Microcephaly and Tracheoesophageal Fistula in a newborn with *PNKP* mutation

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Microcephaly is highly heterogeneous and making a genetic diagnosis is therefore challenging in young infants where recognizable phenotypes may be lacking. In this setting NGS panels, or whole exome sequencing (WES) may be the optimal approach to diagnosis. We present a full-term male infant with primary microcephaly and distal type 3 tracheoesophageal fistula (TEF). He was the first child for a 21year old mother and 23 year old father of Ashkenazi Jewish descent, with no history of consanguinity. Microcephaly was initially noted on prenatal ultrasound at 32 weeks with head circumference plotting at the 8th percentile, progressing to 0 percentile by 38 weeks. Distal type 3 TEF was diagnosed after birth. Examination was notable for microcephaly (28.5cm, Z score - 4.28), with overriding sutures and no palpable anterior fontanel. He was otherwise non-dysmorphic and active with normal strength, tone and intact neonatal reflexes. CT head did not show craniosynostosis. MRI of the brain showed a structurally normal brain but small cerebral hemispheres, prominent subarachnoid spaces and small calvarium. Renal ultrasound showed a right pelvic kidney. No cardiac defects or other anomalies were present. He underwent uncomplicated surgical repair of the TEF at 1 week of life. At 2 months age, he began to have intractable seizures. By 8 months, he showed significant global developmental delays and had occasional seizures on Keppra and Topamax. His head circumference was 33 cm, 0 percentile (Z score -8.6). EEG showed diffuse cerebral dysfunction and potential epileptogenicity of bilateral frontal and temporal regions. The patient's presentation initially prompted consideration of VACTERL association or Fanconi anemia, though the severity of microcephaly was unusual. Genetic testing included normal chromosome analysis, microarray and DEB breakage studies. Clinical diagnostic exome sequencing (DES) revealed a homozygous missense mutation in exon 15 of the Polynucleotide kinase 3'-phosphatase (*PNKP*) gene (NM_007254, c.1385 G>C, p.R462P). Co-segregation analysis revealed biparental inheritance from his heterozygous unaffected mother and father. Mutations in *PNKP* have been associated with adult onset ataxia-oculomotor apraxia type 4 in Portugese families (AOA4, OMIM #605610), as well as microcephaly, seizures and developmental delay (MCSZ, OMIM#613402). MCSZ is characterized by primary microcephaly, global developmental delay, and early infantile epileptic encephalopathy with refractory early onset seizures. Some affected patients appear to have a shared behavioral phenotype with hyperactivity (Shen et al. 2010). Our patient's mutation was previously reported in a female infant, also in homozygous form, with microcephaly, developmental delays and intractable seizures. Her phenotype included primordial dwarfism, brain atrophy, agenesis of the corpus callosum, and choanal atresia (Nair et al. 2016). This appears to be the first report of *PNKP* mutations with birth defects in the VACTERL

spectrum. The PNKP enzyme has an important role in DNA repair and further investigation is required to characterize this association, which is also noted in Fanconi anemia, another disorder of DNA repair. Lastly, early diagnosis achieved through WES was important in order to understand prognosis, provide appropriate interventions and for future family planning for the parents.