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Case Report

Disruption of *POGZ* and Syndromic Intellectual Disability: Report of 4 Portuguese Cases

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Abstract

Introduction: White-Sutton syndrome (WHSUS) is a rare monogenic, autosomal dominant neurodevelopmental disorder. The diagnosis is established in a proband with a suggestive phenotype and a heterozygous pathogenic variant in the POGZ gene. Here we report 4 unrelated Portuguese individuals with WHSUS.

Case Report: Case 1: 7-year-old boy with intellectual disability (ID), disruptive behaviour and a pathogenic variant POGZ: c.3001C>T p. (Arg1001*). Case 2: 7-year-old boy with ID and obesity and a pathogenic variant POGZ: c.1837del p. (His613Metfs*13). Case 3: 5-year-old boy with developmental delay, behavioural problems, obesity and a likely pathogenic variant POGZ: c.3624del p. (Trp1208Cysfs*20). Case 4: 9-year-old boy with ID and ASD with a variant of unknown significance in POGZ: c.2459G>A (p.C820Y).

Discussion: WHSUS is a rare and likely underdiagnosed neurodevelopmental disorder with a non-specific phenotype. The vast majority of cases have truncating variants; the role of missense variants is still unclear (associated with disruptive behaviour but not clearly associated with ID).

Keywords: White-Sutton syndrome; Phenotype; POGZ; Intellectual Disability; Variants

Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; ID: Intellectual Disability; WES: Whole Exome Sequencing; WHSUS: White-Sutton syndrome

Introduction

Intellectual disability (ID) is a common, but extremely heterogeneous disorder. To date, more than 1300 genes have been implicated in a wide range of ID syndromes with diverse clinical presentations [1].

White-Sutton syndrome (WHSUS, MIM #616364), also known as *POGZ*-related intellectual disability syndrome, is a monogenic autosomal dominant neurodevelopmental disorder first identified by the Deciphering Developmental Disorders Study in 2015 [2]. WHSUS is characterized by a broad spectrum of symptoms, encompassing cognitive dysfunction, developmental delay (particularly speech and language) and dysmorphic features. A significant number of patients have autism spectrum disorder (ASD) or other behavioural problems [4]. Other features may include hypotonia, visual impairment and gastrointestinal problems. The diagnosis of WHSUS is made in a proband with suggestive findings and a heterozygous pathogenic variant in *POGZ* [5].

The pogo transposable element with zinc finger domain (*POGZ*) gene is located on chromosome 1q21.3 and expressed in most tissues, particularly the pituitary and cerebellum. It encodes a heterochromatin protein 1α-binding protein containing a cluster of multiple C2H2-type zinc fingers that can regulate gene expression, and a centromere protein B-like DNA-binding domain [3,7]. The largest transcript (ENSEMBL Transcript ID: ENST00000271715.6) has 19 exons (out of which 18 are coding). There is increasing evidence that *POGZ* is involved in transcriptional dysregulation, chromosome segregation and neuronal proliferation [6]. Therefore, dysregulation of *POGZ* causes premature mitotic exit with consequent depletion of neurogenic progenitor cells [9].

To date, only about one hundred cases have been reported, none of them from Portugal. Here we report 4 unrelated Portuguese individuals with heterozygous variants in *POGZ* and a clinical phenotype compatible with WHSUS.

Case Report

CASE 1

Seven-year-old boy referred for genetic consultation due to neurodevelopmental delay and behavioural problems. Family history was not relevant.

During the first two years, milestones were globally delayed. Language skills were severely impaired. Physical examination revealed brachycephaly, coarse flat face, long palpebral fissure, low set ears, prominent nasal tip with wide nasal ridge, anteverted nares, long philtrum, macroglossia, wide triangular mouth and single transverse palmar crease.

The first formal neurodevelopmental assessment at the age of 3 years revealed a below average general developmental quotient of 39.5 (Griffiths Mental Development Scales). The boy developed behavioural problems and was diagnosed with ID, ASD and attention deficit hyperactivity disorder (ADHD).

Clinical investigations included: normal metabolic study and neuroimaging (reduced encephalic volume with late myelinization). Initial genetic evaluation included conventional karyotype, molecular fragile X study, and comparative genomic hybridization (CGH) array all negative.

At the age of 16, an next-generation sequencing (NGS)-based ID gene panel revealed a *de novo* pathogenic variant NM_015100.3:c.3001C>T p.(Arg1001*) in heterozygosity in the *POGZ* gene. It's a nonsense variant located in exon 19. This variant was previously reported in patients with WHSUS (ClinVar ID 224724).

Case 2

Seven-year-old boy referred for genetic consultation due to ID, obesity and dysmorphic features. Family history included learning difficulties (father and siblings).

The boy was born with microcephaly and right *talipes equinovarus*. Infant weight started to increase after 18 months and exceeded the 97th percentile at the age of 7 years-old; length developed within the 25-50th precentile with persistent microcephaly.

Dysmorphic features included asymmetric round face, dysmorphic ears, broad eyebrow, upslanted palpebral fissure, hypertelorism, small nose with anteverted nares. Joint hypermobility and clinodactyly of 4-5 fingers were described.

Neurodevelopment was described as normal in the first year. He was referred at 30 months for speech delay. The boy had his first formal neurodevelopmental assessment at the age of 6 years, with an intelligence coefficient (IQ) of 44 (Wechsler Preschool and Primary Scale of Intelligence, version 3). He had also reports of disruptive behaviour, including hetero-aggressiveness.

Investigations included: metabolic study, neuroimaging, karyotype, molecular fragile X study and array CGH, all normal.

An NGS-based ID gene panel was remarkable for the likely pathogenic variant NM_015100.3:c.1837del p.(His613Metfs*13) in heterozygosity in *POGZ* , located in exon 12. This was a previously unreported frameshift variant, predictably resulting in a premature stop codon with a consequently truncated protein. Both parents opted out of testing.

Case 3

A five-year-old boy was referred for genetic consultation due to developmental delay. Family history included the father who died of lung cancer, the mother with idiopathic thrombocytopenic purpura who underwent splenectomy at the age of 25, and two healthy siblings.

Motor acquisition was borderline in the first year. Speech delay and behavioural problems (hyperkinetic and limited social interactions) were the first remarkable signs. Other health problems included hydrocele and astigmatism. Weight had exceeded 97th percentile at 3 years. Dysmorphic facial features included epicanthus and mild ectropion, wide nasal bridge with prominent nasal tip, anteverted nares, large fleshy low set ears, long philtrum, triangular mouth with high palate.

Formal neurodevelopmental assessment reported a below average developmental quotient, with a score of 54. He was later diagnosed with ADHD and developed an anxiety disorder.

Investigation included neuroimaging, metabolic study, molecular fragile X study, karyotype and assessment of deletions/duplications of subtelomeric regions my multiplex ligation-dependent probe amplification (MLPA), all normal.

Seven years later, a re-evaluation including array CGH (normal) and NGS-based ID gene panel detected an heterozygous likely pathogenic variant in *POGZ* (NM_015100.3):c.3624del p.(Trp1208Cysfs*20) in exon 19. This variant is a frameshift with a premature stop codon and predictably truncated protein, not previously reported. The maternal study was negative.

Case 4

Nine-year-old boy referred for a Medical Genetics consultation due to ID. Both mother and father had learning difficulties; the father died in a car accident at the age of 32.

At birth, physical examination revealed facial dysmorphisms (high forehead, broad columella, narrow nasal bridge, anteverted nares, underdeveloped nasolabial fold, thin upper lip vermilion, short lingual frenulum), frontal angioma, and axial hypotonia. The newborn presented feeding difficulties in the first days of life, with poor sucking and frequent choking. Nevertheless, anthropometry was still adequate.

Neurodevelopmental milestones were described as normal in the first year of life, but language and communication skills were severely delayed and the boy was diagnosed with ASD and ADHD at the age of six. Other health problems included delayed dental erosion, astigmatism and an epigastric hernia.

Genetic investigation included karyotype, molecular fragile X study and array CGH, all normal. Neuroimaging did not show any significant changes.

An NGS-based ID gene panel revealed NM_015100.3:c.2459G>A p.(Cys820Tyr) heterozygous variant in *POGZ*. This missense variant in codon 17 has not been previously reported. It was classified as a variant of uncertain significance (VUS). No other relevant variants were found in this study. The maternal study was negative.

Discussion

The diagnosis of WHSUS is established in a proband with suggestive findings and an heterozygous pathogenic variant in *POGZ*. Craniofacial features are non-specific and may include microcephaly, brachycephaly, broad forehead, hypertelorism, high nasal

root, anteverted nares, long malar region with midface hypoplasia, prognathism, palatal anomalies and low set ears [5]. Our patients had several of these features, but without a consistent pattern, as expected. Table 1 summarizes the findings in our patients that fit the phenotype of WHSUS.

Clinical features	Case 1	Case 2	Case 3	Case 4
Dysmorphic features	Brachycephaly, low set ears, anteverted nares	Microcephaly, hypertelorism, anteverted nares	Anteverted nares, low set ears, high palate	High forehead, anteverted nares
Intellectual disability	Moderate	Moderate	Moderate	Mild
Speech delay	x	x	x	x
Motor delay/Hypotonia	x			
ASD	x			x
Other behavioural problems	x	x	x	x
Obesity		x	x	
Ophthalmologic features			x	x
Musculoskeletal anomalies		x		

Table 1: Clinical features present in each case that fit WHSUS phenotype. (Legend: ASD-autism spectrum disorder).

In terms of neurodevelopmental manifestations, a wide range of developmental delay (particularly in speech), ID and behavioural problems are described [5]. In line with the literature, all our patients had ID and speech delay, two of them with moderate ID. Behavioural problems were over-reported in our patients, compared with an incidence of 50-60% in the literature. These results may be due to reference bias (as mild cases may not be referred for study) and the small sample size of this series.

Feeding difficulties affect over 50% and may be severe enough to require a nasogastric tube or gastrostomy. None of our patients had severe feeding difficulties and only patient 4 had mild feeding difficulties in the first days of life. Despite initial feeding difficulties, a significant proportion of children become overweight [5]. Both cases 2 and 3 are obese, the latter also with tall stature (a feature not previously associated with WHSUS).

Our patients, as reported in the literature, have a variable and non-specific phenotype common to various ID syndromes. Therefore, a definitive clinical diagnosis of WHSUS cannot be based on phenotypic features alone and requires molecular confirmation.

Among deleterious WHSUS genetic variants, most are frameshift (41%) and nonsense (40%); to a lesser extent, missense (8.5%), splice site (7%) and deletions (3.5%) have been reported [6].

In the present work, we report four different *POGZ* variants (Table 2).

	Variant	Type	Previously Reported	Pathogenicity	Family Study
Case 1	*POGZ* c.3001C>T p. (Arg1001*)	Nonsense (premature stop codon)	Yes (ClinVar ID 226507)	Pathogenic (PVS1_STR, PS4, PM2_SUP)	Negative
Case 2	*POGZ* c.1837del p. (His-613Metfs*13)	Nonsense (premature stop codon)	No	Likely Pathogenic (PVS1, PM2_SUP)	Unknown
Case 3	*POGZ* c.3624del p. (Trp-1208Cysfs*20)	Frameshift (premature stop codon)	No	VUS (PVS1_STR, PM2_SUP	N/A
Case 4	*POGZ* c.2459G>A p. (Cys820Tyr)	Missense	Yes (ClinVar ID 578764)	VUS (PM2_SUP, PP2)	Mother negative. Father N/A

Table 2: Variant description including type of variant, previous reports, pathogenicity classification (and respective ACMG criteria) and family study.

Legend: N/A-Not Available; VUS- Variant of Uncertain Significance).

Three variants were classified as pathogenic (all nonsense) or likely pathogenic (one frameshift), all occurring in exon 19. The literature suggests that most pathogenic truncating variants occur in this exon [3,8].

The last variant is a missense variant (case 4), which is classified as a VUS. While the presentation is compatible with WHSUS, clinical compatibility is uninformative due the non-specificity of the phenotype. Variant segregation in the family was suggested to help reclassify the variant. Unfortunately, only maternal study was available.

Missense variants are quite rare and distributed throughout the gene without a specific pattern. These variants are not clearly associated with ID, but appear to be associated with behavioural problems. Recent studies suggest that missense variants may not be pathogenic, or at least may not cause WHSUS. Published data suggest that all nonsense *POGZ* variants are fully penetrant, but that missense *POGZ* variants may have reduced penetrance; however, data are limited and further studies are needed [3,8]. In case 4, since both parents presented learning difficulties we cannot exclude other causes for the boy's ID; it is currently only an hypothesis that disruptive behaviour is attributable to missense variant, and ID to other causes.

In summary, WHSUS is a pleiotropic disorder with a broad spectrum of neurocognitive manifestations and a non-specific phenotype. Therefore, a definitive clinical diagnosis requires molecular confirmation and is probably under-reported. This paper describes the first cohort of Portuguese patients with WHSUS. As expected, our patients present a non-specific phenotype with a higher-than-expected incidence of behavioural problems. The vast majority of cases have a truncating variant in the 19th exon; the role of missense variants is still unclear. With this study, the authors aim to further characterise the WHSUS phenotype and genetic alterations, and also alert physicians to this rare and recently discovered syndrome.

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Conflict of Interest

The authors have stated that they had no interests which might be perceived as posing a conflict or bias.

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