

 Theme: Genetics

**Exome sequencing aids in the treatment of a child with type I interferonopathy** (*N Engl J Med.* 2020; 382(3):256-65)

Ubiquitin-specific protease 18 (USP18) deficiency [Pseudo-TORCH syndrome 2 (MIM# 617397)], due to homozygous or compound heterozygous variants in *USP18*, is a severe monogenic autoinflammatory disorder. USP18 restricts the access of Janus-associated kinase 1 (JAK1) to type I interferon receptor, thus preventing excessive interferon signaling. Individuals with USP18 deficiency present in the neonatal period with intracranial calcification, hemorrhage, liver dysfunction, septic shock, and thrombocytopenia, resembling congenital intrauterine infections. A Saudi Arabian boy, born to first-cousin parents, and diagnosed in the first month was treated with oral ruxolitinib, a JAK1/2 inhibitor. The child showed clinical improvement and was discharged from the intensive care unit at 9 months. At 3 years of age, this child is the oldest surviving individual with this rare condition. The case reiterated the importance of a rapid genetic diagnosis by ES, which specifically helped in initiating therapy and changing the course of the illness.

**Genome sequencing in pediatric heart disease** (*Genet Med.* 2020;22:1015-24)

Congenital heart disease (CHD) is one of the most common anomalies in humans. The Cardiac Genome Clinic was established in the Hospital for Sick Children, Canada, to assess the utility of genome sequencing (GS) in children with heart diseases. Individuals from 111 families with cardiac diseases like cardiomyopathy, laterality defects, and outflow tract obstructions were recruited from January, 2017 to December, 2018. Trio/ quartet (child and parents) GS was done and data were generated for 328 individuals from 111 families. Using a specific research protocol for variant prioritization, candidate variants were identified. Causative pathogenic or likely pathogenic variants were identified in 14 of the 111 families (12.6%). Seven families had *denovo* variants in genes like *ANKRD11* (KBG syndrome), *KMT2D* (Kabuki syndrome), *NR2F2* (NR2F2-related CHD), *POGZ* (White-Sutton syndrome), *PTPN11* (Noonan syndrome), *PTEN* (PTEN hamartoma syndrome), and *SALL1* (Townes-Brocks syndrome). Novel candidate genes for cardiac phenotypes identified in this cohort were *FGD5*, *CDC42BPA*, *VASP* or *TLN2*, *TRPM4*, *SMARCC1*, *TPCN1*, and *UBXN10*. Structural variants of sizes ranging from 9.1kb to 8.3Mb were also identified and the detection rate was more than chromosomal microarray. The evidence generated in this study is likely to pave the way for GS as a first-tier diagnostic test for pediatric heart disease.

**Ultra-rapid exome sequencing in critically ill children with monogenic conditions** (*JAMA.* 2020;323:2503-11)

This study was conducted in Australia to evaluate the utility of ultra-rapid exome sequencing in critically ill pediatric patients with suspected monogenic diseases. A total of 108 patients were recruited prospectively from neonatal and pediatric intensive care units from March, 2018 to February, 2019. Trio exome sequencing was performed in 105 families and singleton exome was performed in three families. The median age of study participants was 28 days (range 0-17 years). 62 patients were from NICU (57%), 36 from PICU (33%) and 10 were from other hospital wards. The majority of patients had neurological symptoms like seizures or hypotonia. The mean time from sample receipt to the generation of a report (primary outcome) was 3.3 days (95% CI, 3.2-3.5 days). Fifty-six genetic conditions were diagnosed in 55 patients (51%). Two novel candidate genes were identified. A change in clinical management after the report was observed in 44% patients. The diagnosis helped in targeted therapy in 12 patients (11%), palliative care discussions in 14 patients (13%), and surveillance plans in 19 patients (18%). The authors underlined the need for more evidence for assessing the clinical utility of ultra-rapid exome sequencing in other settings.

**Genetic causes of neonatal encephalopathy** (*Clin Genet.* 2020 Jul 26. 10.1111/cge.13818)

Neonatal encephalopathy is a common condition that presents in the newborn period with seizures, altered consciousness, poor muscle tone, and abnormal electroencephalogram, and magnetic resonance imaging of the brain. The authors recruited 366 neonates with encephalopathy from 2015 to 2017, and performed trio/singleton exome sequencing. A definitive molecular diagnosis was established in 43 neonates (11.7%), with pathogenic or likely pathogenic variants. The variants were identified in 30 genes which were classified into four different categories: epileptic (58.5%), metabolic (18.9%), mitochondrial (3.8%), and syndromic-related genes (18.9%). The most common genes to be involved were *KCNQ2* and *SCN2A*, causing epileptic encephalopathy. On follow up, it was observed that death rate and severe development delay were higher in neonates with a genetic diagnosis. Several personalized therapeutic interventions were possible in some of the genetic neonatal encephalopathies. Thus exome sequencing should be considered in the workup of neonatal encephalopathy.

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