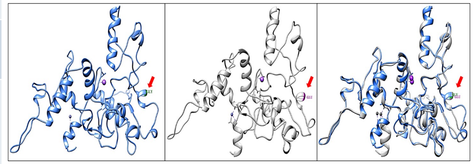

Figure 3 shows the three-dimensional structures of the homology modelled SGCB wild type (Figure 3a) as well as mutant protein (Figure 3b). The superposition of both structures (Figure 3c) was carried out in the UCSF Chimera software with 0.679 Å. There was only one change found at the p.Gly228Glu position and mentioned in the Figure 3.

Conclusions

References

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