Case Study: **XomeDx used to diagnose a child with mild Rubinstein-Taybi syndrome**

**Clinical Overview:**
A 6-month-old infant presents to a genetics clinic with a history of developmental delay (DD), hypotonia, dysmorphic facies and an atrial septal defect (ASD). The parents are healthy and there is no family history of a similar disorder. The geneticist initially suspects DiGeorge syndrome. However, after a karyotype, an array CGH and TBX1 sequencing are all normal, the physician rules out DiGeorge syndrome and orders whole exome sequencing. XomeDx is performed on the infant and the two parents, and a de novo nonsense mutation is identified in the EP300 gene, leading to a diagnosis of Rubinstein-Taybi syndrome.

**Patient Information:**
- **Age:** 6 months
- **Specimen:** Blood
- **Prenatal History:** IVF conception
- **Clinical History:** DD, hypotonia, mild dysmorphic features, ASD
- **Family History:** None
- **Previous Testing:**
  - Karyotype: Normal
  - Array CGH: “likely benign variant”, maternally inherited
  - TBX1 sequencing: Negative

**Diagnostic Summary:**
**POSITIVE.** De novo R1281X mutation in the EP300 gene.

**XomeDx:** Whole exome sequencing was performed on the proband and both parents. The resulting data was filtered to identify clinically significant variants, under various inheritance models. A search for de novo changes revealed the EP300 R1281X mutation. Sanger sequencing confirmed the mutation was present in the proband, and absent from each parents’ sample. EP300 is a rare (3-4%) cause of Rubinstein-Taybi syndrome (RTS).\(^1\) RTS is typically de novo and is characterized by distinctive facial features including downsloping palpebral fissures, beaked nose, and a high arched palate, as well as broad thumbs and great toes, short stature, and moderate to severe intellectual disability.\(^1\) To date, roughly nine EP300 mutations associated with RTS have been reported in the literature, all of which are predicted to result in protein truncation or haploinsufficiency.\(^2\) Some literature suggests that patients with EP300 mutations may have a milder presentation than those with CREBBP mutations.\(^3\)

**Diagnostic Implications:**
Now that the molecular cause of the child’s symptoms is identified, the parents are told that their child has a clinical diagnosis of RTS. The family is counseled about the prognosis and management of RTS, and given information about an RTS patient advocacy organization. It is explained to the parents that the cause of their child’s disorder is de novo and that the chance of having another child with this condition is roughly 0.1%, due to the risk of germline mosaicism.\(^1\) The identification of the molecular basis of their child’s condition allows the family to consider management needs and family planning options, including pre-implantation genetic diagnosis (PGD) in conjunction with IVF, or prenatal diagnosis.

**References:**