Supplemental Information

Supplementary Clinical Information

Patient 1: **variant/inheritance:** c.2590C>T, p.(Arg864*); maternal inherited; There was evidence for mosaicism of this variant in the mother that was confirmed by both whole exome sequencing (with 175 reference reads and 35 alternate reads at this position) and the Sanger sequencing traces. A more even distribution (120 reference reads, 79 alternate reads) was observed at this position in the proband, which is suggestive of a heterozygous variant that is present in all cells tested (which also matched the observed Sanger traces for the proband). This variant was not detected in the father; **age at last visit:** 16 months **sex:** male; **ethnicity:** Asian and Caucasian**; brain imaging:** normal brain MRI at 5 months of age **; developmental history:** gross motor delay, crawling at 16 months, no language at 16 months; **gastrointestinal history:** poor feeding and aspiration, status-post Nissen fundoplication and now requiring g-tube; failure to thrive **other**: umbilical hernia; hypertelorism, low set ears, high arched palate, fifth finger clinodactyly; palate, fifth finger clinodactyly; *

Patient 2: **variant/inheritance:** c.2542delT;p.Cys848Valfs*66; *de novo*; **age at last visit:** 10 years; **sex:** male; **ethnicity:** Caucasian; **growth parameters:** normal height and weight, OFC at -2 SD; **brain imaging:** brain MRI at 4y 8 m was normal, without corpus callosum agenesis; **developmental history:** sensorial hypersensitivity; walked at 12; delayed language (first associations at 3.5-4 y.), toilet trained (night and day) at 2y3m; severe ADHD, motor and verbal dyspraxia, autism spectrum disorder, and psychologic evaluation concluded mild intellectual disability; **ptosis surgery:** left sided ptosis requiring surgery; **skull shape:** plagiocephaly; skull X-ray at 8 months showed small anterior fontanel; a skull X-ray realized few years later showed no craniosynostosis;, **gastrointestinal history:** feeding issues include refused solid food; **other**: multiple night awakenings; hyperopia, astigmatism/surgery for left cryptorchidism, and small umbilical hernia

Patient 3: **variant/inheritance:** c.831_834del p.(Arg277Serfs*26); *de novo;* **age at last visit:** 6 years; **sex:** male; **ethnicity:** Caucasian; **brain imaging:** MRI normal; **developmental history:** motor/speech delay; walked at 2y2m; **ptosis surgery:** none; **gastrointestinal history:** severe feeding difficulties; gastrostomy tube required; **other**: internal ear malformation (dysplasie des canaux semicirculaires), laryngomalacia, interventricular septal defect, bicuspid aorta

Patient 4: **variant/inheritance:** c.6214_6215del p.(His2072fs*8); *de novo;* **age at last visit:** 2 years and 7 months; **sex:** male; **birth history:** birth weight 3760 g; **growth parameters:** height last exam 86,1 cm (-2.33 SD); head circumference last exam 48 cm (-1.26 SD); **brain imaging:** no MRI done yet; **developmental history:** speech delay; **skull shape:** dolichocephaly, biparietal narrowing; **gastrointestinal history:** severe feeding problems from birth**; other**: unexplained episodes of fever, triangular teeth lower jaw

Patient 5: **variant/inheritance:** c.763C>T; p.(Arg255*); paternal*;* **age at last visit:** 14 years**; sex:** female; **ethnicity:** Latin American **; brain imaging:** none completed to date; **developmental history:** individualized education program (IEP), special education; ADHD requiring medications; mixed receptive-expressive language disorder**; gastrointestinal history:** none; **other**: cleft palate, amblyopia and anisometropia, hearing loss; father has same variant and required surgery for ptosis; she has been carrying clinical diagnosis of Saethre-Chotzen based on acrocephalosyndactyly; eczema and asthma; refractive amblyopia; hearing decreased;

Patient 6: **variant/inheritance:** c.7057-2A>G**;** *de novo;* **age at last visit:** 7 months; **sex:** female; **birth history:** birth weight was 2.905kg/6lb 6.5oz (55th centile); birth length was 48cm (55th centile), birth OFC: 30cm (<2nd centile) for 36 6/7 weeks gestation; **growth parameters:** at 7 months: OFC 38.5cm <2nd centile (50% for 3m); height 61.2cm <1st centile (50% for 3.5m); **brain imaging:** MRI did not detect structural differences**; developmental history:** early developmental delay: at 7m attempting to sit, transfers objects hand to hand**; ptosis surgery:** right sided ptosis, no surgery to date; **skull shape:** normal shape, microcephaly**; gastrointestinal history:** NG tube started early for concern of aspiration pneumonia with swallow study; **other**: close nipples at birth (<3%ile), prominent creases on hands and feet, ears had prominent crus bilaterally with railroad tracking squared off at top; VSD;

Patient 7: **variant/inheritance:** c.6794dup (p.(Tyr2265*); *de novo*; **age at last visit:** 13 years; **sex:** male; **ethnicity:** Caucasian; **brain imaging:** none; **developmental history:** autism spectrum disorder; **skull shape:** metopic ridge; **other**: originally diagnosed with branchio-oto-renal syndrome, double urinary system, a median branchial cyst and prominent ears with ear pits. DNA testing for BOR (SIX1, EYA1), SNP array, and whole exome sequencing for renal diseases were all negative; glossptosis (he had a frenulectomy), mild hearing loss, and hypodontia (2 permanent teeth). He has a small mandible, mild facial asymmetry, and a full lower lip, tip, pectus excavatum.

Patient 8: **variant/inheritance:** c.882dupC p.(Ser295fs*64); *de novo;* **age at last visit:** 2 years; **sex:** male; **ethnicity:** Caucasian; **brain imaging:** agenesis of corpus callosum; **developmental history:** delayed speech; **ptosis surgery:** ptosis present but no surgery; **skull shape:** normal; **gastrointestinal history:**

Patient 9: **variant/inheritance:** c.4165C>T, p.Gln1389*; *de novo;* **age at last visit:** 15 years; **sex:** male; **ethnicity:** Caucasian; **growth parameters:** height 75th centile, weight 75th centile, OFC +2SD; **brain imaging:** no imaging done; **developmental history:** global developmental delay, mild intellectual disability; mainstream school with extra assistance; **ptosis surgery:** none; **skull shape:** normal head shape; **gastrointestinal history:** struggled to breast feed; **other**: low set ears

Patient 10: **variant/inheritance:** c.1234_1235insAA; p.Ser412*fs; unknown inheritance; **age at last visit:** 8 years; **sex:** male; **birth history:** born by C-section at 40 weeks gestation; birth weight: 2.977 kg (6 lb. 9 oz); HC 49.5 cm (19.49");

Apgar five: 9, ten: 9; 2 vessel cord noted prenatally; **growth parameters:** weight 27.2 kg (53th centile), height 17 119.5 cm (3rd centile), OFC 50.8; **brain imaging:** MRI normal**; developmental history:** ADHD; receptive/ expressive language disorder, early intervention counseling, speech and occupational therapy received ; sensory processing condition, IEP for communication impairment in addition to a math disability. **ptosis surgery:** bilateral ptosis repair; **gastrointestinal history:** dysphagia, eosinophilic esophagitis and possible reflux; **other**: transient tic; motor apraxia; evaluated by pediatric endocrinology for short stature. mild low tone; bilateral tympanostomy tube placement; inner ear surgery for perforated ear drum; simple, mildly cupped ears; prominent nasal root; retrognathia

Patient 11: **variant/inheritance:** c.6214_6215del p.(His2072Tyrfs*8); *de novo;* **age at last visit:** 2.5 years; **sex:** female; **developmental history:** normal; **ptosis surgery:** bilateral ptosis but no surgery; **gastrointestinal history:** feeding dysfunction requiring a G-tube; **other**: hypotonia;

Patient 12: **variant/inheritance:** c.2049dup p.(Pro684Serfs*14); *de novo;* **age at last visit:** 9 months; **sex:** male; **ethnicity:** Caucasian; **brain imaging:** normal brain MRI; **developmental history:** developmental delay: gross motor skill delay; **ptosis surgery:** ptosis present but no surgical correction; **skull shape: gastrointestinal history:** no feeding issues;

Patient 13: **variant/inheritance:** c.6631delC; p.Arg2211Glyfs*59; *de novo***; age at last visit:** 8 years 7 months; **sex:** male; **ethnicity: birth history:** birth weight 3710g; **growth parameters:** height 107 cm at 5yo (25-50 centile); OFC 53cm at 8y7m (68th centile); **brain imaging:** MRI not done; **developmental history:** normal; **ptosis surgery:** ptosis surgery completed; **other**: blocked lacrimal ducts bilaterally; brachydactyly with 5th finger clinodactyly bilaterally

Patient 14: **variant/inheritance:** c.2695G>T; p.(E899*) unknown inheritance; **age at last visit:** 8 years; **sex:** female; **brain imaging:** normal brain MRI; **developmental history:** participant in life skills program; currently in grade 3 in a special class; **ptosis surgery:** no ptosis; **gastrointestinal history:** NG tube in neonatal period; **other**: wide forehead; deep-set eyes; hypertelorism, broad nasal root, hypoplastic alae nasi, full eyebrows with lateral flare, smooth philtrum, thin upper lip, transverse smile; strabismus; mild eczema; poor sleep (4-6 hours per night); ADHD

Supplementary Table 1. Binary comparisons for mean results.

BINARY COMPARISONS	CASES	FRONTAL IMAGES	MEAN AUC	AUC STD
ZNF462 vs. Noonan syndrome	21 vs. 16	21 vs. 16	0.97	0.02

BINARY COMPARISONS	CASES	FRONTAL IMAGES	MEAN AUC	AUC STD
ZNF462 vs. Unaffected Controls (for "Cohort 1 - ZNF462")	21 vs. 21	21 vs. 21	0.96	0.03

AUC, area under the curve; STD, standard deviation

Supplementary Figure 1. Receiver operating characteristic for aggregated splits.