Importance of genetic counseling in prenatal diagnosis : A case of a couple molecularly diagnosed with Limb-girdle muscular dystrophy (LGMD)

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Introduction

- Limb-girdle muscular dystrophy (LGMD) is a genotypically and phenotypically heterogeneous group of disorders
- More than 30 different genetic subtypes of LGMD have been identified.
- Clinical spectrum: weakening and atrophy of proximal limb-girdle muscles, gait difficulty, and muscle wasting.
- The severity, age of onset, and progression of symptoms may vary among the subtypes and may differ between family members with the same condition.
- Two main groups :

1) LGMD1 : Autosomal dominant forms [e.g, LGMD1A LGMD1B , etc]

2) LGMD2 : Autosomal recessive forms [e.g, LGMD2K, LGMD2L, etc]

Aims & Objectives

We present a case of a couple diagnosed with LGMD with the aim :

To highlight the challenges faced during the post test counselling for conditions with genetic and phenotypic heterogeneity

Objectives : To emphasize that

Genetic counselling plays an important role to explain actual risk for the fetus based on the pattern of inheritance and affection status of parents

Pretest and post test genetic counseling in prenatal diagnosis can help take informed reproductive decisions

Case details and Investigations

Mr A (25 Years) and Mrs B (30 Years) are non-consanguineously married couple.

- The couple spontaneously conceived a pregnancy and there was no history of any abortion as well as MTP.
- Both of them are clinically diagnosed with LGMD, clinical exome sequencing had confirmed their diagnosis.
- They had undergone prenatal clinical exome testing of ongoing pregnancy via CVS sample at 14 weeks of gestation.
- They were referred to understand the affection status and plan reproductive action.

Results:

Table 1. Clinical Exome sequencing results of couple and fetus

	Gene	Variant	Zygosity	Affection Status	OMIM Phenotype
Mr A [Father]	*CAPN3*	Likely pathogenic deletion of ~2.94 kb size [included 7 exons]	Homozygous	Affected	Autosomal recessive LGMD type 1
Mrs B [Mother]	*LAMA2*	Likely pathogenic missense variant c.442C>T (p.Arg148Trp)	Probable compound heterozygous	Affected	Autosomal recessive LGMD Type 23 and Merosin-deficient congenital muscular dystrophy Type 1A
		Likely pathogenic deletion of ~176.66 kb size			
Fetus	*CAPN3*	Deletion of ~2.94 kb	Heterozygous	Carrier of paternal variant / unaffected	
	LAMA2	c.442C>T (p.Arg148Trp)	Heterozygous	Carrier of maternal variant / unaffected	

Discussion

Challenges faced :

Information available to the couple : a) They were informed that the fetus is affected and they need to terminate the pregnancy b) The mode of inheritance explained was of an X linked recessive condition and not an autosomal recessive condition and not an autosomal recessive condition c) They were seeking 100% assurance that their child will not be affected with LGMD.

Counselling done :

- The CVS report was reviewed and it was explained that the fetus is just a carrier for the variants of genes detected in the couple and hence is NOT AFFECTED as both the variants are present in two different genes.
- They were relieved to hear this.
- Both conditions are AR - This information was also relieving to them as they had concluded that every male fetus would be affected.
- Carrier status for both the genes in opposite partners was not mentioned in their CES report.
- Since they wanted assurance, additional points were discussed :
  i) They have been advised to request the primary lab to look for the carrier status of any other significant variants in the *LAMA2* gene in husband and *CAPN3* gene in the wife
  ii) They have been explained about the background risk of any other genetic disorder due to limitations of the current technology or limitation of literature evidence in view of undiscovered genes , new disease conditions cannot be ruled out
- They have also been suggested to test for aneuploidy by FISH + Microarray on the stored CVS sample to rule out the risk of common chromosomal aneuploidies like Trisomy 13/18/21.
- The couple was relieved to know the risk for LGMD is low based on the genetic report.
- The couple opted to continue the pregnancy.

Conclusion

- This case shows how pretest and post test Genetic Counseling can play an important role to explain the actual risk for the fetus based on the pattern of inheritance and genes involved.
- This case highlights that if pretest Genetic Counseling would have been done for this couple, invasive prenatal testing could have been avoided after confirming that wife is not a carrier for pathogenic/likely pathogenic variants in *CAPN3* gene and husband for *LAMA2* gene.
- In rare genetic disorders with genetic heterogeneity there could be complex combinations in multiple genes and it is important to explain these in simple terms to couples to help them take informed reproductive decisions.

Reference

Strafella C, Caputo V, Campoli G, Galota RM, Mela J, Zampatti S, Minozzi G, Sancricca C, Servidei S, Giardina E, Cascella R. Genetic Counseling and NGS Screening for Recessive LGMD2A Families. High Throughput. 2020 May 10;9(2):13. doi: 10.3390/ht9020013. PMID: 32397577; PMCID: PMC7349198.

Acknowledgment

We would like to thank Neuberg Centre for Genomic Medicine for providing a platform for the genetic counseling session for this case