Clinical Whole Exome Sequencing Reveals a De Novo PTPN11 Pathogenic Variant in Association with an Unusual Presentation of Noonan Syndrome

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Introduction

- Clinical features of Noonan syndrome include congenital heart defects, bleeding diathesis, characteristic facies, pulmonary valve stenosis, pulmonary artery stenosis, and cryptorchidism (Table 1). Although rare, there are isolated case reports of craniosynostosis in individuals with Noonan syndrome. Approximately 50% of individuals with Noonan syndrome have a pathogenic variant in PTPN11.
- Whole exome sequencing should be considered for clinical diagnostic assessment in patients with multiple congenital anomalies, including features that do not specifically correspond with a single unique genetic etiology. WES has been demonstrated to identify a clinical genetic diagnosis in 25-55% of patients undergoing assessment for features suggestive of a genetic condition (Yang 2014, Soden 2014, Willig 2015, Retterer 2015).

Case Presentation

- A male was born at 35 weeks by Cesarean section after premature rupture of membranes and placental abruption, weighing 1720 g and 45.9 cm long.
- Prenatal imaging by fetal MRI at 34 weeks gestation demonstrated right pulmonary agenesis, dextroposition of the heart and mediastinum, tracheoesophageal fistula with esophageal atresia, polyhydramnios and craniosynostosis. Clinical evaluation at birth confirmed right pulmonary agenesis with right-sided pulmonary artery agenesis and diaphragmatic hernia, dextrocardia, atrial septal defect, Type C tracheoesophageal fistula with esophageal atresia, asymmetric lambdoid suture craniosynostosis, low set ears, widely spaced nipples, short papebral fissures, prominent forehead and unilateral cryptorchidism (Figure 1, Figure 2). The patient was evaluated clinically by a geneticist with a working diagnosis of non-syndromic developmental field defect with a normal karyotype (46,XY).
- Following tracheoesophageal fistula repair on day 3 of life, the newborn required mechanical ventilation for 13 days followed by continuous supplemental oxygen. At 74 days of life, the patient had a successful endoscopic-assisted lambdoid suturoectomy and began occupational therapy and cranial modeling with helmet prophylaxis. At 3 months of age and 3500 g, the patient underwent a successful esophageal atresia repair. The post-operative course was complicated by pulmonary hypertension followed by pulmonary hemorrhage on post-op day 7, at which time the family elected ECMO. The patient remained on ECMO for 15 days. Following ultrasound observation of subdural and temporal lobe cerebral hemorrhage, ECMO was withdrawn and the infant expired 7 days later on day of life 118.

Methods

- Exome sequencing at GeneDx was performed on exon targets isolated by capture using Agilent Clinical Research Exome Kit.
- The sequencing methodology and variant interpretation protocol has been previously described (Tanaka et al. 2015).
- Criteria used to assess the pathogenicity of the variant include: frequency in general population, publication, in silico predictions, functional evidence, variant location, de novo. Data were analyzed prior to the implementation of the updated ACMG Standards and Guidelines for the classification of sequence variants.

Results

- The family elected post-mortem trio whole exome sequencing (WES) which identified a previously reported pathogenic variant: PTPN11 c.802G>T, p.Gly268Cys in exon 7 (PTPN11 NM_002834.3), consistent with a diagnosis of Noonan syndrome.
- Both parents were negative for this pathogenic variant, confirming a de novo presentation.

Conclusions

- Clinical whole exome sequencing has utility for patients with multiple congenital anomalies.
- In this case, while a diagnosis of Noonan syndrome was not clinically suspected, it was beneficial for the family in understanding the challenging peri-operative course and instrumental in emotional closure.
- Early diagnosis of a genetic disorder may have a significant impact on family counseling and management plan of a patient with complex medical and surgical issues.
- WES is optimally utilized as a clinical diagnostic tool but may also have benefit in the post-mortem setting as demonstrated in this case, with both emotional and potential reproductive implications.

References

2. Soden SE et al. (2014) Science Translational Medicine, 6(265):265ra68. (PMID: 25473038)

- Parental permission was obtained for photographs.