Importance of Preconceptional Genetic Counseling in a Family with Genetic Condition: A Case Report

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Abstract

A 28-year-old woman with a known family history of stargardt syndrome sought preconceptional genetic counseling. Stargardt syndrome is an inherited autosomal recessive eye disorder that affects the retina, leading to progressive vision loss. She shared that many individuals are affected in her community including her brother and paternal cousins. She is married to an individual within the same community and was concerned about the potential risk for her future offspring. Genetic testing revealed likely pathogenic compound heterozygous variants in *ABCA4* gene in her brother. Carrier screening was suggested for the couple. The results revealed that the couple are negative for stargardt syndrome, however both are carriers for *NEB* gene implicated in Arthrogryposis multiplex congenita 6 and Nemaline Myopathy 2.These are two distinct congenital conditions that affect muscular skeletal system usually lethal during the first few months of life. Couple were counselled about the condition, recurrence risk, prenatal testing and pre implantation options. This case highlights the importance of preconceptional counselling and comprehensive genetic testing.

Background

- Stargardt disease is an inherited eye condition that causes progressive vision loss due to abnormal accumulation of a fatty yellow pigment (lipofuscin) in the cells within the macula.
- Variants in *ABCA4* gene are associated with stargardt disease and inherited in an autosomal recessive pattern.
- Patients present with progressive visual impairment, usually beginning in the first or second decades of life.

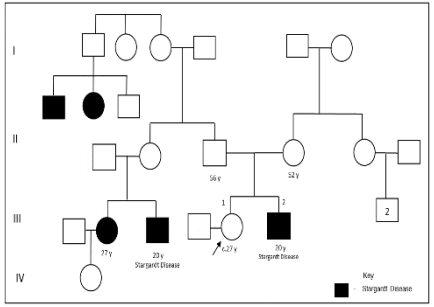
Case Presentation

Referral Reason

A 28 year old normal female anxious to start a family attended the preconceptional genetic counselling with concerns of having a family history of stargardt disease

Pedigree Analysis

- Non-consanguineous couple, married within the same community .
- History of stargardt disease for her brother and paternal cousins. Strong history in the specific community.
- Whole exome sequencing for her brother revealed likely pathogenic compound heterozygous variants in the *ABCA4* gene (c.4731_4732del; p.Gly1578ValfsTer18) and (c.634C>T; p.Arg212Cys) associated with Stargardt disease.



Diagnostic Workup

- Carrier Screening by WES for couples, inclusive of *ABCA4* gene was suggested to rule out other autosomal recessive disorders.
- Carrier screening for couple revealed no significant variant in *ABCA4* gene. However, both were found to be carriers for *NEB* gene implicated in Autosomal Recessive Arthrogryposis multiplex congenita 6 and Nemaline myopathy 2.

Couple carrier screening Analysis - WES

Husband	Wife	Disease
CARRIER **Gene:** *NEB* Exon 126, c.19477G>A (p.Val6493Met), Heterozygous **Classification:** Uncertain Significance **Mode of Inheritance:** Autosomal Recessive	**CARRIER** **Gene:** *NEB* Exon 22, c.2033del (p.Leu678TrpfsTer5), Heterozygous **Classification:** Likely Pathogenic **Mode of Inheritance:** Autosomal Recessive	Arthrogryposis multiplex congenita 6; Nemaline myopathy 2

NEB Gene

- *NEB* gene encodes Nebulin protein, plays an important role in skeletal muscles.
- Mutation in this gene causes Nemaline myopathy 2(NM) and Arthrogryposis multiplex congenita 6.
- The clinical manifestation of NM caused by *NEB* pathogenic variants (NM-NEB) is very broad, ranging from mild to severe phenotype manifesting with generalized weakness, respiratory illness, hypotonia and depressed or absent deep tendon reflexes.
- Age of onset, ranging from a severe congenital-onset (at birth) form that is usually lethal in the first few months of life, through to less severe forms with onset in childhood or adulthood
- Clinical features of Arthrogryposis is non progressive multiple congenital joint contractures that generally result from lack of fetal movement in utero.

Genetic Counseling

- The family were counseled about the nature of the condition, natural history and mode of inheritance.
- Recurrence risk for *NEB* gene variant: offspring have a chance of 25% affected,50% carrier and 25% normal.
- Antenatal monitoring using USG.
- Prenatal Diagnostic testing by Chorionic Villus Sampling at 10-13 weeks of gestation/ Amniocentesis 16-20 weeks and preimplantation genetic testing option was also discussed.

Conclusion

- This case study highlights the importance of Carrier screening in a family with a genetic condition
- Prevention of unexpected genetic conditions and utilization of screening tools to monitor the pregnancy
- Importance of Preconceptional genetic counseling and genetic testing
- Utilization of available NGS Technology for improved family care.

References

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