U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Assia Batzir N, White J, Sutton VR. White-Sutton Syndrome. 2021 Sep 16. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

White-Sutton Syndrome

Synonym: *POGZ*-Related Intellectual Disability Syndrome

Nurit Assia Batzir, MD,[1] Janson White, PhD,[2] and V Reid Sutton, MD[3]

Created: September 16, 2021.

Summary

Clinical characteristics

White-Sutton syndrome is a neurodevelopmental disorder characterized by a wide spectrum of cognitive dysfunction, developmental delays (particularly in speech and language acquisition), hypotonia, autism spectrum disorder, and other behavioral problems. Additional features commonly reported include seizures, refractive errors and strabismus, hearing loss, sleep disturbance (particularly sleep apnea), feeding and gastrointestinal problems, mild genital abnormalities in males, and urinary tract involvement in both males and females.

Diagnosis/testing

The diagnosis of White-Sutton syndrome is established in a proband with suggestive findings and a heterozygous pathogenic variant in *POGZ* identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental delay/intellectual disability, speech and language acquisition, behavioral issues, seizures, refractive errors and strabismus, hearing impairment, sleep disturbance, feeding and gastrointestinal issues, and genitourinary problems are managed by specialists per standard care.

Surveillance: Follow up of the common manifestations at each clinic visit.

Genetic counseling

White-Sutton syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Most probands reported to date whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo POGZ* pathogenic variant. Rarely, individuals with White-Sutton syndrome have the disorder as the result of a *POGZ* pathogenic variant inherited from a heterozygous parent with features such as

Author Affiliations: 1 Pediatric Genetics Clinic, Schneider Children's Medical Center of Israel, Petah Tikva, Israel; Email: nurita3@clalit.org.il. 2 Invitae Corporation, San Francisco, California; Email: janson.white@invitae.com. 3 Professor, Molecular & Human Genetics Baylor College of Medicine; Texas Children's Hospital, Houston, Texas; Email: vrsutton@texaschildrens.org.

developmental delay and/or mild intellectual disability. Once the *POGZ* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for White-Sutton syndrome have been published.

Suggestive Findings

White-Sutton syndrome **should be considered** in individuals with the following clinical and brain MRI findings.

Clinical findings

- Mild-to-severe developmental delay, intellectual disability, or learning difficulties
- Speech delay

AND

- Any of the following features presenting in infancy or childhood:
  Common features
  - Motor delay
  - Generalized hypotonia
  - Behavioral problems such as anxiety, attention-deficit/hyperactivity disorder, aggression towards self or others, and sleep disturbance
  - Autism / autism spectrum disorder
  - Microcephaly
  - Infant feeding difficulties that may require tube feeding or gastrostomy
  - Gastrointestinal manifestations including constipation, gastroesophageal reflux, and cyclic vomiting
  - Tendency toward being overweight

  Less common features
  - Epilepsy with both focal and generalized seizures that generally respond to anti-seizure medications
  - Ophthalmologic abnormalities such as strabismus, optic nerve hypoplasia, and refractive errors including myopia, hypermetropia, and astigmatism
  - Sensorineural hearing impairment / cochlear dysfunction
  - Sleep-disordered breathing
  - Congenital diaphragmatic hernia
  - Mild male genital anomalies such as cryptorchidism or micropenis
  - Congenital anomalies of the kidney and urinary tract such as duplicated collecting system
  - Recurrent infections
  - Palate abnormalities such as high-arched palate, cleft palate, or bifid uvula

While some facial features are frequently observed, the authors believe that this syndrome cannot be definitively diagnosed clinically based on facial or other phenotypic features alone (see Clinical Description and Assia Batzir et al [2020], Figure 2).

Establishing the Diagnosis

The diagnosis of White-Sutton syndrome **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *POGZ* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both

can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *POGZ* variant of uncertain significance itself does not establish or rule out the diagnosis.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability may begin with **chromosomal microarray analysis (CMA)**. Other options include use of a multigene panel or exome sequencing. Note: Single-gene testing (sequence analysis of *POGZ*, followed by gene-targeted deletion/duplication analysis) would generally NOT be recommended, as the phenotypic features of White-Sutton syndrome are relatively nonspecific.

- **An intellectual disability multigene panel** that includes *POGZ* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of White-Sutton syndrome, some panels for intellectual disability may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an ID multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID, whereas some multigene panels may not. **Genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in White-Sutton Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
POGZ	Sequence analysis [3]	99% [4]
	Gene-targeted deletion/duplication analysis [5]	A 32-kb deletion involving exons 4-19 identified in 1 person [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Stessman et al [2016], White et al [2016], Assia Batzir et al [2020], Garde et al [2021]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Ye et al [2015]; also reported in Assia Batzir et al [2020]

Clinical Characteristics

Clinical Description

White-Sutton syndrome is a neurodevelopmental disorder characterized by a wide spectrum of cognitive dysfunction, developmental delays (particularly in speech and language acquisition), and autism spectrum disorder (ASD) as well as other behavioral problems. Additional features commonly reported include hypotonia, gastrointestinal problems, seizures, microcephaly, sensorineural hearing loss, strabismus, short stature, tendency towards obesity, and sleep disturbance (particularly sleep apnea).

To date, more than 90 individuals have been identified with a pathogenic variant in *POGZ* [Gulsuner et al 2013, Gilissen et al 2014, Iossifov et al 2014, Deciphering Developmental Disorders Study Group 2015, Fukai et al 2015, Homsy et al 2015, Ye et al 2015, Hashimoto et al 2016, Stessman et al 2016, Tan et al 2016, White et al 2016, Dentici et al 2017, Du et al 2018, Ferretti et al 2019, Zhao et al 2019, Assia Batzir et al 2020, Pascolini et al 2020, Samanta et al 2020, Dal et al 2021, Donnarumma et al 2021, Garde et al 2021, Liu et al 2021, Trimarchi et al 2021, Türay & Eröz 2021, Wright et al 2022]. Table 2 and the following description of the phenotypic features associated with this condition are based on these reports.

Table 2. Select Features of White-Sutton Syndrome

Feature		# of Persons w/ Feature	Comment
Intellectual disability / Learning difficulties		76/76 (100%)	• LD in 5/19 persons • Mild ID in 8/19 • Moderate ID in 3/19 • Severe ID in 3/19 [1]
Speech delay		74/74 (100%)	
Motor delay		61/76 (80%)	
Hypotonia		34/44 (77%)	
Behavioral problems	**ASD**	33/73 (45%)	Plus at least 4 addl persons w/some features consistent w/ASD
	Other	46/78 (59%)	Biting & aggression toward others, anxiety, stereotypies, withdrawal, hyperactivity, obsessions
Epilepsy		11/71 (15%)	• GTC, partial seizures, drop attacks, absence • Plus 2 addl persons w/ paroxysmal nonepileptic episodes
Ophthalmologic features		40/64 (63%)	
Hearing loss		28/74 (38%)	
Sleep disorders		18/63 (29%)	

Table 2. continued from previous page.

Feature		# of Persons w/ Feature	Comment
Feeding & gastrointestinal problems	**Feeding difficulties**	23/44 (52%)	
	Constipation	17/56 (30%)	
	Cyclic vomiting	11/52 (21%)	Plus 1 person w/vomiting w/o features of CVS
	Diaphragmatic hernia	3/83 (4%)	
	Other GI disorders	6/71(8%)	Intestinal malrotation, pancreatitis, rectal prolapse, ventral hernia, occlusion (presumed to be intestinal obstruction) [2]
Genitourinary abnormalities	**Urinary tract involvement**	5/48 (10%)	Megaureter, duplicated collecting system
	Male genital abnormalities	6/51 (12%) males	Cryptorchidism, hypoplastic testes, micropenis
Musculoskeletal anomalies		22/71 (31%)	

Based on Fukai et al [2015], Ye et al [2015], Stessman et al [2016], Wang et al [2016], White et al [2016], Dentici et al [2017], Ferretti et al [2019], Zhao et al [2019], Assia Batzir et al [2020], Samanta et al [2020], Garde et al [2021], and Trimarchi et al [2021]
ASD = autism spectrum disorder; CVS = cyclic vomiting syndrome; GTC = generalized tonic-clonic; ID = intellectual disability; LD = learning difficulties
1. Based on Garde et al [2021]
2. "Occlusion" as appears in Garde et al [2021]; interpreted by authors as "intestinal obstruction"

Intellectual disability / learning difficulties. Virtually all individuals reported to date have learning difficulties or intellectual disability ranging from mild (36%-50%) to profound (≤32%). Assessment of various cognitive domains in five individuals identified deficiencies in language and attention, as well as executive and social dysfunction that affected their daily lives (especially in communication) [Garde et al 2021]. Although information on cognitive function in adults is limited, some adults are able to work, care for themselves, and raise children [Assia Batzir et al 2020; Garde et al 2021; Liu et al 2021; Wright et al 2022; Authors, personal experience].

Speech delay is seen in nearly all affected individuals, and is generally more pronounced than motor delays. While first words often emerge at an appropriate age, the formation of sentences may be delayed until the school-age years; some remain nonverbal after age six years [Assia Batzir et al 2020, Garde et al 2021]. Despite language difficulties, verbal comprehension appears to be less affected.

Although information on cognitive function in adults is limited, adults may be able to work and care for themselves, and in some instances raise children [Assia Batzir et al 2020; Garde et al 2021; Liu et al 2021; Wright et al 2022; Authors, personal experience].

Motor delay is common. Reported age at onset of walking ranges from before 12 months to six years [Assia Batzir et al 2020, Garde et al 2021]. Delays may be related to hypotonia that presents as early as the first days of life. Hypotonia is seen in the vast majority of individuals and may be the first sign that brings the child to medical attention.

Additional causes for motor delays include medical issues such as complex abdominal surgery and lower limb spasticity. Gait abnormalities including clumsiness and difficulty with coordination have also been reported.

Although a movement disorder is not frequently seen, paroxysmal nonepileptic events have been described in at least two individuals [Ferretti et al 2019, Donnarumma et al 2021].

Behavior problems include issues with attention, anxiety, irritability, and aggression toward oneself or others. In their assessment of neuropsychological profiles of 19 individuals with White-Sutton syndrome, Garde et al [2021] observed common behavioral characteristics including immature behavior (7 individuals), significant slowness (7), and attention disorder (8) that were associated with either excessive inhibition and withdrawal or lack of inhibition leading to agitation, opposition, or provocation.

ASD was observed in up to 50% of individuals reported in the literature. Repetitive behaviors [Wang et al 2016], restricted interests, and stereotypic movements of the hands or mouth have been described [Stessman et al 2016, Dentici et al 2017, Donnarumma et al 2021].

Epilepsy. Both generalized and tonic and focal epilepsy, as well as febrile seizures and EEG abnormalities without overt convulsions, occur in approximately 20% of affected individuals [Pascolini et al 2020, Samanta et al 2020]. Epileptic seizures precipitated by bathing/showering in hot water were reported in one individual [Türay & Eröz 2021].

While onset of seizures ranges from infancy to adolescence, it is typically between ages one and four years. Seizures are generally controlled either by monotherapy or with multiple anti-seizure medications, and may resolve with age. Status epilepticus has not been reported.

Information on EEG patterns is limited. Findings may include epileptic abnormalities localized to the frontal region or bitemporal sharp waves and are not specific to this disorder [Stessman et al 2016, White et al 2016, Ferretti et al 2019, Samanta et al 2020].

Neuroimaging. Brain imaging reveals central nervous system abnormalities in up to two thirds of affected individuals. When present, brain MRI abnormalities are variable and nonspecific. Recurring features include small foci in the deep white matter on T_2/FLAIR imaging, prominence of cerebrospinal fluid in the posterior fossa, and cerebellar dysgenesis [Samanta et al 2020]. Thin corpus callosum, abnormal myelination, polymicrogyria, small optic chiasm / optic nerve hypoplasia, persistent cavum septum pellucidum, and Dandy-Walker spectrum malformations have also been described [Ye et al 2015, Dentici et al 2017, Assia Batzir et al 2020, Samanta et al 2020].

Ophthalmologic abnormalities that can impair vision include retinal dystrophy (3 individuals) [White et al 2016, Assia Batzir et al 2020], optic nerve hypoplasia (3) [White et al 2016, Assia Batzir et al 2020], Horner syndrome (2) [Gilissen et al 2014, White et al 2016], and coloboma (1) [White et al 2016]. Treatable conditions can include refractive errors (astigmatism, myopia, or hyperopia) and strabismus.

Hearing loss, reported in approximately one third of individuals, can be conductive secondary to recurrent middle ear infections or sensorineural with cochlear dysfunction.

Sleep disorders. Families of individuals with White-Sutton syndrome often report problems with sleep (e.g., difficulty falling asleep, frequent awakenings, sleepwalking).

Sleep apnea is known to occur; a sleep disorder survey completed for 12 individuals revealed features suggestive of obstructive sleep apnea in four [Assia Batzir et al 2020].

Feeding/gastrointestinal problems. Feeding difficulties, which are common, may be severe enough to require nasogastric tube feeding or gastrostomy. These problems can be related to gastroesophageal reflux, feeding intolerance with gastric distention, problems with chewing or swallowing, or oversensitivity of the oral region resulting in food aversion.

Vomiting is common. Some individuals experience recurring episodes of vomiting in childhood with or without a cyclical pattern. Vomiting tends to improve or resolve with age; some parents report that nausea and vomiting appear to respond to therapies for "abdominal migraines" [Assia Batzir et al 2020; Authors, personal communication].

Gastrointestinal manifestations requiring surgery can include intestinal malrotation, ventral and inguinal hernia, and rectal prolapse.

Congenital diaphragmatic hernia, although infrequently described, is a recurring finding [White et al 2016, Longoni et al 2017, Assia Batzir et al 2020, Garde et al 2021].

Genitourinary abnormalities. Congenital anomalies of the kidneys and urinary tract can include dysplastic kidneys as well as duplicated collecting system, hydronephrosis, and/or megaureter. Male genital anomalies can include undescended testes, hypoplastic scrotum/testes, and micropenis.

Recurrent infections. Frequent respiratory, ear, and bladder infections were reported in several individuals; one individual was diagnosed with immune deficiency. One individual had low titers to vaccines [Authors, personal experience].

Musculoskeletal. Minor abnormalities of the fingers and toes (e.g., brachydactyly, broad thumbs or first toes, and spatulate fingers) and joint laxity may be seen. Clubfeet, joint contractures, and syndactyly are rare.

Growth. Although growth parameters at birth are usually within the normal range, intrauterine growth restriction has been documented in approximately 20% of individuals for whom data were available.

Height and weight range from below the third percentile to above average. Short stature or failure to gain weight have been reported in approximately 15% of individuals [Fukai et al 2015, Stessman et al 2016, Tan et al 2016, Dentici et al 2017, Ferretti et al 2019, Zhao et al 2019, Assia Batzir et al 2020, Pascolini et al 2020, Garde et al 2021].

Despite initial problems with feeding, a significant proportion of children become overweight, as early as the first years of life [Stessman et al 2016].

Microcephaly (head circumference <3rd percentile) is common.

Other. Although minor cardiovascular abnormalities including atrial septal defect / patent foramen ovale, bicuspid aortic valve, and mild dilatation of the ascending aorta have been reported, it is unclear if these occur at a higher frequency in White-Sutton syndrome than in the general population.

Craniofacial features may include microcephaly, brachycephaly, high and broad forehead, hypertelorism, broad and/or high nasal root, anteverted nares, long malar region with midface hypoplasia/retrusion, prognathism, downturned corners of the mouth, palate abnormalities (high-arched palate, cleft palate, bifid uvula), and low-set ears. While these facial features are frequently observed, the authors believe that a definitive clinical diagnosis of this syndrome cannot be made based solely on facial or other phenotypic features.

Prognosis. It is unknown whether life span in individuals with White-Sutton syndrome is decreased. The oldest known individual was age 36 years at time of report [Wright et al 2022]. One affected individual (age not reported) has an affected son, age 15 years [Liu et al 2021]. Instances of parent-to-child transmission [Assia Batzir et al 2020, Garde et al 2021, Liu et al 2021] demonstrate that survival into adulthood and raising a family are possible.

Genotype-Phenotype Correlations

While no clear genotype-phenotype correlations have been identified, the following are general observations:

- Missense variants are not clearly associated with cognitive problems but appear to be associated with behavioral issues including ASD or autistic-like behaviors [Stessman et al 2016].
- In 20 individuals with White-Sutton syndrome with nonsense, frameshift, or copy number variants in *POGZ*, variants in exons 18-19, which were predicted to escape nonsense-mediated RNA decay (NMD), were more likely to be associated with lack of speech and more severe gastrointestinal complications that

required surgery (such as malrotation, rectal prolapse, and congenital diaphragmatic hernia). Variants that occurred in exons 6, 8, 9, 10, and 15, and one deletion of exons 4-19, predicted to undergo NMD, were more frequently associated with milder neurocognitive deficiencies [Assia Batzir et al 2020].
- Behavioral problems, sleep disorders, gastrointestinal manifestations, and microcephaly were more frequently associated with variants in the DDE domain of the protein (encoded by part of exon 19), whereas central nervous system and genitourinary malformations occurred more often with variants affecting other protein domains [Pascolini et al 2020].

Prevalence

To date, more than 90 individuals with White-Sutton syndrome have been reported.

Exome sequencing of 9,206 individuals with neurodevelopmental disorders identified pathogenic or likely pathogenic variants in *POGZ* in 13 (i.e., 1.4:1,000 or 0.14%) [Assia Batzir et al 2020].

Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Penetrance

To date, when parental data were available, all reported instances of loss-of-function variants in *POGZ* associated with White-Sutton syndrome were either *de novo* or inherited from an affected parent. Published information indicates that all nonsense *POGZ* variants are fully penetrant.

The penetrance of missense *POGZ* variants may be reduced; however, data are limited.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *POGZ*.

Differential Diagnosis

Because the phenotypic features associated with White-Sutton syndrome are not sufficient to diagnose this condition, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Note: *De novo POGZ* pathogenic variants were first identified in individuals with suspected Smith-Magenis syndrome (SMS) [White et al 2016]. SMS, an autosomal dominant disorder typically caused by a *de novo* deletion of or pathogenic variant in *RAI1* on chromosome 17p11.2, is characterized by distinctive physical features (particularly facial features that progress with age), developmental delay, cognitive impairment, behavioral abnormalities, sleep disturbance, and childhood-onset abdominal obesity. Due to behavioral problems, aggression, and some of the associated physical features that may be seen in White-Sutton syndrome (e.g., brachycephaly, brachydactyly, and obesity), SMS can be considered in the differential diagnosis [White et al 2016, Pascolini et al 2020]. However, unlike White-Sutton syndrome, SMS is also known to be associated with sensory issues, significant maladaptive behaviors, closely spaced eyes, and polyembolokoilamania.

Management

No clinical practice guidelines for White-Sutton syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with White-Sutton syndrome, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with White-Sutton Syndrome

System/Concern	Evaluation	Comment
Developmental delay	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Motor delay	Physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Speech & language	Eval by SLP	• Consider need for augmentative communication. • Assess for palatal abnormalities.
Psychiatric/ Behavioral	Eval by developmental pediatrician &/or mental health professional	For those age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD
Neurologic	Neurologic eval	• Consider brain MRI. • Consider EEG if seizures are a concern.
Eyes	Ophthalmologic eval	To assess for refractive error & strabismus
Hearing	Audiologic eval	Assess for hearing loss.
Sleep disorders	Eval for recognizable sleep disorders &/or sleep apnea	Consider need for sleep study if history of suggestive symptoms
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in persons w/ dysphagia &/or aspiration risk.
Genitourinary	Eval for: genital abnormalities in males; CAKUT in males & females	To incl renal ultrasound exam
Growth	Monitor height & weight.	To assess for failure to thrive in infancy or obesity in older persons
Cardiovascular	Baseline echocardiogram	Recommended despite uncertainty re assoc of congenital heart disease in this disorder
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of White-Sutton syndrome to facilitate medical & personal decision making

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; CAKUT = congenital anomalies of the kidney and/or urinary tract; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; SLP = speech-language pathologist

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with White-Sutton Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Hypotonia, spasticity, & gait problems	• PT/OT for muscle strengthening, stretching to help avoid contractures & falls • Orthopedics / physical medicine & rehab as needed	Consider need for positioning & mobility devices, disability parking placard.
Behavioral problems	Behavioral & psychiatric treatment(s) as needed per psychotherapist/psychiatrist for aggressive behavior, extreme withdrawal, or anxiety	Psychiatric eval & follow up as needed
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Ophthalmologic involvement	Standardized treatment per ophthalmologist	Community vision services through early intervention or school district
Hearing	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district
Sleep disorders	Individualized treatment depending on disorder	• Melatonin has improved quality of sleep in some persons. [2] • Standardized treatment for obstructive sleep apnea
Vomiting	Standardized treatment for gastroesophageal reflux & cyclic vomiting	
Bowel dysfunction	Standardized treatment for constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed
Poor weight gain / FTT	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; DD = developmental delay; FTT = failure to thrive; ID = intellectual disability; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.
2. White et al [2016]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- Individualized education plan (IEP) services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating,

assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 5. Recommended Surveillance for Individuals with White-Sutton Syndrome

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	At each visit; follow up w/ psychiatrist as needed for severe behavioral problems
Neurologic	Monitor those w/seizures.	As clinically indicated
	Assess for new manifestations such as seizures or changes in tone.	At each visit
Eyes	For persons w/refractive errors, optic nerve hypoplasia, &/or strabismus: per treating ophthalmologist	As clinically indicated
Hearing	Monitor for hearing loss.	
Sleep disorders	Assess for obstructive sleep apnea & difficulty falling asleep & maintaining sleep.	
Gastrointestinal	Monitor for constipation & vomiting.	At each visit
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	
Genitourinary	For persons w/renal / urinary tract anomalies: per treating urologist &/or nephrologist	As clinically indicated

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	At each visit
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Following studies in mice that suggested a role for the oxytocin system in autism spectrum disorders, Kitagawa et al [2021] observed that intranasal oxytocin administration was able to restore the impaired social behavior in a mouse model heterozygous for the *Pogz* missense variant Gln1038Arg. No studies on the effect of oxytocin treatment in humans have been published to date.

Behavioral abnormalities in a mouse model of White-Sutton syndrome improved when treated with the anti-seizure medication perampanel [Matsumura et al 2020]. Perampanel has NOT been studied in individuals with White-Sutton syndrome.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

White-Sutton syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most probands reported to date with White-Sutton syndrome whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo POGZ* pathogenic variant.
- Rarely, individuals diagnosed with White-Sutton syndrome have the disorder as the result of a *POGZ* pathogenic variant inherited from a heterozygous parent with mild features of the syndrome such as developmental delay and/or mild intellectual disability.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.

- The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is known to have the *POGZ* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the *POGZ* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with White-Sutton syndrome has a 50% chance of inheriting the *POGZ* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *POGZ* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected and to the parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *POGZ* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **White Sutton Syndrome Foundation**
  PO Box 591
  Broken Arrow OK 74103
  Phone: 918-884-7125
  www.whitesutton.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. White-Sutton Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
POGZ	1q21.3	Pogo transposable element with ZNF domain	POGZ	POGZ

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for White-Sutton Syndrome (View All in OMIM)

614787	POGO TRANSPOSABLE ELEMENT-DERIVED PROTEIN WITH ZNF DOMAIN; POGZ
616364	WHITE-SUTTON SYNDROME; WHSUS

Molecular Pathogenesis

POGZ (pogo-transposable element with ZNF domain) encodes a heterochromatin protein involved in chromatin condensation with robust expression in developing neuronal progenitor cells. Functionally, POGZ has been shown to be important for neuronal differentiation and development [Matsumura et al 2020]. Dysregulation of chromatin architecture in developing neurons and the resulting alteration of neuronal transcription likely underlie the cellular pathogenesis. Indeed, disruption of chromatin architecture is an etiology shared among various neurodevelopmental disorders, in which *POGZ* has become one of the most commonly mutated genes observed in large cohorts of neurodevelopmental disorders [Satterstrom et al 2020].

The majority of pathogenic variants reported thus far create premature termination codons, although many are located in the final exon and are thus not expected to undergo nonsense-mediated decay. In addition, some single-nucleotide missense variants have demonstrated functional defects, such as impaired DNA binding [Matsumura et al 2020].

Mechanism of disease causation. Given the preponderance of heterozygous truncating variants and functional characterization of missense alteration, loss of function resulting in haploinsufficiency is the most likely mechanism of pathogenicity.

Table 6. Notable *POGZ* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_015100.3 NP_055915.2	c.3936delT	p.Ile1312MetfsTer7	Most common C-terminal truncating variant reported [Fromer et al 2014]
	c.3001C>T	p.Arg1001Ter	Recurrent variant [Gilissen et al 2014, Assia Batzir et al 2020]
	c.3041delA	p.Gln1014ArgfsTer5	Recurrent variant [Yavarna 2015, Ye et al 2015, Assia Batzir et al 2020]
	c.3456_3457del	p.Glu1154ThrfsTer4	Recurrent variant [Stessman et al 2016, Assia Batzir et al 2020, Satterstrom et al 2020]
	32-kb deletion (incl exons 4-19)	--	Single case of White-Sutton syndrome caused by copy number variant [Ye et al 2015, Assia Batzir et al 2020]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

V Reid Sutton's website: www.bcm.edu

Acknowledgments

We would like to acknowledge James Lupski, Christine Beck, Tamar Harel, and Jennifer Posey, who were instrumental in the initial description of White-Sutton syndrome. The work that led to the initial description was supported by the US National Human Genome Research Institute (NHGRI) / National Heart Lung and Blood Institute (NHLBI) Grant No. HG006542 to the Baylor-Hopkins Center for Mendelian Genomics. We would also like to thank the White-Sutton Syndrome Foundation and families for their continued support in our research endeavors.

Revision History

- 16 September 2021 (bp) Review posted live
- 2 July 2021 (vrs) Original submission

References

Literature Cited

Assia Batzir N, Posey JE, Song X, Akdemir ZC, Rosenfeld JA, Brown CW, Chen E, Holtrop SG, Mizerik E, Nieto Moreno M, Payne K, Raas-Rothschild A, Scott R, Vernon HJ, Zadeh N. Baylor-Hopkins Center for Mendelian G, Lupski JR, Sutton VR. Phenotypic expansion of POGZ-related intellectual disability syndrome (White-Sutton syndrome). Am J Med Genet A. 2020;182:38–52. PubMed PMID: 31782611.

Dal S, Hopper B, du Chattel MVR, Goel H. A case of White-Sutton syndrome with previously described loss-of-function variant in DDE domain of POGZ (p.Arg1211*) and Kartagener syndrome. Am J Med Genet A. 2021;185:1006–7. PubMed PMID: 33377604.

Deciphering Developmental Disorders Study Group. Large-scale discovery of novel genetic causes of developmental disorders. Nature. 2015;519:223–8. PubMed PMID: 25533962.

Dentici ML, Niceta M, Pantaleoni F, Barresi S, Bencivenga P, Dallapiccola B, Digilio MC, Tartaglia M. Expanding the phenotypic spectrum of truncating POGZ mutations: association with CNS malformations, skeletal abnormalities, and distinctive facial dysmorphism. Am J Med Genet A. 2017;173:1965–9. PubMed PMID: 28480548.

Donnarumma B, Riccio MP, Terrone G, Palma M, Strisciuglio P, Scala I. Expanding the neurological and behavioral phenotype of White-Sutton syndrome: a case report. Ital J Pediatr. 2021;47:148. PubMed PMID: 34215294.

Du X, Gao X, Liu X, Shen L, Wang K, Fan Y, Sun Y, Luo X, Liu H, Wang L, Wang Y, Gong Z, Wang J, Yu Y, Li F. Genetic diagnostic evaluation of trio-based whole exome sequencing among children with diagnosed or suspected autism spectrum disorder. Front Genet. 2018;9:594. PubMed PMID: 30555518.

Ferretti A, Barresi S, Trivisano M, Ciolfi A, Dentici ML, Radio FC, Vigevano F, Tartaglia M, Specchio N. POGZ-related epilepsy: case report and review of the literature. Am J Med Genet A. 2019;179:1631–6. PubMed PMID: 31136090.

Fromer M, Pocklington AJ, Kavanagh DH, Williams HJ, Dwyer S, Gormley P, Georgieva L, Rees E, Palta P, Ruderfer DM, Carrera N, Humphreys I, Johnson JS, Roussos P, Barker DD, Banks E, Milanova V, Grant SG, Hannon E, Rose SA, Chambert K, Mahajan M, Scolnick EM, Moran JL, Kirov G, Palotie A, McCarroll SA,

Holmans P, Sklar P, Owen MJ, Purcell SM, O'Donovan MC. De novo mutations in schizophrenia implicate synaptic networks. Nature. 2014;506:179–84. PubMed PMID: 24463507.

Fukai R, Hiraki Y, Yofune H, Tsurusaki Y, Nakashima M, Saitsu H, Tanaka F, Miyake N, Matsumoto N. A case of autism spectrum disorder arising from a de novo missense mutation in POGZ. J Hum Genet. 2015;60:277–9. PubMed PMID: 25694107.

Garde A, Cornaton J, Sorlin A, Moutton S, Nicolas C, Juif C, Genevieve D, Perrin L, Khau-Van-Kien P, Smol T, Vincent-Delorme C, Isidor B, Cogne B, Afenjar A, Keren B, Coubes C, Prieur F, Toutain A, Trousselet Y, Bourgouin S, Gonin-Olympiade C, Giraudat K, Piton A, Gerard B, Odent S, Tessier F, Lemasson L, Heide S, Gelineau AC, Sarret C, Miret A, Schaefer E, Piard J, Mathevet R, Boucon M, Bruel AL, Mau-Them FT, Chevarin M, Vitobello A, Philippe C, Thauvin-Robinet C, Faivre L. Neuropsychological study in 19 French patients with White-Sutton syndrome and POGZ mutations. Clin Genet. 2021;99:407–17. PubMed PMID: 33277917.

Gilissen C, Hehir-Kwa JY, Thung DT, van de Vorst M, van Bon BW, Willemsen MH, Kwint M, Janssen IM, Hoischen A, Schenck A, Leach R, Klein R, Tearle R, Bo T, Pfundt R, Yntema HG, de Vries BB, Kleefstra T, Brunner HG, Vissers LE, Veltman JA. Genome sequencing identifies major causes of severe intellectual disability. Nature. 2014;511:344–7. PubMed PMID: 24896178.

Gulsuner S, Walsh T, Watts AC, Lee MK, Thornton AM, Casadei S, Rippey C, Shahin H. Consortium on the Genetics of S, Group PS, Nimgaonkar VL, Go RC, Savage RM, Swerdlow NR, Gur RE, Braff DL, King MC, McClellan JM. Spatial and temporal mapping of de novo mutations in schizophrenia to a fetal prefrontal cortical network. Cell. 2013;154:518–29. PubMed PMID: 23911319.

Hashimoto R, Nakazawa T, Tsurusaki Y, Yasuda Y, Nagayasu K, Matsumura K, Kawashima H, Yamamori H, Fujimoto M, Ohi K, Umeda-Yano S, Fukunaga M, Fujino H, Kasai A, Hayata-Takano A, Shintani N, Takeda M, Matsumoto N, Hashimoto H. Whole-exome sequencing and neurite outgrowth analysis in autism spectrum disorder. J Hum Genet. 2016;61:199–206. PubMed PMID: 26582266.

Homsy J, Zaidi S, Shen Y, Ware JS, Samocha KE, Karczewski KJ, DePalma SR, McKean D, Wakimoto H, Gorham J, Jin SC, Deanfield J, Giardini A, Porter GA Jr, Kim R, Bilguvar K, Lopez-Giraldez F, Tikhonova I, Mane S, Romano-Adesman A, Qi H, Vardarajan B, Ma L, Daly M, Roberts AE, Russell MW, Mital S, Newburger JW, Gaynor JW, Breitbart RE, Iossifov I, Ronemus M, Sanders SJ, Kaltman JR, Seidman JG, Brueckner M, Gelb BD, Goldmuntz E, Lifton RP, Seidman CE, Chung WK. De novo mutations in congenital heart disease with neurodevelopmental and other congenital anomalies. Science. 2015;350:1262–6. PubMed PMID: 26785492.

Iossifov I, O'Roak BJ, Sanders SJ, Ronemus M, Krumm N, Levy D, Stessman HA, Witherspoon KT, Vives L, Patterson KE, Smith JD, Paeper B, Nickerson DA, Dea J, Dong S, Gonzalez LE, Mandell JD, Mane SM, Murtha MT, Sullivan CA, Walker MF, Waqar Z, Wei L, Willsey AJ, Yamrom B, Lee YH, Grabowska E, Dalkic E, Wang Z, Marks S, Andrews P, Leotta A, Kendall J, Hakker I, Rosenbaum J, Ma B, Rodgers L, Troge J, Narzisi G, Yoon S, Schatz MC, Ye K, McCombie WR, Shendure J, Eichler EE, State MW, Wigler M. The contribution of de novo coding mutations to autism spectrum disorder. Nature. 2014;515:216–21. PubMed PMID: 25363768.

Kitagawa K, Matsumura K, Baba M, Kondo M, Takemoto T, Nagayasu K, Ago Y, Seiriki K, Hayata-Takano A, Kasai A, Takuma K, Hashimoto R, Hashimoto H, Nakazawa T. Intranasal oxytocin administration ameliorates social behavioral deficits in a POGZ(WT/Q1038R) mouse model of autism spectrum disorder. Mol Brain. 2021;14:56. PubMed PMID: 33726803.

Longoni M, High FA, Qi H, Joy MP, Hila R, Coletti CM, Wynn J, Loscertales M, Shan L, Bult CJ, Wilson JM, Shen Y, Chung WK, Donahoe PK. Genome-wide enrichment of damaging de novo variants in patients with isolated and complex congenital diaphragmatic hernia. Hum Genet. 2017;136:679–91. PubMed PMID: 28303347.

Liu S, Yan Z, Huang Y, Zheng W, Deng Y, Zou Y, Xie H. A case of White-Sutton syndrome arising from a maternally-inherited mutation in POGZ. Psychiatr Genet. 2021;31:135–9. PubMed PMID: 34133408.

Matsumura K, Seiriki K, Okada S, Nagase M, Ayabe S, Yamada I, Furuse T, Shibuya H, Yasuda Y, Yamamori H, Fujimoto M, Nagayasu K, Yamamoto K, Kitagawa K, Miura H, Gotoda-Nishimura N, Igarashi H, Hayashida M, Baba M, Kondo M, Hasebe S, Ueshima K, Kasai A, Ago Y, Hayata-Takano A, Shintani N, Iguchi T, Sato M, Yamaguchi S, Tamura M, Wakana S, Yoshiki A, Watabe AM, Okano H, Takuma K, Hashimoto R, Hashimoto H, Nakazawa T. Pathogenic POGZ mutation causes impaired cortical development and reversible autism-like phenotypes. Nat Commun. 2020;11:859. PubMed PMID: 32103003.

Pascolini G, Agolini E, Fleischer N, Gulotta E, Cesario C, D'Elia G, Novelli A, Majore S, Grammatico P. A novel patient with White-Sutton syndrome refines the mutational and clinical repertoire of the POGZ-related phenotype and suggests further observations. Am J Med Genet A. 2020;182:1791–5. PubMed PMID: 32359026.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Samanta D, Ramakrishnaiah R, Schaefer B. The neurological aspects related to POGZ mutation: case report and review of CNS malformations and epilepsy. Acta Neurol Belg. 2020;120:447–50. PubMed PMID: 30879264.

Satterstrom FK, Kosmicki JA, Wang J, Breen MS, De Rubeis S, An JY, Peng M, Collins R, Grove J, Klei L, Stevens C, Reichert J, Mulhern MS, Artomov M, Gerges S, Sheppard B, Xu X, Bhaduri A, Norman U, Brand H, Schwartz G, Nguyen R, Guerrero EE, Dias C; Autism Sequencing Consortium. iPSYCH-Broad Consortium, Betancur C, Cook EH, Gallagher L, Gill M, Sutcliffe JS, Thurm A, Zwick ME, Børglum AD, State MW, Cicek AE, Talkowski ME, Cutler DJ, Devlin B, Sanders SJ, Roeder K, Daly MJ, Buxbaum JD. Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. Cell. 2020;180:568–84.e23. PubMed PMID: 31981491.

Stessman HAF, Willemsen MH, Fenckova M, Penn O, Hoischen A, Xiong B, Wang T, Hoekzema K, Vives L, Vogel I, Brunner HG, van der Burgt I, Ockeloen CW, Schuurs-Hoeijmakers JH, Klein Wassink-Ruiter JS, Stumpel C, Stevens SJC, Vles HS, Marcelis CM, van Bokhoven H, Cantagrel V, Colleaux L, Nicouleau M, Lyonnet S, Bernier RA, Gerdts J, Coe BP, Romano C, Alberti A, Grillo L, Scuderi C, Nordenskjold M, Kvarnung M, Guo H, Xia K, Piton A, Gerard B, Genevieve D, Delobel B, Lehalle D, Perrin L, Prieur F, Thevenon J, Gecz J, Shaw M, Pfundt R, Keren B, Jacquette A, Schenck A, Eichler EE, Kleefstra T. Disruption of POGZ is associated with intellectual disability and autism spectrum disorders. Am J Hum Genet. 2016;98:541–52. PubMed PMID: 26942287.

Tan B, Zou Y, Zhang Y, Zhang R, Ou J, Shen Y, Zhao J, Luo X, Guo J, Zeng L, Hu Y, Zheng Y, Pan Q, Liang D, Wu L. A novel de novo POGZ mutation in a patient with intellectual disability. J Hum Genet. 2016;61:357–9. PubMed PMID: 26763879.

Trimarchi G, Caraffi SG, Radio FC, Barresi S, Contrò G, Pizzi S, Maini I, Pollazzon M, Fusco C, Sassi S, Nicoli D, Napoli M, Pascarella R, Gargano G, Zuffardi O, Tartaglia M, Garavelli L. Adducted thumb and peripheral polyneuropathy: diagnostic supports in suspecting White-Sutton syndrome: case report and review of the literature. Genes (Basel). 2021;12:950. PubMed PMID: 34206215.

Türay S, Eröz R. White-Sutton syndrome with hot water epilepsy and coexistence of SHOX gene variations. Acta Neurol Belg. 2021;121:749–55. PubMed PMID: 33837909.

Wang T, Guo H, Xiong B, Stessman HA, Wu H, Coe BP, Turner TN, Liu Y, Zhao W, Hoekzema K, Vives L, Xia L, Tang M, Ou J, Chen B, Shen Y, Xun G, Long M, Lin J, Kronenberg ZN, Peng Y, Bai T, Li H, Ke X, Hu Z, Zhao J, Zou X, Xia K, Eichler EE. De novo genic mutations among a Chinese autism spectrum disorder cohort. Nat Commun. 2016;7:13316. PubMed PMID: 27824329.

White J, Beck CR, Harel T, Posey JE, Jhangiani SN, Tang S, Farwell KD, Powis Z, Mendelsohn NJ, Baker JA, Pollack L, Mason KJ, Wierenga KJ, Arrington DK, Hall M, Psychogios A, Fairbrother L, Walkiewicz M, Person RE, Niu Z, Zhang J, Rosenfeld JA, Muzny DM, Eng C, Beaudet AL, Lupski JR, Boerwinkle E, Gibbs RA, Yang Y, Xia F, Sutton VR. POGZ truncating alleles cause syndromic intellectual disability. Genome Med. 2016;8:3. PubMed PMID: 26739615.

Wright CM, Guter SJ, Cook Eh. Case report: association of comorbid psychiatric disorders and sigmoid prolapse with de novo POGZ mutation. J Autism Dev Disord. 2022;52:1408–11. PubMed PMID: 33909211.

Yavarna T. High diagnostic yield of clinical exome sequencing in Middle Eastern patients with Mendelian disorders. Hum Genet. 2015;134:967–80. PubMed PMID: 26077850.

Ye Y, Cho MT, Retterer K, Alexander N, Ben-Omran T, Al-Mureikhi M, Cristian I, Wheeler PG, Crain C, Zand D, Weinstein V, Vernon HJ, McClellan R, Krishnamurthy V, Vitazka P, Millan F, Chung WK. De novo POGZ mutations are associated with neurodevelopmental disorders and microcephaly. Cold Spring Harb Mol Case Stud. 2015;1:a000455. PubMed PMID: 27148570.

Zhao W, Tan J, Zhu T, Ou J, Li Y, Shen L, Wu H, Han L, Liu Y, Jia X, Bai T, Li H, Ke X, Zhao J, Zou X, Hu Z, Guo H, Xia K. Rare inherited missense variants of POGZ associate with autism risk and disrupt neuronal development. J Genet Genomics. 2019;46:247–57. PubMed PMID: 31196716.

License