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CLINICAL REPORT

Phenotypic comparison of patients affected with DeSanto-Shinawi syndrome: Point mutations in *WAC* gene versus a 10p12.1 microdeletion including *WAC*

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Abstract

Introduction: DeSanto-Shinawi syndrome is a rare neurodevelopmental disorder caused by loss-of-function variants of *WAC*, located on chromosome 10p12.1. This syndrome is characterized by dysmorphic facial features, intellectual disability, and behavioral problems.

Case report: In this case report, we present a new deletion case and summarize the clinical data of previously reported individuals, comparing the similarities and differences between cases caused by point mutations versus those which are caused by deletions in the 10p region.

Conclusion: Some differential features could facilitate the diagnostic suspicion guiding the optimal diagnostic tests that should be requested in each case scenario.

KEYWORDS

10p deletion, array CGH, DeSanto-Shinawi syndrome, global developmental delay, *WAC*

1 | INTRODUCTION

DeSanto-Shinawi syndrome (DESSH, OMIM #616708) was first described by de Santo et al. (2015). It is a rare neurodevelopmental disorder characterized by global developmental delay, behavioral abnormalities beginning in early childhood, and characteristic dysmorphic facial features.

It is caused by loss-of-function variants of *WAC* (OMIM #615049), located on chromosome 10p12.1. It encodes WW domain-containing adaptor with coiled-coil region (WAC), a nuclear protein that regulates histone H2B ubiquitination through interaction with RNF20/40, chromatin organization and ultimately gene transcription and cell cycle checkpoint activation in response to genotoxic stress (Alawadhi et al., 2021; de Santo et al., 2015). The protein encoded by this gene plays a vital role in gene transcription, microtubule development, autophagy, and Golgi apparatus function (Alsahlawi et al., 2020).

To our knowledge, an extensive clinical description has been reported in the literature for only 25 cases of point mutations (Alsahlawi et al., 2020; de Santo et al., 2015; Leonardi et al., 2020; Lugtenberg et al., 2016; Uehara et al., 2018; Vanegas et al., 2018; Zhang et al., 2019). Before

the full description of the syndrome by DeSanto et al. in 2015, several studies had described the common phenotypic characteristics of patients with deletions in the *WAC* gene (Okamoto et al., 2012; Shahdadpuri et al., 2008; Wentzel et al., 2011).

2 | MATERIAL AND METHODS

We report a case from a 6-year-old female patient who was born to non-consanguineous Caucasian parents after a 41-week, uncomplicated pregnancy. Father reported a mild gait delay, but both parents were not known to have any genetic or chronic disease.

At birth, Apgar score was 10/10, she weighed 2.970 Kg (10th centile), length 50.5 cm (60th centile), and her occipitofrontal head circumference (OFC) was 32 cm (10th centile).

Developmental delay was first noticed at 19 months old, when patient was unable to walk. She started crawling at 14 months. Language development was also delayed, with first words spoken at 14 months. By the time of her first clinical evaluation (at 20 months old), she could say less than 10 words. She also presented repetitive behavior patterns, such as turning lights on and off. She showed characteristic facial dysmorphic features (Figure 1): synophrys with deeply set eyes, down slanted palpebral fissures, a bulbous nose with depressed nasal bridge, and posteriorly rotated ears with preauricular pits. She had the tendency to keep the mouth open with tongue protrusion, and she also presented diastema and an everted vermilion of the upper lip. Since early childhood she had sleep difficulties, such as snoring with occasional apnea pauses, sleep terrors, and enuresis.

The patient is currently enrolled in early childhood education with educational and speech therapy support. She presents a mild gross motor clumsiness and social development and interactional difficulties due to her impulsive and aggressive behavior with her peers.

A comparative genomic hybridization (aCGH) was performed from peripheral blood sample obtained with prior written informed consent from parents. Analysis was carried out using 60 K SurePrint G3 Human CGH ISCA v2 Microarray from Agilent Technologies. Samples from patient and her parents were hybridized against a same-sex hybridization control (Human Reference DNA, from Agilent Technologies).

3 | RESULTS

A single dose of the 10p12.1p11.23 region was found in the proband. This deletion on 10 chromosome was approximately 2.49 Mb in size: arr[GRCh37] 10p12.1p11.23(27727630_30222261)x1, and included seven genes, where *WAC* gene was contained. Chromosomal formula is expressed according to the ISCN nomenclature against the GRCh37 reference assembly. Results have been aligned against the reference human genome and their possible pathogenicity was evaluated by querying databases.

Major features are summarized in Table 1 next to their HPO codes, as well as other clinical findings in the proband, comparing them with other cases published

FIGURE 1 Patient's facial dysmorphic features

TABLE 1 Clinical features of the case reported compared to individuals previously reported in the literature

		Deletions							
		This report	Okamoto et al. (2012)	Wentzel et al. (2011)	Shahdadpuri et al. (2008)	Deletions		Point mutations	
	Sample	1 patient	2 patients	6 patients	1 patient	10 patients	%	25 patients	%
	Sex	F	1 F, 1 M	4 F, 2 M	1 M	6F, 4 M		13 F, 12 M	
	Age	6 y/o	6, 7–7, 8 y/o	3, 4–11 y/o	1, 3 y/o	1, 3–11 y/o		1, 3–22 y/o	
	Delayed growth	–	0/2	4/6	–	4/10	40.00%	11/25	44.00%
	Perinatal abnormalities	–	0/2	2/6	–	2/10	20.00%	9/25	36.00%
	Development								
HP:0001270	Motor delay	+	2/2	6/6	+	10/10	100.00%	24/25	96.00%
HP:0000750	Delayed speech and language development	+	1/2	5/6	+	8/10	80.00%	24/25	96.00%
	Dismorphic features								
HP:0000664	Synophrys	+	2/2	5/6	NR	8/9	88.89%	9/25	36.00%
HP:0000490	Deeply set eye	+	2/2	4/6	+	8/10	80.00%	12/25	48.00%
HP:0000414	Bulbous nose	+	1/2	4/6	+	7/10	70.00%	13/15	86.67%
HP:0000158	Macroglossia	–	2/2	NR	NR	2/3	66.67%	12/12	100.00%
HP:0004467	Preauricular pit	+	1/2	NR	–	2/4	50.00%	2/12	16.67%
HP:0011297	Abnormal digit morphology	+	1/2	3/6	–	5/10	50.00%	14/21	66.67%
HP:0005280	Depressed nasal bridge	+	2/2	1/6	NR	4/9	44.44%	9/9	100.00%
HP:0001007	Hirsutism	+	NR	2/6	NR	3/7	42.86%	7/25	28.00%
HP:0011220	Prominent forehead	–	2/2	1/6	–	3/10	30.00%	21/25	84.00%
HP:0000316	Hypertelorism	–	0/2	NR	+	1/4	25.00%	14/19	73.68%
HP:0000369	Low-set ears	–	0/2	NR	+	1/4	25.00%	5/15	33.33%
HP:0000272	Malar flattening	–	0/2	1/6	NR	1/9	11.11%	4/9	44.44%
	Behavioral problems								
HP:0000752	Hyperactivity	+	NR	4/6	NR	5/7	71.43%	9/24	37.50%
HP:0100852	Anxiety-related behavior	+	NR	3/6	NR	4/7	57.14%	9/24	37.50%
HP:0002360	Sleep disturbance	+	NR	3/6	NR	4/7	57.14%	12/25	48.00%
HP:0000729	Autistic behavior	+	NR	2/6	NR	3/7	42.86%	7/23	30.43%
	Neurological								
HP:0001252	Hypotonia	–	0/2	3/6	+	4/10	40.00%	18/24	75.00%

(Continues)

TABLE 1 (Continued)

		Deletions				Deletions		Point mutations	
		This report	Okamoto et al. (2012)	Wentzel et al. (2011)	Shahdadpuri et al. (2008)				
	Sample	1 patient	2 patients	6 patients	1 patient	10 patients	%	25 patients	%
HP:0001250	Seizures	–	0/2	2/6	NR	2/9	22.22%	6/24	25.00%
	Other								
HP:0000486	Strabismus	–	NR	3/6	–	3/8	37.50%	8/24	33.33%
HP:0002019	Constipation	–	1/2	2/6	NR	3/9	33.33%	8/14	57.14%
HP:0011968	Feeding difficulties	–	1/2	1/6	NR	2/9	22.22%	10/24	41.67%
	Diagnostic tests								
HP:0002353	EEG abnormalities	+	NR	NR	NR	1/1	100.00%	2/8	25.00%
HP:0002500	MRI abnormalities	NR	0/2	4/6	+	5/9	55.56%	6/21	28.57%
HP:0000364	Hearing abnormality	–	1/2	2/6	+	4/10	40.00%	3/15	20.00%

Note: NR, not reported; +, present; –, absent.

before deletions from 15.7 to 2 Mb that include *WAC* gene (Okamoto et al., 2012; Shahdadpuri et al., 2008; Wentzel et al., 2011) among other genes versus point mutations in *WAC* gene (Alsahlawi et al., 2020; de Santo et al., 2015; Leonardi et al., 2020; Lugtenberg et al., 2016; Uehara et al., 2018; Vanegas et al., 2018; Zhang et al., 2019).

4 | DISCUSSION

Almost all patients described in cases of point mutations and in the deletion group presented motor developmental delay. More than 80% of them presented language difficulties as well, without significant differences between the two groups.

According to the dysmorphic characteristics, there were some recognizable craniofacial characteristics in both groups. Nevertheless, some of them were described with significant differences between them, being more frequent in the deletion group, such as synophrys (8/9), deeply set eyes (8/10), or depressed nasal bridge (4/9) (Okamoto et al., 2012; Shahdadpuri et al., 2008; Wentzel et al., 2011).

On the other hand, features such as prominent forehead (3/10) or malar flattening (1/9) were less frequent in this group compared to the point mutations one (Alsahlawi et al., 2020; de Santo et al., 2015; Leonardi et al., 2020; Lugtenberg et al., 2016; Uehara et al., 2018; Vanegas et al., 2018; Zhang et al., 2019).

Some dysmorphic characteristics like bulbous nose or abnormal digit morphology were reported without significant differences between both groups.

Most of the patients presented behavioral problems. In the deletion group, ADHD was detected in greater than 70% of the cases (Okamoto et al., 2012; Shahdadpuri et al., 2008; Wentzel et al., 2011). Anxiety-related behavior, sleep disturbances, or autistic features were also described in both groups.

In the patient described in this report, no anomalies were found in metabolic and immunology tests, polysomnography, or auditory evoked potentials.

The EEG showed a normal background activity with right middle temporal epileptiform activity more intense during sleep. However, no clinical crises have been reported to date.

Seizures or epilepsy had been described only in patients with *WAC* point mutations. The typical EEG pattern of electrical status epilepticus during slow sleep, has been reported only in one patient by Leonardi et al. (2020), but due to the importance of early diagnosis it should be taken into account from now on in new diagnoses of DESSH.

5 | CONCLUSION

So far, few cases have been reported. We intend to further delineate the phenotypic spectrum of DESSH, emphasizing the possible differences depending on the type of variant found. As we describe in this report, synophrys, deeply set eyes, or depressed nasal bridge were features found more frequently in the large deletions group, which were detected by aCGH. However, patients who showed a prominent forehead or malar flattening, were more likely to present a point mutation, in which we would perform the sequencing of the *WAC* gene.

We could improve the genotype–phenotype correlations described in DESSH patients and we could decide which is the technical method used in each case.

Broadening the knowledge about WAC-DESSH phenotype may contribute to improving the management of patients and the counseling to the families.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Cristina Toledo-Gotor: collected the data, contributed data or analysis tools, and wrote the paper. Cristina García-Muro: collected the data, contributed data, or analysis tools. Alberto García-Oguiza: contributed data or analysis tools, revised the draft. Mª Luisa Poch-Olivé: revised the draft critically for important intellectual content. Mª Yolanda Ruiz-del Prado: approved the version to be published. Elena Domínguez-Garrido: conceived and designed the analysis, revised the draft, approved the version to be published.

ETHICAL APPROVAL

All procedures performed were in accordance with the ethical standards with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Patient's family provided written informed consent.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article (and its supplementary information files). If you have any further questions, data are available from the corresponding author upon reasonable request.

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