Clinical Vignette

Rare Type of Epidermolysis Bullosa Associated with the *ITGB4* Gene: Journey with the Patient's Family

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Introduction

Next generation sequencing (NGS) is a boon for patients with rare monogenic disorders and their physicians. Epidermolysis bullosa (EB) is a genetic disorder with genetic and phenotypic variability. This report discusses the case of a neonate with a rare type of EB caused by biallelic pathogenic variants in the *ITGB4* gene and the long term follow up of the family as well as their reproductive decisions. Communication of the clinician with the laboratory on the one hand and with the patient's family on the other hand is necessary for the success of the diagnostic and genetic counseling process.

Case Report

A young father brought a photograph of his 10 days- old sick neonate admitted in another hospital. The photograph showed was consistent with the referral diagnosis of epidermolysis bullosa and showed patches of raw areas with some blisters over the entire body. Clinical exome sequencing was ordered to look for sequence variations in genes for EB. The parents were non-consanguineous and their first child had similar manifestations during the neonatal period and had succumbed to the illness. The father had brought 2 ml of blood of the neonate which was given to the laboratory (outsourced) with the clinical diagnosis of EB. The family reported that the baby died within the next few days. The report showed a truncating sequence variation c.4734dup (p.Asn1579Glnfs*35) in exon 36 of *ITGB4* gene in heterozygous form. This variant was not reported in 1000Genome and ExAC databases. The variant was predicted to be damaging by MutationTaster2. Biallelic variants in *ITGB4* gene are known to cause EB, junctional, non-Herlitz type (MIM #226650) and EB, junctional with pyloric atresia (MIM #226730). Epidermolysis bullosa of hands and feet, a mild form of EB has been reported in a patient with heterozygous mutation in the *ITGB4* gene (Jonkman et al., 2002). Since our subject had a severe phenotype, we requested the laboratory to re-analyse the data and look specifically for other sequence variants which could explain the phenotype. The laboratory reported another splice site variant in intron 24, c.2783-2A>A/G (3' Splice site) which was reported as likely pathogenic in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/RCV000190599/). Sanger sequencing confirmed the segregation of the variant c.4734dup in exon 36 in the mother in heterozygous form and c.2783-2A>G in intron 24 in the father in heterozygous form. This supported biallelic pathogenic sequence variations as the cause of severe type of EB in the neonate. However, the presence of a truncating variant and a lethal outcome in the baby suggested that the baby had probably EB, junctional with pyloric atresia rather than the EB, junctional, non-Herlitz type, which is mostly non lethal. While discussing the report with the parents, we specifically asked for history of vomiting in the neonate suggesting the possibility of pyloric obstruction. They confirmed that the baby was diagnosed to have pyloric stenosis and operated, but succumbed to the illness. This clinical information correlated with the causative gene and the type of pathogenic sequence variant identified.

The family was counseled about the recurrence risk of 25% in each offspring and the option of prenatal genetic testing through chorionic villus sampling in subsequent pregnancies. The couple discussed these issues with their obstetrician. In view of previous two Caesarean section deliveries, they were anxious and reluctant to terminate the pregnancy in case prenatal testing revealed an affected fetus. The obstetrician suggested the option of assisted fertilization with a donor gamete to minimize the risk of recurrence. The couple chose the option of donor sperm from an unrelated individual. However, the donor was not evaluated

for DNA sequence variations in the *ITGB4* gene. After successful conception the family reported at 15 weeks to consider the option of prenatal testing for EB. As the donor was unrelated, the possibility of the donor being a carrier for a rare variant in the *ITGB4* gene was considered negligible and prenatal genetic testing was not done. The family opted to continue the pregnancy with routine antenatal care.

Discussion

EB with pyloric atresia is a rare type of EB with associated non-dermatological features. Vidal et al. (1995) identified 2 mutations in *ITGB4* gene in compound heterozygous form in a patient with junctional epidermolysis bullosa associated with pyloric atresia. A gene that codes for another integrin subunit, *IGTA6*, is known to be associated with a similar phenotype of EB with pyloric stenosis (MIM #226730). Pyloric atresia may be the result of involvement of the gastrointestinal mucosa, as patients surviving the neonatal period later develop oesophageal, gut and genitourinary involvement (Mencía et al., 2016). Because of obstruction to the upper gastrointestinal tract, prenatal diagnosis by ultrasonography has been reported (Dural et al., 2014). Available literature suggests a genotype phenotype correlation, with truncating mutations being more common in the lethal variety of EB with pyloric atresia. Missense sequence variants have also been reported (Nakano et al., 2001). Mencia et al. (2016) reported 2 large deletions, 1 splice-site variant and 3 missense variants in 6 patients with EB with pyloric atresia.

This case highlights the importance of accurate phenotypic description and also good communication with the laboratory doing NGS analysis. Lack of genetic testing of the first similarly affected child and lack of timely referral to a medical genetics specialty unit lead to recurrence. Identification of disease-causing sequence variants provides an easy option of prenatal diagnosis which is mostly acceptable. However, with the repeated occurrence of a serious disorder, for some families the 25% risk of recurrence may not be acceptable and they may like to consider other options. Use of donor gamete is an option for prevention of autosomal recessive disorders. However, avoiding a related donor and preferably testing for the causative gene in the prospective donor should be considered. The family should be provided information about the rare possibility of the donor being a carrier for the same disorder, though the possibility may be extremely rare for such rare disorders. Also, the background risk of any birth defect and genetic disorder inherent in every pregnancy should be communicated to the family. The complexities of such situations are immense and good communication with the family is essential. Offering an option of donor gametes is also a delicate issue. If assisted reproductive techniques are considered for donor ovum or preimplantation diagnosis, the success rate of in vitro fertilization and increased risk of prematurity and birth defects as compared to natural conceptions, also need to be conveyed to the family to help in decision making.

To summarize, newer advances in technology offers unlimited diagnostic opportunities in medical genetics but simultaneously calls for the need of good communication skills for the clinician and the genetic counselor. Increasing awareness amongst clinicians and improving availability of genetic counseling services is the need of the hour. The accurate diagnosis of rare disorders is not only important for preventing recurrences, but also for pursuing the hope of novel treatment strategies as shown recently for EB (Hirsch et al., 2017) and ectodermal dysplasia (Schneider et al., 2018).

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References

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