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Skraban-Deardorff syndrome: six new cases of *WDR26*- related disease and expansion of the clinical phenotype

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Data availability statement: The *WDR26* variants and associated phenotypes have been submitted to the ClinVar database (<https://www.ncbi.nlm.nih.gov/clinvar/>). Further data supporting the study's findings are available from the corresponding author upon reasonable request.

Abstract:

Skraban-Deardorff syndrome (a disease related to variations in the *WDR26* gene; OMIM #617616) was first described in a cohort of 15 individuals in 2017. The syndrome comprises intellectual deficiency, severe speech impairment, ataxic gait, seizures, mild hypotonia with feeding difficulties during infancy, and dysmorphic features. Here, we report on six novel heterozygous *de novo* pathogenic variants in *WDR26* in six probands. The patients' phenotypes were consistent with original publication. One patient displayed marked hypotonia with an abnormal muscle biopsy; this finding warrants further investigation. Gait must be closely monitored, in order to highlight any musculoskeletal or neurological abnormalities and prompt further examinations. Speech therapy and alternative communication methods should be initiated early in the clinical follow-up, in order to improve language and oral eating and drinking.

Keywords: Skraban-Deardorff syndrome; *WDR26*; intellectual disability; phenotype; speech therapy; hypotonia; language development disorders

Introduction:

Syndromic forms of intellectual disability can be difficult to recognize clinically, given the variable severity and great heterogeneity in the disease features. The *WDR26* gene is located in chromosomal region 1q42, which was first described in 1q41q42 microdeletion syndrome (OMIM #612530). Seven probands with deletions ranging from 2.6 to 10 Mb in size were described; the disease features were developmental delay, microcephaly, cleft palate, club foot, seizures, short stature, and dysmorphic features (frontal bossing, deep-set eyes, broad nasal tip, anteverted nares, coarse facial features)¹.

In 2017, Skraban et al. described a *WDR26*-related disease in a cohort of 15 individuals with *de novo* pathogenic variants². Skraban-Deardorff syndrome combines intellectual disability, seizures, developmental delay, abnormal gait, and characteristic facial features. Skraban et al.² pointed out the overlap between the clinical features of individuals with *WDR26 de novo* variants and those with 1q41q42 microdeletion, and suggested that the syndrome results from *WDR26* haploinsufficiency. They also reported that frameshift variants of *WDR26* were associated with abnormally low total mRNA levels and *WDR26* protein levels. *WDR26* missense variants are located in highly conserved region and are thought to lead to a less stable, less active protein.

Recently, a large-insert genome sequencing study identified an apparently balanced translocation disrupting *ANKS1B* and *WDR26* in a proband with a *WDR26*-disease phenotype compatible³.

Here, we report six novel cases with *de novo WDR26* variants. We provide additional clinical and molecular data and compare the probands' phenotypes with the literature data.

Patients and methods:

We collected clinical and molecular data from six patients (3 males and 3 females, aged from 9 months to 16 years) treated at four different university hospitals in France. Multicentre national recruitment was made possible by a call for collaboration via the “AnDDi-rares” study network for rare developmental disorders. In line with French legislation and the Declaration of Helsinki, the patients’ parents gave their informed consent to genetic analysis and to publication of the photographs included in the present manuscript. Genomic DNA was extracted from a peripheral blood sample. *WDR26* variants were detected with next-generation sequencing (whole exome sequencing or screening against an intellectual deficiency and epilepsy gene panel).

Results (Table 1):

Molecular data:

We found six novel *de novo* variants: 1 missense, 3 nonsense, 1 frameshift and 1 splice site variants.

In patient #1, screening against the intellectual deficiency gene panel revealed 3 variants: the wild-type allele NM_025160.6:c.1644+1G and two substitutions c.1644+1G>C and c.1644+1G>A (Figure 1). These variants affected the first base of the exon 11 splice donor canonical site. RNA analysis revealed the exclusion of exon 11 from the mRNA, leading to a frameshift and a premature stop codon (American College of Medical Genetics (ACMG)⁴ class 5). For patient #6, the missense variant was NM_025160.6:c.1529G>A, p.(Arg510Gln), affecting a highly conserved nucleotide/amino acid. Most models predicted an effect on the protein. This variant was not present in population database GnomAD.

Clinical description:

Four patients had intrauterine growth restriction. For patients #3 and #6, pregnancy was marked by second-trimester polyhydramnios and third-trimester oligohydramnios, respectively.

During early development, all our patients (other than #6) had feeding difficulties; this ranged from difficulty swallowing pieces of food to inability to eat. Patient #3 had a suspected Pierre-Robin sequence, in view of the antenatal polyhydramnios and the presence of abnormal tongue placement and an excessively marked nausea reflex. A nasogastric tube was required from birth, due to oral difficulties, emesis, and poor weight gain. At 9 months of age, she underwent a gastrostomy for exclusively enteral nutrition. Patient #6 did not present feeding difficulties during infancy but developed a pica disorder. Patient #1 and #5 had repeated ENT infections and sinusitis, respectively.

All individuals presented with developmental delay in general and language delay in particular. Oral expression started at between 3 and 8 years of age and at best, patients used single words or two-word combination. Comprehension appeared to be relatively unaffected. Pictogram-based communication was established in all cases. At 14 months of age, patient #3 chewed and mumbled constantly and did not pronounce any single words. Patient #6 had a good understanding of simple instructions when attentive but was limited by major behavioural disorders at the age of 8 years.

Four patients underwent a neuropsychological assessment. Patient #1 Psycho-Educational Profile (3rd edition)⁵ results for expression, communication, comprehension, and motor skills were that of a 12, 15, 19 and 25-month-old infant, respectively, at 3 years and 9 months-old. She had very poor attentional capabilities, and non-verbal communication fluctuated between withdrawal and interaction. At 10 years-old, patient #2's assessment on the Brunet-Lézine⁶

revealed a moderate developmental delay. Motor skills were relatively unaffected – in contrast to the language skills and socialization abilities. Patient #3 had a Brunet-Lézine⁶ assessment at 17 months of age. Results for socialization, gross and fine motor skills were that of a 14, 8 and 9-month-old, respectively. She had a good level of understanding, presented appropriate tonic-emotional reactions, and was interested by non-verbal communication such as the Makaton Language Programme (speech/signs/symbols) and sign language. Patient #5 estimated intellectual quotient was between 46 and 62 at 8 years-old. All six patients were described as having happy, friendly personalities.

Dysmorphism and other phenotypic characteristics (Figure 2):

Our patients with *WDR26*-related syndrome had a pronounced subpalpebral crease (5 out of 6), rounded palpebral fissures and relatively large irises (4 out of 6), not described in the original Skraban-Deardorff cohort². Dysmorphic features were similar to those described in 2017.

During the neonatal period, patient#3 hypotonia prompted a muscle biopsy. Light microscopy was normal but electron microscopy showed Z-line disorganization and multiminicores. Echocardiography revealed lipomatous hypertrophy of the interatrial septum and a short (2 mm) atrial septal defect.

Discussion:

Here, we reported on six new cases of Skraban-Deardorff syndrome caused by six novel *de novo* variants in *WDR26*. The latter gene is thought to be a negative regulator of MAP kinase signalling pathways and might therefore have a major role in cell signal transduction⁷. *WDR26* is transcribed ubiquitously, although expression levels are higher in skeletal muscle, brain, liver, lung and heart in the foetus and in skeletal muscle and heart in the adult. This ubiquitous expression might explain the diversity of disease symptoms.

The phenotypic description is concordant with the initial syndromic description by Skraban et al.², we confirm the large occurrence of various neurological malformations, autistic behaviour, seizures, skeletal manifestations and ataxic gait. Seizures or subclinically abnormal EEG patterns and autistic behaviour were observed in all but one (a 18-month-old infant) of the members of both cohorts. Skraban et al. reported that the age at onset of epilepsy ranged from neonatal to the age of seven years.

Patient #3 presented with a Z-line disorganization, multiminicores, and an atrial septal defect. This muscle/cardiac phenotype has not previously been described in a case of *WDR26*-related disease. Differential diagnoses for Z-line disorganization and multiminicores include variants in *TTN*⁸ and *ACTN2*⁹ but a trio exome analysis did not reveal any variants in these genes. Exome sequencing also revealed a *de novo NR4A3* variant, a gene better known in the field of oncogenetics¹⁰. At the time of writing, the patient had not shown any signs of neoplasia.

Five patients had feeding difficulties during infancy in our cohort. One patient had a suspected Pierre-Robin sequence and abnormal tongue placement, oral feeding was still not possible at the age of 11 months - prompting a gastrostomy. Another of our patients had a velar cleft palate. Six patients in Skraban et al.'s cohort had failure to thrive or feeding difficulties in the absence of major respiratory or gastrointestinal malformations, and one individual had a cleft palate. These difficulties might have resulted from hypotonia in the neonatal period. Cleft palate might be underdiagnosed; it might be worth (i) an evaluation by a specialist and (ii) asking caregivers to look for signs of velopharyngeal inadequacy (nasal emissions and hypernasality).

Language appears to be limited to single words or two-word associations, which limits the person's ability to express frustration or explain emotional or physical distress. In turn, this can exacerbate psychiatric disorders¹¹. Early speech therapy and augmentative/alternative communication methods are essential for the management of children with Skraban-Deardorff

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syndrome. This management can improve language development¹² and reduce behavioural disorders by promoting communication and social skills¹³.

Conclusion:

The present clinical report is the second description of *WDR26*-related disease. The phenotypes observed in the six new cases are consistent with Skraban et al.'s description in 2017²: intellectual disability, developmental delay (predominantly for the language), characteristic dysmorphism, epilepsy, skeletal manifestations, abnormal gait, and a happy/friendly personality. We additionally observed abnormal features in a muscle biopsy; these might be related to the *WDR26* defect. Skeletal manifestations, feeding difficulties in infancy (with or without a velar cleft palate) and early-onset epilepsy are present in most patients.

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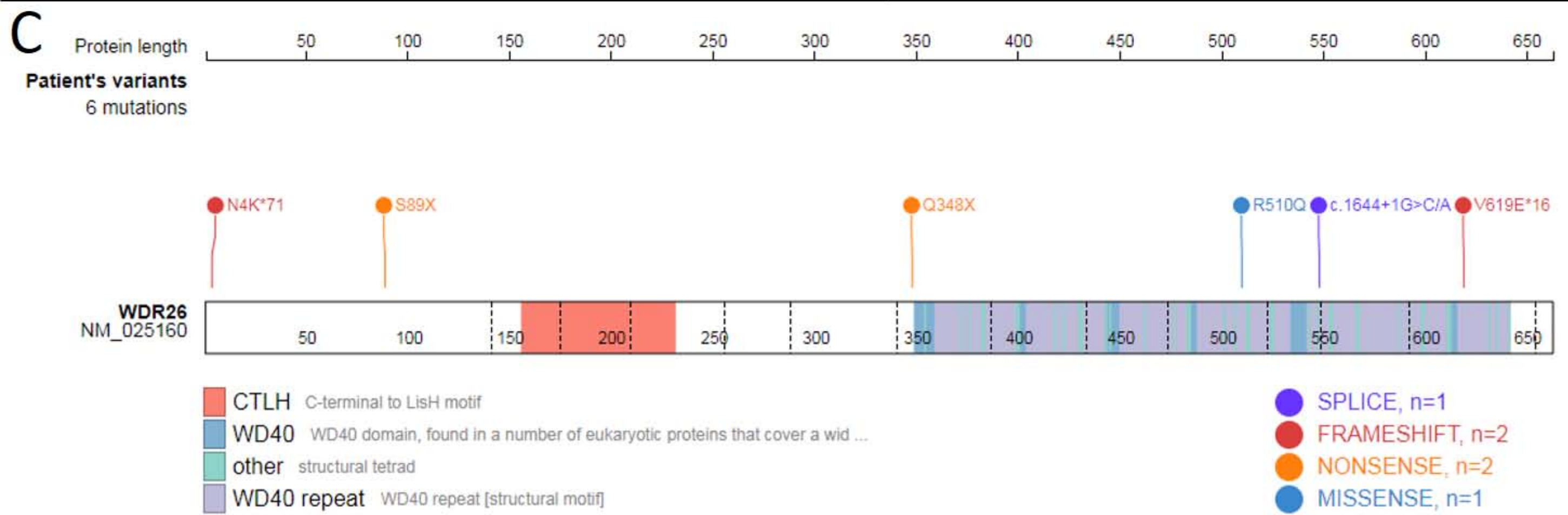
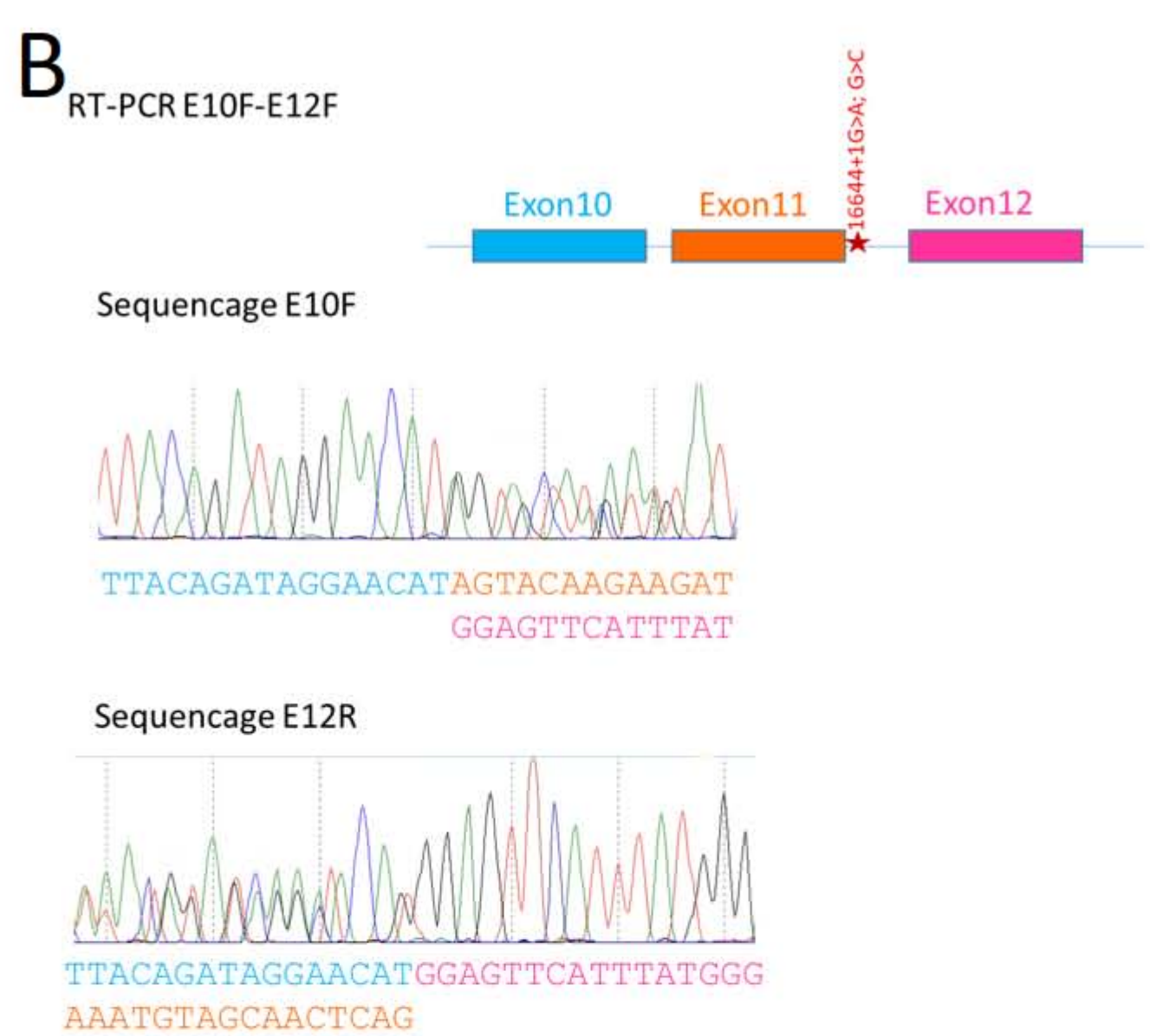
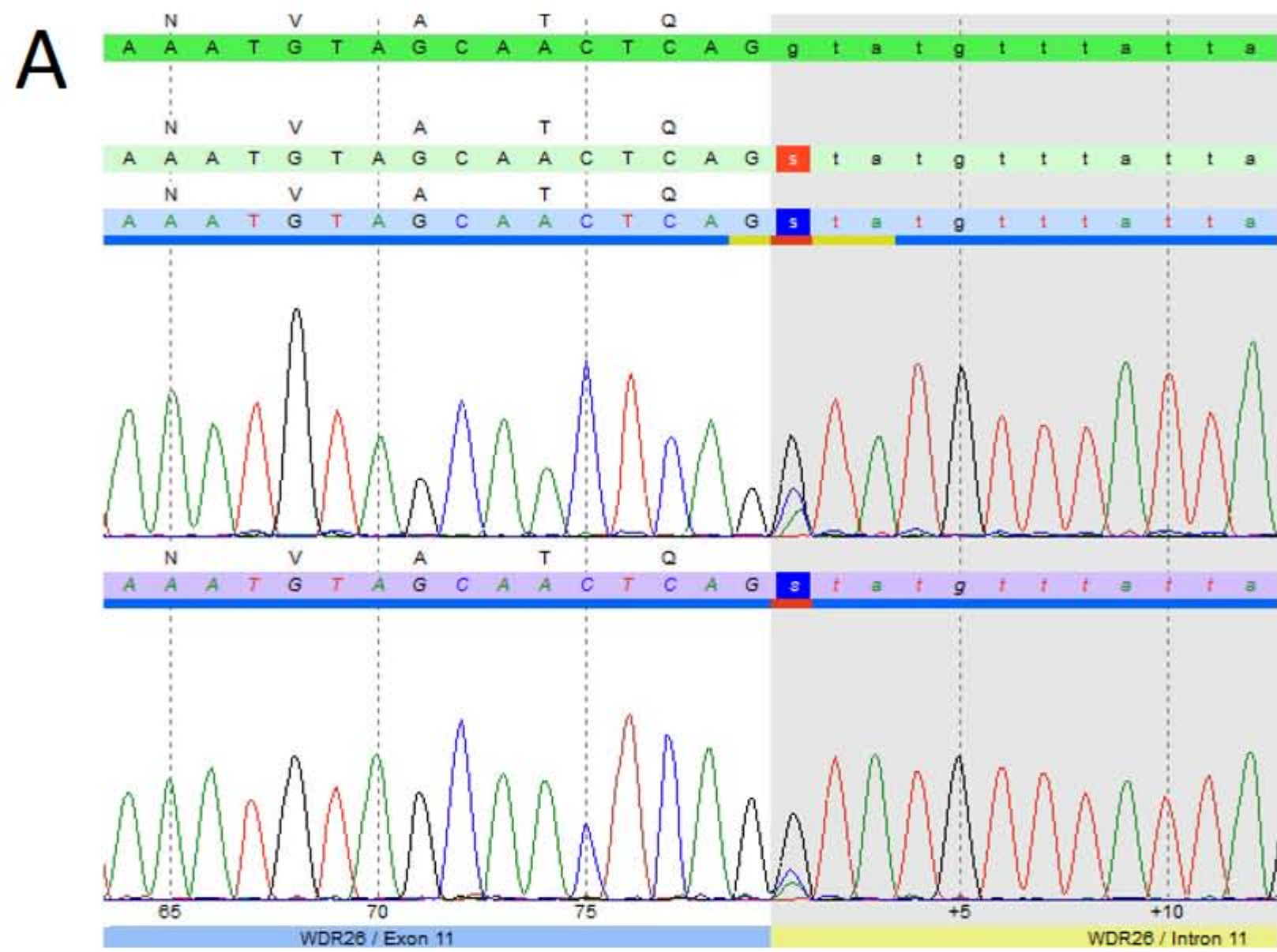
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Legends:

Table 1: Molecular and clinical characteristics of six patients with novel WDR26 pathogenic variants. ADHD: attention deficit/hyperactivity disorder; IUGR: intrauterine growth restriction; p: percentile on the *Association des Utilisateurs de Dossiers Informatisés en Pédiatrie, Obstétrique et Gynécologie* charts for neonates (<https://www.audipog.net>); SD: standard deviation on Sempé's growth charts¹⁴; TCS: tonic-clonic seizure.

Figure 1: A) Chromatogram of the DNA sequence, showing the wild-type allele NM_025160.6:c.1644+1G and the two substitutions c.1644+1G>C and c.1644+1G>A in the forward sequence (upper transcript) and the reverse sequence (lower transcript). The variation affects the first nucleotide of intron 11. B) RT-PCR results showing the splicing alteration due to the two substitutions c.1644+1G>C and c.1644+1G>A, which lead to exon 11 being skipped in the RNA sequence. The forward sequence (upper transcript) shows the superposition of the exon 11 transcript and the alternative exon 12 transcript. The reverse sequence (lower transcript) shows the superposition of exon 10 and exon 11 transcripts, which proves that exon 11 has been skipped. C) Representation of the six novel variants in the protein sequence. The red box corresponds to the C-terminal to LisH motif (CTLH) domain, and the blue and purple boxes correspond to the WD40 domains and repeats, respectively. This figure was created with Proteinpaint (<https://pecan.stjude.cloud/proteinpaint>).

Figure 2: Photographs of the six patients with WDR26 variants found by exome sequencing. The patient numbers are those used in the text.





	Skraban-Deardorff cohort	Present cohort	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6
<i>WDR26 variants (de novo)</i>								
cDNA notation (NM_025160.6)			3 alleles: c.1644+1G c.1644+1G>C c.1644+1G>A	c.12del	c.266C>G	c.1042C>T	c.1856_1857del	c.1529G>A
Predicted effect on protein			splice site p.(Ile522Metfs*13)	p.(Asn4Lysfs*71)	p.(Ser89*)	p.(Gln348*)	p.(Val619Glufs*16)	p.(Arg510Gln)
Pregnancy, neonatal and growth parameters								
Particular features of pregnancy or delivery		4/6	none	none	IUGR (2 nd trimester) polyhydramnios	IUGR	IUGR (last month)	IUGR (3 rd trimester) oligohydramnios
Sex (M/F)		3F/3M	F	M	F	F	M	M
Age at last follow-up (y: years, m: months)			8 y	16 y	18 m	4 y 9 m	8 y 4 m	14 y
<i>Parameters at birth</i>								
APGAR 1'/3'			10/10	10/10	8/9	10/10	10/10	9/10
Gestation term (weeks)			37	38	37	34	37	39
Weight g (p.)			2820 (16)	3500 (50)	2675 (8)	2450 (38)	2370 (<1)	2230 (<1)
Length cm (p.)			47 (12)	48 (8)	47 (12)	44 (12)	48.5 (22)	46 (<1)
Head circumference cm (p.)			32 (5)	35 (48)	33 (20)	31 (12)	33.5 (19)	32 (1)
<i>Parameters at last follow-up</i>								
Weight, kg (SD)			21.4 (0)	50.6 (-1)	6.340 (- 2)	16.3 (-1)	20 (-1)	49.6 (0)
Height, cm (SD)			118 (0)	168.9 (-0.5)	64.5 (-1.75)	109.3 (+0.5)	124.5 (0)	160.5 (-0.5)
Head circumference, cm (SD)			49 (-2)	54.5 (-1.5)	43 (-1)	49 (-1)	51.5 (-1)	52.8 (-1.5) at 13 y.
Psychomotor development								
Hypotonia	9/12	4/6	yes	no	yes	yes	no	yes
Developmental delay or intellectual disability	15/15	6/6	yes	yes	yes	yes	yes	yes
Motor development			sitting up at 12 m, started walking at 2 y	started walking at 2 y	sitting up at 11 m, rolling over onto back at 17 m, not walking at 18 m	hold her head at 12 m, started walking at 2.5 y	sitting alone at 16 m, started walking at 2.5 y. Dyspraxia	sitting up at 8 m, started walking at 18 m
<i>Abnormal gait</i>		3/6	ataxic	ataxic	-	no	no	coordination difficulties

Level of language			Not talking at 2 y, simple word associations at 5 y. Regression period with loss of word in childhood	first words at 4 y	babbling at 17 m	three words at 4 y, babbling	first words at 8 y	Not talking at 17 m, then simple word associations during childhood
Dysmorphism								
Abnormal eyebrows (horizontal)	6/15	4/6	yes	yes	no	no	yes	yes
Depressed nasal root	5/15	5/6	yes	yes	yes	yes	yes	no
Anteverted nares	8/15	5/6	yes	yes	yes	yes	no	yes
Full nasal tip	11/15	6/6	yes	yes	yes	yes	yes	yes
Full cheeks as a child	11/13	5/6	yes	yes	yes	yes	no	yes
Prominent maxilla and protruding upper lip	13/15	3/6	yes	yes	no	no	yes	no
Decreased cupid's bow	11/15	5/6	yes	yes	no	yes	yes	yes
Widely spaced teeth	13/15	3/4	yes	yes	-	yes	-	no
Abnormal gums	9/15	2/2	yes	yes	-	-	-	-
Coarse facial features	12/15	2/6	no	yes	no	no	yes	no
Pronounced subpalpebral crease		5/6	yes	yes	yes	yes	yes	no
Rounded palpebral fissures and relatively large irises		4/6	yes	no	yes	yes	no	yes
Other								
Epilepsy/EEG abnormalities	15/15	5/6	TCS and absences	one febrile seizure	-	infra-clinical focal point of straight central waves	one febrile TCS	TCS, bifrontal foci
Brain MRI	10/14	4/6	bilateral frontal polymicrogyria	normal	ventriculomegaly, thin corpus callosum	normal	pineal cyst, left olfactory bulb agenesis	thin corpus callosum
Psychiatric disorders	-	4/6	anxiety, sudden changes in behaviour, unmotivated laughter	anxiety	-	-	anxiety	ADHD, disinhibition, auto/hetero aggressivity
Autism and repetitive behaviour	5/9	5/6	yes	yes	-	yes	yes	yes
Orthopaedic disorders	5/15	4/6	bilateral genu valgum	lower limb joint stiffness, flat feet	-	unilateral congenital hip dislocation	-	pectus carinatum, thoracic kyphosis
Oral condition			-	velar cleft, agenesis of two lateral incisors	suspected Pierre-Robin sequence as a neonate, with abnormal tongue placement	-	delayed loss of deciduous teeth	macrodontia (incisors)

Other features		-	-	abnormal muscle biopsy (Z-line disorganization and multiminicores) and echocardiography	Surgically treated umbilical hernia	unilateral cryptorchidism, auditive acuity: 30 dB (behavioural audiometry)	convergent strabismus, nevus on left iris, hairy nevus on left forearm
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