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Phenotypic expansion of *POGZ*-related intellectual disability syndrome (White-Sutton syndrome)

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Conflict of Interest:

Baylor College of Medicine (BCM) and Miraca Holdings Inc. have formed a joint venture with shared ownership and governance of BG, formerly the Baylor Miraca Genetics Laboratories (BMGL), which performs clinical exome sequencing and chromosomal microarray analysis for genome-wide detection of copy number variants. J.R.L. serves on the Scientific Advisory Board of BG. J.R.L. has stock ownership in 23andMe, is a paid consultant for Regeneron Pharmaceuticals, and is a co-inventor on multiple United States and European patents related to molecular diagnostics for inherited neuropathies, eye diseases and bacterial genomic fingerprinting. V.R.S serves on the medical advisory board of the White-Sutton Syndrome Foundation. The other authors declare no conflict of interest.

Abstract

White-Sutton syndrome (WHSUS) is a recently-identified genetic disorder resulting from *de novo* heterozygous pathogenic variants in *POGZ*. Thus far, over 50 individuals have been reported worldwide, however phenotypic characterization and data regarding the natural history are still incomplete. Here we report the clinical features of 22 individuals with 21 unique loss of function *POGZ* variants. We observed a broad spectrum of intellectual disability and/or developmental delay with or without autism, and speech delay in all individuals. Other common problems included ocular abnormalities, hearing loss and gait abnormalities. A validated sleep disordered breathing questionnaire identified symptoms of obstructive sleep apnea in 4/12 (33%) individuals. A higher-than-expected proportion of cases also had gastrointestinal phenotypes, both functional and anatomical, as well as genitourinary anomalies. In line with previous publications, we observed an increased body mass index (BMI) z-score compared to the general population (mean 0.59, median 0.9; p 0.0253). Common facial features included microcephaly, broad forehead, midface hypoplasia, triangular mouth, broad nasal root and flat nasal bridge. Analysis of the Baylor Genetics clinical laboratory database revealed that *POGZ* variants were implicated in approximately 0.14% of cases who underwent clinical exome sequencing for neurological indications with or without involvement of other body systems. This study describes a greater allelic series and expands the phenotypic spectrum of this new syndromic form of intellectual disability and autism.

Keywords

POGZ; intellectual disability; autism; developmental delay; speech delay

Introduction

The growing application of comprehensive genomic sequencing has led to a multitude of novel gene discoveries (Choi et al., 2009; Ng et al., 2010; Posey et al., 2019; J. J. White et al., 2018). Traditionally, analysis of cohorts of individuals with shared phenotypic features has led to identification of disease-causing genes and pathways; however, it is increasingly common that genetic etiologies are identified, and subsequent deeper characterization of patient cohorts can identify shared phenotypes to define a new syndrome using a gene- or genotype-first approach. Delineating the full phenotypic spectrum for Mendelian conditions has important implications for guiding diagnostic testing and informing expectant management, and potentially directing development of targeted therapeutic intervention.

The analysis of variations in the pogo transposable element with zinc finger domain gene (*POGZ)* that led to the identification of White-Sutton Syndrome (WHSUS, OMIM: 616364) is an example of this “genotype-first” approach. WHSUS results from *de novo* heterozygous pathogenic variants in *POGZ* on chromosome 1q21.3. There are 21 isoforms in ENSEMBL (Zerbino et al., 2018), five of which correspond to curated RefSeq/concensus CDS isoforms. The longest transcript (ENSEMBL Transcript ID: ENST00000271715.6, RefSeq: NM_015100.3) has 19 exons, of which 18 are coding (exons 2-19). *POGZ* is constitutively expressed across most tissues, particularly the pituitary and cerebellum (Stessman et al., 2016). The protein encoded by this gene has a zinc finger cluster, an HP1-binding motif, a

centromere protein-B-like DNA binding (CENPB-DB) domain and a transposase-derived DDE domain (Nozawa et al., 2010). It acts as a regulator of chromatin remodeling and plays a role in chromosomal segregation and mitotic progression through the assembly of the kinetochore, interactions with HP1α and activation of aurora B kinase. It is also involved in regulation of neuronal proliferation (Nozawa et al., 2010). Expression is highest in the embryonal period around week 8-9 of gestation, decreases gradually until birth, and remains at low levels into adulthood (Stessman et al., 2016).

Prior to the characterization of WHSUS, variants in *POGZ* had been reported in several large cohorts of subjects with intellectual disability, developmental delay and autism spectrum disorder (Deciphering Developmental Disorders, 2015; Fromer et al., 2014; Gilissen et al., 2014; Iossifov et al., 2014; Neale et al., 2012), and subsequently *POGZ* was reported to be one of the most recurrently mutated genes in intellectual disability and autism (Matsumura et al., 2016). It was only after the observation that subjects with pathogenic variants in *POGZ* also shared similar facial characteristics as well as other phenotypic features that this became recognized as a pleiotropic intellectual disability syndrome (J. White et al., 2016; Ye et al., 2015).

To date, over 50 cases have been reported in the literature (Dentici et al., 2017; Du et al., 2018; Fromer et al., 2014; Fukai et al., 2015; Gilissen et al., 2014; Gulsuner et al., 2013; Hashimoto et al., 2016; Homsy et al., 2015; Iossifov et al., 2014; Longoni et al., 2017; Matsumura et al., 2016; Neale et al., 2012; Stessman et al., 2016; J. White et al., 2016; Yavarna et al., 2015; Ye et al., 2015). Here we report insights from an allelic series of 21 distinct *POGZ* variants in 22 individuals with WHSUS. The results of this study provide additional information on the natural history, genotypic architecture and genotype-phenotype correlations associated with *POGZ*.

Methods

Editorial Policies and Ethical Considerations

The study was approved by the Baylor College of Medicine Institutional Review Board (IRB).

Recruitment and data collection

Subjects were recruited through clinicians and self-referral. Participants were also recruited through the White-Sutton Syndrome Foundation website (whitesuttonsyndrome.org) and Facebook® group. Medical information including genetic test results were collected from subjects and healthcare providers. In order to collect a more detailed and consistent set of phenotypic data across the cohort, a clinical survey was sent to all but one participating families, for whom contact information was no longer available. The survey entailed potential medical conditions in the participants, their developmental milestones, as well as a sleep disordered breathing questionnaire (Chervin, Hedger, Dillon, & Pituch, 2000). For functional gastrointestinal disorders, definitions for diagnostic criteria of diarrhea, constipation and cyclic vomiting were provided based on the Rome IV Criteria

(Zeevenhooven, Koppen, & Benninga, 2017). The detailed survey can be found in the Supplementary Materials.

Data on height and weight from clinic measurements and parental reports were used to calculate body mass index (BMI). BMI z-scores were plotted from age-based pediatric growth reference charts for children ages 2-20 years based on publicly available data from the National Health and Nutrition Examination Survey (Centers for Disease Control and Prevention, U.S. Department of Health and Human Services) using an online tool (https://www.bcm.edu/bodycomplab/Flashapps/bmiVAgeChartpage.html, USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine, Houston, Texas).

POGZ Variants in the Baylor Genetics Laboratory Database

In addition, we sought to estimate the frequency of pathogenic/likely pathogenic variants in *POGZ* in cases with autism and/or intellectual disability. The Baylor Genetics (BG) clinical laboratory database (which contains over 12,500 clinical exomes) was queried for *POGZ* sequence variants based on categories for testing. Categories in the BG database include "neurological", "neurological plus other organ systems" and "non-neurological"; cases where no category was assigned by the lab are "uncategorized". The search was then narrowed to specific indications including autism spectrum disorders, developmental delays, intellectual disability/learning difficulties and attention deficit hyperactivity disorder (ADHD). Limited, de-identified clinical information was extracted for these subjects for statistical purposes only, unless specifically consented for the study.

Results

Overview

Molecular data for subjects in the study are summarized in Table 1. Twenty-two individuals from 21 families (PT22 is the mother of PT21) with pathogenic/likely damaging *POGZ* variants enrolled in the study, including 15 males and seven females. Detailed clinical information was obtained from medical records and parental report and was included for phenotypic characterization. Of these individuals, two had previously been included in other *POGZ*-related publications: PT15 (J. White et al., 2016) and PT12 (Ye et al., 2015).

Twenty-one distinct variants in *POGZ* were identified, including 20 sequence variants and one 32kb deletion. Eighteen of the sequence variants were detected through clinical exome sequencing. PT10 and PT11 were diagnosed through the Deciphering Developmental Disorders (DDD) study (Deciphering Developmental Disorders, 2015) and results were reviewed through a clinical laboratory. PT25 was diagnosed through the Simons Powering Autism Research (SPARK) and the *POGZ* variant was confirmed by Sanger sequencing. Variant data were obtained from lab reports that were available for all but three of the cases (PT1, PT12, PT20), for which data were provided by the subjects' clinicians.

For some of the subjects, results of prior genetic testing were available either through lab reports or clinical notes describing those studies. These tests, including chromosomal microarray analysis (CMA) and targeted gene analysis, were generally normal/non-diagnostic. Variants of uncertain clinical significance (VUS) in genes other than *POGZ* were

reported in five subjects, however upon review, these variants either did not fit the phenotype, single variants were reported for autosomal recessive disorders or the variant was inherited from a phenotypically normal parent. PT17 also had a pathogenic variant and a VUS in *GJB2*, a gene known to be associated with hearing loss. He had a history of mild to moderate hearing loss with right eustachian tube dysfunction and left middle ear effusion, however repeat hearing evaluation was normal. In one subject, an incidental finding of a heterozygous pathogenic variant in the *LDLR* gene associated with familial hypercholesterolemia was detected. Results of additional genetic testing for the subjects in the cohort can be found in Supplementary Table 1.

POGZ variants

Twenty-one distinct *POGZ* heterozygous variants were identified in 22 individuals. Eighteen variants occurred *de novo*, and one (PT21) was inherited from a mother who has mild intellectual disability and obesity (PT22). Based on exome and Sanger sequencing data there was no evidence to suggest mosaicism in the mother, in whom the variant was detected in 19 out of 56 total reads on next generation sequencing; however, given that the assay was not designed to detect mosaicism and that genetic testing was performed on one tissue type, mosaicism cannot be excluded. Parental data were unavailable for the mother (PT22) and two other individuals in the study. Twelve of the 21 variants (57%) involved exon 19, the last and largest exon. The data that support the findings of this study are available from the corresponding author upon reasonable request.

All 21 variants in the cohort are truncating or splice-site variants. Nineteen are variants predicted to lead to a premature termination of the protein, including one large deletion encompassing exons 4-19 of the gene, ten missense variants and eight indels leading to frameshifts. Six of the truncating variants are predicted to undergo nonsense-mediated RNA decay (NMD) by computational analysis and 13 are predicted to escape NMD (Coban-Akdemir et al., 2018).

Two variants occurred at splice sites and are predicted to likely obliterate the wild type acceptor sites at exon 4 (c.460-2A>C) and exon 17 (c.2433-1G>A) (Desmet et al., 2009). The former affects all but one RefSeq curated transcript of the gene. All the other variants in the study affect all curated transcripts.

Figure 1 shows a schematic representation of *POGZ* variants in the present study and variants from previous reports in the literature.

Presentation and time to diagnosis

Reasons for genetic evaluation were neurobehavioral and neurocognitive disorders in the majority of subjects, including developmental delay, learning difficulties, intellectual disability and autism. PT 22 was identified following molecular diagnosis of her son (PT 21). Two subjects also had significant gastrointestinal abnormalities including intussusception (1 subject) and malrotation (1 subject). One subject presented with congenital diaphragmatic hernia. Ages at first medical evaluation ranged from one week (presenting with birth defects) to 28 years (subject seen for calcinosis cutis, and noted to have mild intellectual disability and polydactyly). Median age at diagnosis was eight years,

and the time from initial concern to diagnosis ranged from two months to over 15 years. Paternal ages at time of birth of individuals in the cohort ranged from 26 years to 46 years (mean 34 years, median 33 years); maternal ages ranged from 24 years to 44 years (mean 33 years, median 32.5 years).

Phenotypic features

Clinical features were ascertained from available records from clinic visits, history provided by the parents, review of photographs and from family survey.

a. Growth parameters and facial features—Description of facial characteristics was available from clinic notes and/or patient photos for 18 of the subjects. The most common features included a high and broad forehead, tented or triangular mouth with downturned corners of the mouth, midface hypoplasia or retrusion, a broad nasal root and flat nasal bridge. Five individuals had anteverted nares. Two subjects had a bifid uvula, and one subject had a high-arched palate. Protruding tongue was seen in four of the subjects, and at least three subjects had widely-spaced teeth. Ear abnormalities included overfolded or abnormally-folded helices or pinna anomalies in four subjects, low-set ears in eight subjects and pre-auricular skin tags in one subject. Figure 2 depicts subjects from the study and Table 2 summarizes the main facial features noted in the cohort.

Growth parameters were documented from clinic visits or reported for 15 subjects. Body mass index (BMI) z-scores were calculated for 14 of the subjects who had height and weight measurements at ages between two and 20 years (the ages for which standardized growth charts are available). Z-scores ranged from −1.9 to 2.1, median 0.9, mean 0.59. Nine subjects (9/14, 64.3%) had a BMI in the healthy range, three were overweight (3/14, 21.4%), one was obese (1/14, 7.1%) and one was underweight (7.1%). These results indicate a higher average BMI in this group compared to the general population. The results are statistically-significant using a one-sided *t*-test (p 0.0253) but borderline using a two-sided *t*-test (p 0.0506). Data were available for two additional adult patients over age 20 years; both had BMIs in the range of obesity. Overall, 6/16 (37.5%) were overweight or obese. Height and weight below the 3rd percentile were present in 2/16 (12.5%) individuals.

b. Neurocognitive development—Neurocognitive and neurobehavioral symptoms were a global feature of cases in the cohort, however the degree to which they were affected varied greatly. Presentations ranged from severe developmental delays to high-functioning individuals with low-normal intelligence, with or without autism spectrum disorder. It is notable that the majority of cases had mild to moderate delays. One subject (PT13) was intellectually on the low average level for age but had dyspraxia, abnormal executive function, problems with visuo-spatial planning and working memory as well as difficulties with “affect recognition”.

Speech delay was universal, and seven subjects were non-verbal at time of assessment, ages ranging from two to 16 years. One subject (PT15) had an articulation disorder and a receptive-expressive language disorder. At age seven years he was noted to speak at an 18-month level (two-word sentences) although from a cognitive standpoint he only had mild intellectual disability. PT13, who also had cerebellar involvement, had delayed emergence of

speech. While she said her first word around the age of one year, she did not use sentences until around the age of five years. Some degree of motor delay was reported for 19/22 (86%) patients (delay was questionable in one additional case). Figure 3 depicts age at acquisition of developmental milestones of subjects in the study compared to the general population.

Six subjects had been diagnosed with autism spectrum disorders and three additional cases had some features consistent with autism. Behavior problems or disruptive behavior that included biting and aggression towards others was reported for six individuals, four of whom had a diagnosis of autism. Another individual had temper tantrums as a toddler, however as an older child she was social and did not have behavioral problems.

The neurocognitive features are summarized in Table 3.

c. Neurological abnormalities—Hypotonia was noted in all subjects for whom neurological exam findings were available (17/17, 100%). Five out of 17 subjects (30%) had seizures of different types (including generalized tonic-clonic, partial seizures, drop attacks, staring spells and absence) starting as early as the first weeks of life and as late as age 16 years. A sixth subject had episodes of “absence” but no medical diagnosis of seizures at the time of report. Seizures generally responded to one or two medications, but in two cases the treatment regimen was influenced by behavioral problems resulting in change of treatment or addition of other medications. Reports of head imaging were available for 15 subjects, and results were abnormal in 10/15 (67%). Findings included nonspecific white matter changes, abnormalities of myelination, ventricular enlargement, evidence of volume loss, cavum septum pellucidum and discrete vermian atrophy with clinical manifestations of ataxia which later resolved. The subject with the latter findings also had a diagnosis of dyspraxia, synkinesis and dysexecutive syndrome. Gait abnormalities were reported in seven additional subjects and were related to spasticity, hypotonia or discoordination. The major neurological features are summarized in Table 4.

d. Ophthalmologic problems and hearing loss—Fourteen of 19 subjects (74%) for whom data were available had ophthalmological abnormalities, including strabismus, nystagmus and vision disturbance (myopia, hyperopia and astigmatism). Retinal dystrophy was reported in one subject. One case reported amblyopia without mention of other abnormalities, and one had a bilateral squint with normal visual evoked potentials/ electroretinography (VEP/ERG). For 16 subjects, results of hearing evaluation or subjective report of normal/abnormal hearing were available. Of those, hearing loss was reported in 6/16 (37.5%) of cases, which was sensorineural in at least one case and associated with cochlear dysfunction in another.

e. Musculoskeletal—Mild musculoskeletal abnormalities were also described in some of the participants in the study. Description of the extremities was available for twelve of the subjects. Previous studies reported brachydactyly in 3/30 patients with *POGZ* variants (Stessman et al., 2016; J. White et al., 2016). In our cohort, small hands or short fingers were reported in 5/12 (42%), including three with brachydactyly and two others with brachymetacarpia or small hands and feet. Two subjects (17%), however, were noted to have long fingers (one of whom also had mitral valve prolapse and pectus excavatum). Large

halluces were reported in two subjects, and two others had spatulate fingers or nails. Syndactyly was noted in two subjects (17%), one involving the fingers and one involving the toes. The latter subject also had polydactyly; in this case, however, this was a familial trait, and polydactyly was not reported in any of the other cases. Data on lower limb abnormalities was available for ten subjects. Lower limb abnormalities other than toe syndactyly were arthrogryposis and spastic quadriplegia (1/10, 10%), clubfeet (2/10, 20%), some degree of ankle contracture (1/10) or increased lower extremity tone (1/10). Pes planus (1/10) and leg length discrepancy (1/10) were also reported. Notably, four individuals in the cohort were described in physician records to have joint laxity, however information on mobility of the joints was only identified for eight subjects.

f. Gastrointestinal (GI) involvement—GI involvement occurred in the majority (17/19, 89%) of the individuals for whom information was available. Nine subjects (9/17, 53%) had dysphagia/swallowing problems, and eight (8/17, 47%) had constipation. Eleven (11/18, 61%) had a history of feeding difficulties. Notably, some of the subjects reported resolution or improvement with age. Multiple subjects reported gastroesophageal reflux. Cyclic vomiting was reported in 6/16 (37.5%) of subjects (one of whom reported bouts of vomiting accompanied by behavioral changes over the next 2-3 days), and a seventh subject now 16 years old had a history of vomiting episodes between ages eight to ten years. Cyclic vomiting has been previously reported in subjects with *POGZ* (Stessman et al., 2016; Ye et al., 2015), and the relatively high frequency of this symptom suggests that this may be an important feature. Some parents have reported that therapies prescribed for abdominal migraines have been helpful. A significant proportion (3/19, 16%) had severe gastrointestinal involvement including intestinal malrotation, pancreatitis, rectal prolapse, and congenital diaphragmatic hernia (CDH). Four of 17 (23.5%) subjects received a gastrostomy tube for severe gastroesophageal reflux or feeding difficulties, two of whom had also undergone abdominal surgery for CDH or malrotation repair. One subject had a temporary colostomy following abdominal surgery for rectal prolapse and intussusception. Gastrointestinal symptoms are summarized in Table 5.

g. Other anomalies—Mild male genital anomalies were reported in four of 14 (28.6%) male subjects including undescended testes, hypoplastic scrotum, hypoplastic testes and micropenis, and redundant foreskin with phimosis. One adolescent female had primary amenorrhea at age 16 years, but this is within the upper range of normal.

Major cardiovascular anomalies were not frequent in the study group. Out of eight subjects for whom data from echocardiography was available or reported, two subjects had an atrial septal defect/patent foramen ovale, and one subject had a mild aortic root dilatation. PT23 had mitral valve prolapse as well as pectus excavatum and arachnodactyly, features that are not typically seen in individuals with WHSUS and may suggest another underlying genetic etiology. This individual had normal homocysteine levels, a normal chromosome analysis and testing for Fragile X, and no variants in *FBN1* or other genes relevant to these features were reported on exome sequencing. No documentation of a chromosomal microarray was available.

One subject had type 1 diabetes mellitus, however given that no other major endocrine disorders have been identified in our cohort or previous publications of subjects with *POGZ* variants, this may be an unrelated malady. Pain was also not a frequent complaint, reported in 2/14 (14%) subjects for whom the questionnaire was completed.

h. Sleep disorders—Sleep abnormalities have been previously associated with WHSUS (Stessman et al., 2016; J. White et al., 2016). Disordered sleep was reported in six subjects in the study, including at least two cases treated with melatonin. One additional subject was described as having “light sleep”, and one subject had a sleep study for unknown indications which was normal. To further assess for obstructive sleep apnea, a Pediatric Sleep Questionnaire (PSQ) (Chervin et al., 2000) pertaining to sleep disordered breathing was sent to families of 21/22 subjects for whom contact information was available. The survey was completed for 12 of the participants in the study, and results were consistent with a clinical diagnosis of obstructive sleep apnea (SRBD score >= 0.3) in four cases (33%). Notably, these subjects were the same subjects for whom medical records also supported this diagnosis. Respiratory support was not required for any of the participants in the study except for one who had surgical correction of CDH, and had a tracheostomy.

Genotype-phenotype correlations

No clear genotype-phenotype correlations were observed in the cohort. However, it is notable that three individuals with CDH (an individual from our study, a case from a previously published *POGZ* cohort and a subject from a cohort of patients with CDH) had indels causing frameshifts that affected exon 19 (c.2849dupC, reported here (PT19); c.2763dupC (J. White et al., 2016); (c.2635_2638del) (Longoni et al., 2017)). Moreover, the two other subjects in our study who had anatomical gastrointestinal disorders (PT4 with malrotation and hiatal hernia and PT5 with rectal prolapse, intussusception and abdominal wall hernia) as well as a patient with malrotation from a previous study (Stessman et al., 2016) all had variants in this exon although not confined to a specific domain.

Of the eight indel variants reported here, seven were predicted to escape nonsense-mediated decay (NMD) by a computational analysis tool, NMDEscPredictor (Coban-Akdemir et al., 2018). The eighth case (PT20) had an indel in exon 8 predicted to undergo NMD. In addition, NMD was predicted for four of ten cases with nonsense variants as well as another subject (PT12, previously reported (Ye et al., 2015)) that had a large 32Kb deletion encompassing exons 4-19. Overall, individuals in both groups (NMD and non-NMD) presented with a wide range of severity of cognitive functions and other phenotypes, although interestingly 4/5 cases who required surgery or gastrostomy tube for gastrointestinal manifestations and virtually all the individuals that were non-verbal had variants predicted to escape NMD, whereas all but one case predicted not to escape NMD had rather mild neurocognitive disorders. On the other hand, escape from NMD was also predicted for PT22 who was diagnosed in adulthood, only had mild ID and no gastrointestinal manifestations (Table 6).

There are several recurrently-mutated sites in *POGZ* in ClinVar (Harrison et al., 2016). Three individuals in the study had variants previously reported in the literature (PT14,

c.3001C>T (Stessman et al., 2016); PT18, c.3041delA (Yavarna et al., 2015; Ye et al., 2015); PT25, c.3456_3457del (Gilissen et al., 2014; Stessman et al., 2016)). An additional case (PT11, c.2709delC) had a deletion affecting the same residue where a nonsense variant was previously reported (c.2711T>A (Deciphering Developmental Disorders, 2015)). We compared the phenotypes of individuals with similar variants, however they did not display any striking similarities that set them apart from the rest of the cohort, other than the fact that obesity/overweight reported for all individuals with the c.3041del A variant as well as a case with a nonsense variant affecting the same residue (c.3040C>T (Stessman et al., 2016)). Given that none of the clinical characteristics are pathognomonic to *POGZ*/WHSUS, it may be difficult to tease out the contribution of specific *POGZ* alleles from influences inflicted by other loci/genes. Of note, the c.3001C>T variant occurs at a CpG dinucleotide potentially accounting for a higher frequency of de novo mutations at this site, although the paternal age of PT14 was not advanced (31 years).

POGZ variants in the Baylor Genetics (BG) Laboratory database

The BG clinical laboratory database holds over 12,500 exome sequencing cases. In this database, *POGZ* was implicated or highly suspected to be causative of the phenotype in 18 cases (of which three - PT2, PT8 and PT19 - consented to participation in the study and are included in the clinical analysis above). Of 2275 cases that were referred for “Neurologic” indications, including developmental delay, speech delay, intellectual disability and seizures, one case was identified to have a pathogenic *POGZ* variant. Of 6931 cases referred for an indication of “Neurologic plus other organ systems”, 12 had causative or likely causative *POGZ* variants. Overall, *POGZ* was implicated in 13 out of 9206 (1.4:1,000 or 0.14%) cases who underwent exome sequencing for neurodevelopmental disorders with or without other system involvement. *POGZ* was also the likely causative gene in one out of 2722 cases referred for non-neurological indications (a newborn with cardiovascular anomalies, dysmorphic features and undescended testes), however the subject may have been too young to reliably assess for neurodevelopmental outcomes. Two additional cases were uncategorized in the lab’s database; both had developmental delays and additional phenotypes that could fit within the spectrum of *POGZ*-related disorders.

Seven cases in the database of approximately 65,000 individuals undergoing clinical chromosomal microarray had an apparently recurrent, ~70kb duplication overlapping the 3’ end of *POGZ,* which may not impact the function of the gene, as a functional copy of *POGZ* may remain intact. Indications in those cases included congenital malformations (including one case of fetal hydrops) and dysmorphic features in three cases, gross motor delay (one case), seizures (one case), autism with aphasia (one case) and hypotonia with dysphagia (one case). There were no deletions or other small (<10 Mb) duplications involving *POGZ.*

The BG database was then queried for specific phenotypes, and causative/likely causative variants in *POGZ* were detected in 0.12% of cases with autism, 0.19% of cases with developmental delay (including motor and/or speech delay), 0.18% with intellectual disability/learning difficulties and none of the cases with ADHD. The findings are summarized in Table 7 and Table 8.

Discussion

In the present study, we report 21 unique *POGZ* variants in a total of 22 individuals; 15 of these variants have not been previously reported, providing the opportunity for further characterization of genotype-phenotype relationships in individuals with WHSUS. An analysis of clinical records and parent-completed surveys demonstrated a higher than expected proportion of cases with a gastrointestinal phenotype, both functional (feeding and swallowing difficulties, cyclic vomiting) and anatomical (malrotation, CDH). Neurocognitive/behavioral features are universal but are highly variable from low-normal intellect to severe intellectual disability. Learning and behavioral abnormalities are also observed in *Drosophila* and mouse models (Stessman et al., 2016; Suliman et al., 2018).

The incidence of CDH appears to be higher than expected in individuals with WHSUS. CDH has been reported in one subject in our study (PT19), as well as a previously-published case with a gene-disruptive variant in *POGZ* (J. White et al., 2016). Further review of the literature revealed that *POGZ* was one of the candidate genes reported in a cohort of individuals with CDH (Longoni et al., 2017). In that report, one subject had a pathogenic truncating *de novo* variant in *POGZ* (NM_015100: c.2635_2638del; p.F879P*fs*). This subject presented with right-sided Morgagni hernia and other features that may fit with *POGZ*-associated phenotypes including microcephaly, seizures, abnormal ears, micropenis, facial dysmorphism and optic nerve hypoplasia. The authors hypothesized that the pathogenesis of CDH in these subjects may be the pleiotropic effects of *POGZ* on the development of organs during embryogenesis due to its role in kinetochore assembly and mitotic chromosome segregation. CDH occurs with an estimated frequency of 1 in 2,500-3,000 births worldwide (Longoni et al., 2017). The occurrence of CDH in three unrelated individuals with pathogenic/likely pathogenic variants in *POGZ* suggests that CDH is a part of the WHSUS phenotypic spectrum. It is noted that two additional subjects from the CDH cohort had missense variants in *POGZ*, one of which had isolated CDH (c.4086A>C; p.Glu1362Asp) and one had CDH and an atrial septal defect (c.3854G>A; p.R1285Q). Intellectual disability or autism were not reported in these subjects. Both of the variants were inherited from asymptomatic parents and therefore their contribution to the phenotype in these cases is unclear, given the rarity of pathogenic missense mutations in *POGZ* and the lack of neurodevelopmental features.

GI involvement in WHSUS has been previously reported (Dentici et al., 2017; Stessman et al., 2016; J. White et al., 2016) but appears to be a significant and yet under-characterized feature. This could possibly result in part from under-reporting of mild symptoms that are relatively common in the general population such as constipation and gastroesophageal reflux. Cyclic vomiting was also seen in a number of the subjects as well as cases from previous reports. In one subject, parents reported a significant improvement in these episodes with the use of acetaminophen. A possible explanation is the association of cyclic vomiting with migraines in children (Rothner, 2018). Intestinal malrotation, one of the most common congenital anomalies of the intestine, occurs in 0.2%-1% of the normal population, and presents with symptoms in about 1 in 2500 infants (Adams & Stanton, 2014). Malrotation/non-rotation occurred in two subjects in our cohort (PT4, PT19), and in at least one previously published case (Stessman et al., 2016). An additional case reported here

underwent surgery for intussusception that was thought possibly to be secondary to malrotation (PT5). Taken together, these data suggest *POGZ* may be involved in the pathogenesis of intestinal tract abnormalities and perhaps gastrointestinal motility.

Another observation we report here is the presence of mild genital abnormalities (undescended testes, hypoplasia of the scrotum). Other reports of duplicate collecting system as well as other anomalies of the genitourinary system such as hydronephrosis and dysplastic kidney were also seen in subjects with WHSUS (Gilissen et al., 2014; Stessman et al., 2016; J. White et al., 2016). Genitourinary manifestations may also be a rare feature of this syndrome, however given the relatively high frequency of these anomalies in the general population (duplicate collecting system is estimated to occur in 0.7-4% of the general population (Privett, Jeans, & Roylance, 1976)), this needs to be further characterized.

Our study had some inherent limitations. Clinical ascertainment is susceptible to bias resulting from available clinical records. As is often the case in rare disease cohorts, subjects were recruited from different primary care centers in different countries, and available records were not uniform. In some cases, very detailed medical records were provided, while others had only brief reports. For the sake of accuracy we only included in our analysis information that was explicitly mentioned, for either negative or positive features. This may result in the underestimation or overestimation of the frequency of some of the features, as negative information (such as not having sleep problems) or mild/common phenotypes (such as constipation) may not always be reported. We utilized a clinical survey in attempt to collect more consistent data across the cohort, however we were unable to get fully completed surveys returned from all subjects consented. Nevertheless, the aggregate of phenotypes points to recurring clinical characteristics that are enriched in individuals with causative variants in *POGZ*. The variability of clinical phenotypes and wide range of severities in neurocognitive function as well as other manifestations may be related to differences in the pathogenicity of alleles, reduced penetrance or age-dependent penetrance of some of the features. However, such “clinical inconsistencies” may also represent the contribution of additional genetic factors and potential second diagnoses with blended, overlapping or distinct clinical phenotypes in these individuals. This is particularly true for recurrently-mutated loci where phenotypic homogeneity may be expected. Allelic series are important to further delineate and isolate the *POGZ*-related characteristics.

The mechanism of variant pathogenicity in *POGZ* has been suggested to be haploinsufficiency, as the vast majority of pathogenic variants lead to premature stop codons. The probability of loss-of-function intolerance (pLI) score for this gene is 1 (Lek et al., 2016), further supporting the notion that loss of function variants have deleterious effects. Previous studies demonstrated that *POGZ* knockdown in cells resulted in disruption of HP1α dissociation from the chromosome arms during mitosis, leading to impaired kinetochore structure and function (Nozawa et al., 2010). On the other hand, reduced levels of wild-type POGZ protein as well as truncated protein were found in a subject with mild intellectual disability without autism who had a truncating variant in exon 9 (of 19 total exons) of *POGZ* (c.1277insC; p.E427*)(Tan et al., 2016). This variant results in a frameshift leading to a premature stop codon, predicted to undergo nonsense-mediated RNA decay (NMD) by computational analysis (Coban-Akdemir et al., 2018); the detection (at least to

some extent) of abnormal protein suggests that it is not completely degraded by NMD. In the present study, 13/19 (68.5%) of the truncating variants are predicted to escape NMD. Interestingly, while severe and mild phenotypes were observed both in the cases predicted to undergo NMD as well as those predicted to escape NMD, there appeared to be a preponderance towards greater severity in those predicted to escape NMD. This raises the question whether a dominant negative effect or gain of function might be involved in the pathogenesis in these cases as a result of the truncated protein.

The fact that most pathogenic truncating variants occurred in the last exon is interesting given that the small number of missense variants reported in the literature were seen more evenly spread throughout the gene (Figure 1) (Fukai et al., 2015; Gulsuner et al., 2013; Hashimoto et al., 2016; Homsy et al., 2015; Stessman et al., 2016). This supports the importance of this exon, encoding the DDE transposase domain and the centromere protein B (CENP-B) DNA binding domain, in the function of the protein encoded by *POGZ*. It also raises the possibility that missense variants are not pathogenic, or at least may not cause WHSUS.

In conclusion, White-Sutton syndrome is a pleiotropic disorder with a wide spectrum of neurocognitive delays, particularly speech delay, as well as mild to severe gastrointestinal symptoms and characteristic facial features. The vast majority of cases have truncating variants and splice site mutations, most of which occur within the last (19^{th}) exon, highlighting the importance of this exon in *POGZ* function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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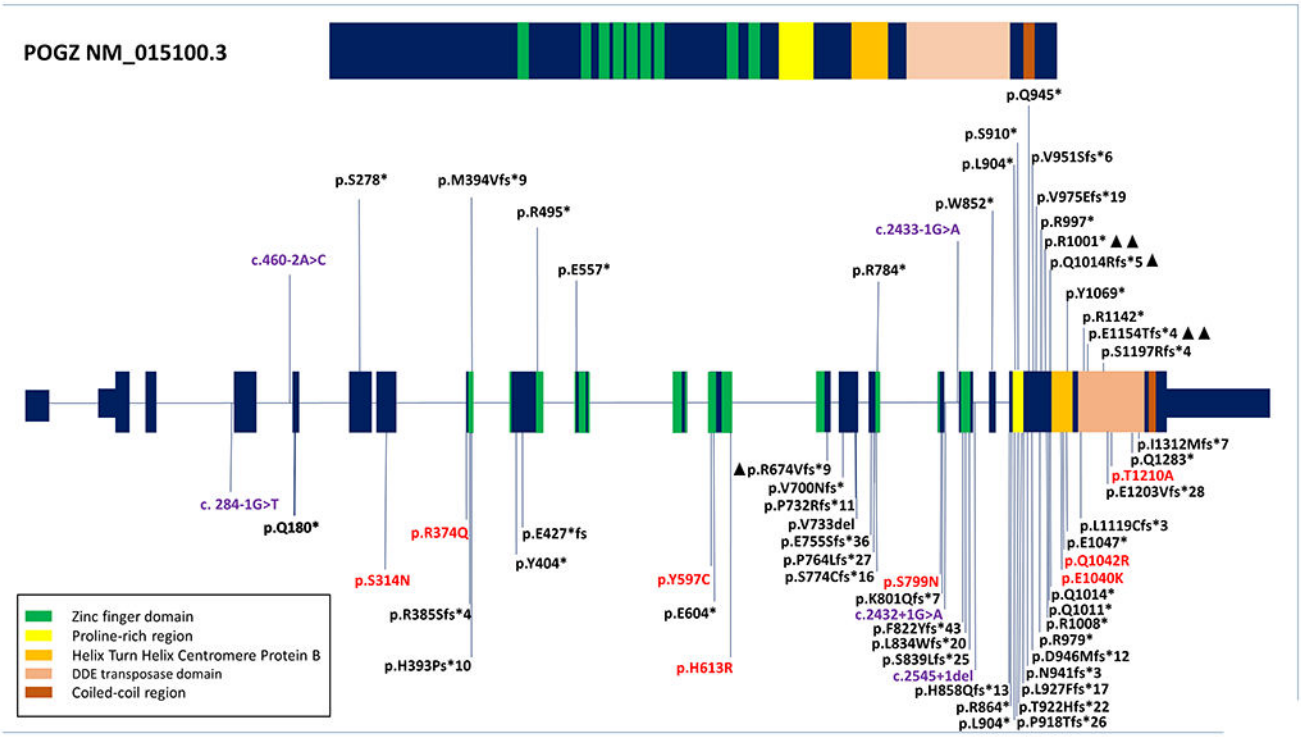

Figure 1.

Schematic representation of the POGZ protein and POGZ gene. Pathogenic variants in the present study shown above the exon structure and variants previously reported in the literature shown below. Black font—frameshift or nonsense variants. Purple font—splice variants. Red font—missense variants. Triangles mark additional reports of the same variant

Figure 2.

Individuals from the study cohort. (a) PT5, 1 year. (b) PT5, 3.5 years. (c) PT15, 1.5 years. (d) PT15, 6 years. (e, f) PT8, 4 years. (g) PT18, 2 years. (h) PT21, age 10 months. (i) PT7, age unknown. (j) PT7, 3 years. (k) PT13, 4 months. (l) PT10, 14.5 years

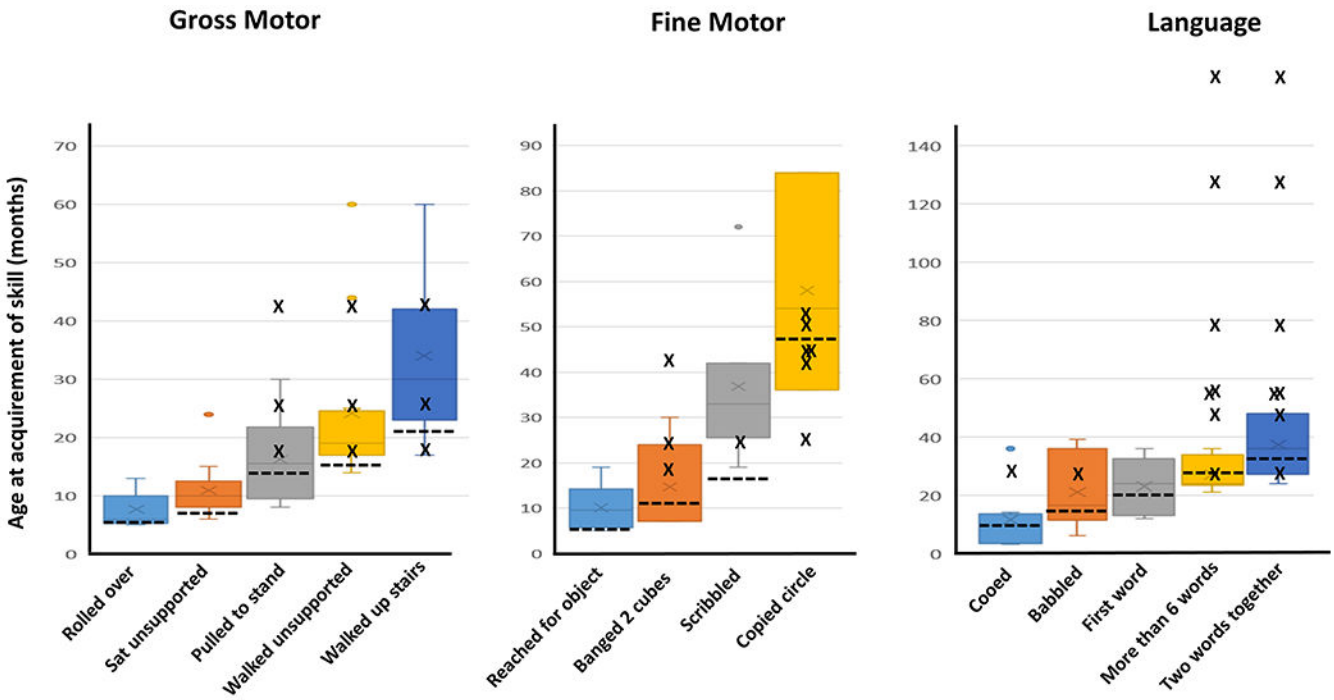

Figure 3.

Developmental milestones in the cohort. Bar plots represent different milestones in the gross motor, fine motor and language categories. Dashed lines mark age when 90% of children have achieved the milestone based on Denver II Developmental Scale (Frankenburg, Dodds, Archer, Shapiro, & Bresnick, 1992). Xs mark age at report when milestone was not achieved

Table 1 –

***POGZ* variants in the cohort.**

N/A – not applicable. NR – not reported. Variants are reported on isoform NM_015100.3.

ID	Nucleotide change	Amino acid	exon	Heredity	Zygosity
PT1	c.2924_2925delTG	p.V975Efs*19	19	*de novo*	Het
PT2	c.1483C>T	p.R495*	9	*de novo*	Het
PT4	c.2729C>A	p.S910*	19	*de novo*	Het
PT5	c.2833C>T	p.Q945*	19	*de novo*	Het
PT6	c.3424C>T	p.R1142*	19	NR	Het
PT7	c.2989C>T	p.R997*	19	*de novo*	Het
PT8	c.2555G>A	p.W852*	18	*de novo*	Het
PT9	c.2350C>T	p.R784*	15	*de novo*	Het
PT10	c.2433-1G>A	N/A	intron 16	*de novo*	Het
PT11	c.2709delC	p.L904*	19	*de novo*	Het
PT12	32kb deletion on 1q21.3 (exons 4-19)	N/A	4-19	*de novo*	Het
PT13	c.3206_3207delAT	p.Y1069*	19	*de novo*	Het
PT14	c.3001C>T	p.R1001*	19	*de novo*	Het
PT15	c.833C>G	p.S278*	6	*de novo*	Het
PT17	c.460-2A>C	N/A	intron 5	*de novo*	Het
PT18	c.3041del	p.Q1014Rfs*5	19	*de novo*	Het
PT19	c.2849dupC	p.V951Sfs*6	19	NR	Het
PT20	c.1180_1181delAT	p.M394Vfs*9	8	*de novo*	Het
PT21	c.3591_3592delTG	p.S1197Rfs*4	19	maternally-inherited	Het
PT22	c.3591_3592delTG	p.S1197Rfs*4	19	NR	Het
PT23	c.1669G>T	p.E557*	10	*de novo*	Het
PT25	c.3456_3457del	p.E1154Tfs*4	19	*de novo*	Het

Table 2 –

Facial features observed in the cohort.

Head	
Microcephaly	13/18
Plagiocephaly	4/14
Brachycephaly	2/14
Forehead	
High, broad forehead / frontal bossing	7/8
Bitemporal narrowing	2/8
Eyes	
Sparse eyebrows	6/6
Hypertelorism	3/5
Palpebral fissures	
Downslanting	2/5
Upslanting	1/5
Midface	
Midface hypoplasia	10/11
Midface retrusion	4/11
Nose	
Broad nasal root or bridge	8/12
Flat nasal bridge	4/12
Anteverted nares / upturned nasal tip	5/12
Mouth	
Tented / triangular	6/8
Oropharynx	
Bifid uvula	2/11
High-arched palate	1/11
Protruding tongue	4/5
Chin	
Micrognathia	2/6
Retrognathia	1/6
Ears	
Low-set	8/10
Abnormally-folded	4/10
Posteriorly-rotated	1/10
Pre-auricular tags	1/10

Table 3 –
Neurocognitive features of patients in the study.

+ indicates mild-moderate presentation. ++ indicates severe presentation. +/− indicates some features were present. Mo – months. N/A – not applicable (patient too young to assess). NR – not reported. Yr – year(s).

ID	Mutation	Sex	Age at presentation	Age at diagnosis	Motor delay	Speech Delay	Intellectual disability	Learning difficulties	Autism
PT1	c.2924_2925delTG	F	3 yr	4 yr	+	++	+	N/A	+
PT2	c.1483C>T	M	28 yr	28 yr	mild?	+	+	+	−
PT4	c.2729C>A	F	<1 yr	16 yr	+	++	+	+	NR
PT5	c.2833C>T	M	Birth (dysmorphism)	22 mo	+	++	+	+	−
PT6	c.3424C>T	M	6 mo	4 yr 10 mo	+	++	+	+	+/−
PT7	c.2989C>T	F	5 mo	20 mo	+ mild	+	+	+	−
PT8	c.2555G>A	M	3 mo	21mo	+	++	+	+	+/−
PT9	c.2350C>T	F	1 yr 3 mo	16 yr 6 mo	+	+	+	+	NR
PT10	c.2433-1G>A	M	<2yr	12 yr 10 mo	+	+	NR	+	+
PT11	c.2709delC	M	NR	8yr	+	++	+	+	−
PT12	32kb deletion on 1q21.3 (exons 4-19)	F	7 mo	9 yr 6 mo	+	+	+	+	+/−
PT13	c.3206_3207delAT	F	<1 yr	11 yr 6 mo	+	++	−	+	NR
PT14	c.3001C>T	M	4 mo	18 mo	+	+	NR	+	+
PT15	c.833C>G	M	5 wk (seizure)	6 yr 6 mo	+	++ †	+	+	+
PT17	c.460-2A>C	M	3 mo	19 mo	+	+	NR	+	+
PT18	c.3041del	M	6 mo	21 mo	+	+/++	NR	+	−
PT19	c.2849dupC	M	prenatal (CDH)	2.5 mo	+	N/A	N/A	N/A	N/A
PT20	c.1180_1181delAT	M	5 yr	20 yr	−	+	−	+	−
PT21	c.3591_3592delTG	M	4 mo	18 mo	+	+	N/A	N/A	N/A
PT22	c.3591_3592delTG	F	5 yr	26 yr	−	+	+	+	NR
PT23	c.1669G>T	M	2 yr	16yr	−	+	+	+	−
PT25	c.3456_3457del	M	1yr	10yr 9mo	+	+	NR	+	+
Total					19/22 (86%)	21/21 (100%)	13/15 (87%)	19/19 (100%)	6/16 (37.5%)

† Articulation problems, receptive-expressive disorder.

Table 4 –
Neurologic features reported in the cohort.

+ indicates feature is present. - indicates feature is absent. Abnl. – abnormal. Bil. – bilateral. CC – corpus callosum. D – desaturations. DVM - delayed visual maturation. E – eye twitching. GTC – generalized tonic-clonic. IS – infantile spasms. IVH-1 – intraventricular hemorrhage grade 1. Optic n. – optic nerve. P – partial seizures. RD – retinal dystrophy. ROP – retinopathy of prematurity. ND – Not done. NR – not reported. S – syncopal episodes. SNHL – sensorineural hearing loss. St – staring spells.

ID	Mutation	Seizures	Abnormal brain imaging	Eye abnormality	Hearing loss	Microcephaly
PT1	c.2924_2925delTG	–	Slightly delayed/borderline-normal myelination at 8 months, mildly thin CC with normal myelination at 2 years	Exotropia	–	+
PT2	c.1483C>T	NR	NR	NR	–	NR
PT4	c.2729C>A	+ (S, GTC)	Extra-axial fluid collection of various ages at 8mo, 3rd + lat. ventriculomegaly, severe atrophy at 2 years	Exotropia, nystagmus, optic n. hypoplasia	+	+
PT5	c.2833C>T	–	IVH-1, very mildly enlarged 3rd ventricle with small cavum septum pellucidum	Strabismus, small optic n., astigmatism. Wears glasses	+ Bil. abnl. cochlear function	+
PT6	c.3424C>T	NR	NR	Hypermetropia	+	NR
PT7	c.2989C>T	–	Mild delay in myelination	Myopia, astigmatism	NR	+
PT8	c.2555G>A	–	Mild hypomyelination near temporal parietal-occipital areas	Strabismus, nystagmus, DVM	–	+
PT9	c.2350C>T	NR	–	NR	–	+
PT10	c.2433-1G>A	–	ND	–	NR	+
PT11	c.2709delC	–	Suspected mild pontocerebellar hyperplasia	Strabismus, bil. squint. Normal VEP/ERG	+ Mild/mod SNHL	+
PT12	del ex. 4-19	–	–	–	–	–
PT13	c.3206_3207delAT	NR	Discrete vermian atrophy	NR	NR	NR
PT14	c.3001C>T	+ (St, D, E+S)	–	Amblyopia, right hypermetropia. RD?	–	+
PT15	c.833C>G	+ (P, S, eye deviation)	At 2yr - normal, at 5yr - foci of white matter signal abnormality in subcortical white matter of frontal lobes, unmyelinated subcortical white matter in temporal poles	Strabismus, hypermetropia, astigmatism	–	+
PT17	c.460-2A>C	–	ND	–	–	+
PT18	c.3041delA	–	Long-standing dysmorphic (slightly prominent) ventricles with increased T2 signal in the corona radiata and occipital lobes (possible perinatal event)	Astigmatism	NR	–
PT19	c.2849dupC	+ (D, St)	Mild central white matter volume loss with secondary thinning of the CC. Small subdural effusion/ hygroma	Strabismus, ROP	+	+

ID	Mutation	Seizures	Abnormal brain imaging	Eye abnormality	Hearing loss	Microcephaly
PT20	c.1180_1181delAT	+ (IS, P, episodes of vomiting and drooling)	ND	−	−	−
PT21	c.3591_3592delTG	−	−	Amblyopia	+	+
PT22	c.3591_3592delTG	−	ND	−	NR	−
PT23	c.1669G>T	−	−	Myopia, astigmatism	NR	−
PT25	c.3456_3457del	−	NR	Astigmatism, hyperopia	−	NR

Table 5 –
Gastrointestinal features reported for the cohort.

CDH – congenital diaphragmatic hernia.

Symptom	Frequency in cohort (%)
Constipation	8/17 (47%)
Diarrhea	3/15 (20%)
Feeding difficulties	11/18 (65%) (3 – resolved/improved)
Cyclic vomiting	6/16 + 1 suspected (37.5-43.75%)
Gastroesophageal reflux	9/18 (50%)
Swallowing difficulties	9/17 (53%)
G-tube feeds	4/17 (23.5%)
GI procedure	5/17 (29%)
Major GI involvement	3/18 (16.6%)
	Malrotation/non-rotation: 2
	Intussusception: 1
	Hernia: 3 (abdominal wall, hiatal, CDH)
	Pancreatitis: 1

Table 6 –

Clinical characteristics in subjects with variants predicted to escape versus variants predicted to undergo nonsense-mediated RNA decay (NMD).

Individuals who had intronic variants are not shown. + indicates mild-moderate presentation. ++ indicates severe presentation. +/− indicates some features were present. CDH – congenital diaphragmatic hernia. G-tube – gastrostomy tube. N/A – not applicable (patient too young to assess). NR – not reported. NV – non-verbal. Yr – year(s).

NMD	ID	Variant	Motor delay	Speech delay	Intellectual disability/ learning problems	autism	GI procedure
Escapes NMD	PT1	p.V975Efs*19	+	NV (4yr)	++	+	NR
	PT4	p.S910*	+	NV	++	NR	+ (malrotation repair, splenectomy, fundoplication, G-tube)
	PT5	p.Q945*	+	NV (3.5yr)	++	−	+ (repair of malrotation/intussusception, colostomy)
	PT6	p.R1142*	+	Few words	++	+/−	NR
	PT7	p.R997*	mild	+	+	−	−
	PT8	p.W852*	+	NV (3.4yr)	++	+/−	−
	PT11	p.L904*	+	NV	++	−	G-tube
	PT13	p.Y1069*	+	++	+	NR	NR
	PT14	p.R1001*	+	+	+	+	−
	PT18	p.Q1014Rfs*5	+	NV (2yr)	+	−	−
	PT19	p.V951Sfs*6	+	N/A	N/A	N/A	CDH repair, fundoplication, G-tube
	PT21	p.S1197Rfs*4	+	+	N/A	N/A	−
	PT22	p.S1197Rfs*4	−	+	+	NR	−
	PT25	p.E1154Tfs*4	+	+	+	+	−
Undergoes NMD	PT2	p.R495*	mild?	+	+	−	NR
	PT9	p.R784*	+	+	++	NR	NR
	PT12	del exons 4-19	+	+	+	+/−	−
	PT15	p.S278*	+	++	+	+	G-tube
	PT20	p.M394Vfs*9	−	+	+ dyscalculia	−	−
	PT23	p.E557*	−	+	+	−	−

Table 7 –

Frequency of causative *POGZ* variants in the Baylor Genetics laboratory database by indication category.

P/LP - pathogenic/likely pathogenic.

Indication category	No. cases	No. with P/LP *POGZ* variants (%)
Neurologic	2275	1 (0.044%)
Neurologic plus other organ systems	6931	12 (0.17%)
Non-neurologic	2722	1 (0.037%)
Uncategorized		2

Table 8

Frequency of causative *POGZ* variants in the Baylor Genetics laboratory database for specific phenotypes (including personal or family history of the symptoms).

P/LP - pathogenic/likely pathogenic.

Phenotype	**No. cases**	**No. with P/LP *POGZ* variants (%)**
Autism spectrum disorders	1668	2 (0.12%)
Search terms:		
Autism		
Autistic		
Developmental delay	6709	13 (0.19%)
Search terms:		
Global developmental delay		
Delayed motor milestones		
Fine motor disorder		
Motor delay		
Speech delay		
Developmental delay		
Delayed speech		
Intellectual disability, Learning difficulties	3241	6 (0.18%)
Search terms:		
Learning disability		
Intellectual disability		
Learning difficulties		
Attention deficit hyperactivity disorder	275	0
Search terms:		
Attention deficit hyperactivity disorder		
ADHD		