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Case Report

Ocular manifestations of Nabais Sa-de Vries Syndrome type 1

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Abstract: Nabais Sa-de Vries syndrome (NSDVS) is a neurodevelopmental disorder first described in 2020. The syndrome is caused by de novo missense mutations in speckle-type pox virus and zinc finger protein (*SPOP*) on chromosome 17q21. The syndrome is divided into two forms (NSDVS Type 1 and NSDVS Type 2) based on the consequence of the mutation involved. In this report, we present the clinical features in a young male patient with suspected NSDVS1 and summarize the features of the reported affected individuals thus far, with a focus on the ophthalmic manifestations. Similar to other individuals with NSDVS1, he had features of congenital microcephaly, developmental delay, behavioral abnormalities, hearing loss, and facial dysmorphisms. Ocular and periorbital manifestations in this patient included thick high-arched eyebrows, mild synophrys, long eyelashes, ptosis, and downslanting palpebral fissures; comparable to features described in other individuals with NSDVS1. In addition, this patient had esotropia that required multiple strabismus surgeries and a refractive error that required the use of corrective lenses. Although the consequences of specific mutations may result in a portion of the phenotypic differences between NSDVS1 and NSDVS2, the ophthalmic abnormalities between the two types may have significant overlap not explained by these bidirectional mutational effects.

Keywords: SPOP, Nabais Sa-de Vries Syndrome, NSDVS1, NSDVS2, neurodevelopmental disorder, craniofacial dysmorphisms, microcephaly

Introduction

Nabais Sa-de Vries Syndrome, an autosomal dominant inherited disease caused by de novo missense mutations in speckle-type pox virus and zinc finger protein (*SPOP*) on chromosome 17q21, has been found to cause two clinically distinct neurodevelopmental disorders causing syndromic forms of intellectual disability [1].

The SPOP protein functions as a context-dependent adaptor in tumorigenesis. The *SPOP* gene plays a role in tumor suppression by destabilizing downstream oncoproteins in some malignancies such as prostate cancer. However, in other malignancies such as endometrial and renal cancers, *SPOP* has an oncogenic role [2]. *SPOP* aids a cullin3-RING-based ubiquitin ligase complex that leads to proteasomal degradation of proteins. The meprin and tumor necrosis factor receptor associated factor homology (MATH) domain of SPOP specifically mediates the degradation of BRD2, BRD3, and BRD4 proteins, collectively termed BETs [3]. In endometrial cancer associated *SPOP* mutations, BETs are increasingly degraded, resulting in cancer cells susceptible to BET inhibitors. However, prostate cancer associated *SPOP* mutations result in impaired degradation of BETs and resistance to pharmacologic BET inhibition may be observed [4]. Missense mutations in *SPOP* frequently occur in prostate and endometrial cancer. *SPOP* was identified as the most frequently mutated gene in prostate cancer, seen in 6-15% of tumors in a prior study [5]. In endometrial cancer, mutations result in gain of function leading to enhanced degradation of BET proteins. In contrast, prostate cancer associated *SPOP* mutations act in

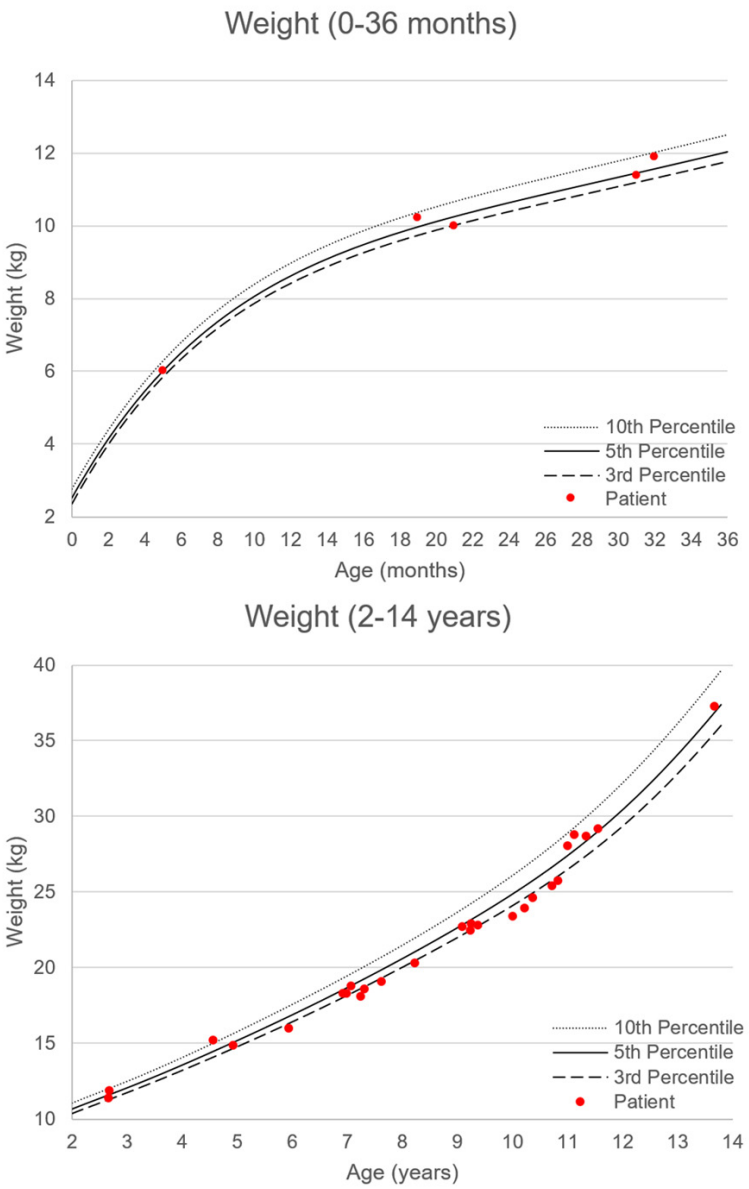

Figure 1. Weight (kg) progression from 0-14 years. Percentile growth curves based on CDC guidelines.

a dominant-negative fashion to inhibit degradation of oncogenic BET proteins, as noted [4].

Nabais Sa-de Vries Syndrome was originally described in seven individuals who had intellectual disability, motor and speech delay, facial dysmorphisms, and congenital anomalies. Among these individuals, six unique de novo missense variants in *SPOP* were identified, with all mutations contained within the MATH domain. However, in two unrelated patients, contrastable craniofacial abnormalities were identified when compared to the other five. These clinical differences resulted in the bifurcation of Nabais Sa-de Vries Syndrome into type 1 (NSDVS1) (MIM #618828), describing the first two individuals, and type 2 (NSDVS2) (MIM #618829), describing the latter five individuals [1]. In this report, we present a new patient with NSDVS1 and summarize the phenotypic features with a focus on the ophthalmic manifestations associated with the condition.

Case report

The patient, now a 13-year-old male, was born full term to a 34-year-old, gravida 4, para 3 mother with a nonremarkable gestational course. Birth weight was 3.2 kg with length at 48.2 cm. Perinatal events were significant for hospitalization after birth for 3 days for respiratory issues as well as neonatal jaundice requiring phototherapy. During 1-2 months of age, there were two seizure-like episodes, however, electroencephalogram testing was normal.

The patient was followed by the clinical genetics service starting at 5 months of age. At that time, he was noted to have brachycephaly with downslanted palpebral fissures, epicanthal folds, and shallow orbits without ptosis. He also had a depressed nasal bridge and a small nose. Ears measured 4.1 cm and were low set, the lateral helix was compressed, and a vertical groove was observed over the helix. Neurological exam revealed slightly increased tone with brisk deep tendon reflexes. Objective measurements at that time showed a weight of 5.9 kg (10th percentile), a length of 65 cm (75th percentile), and a head circumference of 38.5 cm (below the 3rd percentile).

From this point onward, his weight fluctuated from the 3rd percentile to the 10th percentile until present (**Figure 1**). His length/height progressively declined and tracked between the

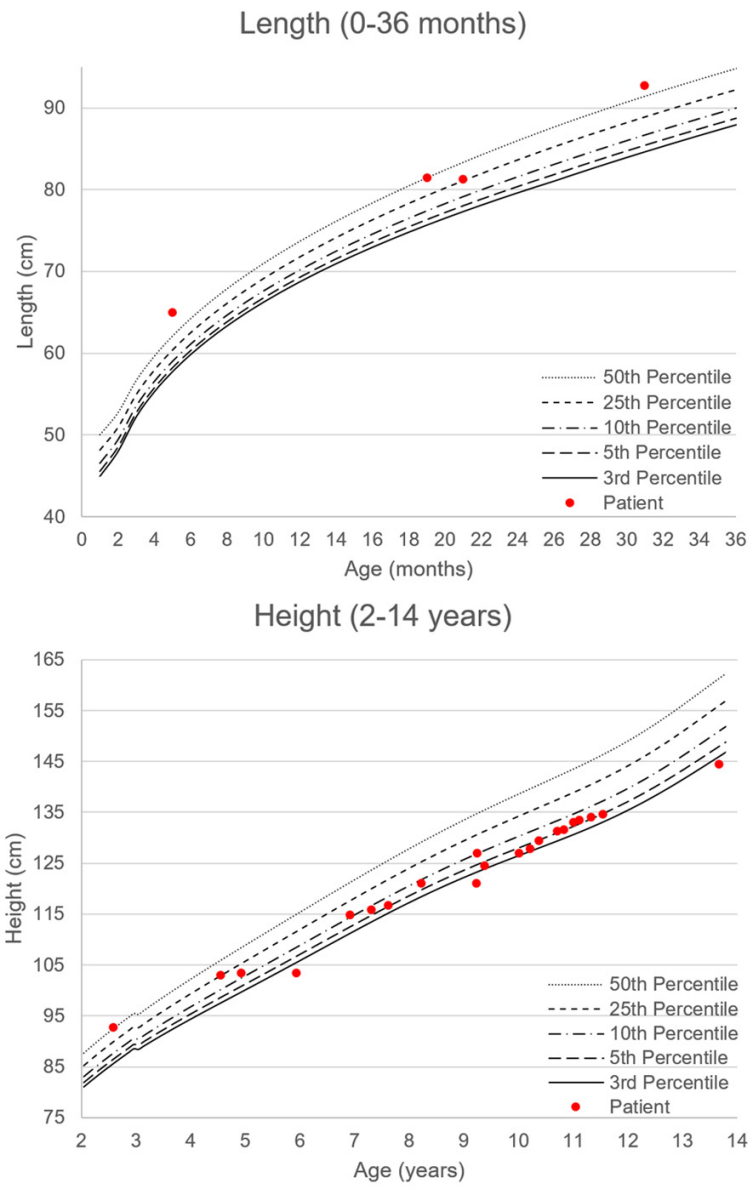

Figure 2. Length/height (cm) progression from 0-14 years. Length/height percentile growth curves based on CDC guidelines.

25-50th percentiles until around age 5, after which it decreased further and remained between the 3rd-10th percentiles until present (**Figure 2**). Head circumference remained significantly below the 3rd percentile until the last documented measurement at age 10 (**Figure 3**).

At 7 months of age, strabismus surgery was performed for congenital esotropia. Two additional strabismus surgeries were required during childhood. He was also discovered to have bilateral hyperopia with astigmatism, and at age 1 he was prescribed glasses. At 8 months of age, a CT scan of the head was performed for suspected craniosynostosis, which showed brachycephaly, however no findings consistent with craniosynostosis were present. MRI at age 1 showed no definite cortical migrational or myelination abnormalities. At 3 years of age, he developed severe early childhood caries requiring full mouth dental rehabilitation with crowns and fillings placed in six teeth.

On a comprehensive documented genetic evaluation at age 4, mild to moderate cognitive delay and slight speech delay were present. Developmental history was notable for smiling at 3 months, rolling over at 8 months, sitting unassisted at 15 months, and speaking his first words at 16 months. At 19 months of age, he still had not acquired the ability to walk or cruise. In addition, at this age, an aggression directed against oneself was noted. A vocabulary of approximately 50 words was present, but he was unable to form 2-3-word sentences and only had the ability to count to 5. In terms of objective measurements, weight was 11 kg (3rd-10th percentile), length was 92.71 cm (25-50th percentile), and head circumference was 44 cm (3 SD below the 3rd percentile). See **Table 1** for a comparison of the physical findings to other documented patients with NSDVS1 and NSDVS2.

At 4 years of age, he developed ear wax build-up resulting in hearing loss and requiring ear tubes placement the same year. Also starting at this age and persisting until the present, he struggled with chronic constipation interfering with toilet training and causing secondary enuresis. Otolaryngologic evaluation at age 7 was notable for a right tympanic membrane

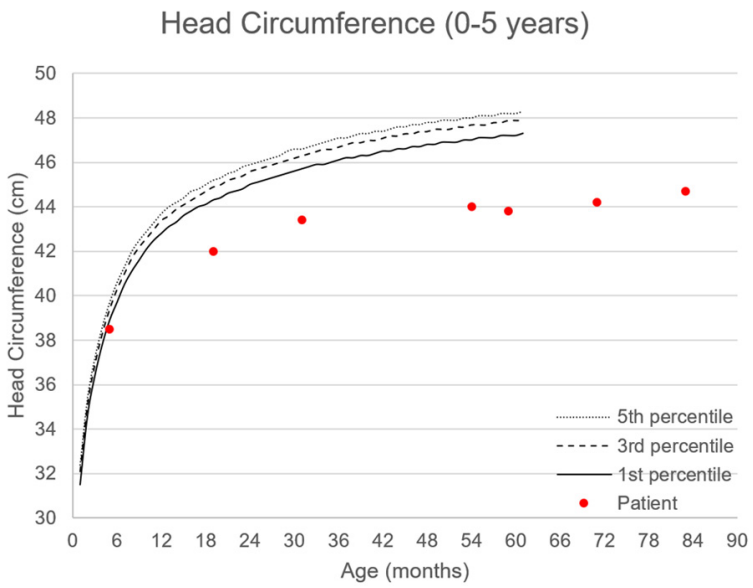

Figure 3. Head circumference (cm) progression from 0-90 months. Head circumference percentile growth curves based on WHO guidelines.

perforation that required surgery. At that time, he was also diagnosed with severe obstructive sleep apnea, requiring adenotonsillectomy and bilateral tonsillectomy. However, repeat polysomnogram post-surgery showed persistent loud snoring, unusual sleep positions, bruxism, and hypoventilation syndrome requiring CPAP usage. He was also evaluated by endocrinology for short stature at age 7 but was found to have normal bone age and growth velocity. At age 10, audiology evaluation showed mild-moderate sensorineural hearing loss bilaterally and the patient was fitted for hearing aids. At age 10, he was evaluated by speech pathology for poor weight gain and choking episodes while eating. A modified barium swallow study revealed moderate oropharyngeal dysphagia complicated by reduced hyolaryngeal excursion, diffuse pharyngeal residue, and delayed swallow initiation. Further assessment at this time revealed failure to thrive with weight and height below 5th percentile and between 5th-10th percentiles, respectively, and BMI/weight for length Z-score was equal to -1.44, indicating mild malnutrition. He was placed on high calorie supplements and thickened liquids that mildly improved his weight gain.

Previous diagnostic genetic testing revealed negative SNRPN testing (age 2), negative chromosomal microarray (age 5) with a benign 485 kb loss at 15q11.2, negative *SRCAP* gene sequencing for Floating Harbor syndrome (age 6), and negative *CREBBP* and *CP300* gene sequencing for Rubinstein-Taybi Syndrome (age 11). Whole exome sequencing done at age 11 did not show pathologic findings initially, but reanalysis in 2020 (age 13) revealed a likely pathogenic missense c.362G>A, p.Arg121Gln variant in the *SPOP* gene, the same mutation as individual 1 in the original paper describing NSDVS1 [1]. After suspecting the diagnosis of NSDVS1, the patient was referred for further evaluation of potential optic nerve hypoplasia and optic atrophy associated with this condition.

At the most recent ophthalmic assessment in April 2021, the now 13-year-old patient had bilateral hyperopia with astigmatism. Amblyopia was present; best corrected visual acuity was 20/80 in the right eye and 20/70 in the left eye. Color plates were full in both eyes. Pupils were 4 mm to 3 mm without afferent pupillary defect, in both eyes. Intraocular pressures were normal, in both eyes. External exam was notable for bilateral downslanting palpebral fissures, thick high-arched eyebrows, mild synophrys, and long eyelashes. Frontal and profile views of the patient are shown in **Figure 4**. Anterior and posterior ocular segments appeared otherwise normal without signs of optic atrophy or optic nerve hypoplasia. Optical coherence tomography (OCT) of the optic nerves was attempted but aborted due to the level of patient cooperation. The patient is followed by ophthalmology to include monitoring for optic nerve changes.

Discussion

From the literature review performed, two individuals with NSDVS1 and five individuals with NSDVS2 have been documented thus far. The feature that most distinguishes NSDVS1 from NSDVS2 is the presence of congenital microcephaly. Both patients had head circumferences of -4 to -5 standard deviations (SD) in childhood, compared to the other 5 individuals with NSDVS2, all with relative macrocephaly.

Table 1. Genotype and Phenotype of Individuals with de novo pathogenic *SPOP* mutations [1]

	Individuals							
	NSDVS1			NVDVS2				
	1	2	Patient of Interest	3	4	5	6	7
Gender/Current Age	F; 4y7m	M; 10y	M; 13y8m	F; 10m	M; 17y11m	M; 17y9m	F; 20y	F; 15y
cDNA change	c.362G>A	c.430G>A	c.362G>A	c.395G>T	c.73A>G	c.412C>T	c.412C>T	c.248A>G
Protein change	p.Arg121Gln	p.Asp144Asn	p.Arg121Gln	p.Gly132Val	p.Thr25Ala	p.Arg138Cys	p.Arg138Cys	p.Tyr83Cys
Head	microcephaly	microcephaly	microcephaly			absolute macrocephaly, but normal HC	absolute macrocephaly, but normal HC	
Effect on BET proteins	gain of function	gain of function	gain of function	loss of function	loss of function	loss of function	loss of function	loss of function
Growth								
Gestational age	40w3d	39w	40w	33w5d	39w	38w	37w	40w
Length at birth (%)	47 cm (10-25%)	NA	48.26 cm (10-25%)	46.4 cm (3-10%)	47 cm (10-25%)	NA	47 cm (10-25%)	54.6 (97%)
Weight at birth (%)	3.033 kg (10-25%)	2.409 kg (3%)	3.203 kg (25-50%)	2.575 kg (3-10%)	2.700 kg (3-10%)	3.020 kg (10-25%)	3.000 kg (10-25%)	3.800 kg (75-90%)
HC at birth (%)	32 cm (-3 SD) at 16d	NA (microcephaly)	NA (microcephaly)	33.5 cm (10-25%)	35 cm (25-50%)	NA	NA	NA (macrocephaly)
Age at measurement	4y7m	16m	4y6m	10m	17y11m	17y9m	20y	15y
Height (%)	104.5 cm (50%)	77 cm (10-25%)	103 cm (25-50%)	65.1 cm (-2.5 SD)	151.8 cm (-3.1 SD)	178.5 cm (50-75%)	172 cm (90-97%)	158.8 cm (25-50%)
Weight (%)	15.3 kg (10-25%)	8.8 kg (-2.3 SD)	15.2 kg (3-10%)	5.6 kg (-4 SD)	49.7 kg (3%)	73 kg (50-75%)	89 kg (97%)	90.7 kg (+2.5 SD)
HC (%)	44 cm (-4 SD)	40.5 cm (-5 SD)	44 cm (-3 SD)	49 cm (+3.5 SD)	NA (25^{th})	56.4 cm (75^{th}-90^{th})	57 cm (+2.5 SD)	56 cm at 5y (+4 SD)
Prenatal and neonatal history								
Prenatal structural anomalies	+ (long bones <3 SD)	-	NA	+ (polyhydramnios; breech presentation)	+ (hypoplastic left heart)	-	-	NA
Congenital abnormalities	+ (congenital microcephaly)	+ (congenital microcephaly)	+ (congenital microcephaly)	+ (congenital heart disease)	+ (congenital heart disease)	NA	+ (congenital heart disease, bilateral CLP)	+ (multicystic kidney dysplasia)
Other neonatal problems	+ (jaundice requiring phototherapy)	+ (jaundice self resolved, respiratory difficulties requiring tracheostomy)	+ (jaundice requiring phototherapy, respiratory difficulties)	+ (hypotonia, swallowing dysfunction and feeding)	+ (bradycardia, dysrhythmia, NA)	NA	-	+ (hypotonia, respiratory and feeding difficulties)
Psychomotor development								
Motor delay	+	+	+	+	+	+	+	+
Age at walking	19m	~36m	>19m	NA	36m	17m	24m	24m
Speech delay	+	+	+	+	+	+	+	NA
Age at first words	60 words at 2y10m	vocalizing at 6y	vocalizing at 16m, 50 words at 4y6m	NA	4y	NA	~5y	NA
Intellectual disability	NA	+ (severe)	+	NA	+ (IQ=46)	+ (IQ=45)	+ (IQ=53)	+ (mild)
Neuropsychiatric abnormalities								

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Epilepsy	-	NA	- (normal EEG but reported seizure like episodes)	-	+	+	NA	-
Neurologic abnormalities	+ (hypertonia)	-	+ (hypertonia)	+ (central hypotonia)	+ (left hemiparesis, intractable migraines, dystonia, chorea)	NA	NA	-
Brain MRI	+ (5y; simplified gyri)	NA	-	+ (4m: enlargement of all ventricles, prominent subarachnoid spaces and bifrontal extra-axial fluid spaces; 17m: mildly increased ventriculo-megaly; symmetrically dysmorphic hippocampi)	+ (16y: borderline enlarged ventricles and slightly small corpus callosum splenium)	- (5y)	NA	-
Behavioral abnormalities	+ (decreased stranger anxiety)	+ (autoaggression)	+ (aggressive behaviors when upset)	NA	+ (overfriendliness, ADHD, agitation)	+ (autism)	+ (severe temper tantrums)	+ (anxiety)
Craniofacial dysmorphisms								
Cranium/Forehead	brachycephaly, prominent glabella	narrow forehead, low anterior hairline	microbrachycephaly, triangular facies	frontal bossing, triangular face	-	large forehead	large forehead	large forehead
Ear	dysplastic simple ears with thickened helix	-	large (5 cm) but normal set	low-set small ears	low-set small ears	protruding ears	low-set posteriorly rotated ears	-
Eye	highly arched eyebrows, underdeveloped supraorbital ridges, downslanted narrow palpebral fissures, deeply set eyes	highly arched eyebrows, synophrys, long eyelashes, epicanthus, telecanthus, narrow palpebral fissures	downslanted palpebral fissures, hooded eyelids, mild ptosis, synophrys, bilateral epicanthal folds, very long eyelashes	hypertelorism, deep set eyes	hypertelorism	hypertelorism, long palpebral fissures, sparse and thin eyebrows	hypertelorism, sparse and thin eyebrows	asymmetric palpebral fissures
Nose	prominent nasal bridge, wide and bulbous nasal tip, underdeveloped nasal alae	low and wide nasal bridge, wide and bulbous nasal tip, short nose	prominent peaked nose with narrow bridge with mild synophrys, bulbous nasal tip, wide base columella with overhang	short, low nasal bridge, upturned nares	-	prominent nasal bridge, bulbous nasal tip	prominent and wide nasal bridge, wide and bulbous nasal tip	prominent nose
Mouth	flat philtrum	flat philtrum	-	wide gums	high-arched palate	-	bilateral CLP	thin lips
Chin	pointed chin	pointed chin	micro/retrognathia	micrognathia	pointed chin	pointed chin		
Hand	Clinodactyly of 5th digits bilaterally	-	Small hands	-	-	NA	distally tapered, long fingers; clinodactyly of the 5th fingers	-
Feet	-	-	-	-	NA	-	short wide feet, pes cavus, short broad halluces	-
System Involvement								
Hearing impairment	+ (sensorineural hearing loss)	+ (bilateral hearing loss)	+ (bilateral sensorineural hearing loss)	-	-	-	-	-

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Ophthalmologic abnormalities	-	+ (bilateral optic nerve hypoplasia)	+ (esotropia requiring strabismus surgery, refraction abnormality)	+ (small optic discs)	+ (refraction abnormality)	-	+ (strabismus)	+ (refraction abnormality)
Cardiovascular	-	-	-	+ (small VSD, PS and supravalvular PS, mild right ventricular outflow obstruction)	+ (variant of hypoplastic left heart syndrome [ASD, small LV, MV and Ao] with left ventricular outflow tract obstruction [subaortic membrane, bicuspid aortic valve, coarctation of the descending Ao])	NA	+ (ASD)	+ (PDA and small VSD)
Respiratory	-	+ (tracheostomy at 3m)	-	-	+ (episode of hemoptysis)	NA	-	-
Gastrointestinal		+ (gastrostomy at 3m)	+ chronic constipation, GERD, pharyngeal dysphagia	+ (choking episodes, GERD, Sandifer syndrome, gastrostomy at 6m)	-	NA	-	+ (chronic constipation, GERD)
Endocrine	-	-	-	-	+ (hypogonadism, testosterone treatment)	+ (hypothyroidism)	NA	+ (hypothyroidism)
Sleep disturbance	-	NA	+ (severe obstructive sleep apnea)	-	+ (sleep apnea)	+	+ (sleep apnea)	+ (sleep apnea)

Key: "NA" = information not available; "-" = negative findings.

Figure 4. Patient with Nabais Sa-de Vries Syndrome Type 1. A 13-year-old male with microcephaly, downslanting palpebral fissures, bilateral epicanthal folds, thick high-arched eyebrows, mild synophrys, long eyelashes, prominent beaked nose with bulbous tip and narrow bridge, overhanging wide base columella.

The differences in presentation between NSDVS1 and NSDVS2 are likely due to the nature of mutational *SPOP* variants leading to phenotypic differences between the two groups, comparable to the differences found between *SPOP* mutations leading to prostate cancer and endometrial cancer [1]. The two individuals with NSDVS1 had a gain-of-function effect with increased *SPOP* activity leading to enhanced ubiquitination and degradation of BET protein amounts, whereas the other five individuals had decreased *SPOP* activity via a dominant-negative effect causing reduced ubiquitination and degradation of BET proteins. This upregulation of BET proteins is thought to be the driving force for increased growth and cell cycle progression, causing relative macrocephaly in the latter five individuals.

Specific ocular dysmorphisms for NSDVS1 described previously include synophrys, blepharophimosis, downslanted/narrow palpebral fissures, and epicanthus. A single individual with NSDVS1 had bilateral optic nerve hypoplasia, however multiple other ophthalmic abnormalities are also seen in individuals with NSDVS2 such as small optic discs, strabismus, and refraction abnormalities.

Our patient was discovered to have the c.362G>A, p.Arg121Gln, likely pathogenic, missense mutation in *SPOP*, the same mutation as individual 1 in the original paper describing NSDVS1.

In concordance with the original paper describing NSDVS1, our patient had significant microcephaly, with a head circumference considerably below the 3rd percentile. Common features included bulbous nasal tip and normal set ears. Several other features that our patient had in common with the other two individuals with NSDVS1 included jaundice at birth (2/2), hypertonia (1/2), aggressive behavior (1/2), hearing loss (2/2), lack of cardiovascular involvement (2/2), lack of endocrine involvement (2/2). One interesting observation was that sleep apnea, which was present in our patient, was also present in 3/5 of NSDVS2 patients.

Regarding ophthalmologic findings, bilateral optic nerve hypoplasia was observed in 1/2 of the patients with NSDVS1. However, NSDVS2 also had ophthalmologic abnormalities, including refraction abnormalities (2/5), strabismus (1/5), and small optic discs (1/5). When comparing facial dysmorphisms involving the eye and periorbital areas between the two syndromes, there exists obvious differences. Whereas NSDVS1 presented with highly arched eyebrows (2/2) and other mixed features such as downslanting (1/2) or narrow palpebral fissures (1/2), long eyelashes (1/2), epicanthus (1/2), deep set eyes (1/2), telecanthus (1/2), synophrys (1/2); the predominating feature of NSDVS2 was hypertelorism (4/5) along with thin eyebrows (2/5), deep set eyes (1/5), long (1/5) or asymmetric (1/5) palpebral fissures.

Our patient shared several facial features with the two other individuals described with NSDVS1 including downslanting palpebral fissures, synophrys, epicanthal folds, and long eyelashes. However, our patient also presented with strabismus and refraction abnormalities, findings reported only in patients with NSDVS2 thus far. Although we are limited by the small sample sizes given the recent identification of this syndrome, differences in mutational consequences (gain of function vs. loss of function) on the effect of eye/periorbital dysmorphisms may be present. The identification and descriptions of further cases will be needed to determine genotype-phenotype correlations.

In summary, this report describes an additional individual that may contribute to the understanding of the relatively newly discovered NSDVS1, in particularly the ocular manifestations involved with this syndrome. Further studies on the role of *SPOP* on ocular pathologies are needed and as more cases are reported we may better elucidate the mechanisms of the associated clinical manifestations and disease course involved.

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Written informed consent was obtained from the patient/family for the publication of the photographs and clinical information presented in this report.

Disclosure of conflict of interest

Natario L. Couser, MD, MS: 1) Retrophin, Inc./Travere Therapeutics, Inc. (Clinical Trial); 2) National Cancer Institute/Children's Oncology Group (Clinical Trial); 3) Elsevier (Book editor); 4) Patient-Centered Outcomes Research Institute (PCORI; Advisory Panel on Rare Disease).

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References

[1] Nabais Sá MJ, El Tekle G, de Brouwer APM, Sawyer SL, Del Gaudio D, Parker MJ, Kanani F, van den Boogaard MH, van Gassen K, Van Allen MI, Wierenga K, Purcarin G, Elias ER, Begtrup A, Keller-Ramey J, Bernasocchi T, van de Wiel L, Gilissen C, Venselaar H, Pfundt R, Vissers LELM, Theurillat JP and de Vries BBA. De novo variants in SPOP cause two clinically distinct neurodevelopmental disorders. Am J Hum Genet 2020; 106: 405-411.

[2] Cheng J, Guo JP, Wang ZW, North BJ, Tao KX, Dai XP and Wei WY. Functional analysis of Cullin 3 E3 ligases in tumorigenesis. Biochim Biophys Acta Rev Cancer 2018; 1869: 11-28.

[3] Zhang P, Wang D, Zhao Y, Ren S, Gao K, Ye Z, Wang S, Pan CW, Zhu Y, Yan Y, Yang Y, Wu D, He Y, Zhang J, Lu D, Liu X, Yu L, Zhao S, Li Y, Lin D, Wang Y, Wang L, Chen Y, Sun Y, Wang C and Huang H. Intrinsic BET inhibitor resistance in SPOP-mutated prostate cancer is mediated by BET protein stabilization and AKT-mTORC1 activation. Nat Med 2017; 23: 1055-1062.

[4] Janouskova H, El Tekle G, Bellini E, Udeshi ND, Rinaldi A, Ulbricht A, Bernasocchi T, Civenni G, Losa M, Svinkina T, Bielski CM, Kryukov GV, Cascione L, Napoli S, Enchev RI, Mutch DG, Carney ME, Berchuck A, Winterhoff BJN, Broaddus RR, Schraml P, Moch H, Bertoni F, Catapano CV, Peter M, Carr SA, Garraway LA, Wild PJ and Theurillat JP. Opposing effects of cancer-type-specific SPOP mutants on BET protein degradation and sensitivity to BET inhibitors. Nat Med 2017; 23: 1046-1054.

[5] Barbieri CE, Baca SC, Lawrence MS, Demichelis F, Blattner M, Theurillat JP, White TA, Stojanov P, Van Allen E, Stransky N, Nickerson E, Chae SS, Boysen G, Auclair D, Onofrio RC, Park K, Kitabayashi N, Macdonald TY, Sheikh K, Vuong T, Guiducci C, Cibulskis K, Sivachenko A, Carter SL, Saksena G, Voet D, Hussain WM, Ramos AH, Winckler W, Redman MC, Ardlie K, Tewari AK, Mosquera JM, Rupp N, Wild PJ, Moch H, Morrissey C, Nelson PS, Kantoff PW, Gabriel SB, Golub TR, Meyerson M, Lander ES, Getz G, Rubin MA and Garraway LA. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. Nat Genet 2012; 44: 685-689.