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White–Sutton Syndrome: Insight of an Italian Cohort of 19 Subjects

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ABSTRACT

White–Sutton syndrome (WHSUS) is a rare neurodevelopmental disorder due to pathogenic variants in the *POGZ* gene. Its phenotype includes developmental delay, behavioral dysfunctions, hypotonia, and dysmorphic features. The condition is still poorly known: comprehensive clinical descriptions and exhaustive genotype–phenotype correlations are lacking, limiting diagnostic and therapeutic advancements. Here, we report molecular, clinical, and instrumental data from the first and largest Italian cohort (19 patients). Our results highlight the importance of an extensive approach at the time of diagnosis—including early nutritional support for preventing obesity-related complications and instrumental screening for congenital malformations. Preliminary data suggest that splicing variants could be associated with more severe phenotypes. This study provides valuable new insights into WHSUS and represents a significant step towards its comprehension.

1 | Introduction

POGZ (OMIM #614787) has been recently identified as the underlying cause of White–Sutton syndrome (WHSUS, OMIM #616364) [1], a rare condition mainly characterized by intellectual disability (ID), developmental delays, behavioral anomalies, such as autistic spectrum disorder, and facial dysmorphic features. Additional manifestations include epilepsy, ophthalmological defects, hearing loss, and congenital abnormalities of the central nervous system (CNS), genitourinary tract, or heart. WHSUS severity is largely variable, ranging from mild to severe. *POGZ* encodes a nuclear protein involved in mitotic progression [2] and chromatin modulation [3]. About a 100 variants are known to date [4] and several studies have investigated genotype–phenotype correlation [4, 5]. Nevertheless, the pathogenic mechanism behind the disease is still unclear.

We report on the first and largest Italian WHSUS cohort, including a rare family (affected mother with two children) and adult cases.

2 | Subjects and Methods

Clinical features were obtained from existing records, clinical and instrumental exams, family surveys, and photographs. Patients have been evaluated across various Italian centers following standardized procedures—for example, validated batteries of neuropsychological tests for cognitive, adaptive, and behavioral assessments. Whole-exome sequencing (WES) was available for all cases: *POGZ* variants in probands and their familial segregation in parents were confirmed through Sanger validation and classified according to ACMG criteria [6], using both Human Gene Mutation Database [7] and ClinVar [8]. WES excluded other known neurodevelopmental pathogenic alleles. Data were revised at the Medical Genetics Service of IRCCS Burlo Garofolo (Trieste).

Genotype–phenotype correlations were analyzed using the scoring system proposed by Nagy et al. [4]. Patients were grouped into three cohorts based on data completeness (Cohort 1: more detailed—Cohort 3: less detailed). NMDEscPredictor [9] suggested whether a frameshift variant escaped NMD. SpliceAI [10] predicted splicing variant impact. Statistical analyses were performed on the 17 unrelated subjects using R V4.4.0 (The R Foundation for Statistical Computing). Severity and total scores were expressed as median and interquartile range (IQR). The Wilcoxon Mann–Whitney test (WMW) was performed to compare variant characteristics, severity, and total scores. $p < 0.05$ was considered statistically significant.

3 | Results

Nineteen patients (12 males and 7 females, aged 8–46; 17 unrelated) were recruited. Three of them had been previously published [11–13].

Main clinical features are summarized in Table 1 (details in Data S1).

Interestingly, 76% of patients presented with overweight or obesity. Microcephaly and short stature were observed in 40% and 25%, respectively. Neurodevelopmental delays and/or behavioral issues were always present. Most patients (89%) had an ID

TABLE 1 | Main clinical manifestations in our WHSUS cohort.

		No. of cases (%)
Neurodevelopment	Intellectual disability	17/19[a] (89)
	Language delay	14/16 (87.5)
	Motor delay	10/16 (62.5)
Neurology	Hypotonia	10/19 (53)
	Seizures	3/16[b] (19)
	CNS abn.	8/13 (61)
Behavior	ASD	5/17 (29)
	Anxiety	11/12 (92)
ENT	Hearing loss	5/16 (31)
Ophthalmology	Refraction defects	11/17 (65)
	Strabismus	9/18 (50)
Dysmorphisms	Facial dysmorph.	18/18 (100)
	Brachydactyly	6/16 (37.5)
Growth parameters	Microcephaly	6/15 (40)
	Overweight/obesity	13/17 (76)
	Short stature	4/16 (25)
Gastroenterology	Feeding difficulties	5/16 (27)
	Cyclic vomiting	2/15 (13)
	Constipation	4/15 (27)
Urology	Renal abn.	2/13 (15)
Cardiology	Heart abn.	4/16 (25)

[a]ID: mild: 9, moderate: 6, severe: 2.
[b]EEG abn. In 9/15 (60%) patients.

TABLE 2 | Genotypes and severity scores of our WHSUS patients.

Nucleotide change	AA change	Type	Loc. on gene	Protein domain	Inheritance	Reported	Patient ID (cohort)	Tot. score, sev. score
c.388C>T	p.Gln130*	Nonsense	Exon 4		De novo	Novel	PT5 (1)	20, 2
c.460-3C>G	p.?	Splicing	Intron 4	ZNF1	De novo	Novel	PT7 (1)	25, 3
c.860-5C>T	p.?	Splicing	Intron 6		Paternal	Novel	PT19 (3)	13, 4
c.1180_1181delAT	p.Met394Valfs*9	Frameshift	Exon 8		Maternal	Assia Batzir et al. [5]; Garde et al. [15]	PT2 (1)	15, 2
c.1180_1181delAT	p.Met394Valfs*9	Frameshift	Exon 8		Maternal	Assia Batzir et al. [5]; Garde et al. [15]	PT3 (1)	15, 2
c.1180_1181delAT	p.Met394Valfs*9	Frameshift	Exon 8		ND	Assia Batzir et al. [5]; Garde et al. [15]	PT4 (1)	16, 2
c.1352C>T	p.Pro451Leu	Missense	Exon 9		De novo	novel	PT18 (3)	5, 2
c.2020delC	p.Arg674Valfs*9	Frameshift	Exon 13		De novo	Stessman et al. [16]	PT16 (3)	6, 2
c.2102C>G	p.Pro701Arg	Missense	Exon 14		De novo	Novel	PT1 (1)	15, 2
c.2195_2196delCT	p.Pro732Argfs*11	Frameshift	Exon 14		De novo		PT17 (3)	8, 3
c.2196delT	p.Val733Serfs*13	Frameshift	Exon 14		ND	Novel	PT8 (1)	25, 3
c.2323_2324delCT	p.Leu775Valfs*4	Frameshift	Exon 15	ZNF8	De novo		PT14 (2)	13, 2
c.2482dupG	p.Asp828Glyfs*36	Frameshift	Exon 17	CBX5 (ZNF9)	De novo	Donnarumma et al. [13]	PT13 (1)	17, 2
c.2546-1G>A	p.?	Splicing	Intron 17		De novo	Trimarchi et al. [12]	PT12 (1)	26, 3
c.2711T>G	p.Leu904*	Nonsense	Exon 19		De novo	Ferretti et al. [11]	PT11 (1)	27, 3
c.3477_3479delAGT	p.Val1160del	In-frame del	Exon 19	DDE-1	Maternal	Novel	PT9 (1)	20, 2
c.4153C>A	p.His1385Asn	Missense	Exon 19	IBM	Paternal	Novel	PT15 (2)	10, 2
Del 1q21.3 (151093150–151574260)	/	/	/		De novo		PT6 (1)	23, 3
Del 1q21.3 (151360615–151448256)	/	/	/		De novo		PT10 (1)	11, 2

Note: Molecular characterization included variant type, localization on gene and protein, mechanism of inheritance. To investigate genotype–phenotype correlations, each subject received a cumulative clinical score ("Total score") which reflected the severity degree of the phenotype ("Severity score," 1: mild to 4: severe); patients were grouped into three cohorts based on how detailed available data were.

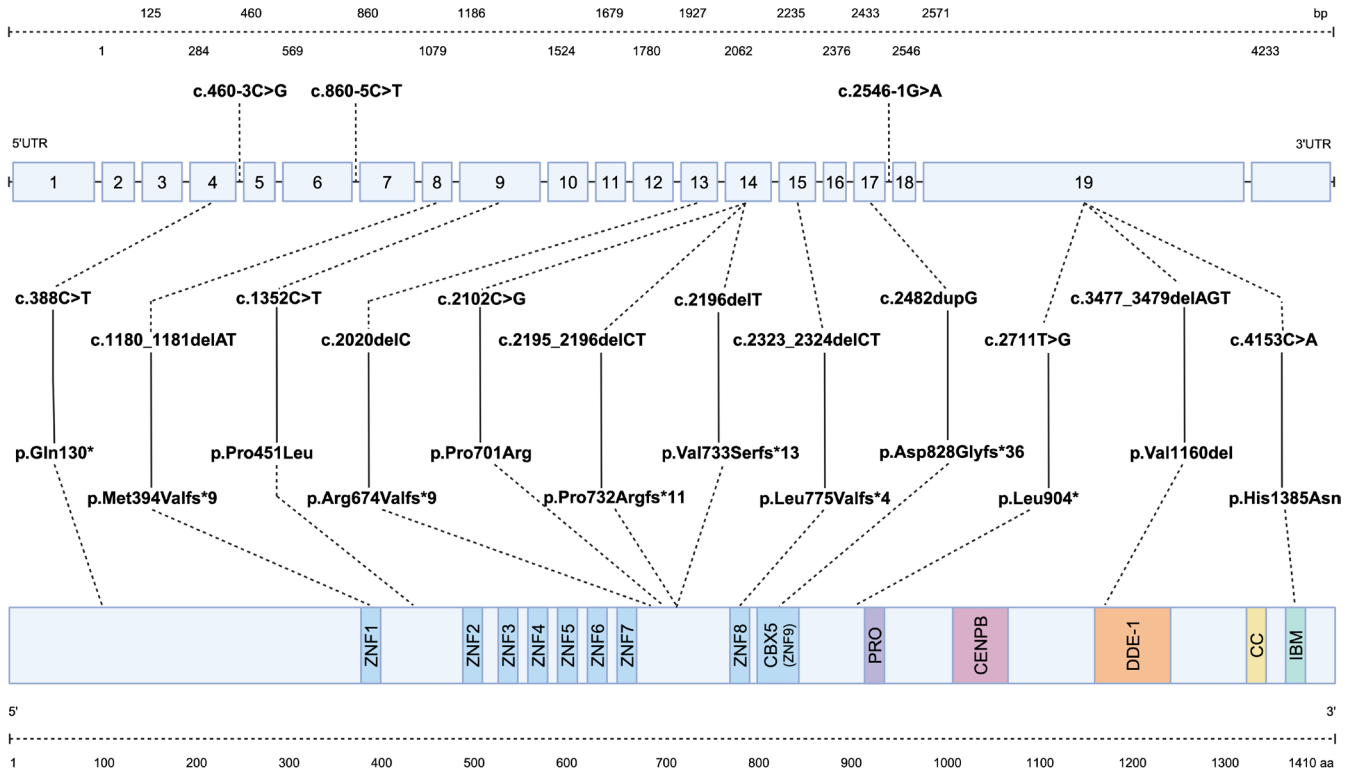

FIGURE 1 | Schematic representation of *POGZ* cDNA and protein structure including the localization of variants identified in our WHSUS patients cohort. NM_015100.4. CBX5, CBX5 (HP1α)-binding domain; CC, coiled-coil domain; CENBP, centromere protein B-binding domain; DDE-1, transposase domain; IBM, integrase-domain binding motif; PRO, proline-rich region; ZNF, zinc-finger domain.

(mild: 9, moderate: 6, severe: 2). Language, learning (87.5%) and motor skills (62.5%) were frequently impaired. Hypotonia was common (53%) and was often present at birth. Behavioral phenotypes were displayed in almost all subjects (95%), with 29% in the autistic spectrum. Anxiety (92%), attention disorder (80%), and sleep cycle alterations (29%) were described. Seizures or paroxysmal events occurred in 19% of cases; however, EEG anomalies were seen in 60%. Brain MRI revealed CNS abnormalities in 61%.

Ophthalmological involvement (79%) included refraction defects and strabismus. Hearing loss affected 31%.

At physical evaluation, all patients displayed dysmorphic features. Most recurrent findings were: broad forehead/frontal bossing (71%), broad nasal root and/or flat nasal bridge (59%), midface hypoplasia and/or midface retrusion (44%), tented or triangular mouth (62.5%), and external ear abnormalities (47%—mainly abnormally folded helices). Small hand and brachydactyly were present in 37.5%, large halluces and broad toes in 50%, and joint laxity in 23.5%.

Gastrointestinal symptoms included gastroesophageal reflux (25%), constipation (27%), and cyclic vomiting (13%). Feeding difficulties such as dysphagia and swallowing problems were also reported for 27%. Finally, renal congenital abnormalities were detected at US in 15%; as for cardiological findings, atrial septal defects with patent foramen ovale were reported for 25%.

As regards molecular study, we described 15 different *POGZ* variants and 2 large deletions encompassing the whole gene or vast part of it (481 and 88 kb, respectively). Ten alleles (eight point variants and the two large deletions) were novel, while the remaining seven were already described. None of them was present in the general population according to gnomAD [14], except for two which, however, were reported with a very low frequency (PT15 c.4153C>A: 0.000003978; PT18 c.1352C>T: 0.000003982). Most cases (six) were frameshift variants causing protein disruption; other types included in-frame deletion, three missense, two nonsense, and three splicing. In silico predictions strongly suggest all splice-site variants to be disruptive of the protein. Variant details are reported in Table 2 and Figure 1. Most variants occurred de novo, while five subjects inherited the allele (three maternally and two paternally), and for two patients, it was not possible to perform segregation analysis. For the two related cases (PT2, PT3), the affected parent (PT4) has been evaluated in detail and included in the study. Preliminary reports about the three other parents carrying the variant suggested mild phenotypes; however, data were limited and they have not yet been included in this study.

Based on Nagy et al. [4] severity scores, patients' phenotypes were classified as follows: none was mild (score 1), 11 were moderate (score 2), six were moderate–severe (score 3), and one was severe (score 4).

Any possible correlation between a variant (i.e., type, site, function) and the clinical phenotype was analyzed, and detailed

results are described in Data S1. Briefly, the severity score was significantly higher in the presence of splice site variants (WMW *p*: 0.017). Contrary to previous reports [17], no correlation was found between the protein domain involved (Figure 1) and the severity of the disease, nor the type of clinical manifestations. Neither loss of function variants potentially escaping NMD [18] were linked to a phenotype.

4 | Discussion

Since WHSUS was first described in 2016 [1], only about a 100 cases have been reported [19]. As this condition remains poorly known, the present study has been conducted to expand our understanding of the disease. Overall, the frequency and type of symptoms were consistent with those previously reported [4, 17] (Data S1) confirming a significant clinical heterogeneity. However, here we describe remarkably higher rates of anxiety issues and overweight/obesity (nearly twice as expected). Moreover, it emerged that congenital malformations (i.e., CNS, urinary tract, and heart) were often silent and only detected when accurately searched by instrumental means. In this light, our findings strongly suggest the importance of a systematic evaluation, including instrumental screening for congenital abnormalities. Neuropsychological support appears crucial to tackle anxiety issues, thus improving the quality of life of patients and their families; also, the inclusion of early nutritional support to reduce the negative consequences of overweight on patients' health seems particularly relevant.

So far only a few WHSUS adult cases have been reported in the literature, and the evolution of the disease with aging is unclear. Clinical data of the four adult patients described here indicate that the course of the disease is stable and unlikely to have any degenerative progression.

Molecular studies led to the description of 10 novel *POGZ* causative alleles and confirmed that the disease typically occurs with a de novo mechanism [17]. Accordingly, WHSUS familial cases are significantly rare. Nevertheless, here we report an unexpectedly high number of inherited variants (five subjects). This extremely interesting finding and the availability of families will be an exciting opportunity for future research aimed at investigating penetrance, expressivity, and mosaicism—as well as at better understanding genotype–phenotype correlations. In fact, we observed that related subjects carrying the same allele shared a similar clinical phenotype. While literature data suggest milder phenotypes associated with missense variants [4, 17], and more severe phenotypes to nonsense, frameshift, and missense variants escaping NMD or involving the proline-rich region of the protein [4], our study failed to find such correspondences. On the other hand, our analysis indicated a statistically significant association between the presence of splicing alleles and more severe phenotypes. Future studies are needed to unravel the functional role of these variants and corroborate our findings.

In conclusion, this work contributes to a more detailed description of WHSUS—from its molecular characterization to the heterogeneous phenotypes—and represents an important step toward a better understanding and management of *POGZ*-related disorders.

Author Contributions

A.F.: patients assessment, data analysis, and manuscript drafting. M.P.C.: statistical analysis and draft revision. S.Z.: molecular data study and draft revision. I.S., C.G., G.T., M.B.: patients assessment, data collection, and draft revision; A.M.I., M.T., A.D.D., L.G., I.D.M., F.M., D.G.: patients assessment and data collection. P.G.: supervision and manuscript revision.

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Ethics Statement

This study was conducted following relevant guidelines and regulations and in accordance with the tenets of the Helsinki Declaration. Patients have been recruited through a routine clinical or diagnostic process in certified and accredited centers belonging to the Italian National Health Care system; they gave consent to genetic tests, signing the appropriate forms.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/cge.70029.

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Supporting Information

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