Diagnostic Exome Sequencing Identifies Alterations in *GLI2* and *PTCH1* in a Previously Undiagnosed Patient with Holoprosencephaly, Seizures, and Hypopituitarism

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Here we describe a 20 year old female who was found to have alterations two genes in the same molecular pathway through diagnostic exome sequencing (DES). DES analysis of the trio revealed that the proband inherited the *GLI2* c.562delG (p.A188Rfs*7) from the unaffected father causing a translational frameshift with a predicted alternate stop codon. These types of alteration are typically considered deleterious in nature. *GLI2* is located on chromosome 2q14.2 and encodes for a vertebral transcription factor that is involved in PTCH1 expression and SHH signal transduction. Mutations are associated with autosomal dominant holoprosencephaly 9 (HPE9). HPE9 has partial penetrance and a variable phenotype, which can include seizures, hypopituitarism, and hypotelorism to full cyclopia.

The proband also inherited a missense alteration *PTCH1* c.4171C>T (p.R1391W) from the unaffected mother. This alteration is considered a variant of uncertain significance. *PTCH1* (Drosphila 'Patched', *PTC*, or *PTCH*) gene, located on 9q22.32, encodes for a transmembrane tumor suppressor protein that is part of the hedgehog signaling pathway. Although typically associated with nevoid basal cell carcinoma syndrome (Gorlin syndrome), but gain of function alterations have been described in families with holoprosencephaly type 7 (HPE7) because of suppression of *PTCH1* in the SHH pathway. Asymptomatic carrier parents have been previously reported, along with familial phenotypic variability.

The patient was born at term by C-section for low lying breech position following a pregnancy complicated by IUGR and oligohydramnios. An unusual head shape was noted prenatally on ultrasound. At birth she was noted to have dysmorphic features, significant GE reflux and retrognathia with glossoptosis and laryngomalacia. She has a single central incisor. Head MRI at 4 months of age showed possible absent anterior pituitary and pan hypopituitarism was diagnosed. Hearing loss was noted in one ear and 2 years of age and bilateral cataracts at age 5 years. She was G-tube fed for 3 years and had a tracheostomy for 2 years. She has a narrow forehead and hypotelorism, hearing loss, and had one lesion on her skin that was biopsied and shown to be an epidermal nevus. All genetics studies over the years were normal. Development has been delayed but she is now a verbal 20 year old who has good life skills and is being trained to work with animals.

To our knowledge this is only the second patient to be reported with double heterozygous alterations in *GLI2* and *PTCH1*. The previously reported patient and first case detected by DES (Rahmimov et al, 2006) was a 5 year old female with bilateral cleft lip/palate, malocclusion, diminished frontonasal angle, hypoplastic anterior nasal spine, hypotelorism, hypoplastic

premaxilla, hypoplastic nose, large ears, and poorly developed philtrum. MRI demonstrated mild gyral asymmetry in the perisylvian areas.

Our patient demonstrates similarities with both HPE7 and HPE9, as well as similarities with the previously reported patient with alterations in both *GLI2* and *PTCH1*. Overall, evidence supports the alteration found in the *GLI2* gene is the most likely cause of the patient's phenotype while the contribution of the *PTCH1* alteration cannot be determined at this time. However, the previously reported case supports that an oligogenic effect and interactions between these genes can produce a phenotype and so cannot be ruled out.