




ORIGINAL ARTICLE

Expansion and further delineation of the *SETD5* phenotype leading to global developmental delay, variable dysmorphic features, and reduced penetrance

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Diagnostic exome sequencing (DES) has aided delineation of the phenotypic spectrum of rare genetic etiologies of intellectual disability (ID). A SET domain containing 5 gene (*SETD5*) phenotype of ID and dysmorphic features has been previously described in relation to patients with 3p25.3 deletions and in a few individuals with de novo sequence alterations. Herein, we present additional patients with pathogenic *SETD5* sequence alterations. The majority of patients in this cohort and previously reported have developmental delay, behavioral/psychiatric issues, and variable hand and skeletal abnormalities. We also present an apparently unaffected carrier mother of an affected individual and a carrier mother with normal intelligence and affected twin sons. We suggest that the phenotype of *SETD5* is more complex and variable than previously presented. Therefore, many features and presentations need to be considered when evaluating a patient for *SETD5* alterations through DES.

KEYWORDS

haploinsufficiency, exome sequencing, intellectual disability, *SETD5*

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1 | INTRODUCTION

The SET domain containing 5 gene (*SETD5*) encodes a highly conserved methyltransferase that is widely expressed throughout the brain.^{1,2} As a methyltransferase, *SETD5* has been shown to control histone acetylation, regulate transcription, and play a vital role in cell cycle progression, and mammalian embryonic development.³ Recent experiments with CRISPR/Cas9 modeling shows *SETD5* loss of function alterations triggers nonsense-mediated decay and haploinsufficiency.⁴ Haploinsufficiency of other histone and epigenetic modifiers such as *KMT2A*, *KMT2D*, *KMT6A*, *KDM5C*, *MECP2*, and *NSD1* are sufficient to cause disease.⁵

Evidence suggests that *SETD5* haploinsufficiency is associated with intellectual disability (ID), language delay, and dysmorphic features and is among the genes deleted in patients with 3p25.3-deletion syndrome (OMIM #613792). *SETD5* is assumed to be the primary gene causing the features known in this deletion syndrome.^{4,6,7} Previously reported individuals with *SETD5* alterations have been described with psychiatric/behavioral anomalies such as autism spectrum disorder (ASD) and stereotypic behaviors, and gastrointestinal abnormalities. Craniofacial abnormalities associated with *SETD5* alterations include a tubular nose with a broad nasal bridge and bulbous tip with anteverted nares, up slanting/down slanting palpebral fissures, long and smooth philtrum, thin upper lip, downturned corners of the mouth, and ear abnormalities.⁷ Additional features include brachycephaly, prominent high forehead with synophrys or striking full and broad eyebrows, significant leg-length discrepancy, congenital heart defects, polydactyly, inguinal hernia, and hypospadias.⁷

Szczaluba et al recently reported the first inherited case of a pathogenic alteration in *SETD5*. The two brothers were reported with ID, triangular facies, micrognathia, abnormal ears and philtrum, and additional variable features. The father, from whom the alteration was inherited, showed only mild ID.⁸ The three carried a previously unreported *SETD5* nonsense alteration (c.2918C>G, p.S973*) along with an alteration in *FGFR1* (c.22863A>G) previously associated with Kallman syndrome.⁹

In this report, we present detailed clinical characteristics of 14 patients with *SETD5* pathogenic alterations demonstrating an expansion of the phenotype beyond the established traits of ID, with dysmorphic features including epicanthal folds, low posterior hairline,

and absence of microcephaly. We present the first unaffected individual with a pathogenic alteration, demonstrating phenotypic variability in *SETD5* presentation.

1.1 | Clinical report

Clinical characterizations of the 14 patients are summarized in Table S1 (Supporting information).

1.1.1 | Patient 1

Patient 1 is a 7.5-year-old Irish male with global developmental delay, dysmorphic features (mild synophrys, upturned nose, cleft palate), hypernasality, ASD, attention deficit hyperactivity disorder (ADHD), encephalopathy, some far-sightedness, occasional temper tantrums, heart murmur (without structural abnormalities), and history of recurrent tonsillitis status-post-tonsillectomy at 2 years. The patient had an unaffected fraternal twin and an unaffected older brother. Family history was significant for a paternal uncle with trisomy 21. Past testing included normal Fragile X testing (30 CGG repeats), *NIPBL* sequencing, chromosome microarray, and Smith-Lemli-Opitz syndrome biochemical testing. Consanguinity was denied.

1.1.2 | Patient 2

Patient 2 is a 6-year-old Ashkenazi Jewish, Italian, and Native American male with developmental disability, dysmorphic features, hypotonia, and pulmonic stenosis with a grade I/VI systolic ejection murmur. He was found to have mildly dilated ventricles and benign enlargement of the subarachnoid spaces. While he has never had a formal IQ test, he is reported to function at less than 50% of his age. He can speak in full sentences and can read but cannot write and is not toilet-trained. Physical features include: double parietal hair whorls, somewhat thickened helices that are "squared off" superiorly, down-slanting eyes, and webbed neck, internipple distance 3rd to 25th percentile with right nipple slightly displaced laterally, minimal pectus carinatum at the left sternal edge, and fifth finger clinodactyly bilaterally. Past testing included normal *PTPN11*, *SOS1*, *KRAS* and *RAF1* sequencing, normal metabolic testing, and chromosomal microarray with a 28 kb loss at 14q11.2 of uncertain significance and unknown

inheritance. Maternal family history is significant for several generations with ovarian and uterine cancer. Consanguinity was denied.

1.1.3 | Patient 3

Patient 3 is a 10-year-old Mexican boy with developmental delays (especially in speech), poor coordination, short stature, submucous cleft of the hard palate, vertebral fusion at T9-T10 with scoliosis, and mild dysmorphic features. His features include flat occiput, bitemporal narrowing smooth philtrum, poor dentition with crowded teeth, thin upper lip, low posterior hairline, coarse hair, mild pectus excavatum, transverse left palmar crease, blunt finger tips, broad hands and feet, and flat feet. His gait is irregular, clumsy, and he walks on his toes. Karyotype, Fragile X, chromosomal microarray, and imaging studies have been nondiagnostic. The family history is significant for his father and paternal half-brother who are said to be "slow," no other details were provided. Consanguinity was denied.

1.1.4 | Patient 4

Patient 4 is a 2-year-old Mexican female with speech delay, motor delay and unsteady gait congenital hypotonia, mildly coarse facial features, aversion to chewing solids, hooded lids, epicanthal folds, brain magnetic resonance imaging (MRI) showed small middle fossa arachnoid cyst. Previous uninformative test results include thyroid function tests, microarray, karyotype, Fragile X, Angelman syndrome methylation, urine mucopolysaccharide screen, urine organic acids, and plasma quantitative amino acids. Family history is significant for a maternal cousin with an unknown type of muscular dystrophy; this cousin's parents are reportedly first cousins. Consanguinity for the proband was denied.

1.1.5 | Patient 5

Patient 5 is a 3-year-old Caucasian male with hypotonia, global developmental delay with significant impairment of expressive speech, and dysmorphic features including tall forehead, right epicanthal fold, low nasal bridge, low-set ears, smooth philtrum, and overhanging upper lip. He has crowded toes that require orthotics. He has a history of gastroesophageal reflux disease (GERD) and has had an adenoidectomy. The patient was first noted to have delayed milestones at 9 months when he could not yet sit unassisted. He sat independently at 12 months and walked at 24 months. He currently receives physical, occupational, and speech therapies. Normal testing includes karyotype, microarray, metabolic studies, and medium-chain acyl-CoA dehydrogenase deficiency mutation analysis, thyroid stimulating hormone, creatine kinase, and brain MRI. The pregnancy and birth history were uncomplicated.

The patient's mother has a paternal first cousin with ID. The patient's father has a mild tic disorder and possible low muscle tone. The tic disorder is also present in a male paternal first cousin of the patient. The family history is otherwise unremarkable. There is no consanguinity.

1.1.6 | Patient 6

Patient 6 is a 20-year-old Hispanic man with ASD, ID, ADHD, epilepsy, macrocephaly, atrial septal defect, scoliosis, short stature, GERD, and pectus excavatum. A brain MRI showed evidence of cerebellar hypoplasia that has been stable. His IQ was measured at 57. He has mood

swings and is sometimes verbally abusive to his mother but does not have suicidal or self-injurious behaviors. At birth he had choanal atresia/stenosis and had surgery when he was a toddler. He also had an adenoidectomy and tympanostomy tubes. Craniofacial features include a large head, small corneas, right preauricular ear pit, port wine stain over the right cheek, and short broad neck. He has tight heel cords, broad gait, and intention tremor. He has a history of seizures of unknown type and onset that are triggered by lack of sleep or illness. Noonan spectrum disorders panel was normal and a microarray found a paternally inherited 558 kb duplication on 11q12.2. His family history is negative for similarly affected individuals. Consanguinity is unknown.

1.1.7 | Patient 7

Patient 7 is a 16-year-old male with autism, ADHD, slight hypertonia, cardiac findings including atrial septal defect, ventricular septal defect (VSD), and holosystolic murmur (grade 2/6). Additional findings include velopharyngeal insufficiency, omphalocele, bilateral inguinal hernias, slightly high-arched palate, horizontal chin crease, accessory left upper tooth, widely spaced nipples, slight asymmetry of the chest wall, bilateral hearing loss, short stature, cutis marmorata, and eczema of the bilateral upper extremities. Dysmorphic features include synophrys, sparse eyebrows, smooth, bulbous nasal tip, fifth digit clinodactyly, long digitalized thumbs with normal placement and architecture, and a crease on the left ear lobe.

1.1.8 | Patient 8

Patient 8 is an 18-month-old male with sleep difficulties, swallowing dysfunction requiring feeding therapy, lower extremity hypertonia, truncal hypotonia, and mild clinodactyly. A brain MRI at age 13 months showed prominence of the ventricles and extra axial spaces. Cardiac examinations show aortic root, aortic annulus, and ascending aorta measuring at the top of normal.

1.1.9 | Patient 9

Patient 9 is an 8-year-old Caucasian male who was born at 33 weeks gestation but did well in the newborn period. He has global developmental delay, hypotonia, mild spastic diplegia, dysarthria, and anxiety. He sat at approximately 12 months, walked at 25 months, began to use single words between 24 and 36 months and 2 to 3 word phrases between 36 and 48 months, and achieved toilet mastery by 60 months of age. He started riding a tricycle at age 4 but is currently unable to ride a bicycle without training wheels. Neuropsychological testing at age 8 years found multiple learning disabilities and variable cognitive skills but no ID. At age 7 years, he developed choreoathetoid movements and dyskinesias, which greatly responded to acetazolamide. Structural anomalies include partial atrioventricular canal defect, postaxial polydactyly of both hands and the left foot, and bilateral inguinal hernias. Facial dysmorphism includes arched eyebrows with slight synophrys, upturned nose with broad nasal tip, and epicanthal folds. He has short stature, failure to thrive, and normal head circumference. Past normal testing included karyotype, chromosomal microarray, 7-dehydrocholesterol, very long chain fatty acids, and metabolic screening. Brain MRI at 16 months of age showed mild periventricular leukomalacia (sequelae of preterm birth).

1.1.10 | Patient 10

Patient 10 is the mother of Patient 9. She was born with bilateral postaxial polydactyly of her hands and has similar craniofacial features as her son except for no epicanthal folds. She has no medical problems, normal growth, development and intelligence, and is a college graduate with a professional career.

1.1.11 | Patient 11

Patient 11 is a 9-month-old female with VSD, failure to thrive, postaxial polydactyly of bilateral hands and feet, natal tooth (single incisor) plagiocephaly, triangular-shaped face, midface hypoplasia, and hypertelorism.

1.1.12 | Patients 12, 13 and 14

Patients 12 and 13 are 21-year-old male fraternal twins born at term. Both patients were reported growth deficiency at 39 months and 21 years, feeding difficulties, hypotonia and unsteady gait. Patient 12 was 3.5 years at his first words and Patient 13 was 4 years at his first words. They currently have a few words and short sentences. Both patients have cognitive delay, ritualized behaviors, obsessive compulsive disorder (OCD), and dysmorphic features. Patient 12 also had a left varicocele and an inguinal hernia. Karyotyping, chromosomal microarrays, and Fragile X testing were performed on both probands with normal results.

1.1.13 | Patient 14

Patient 14 is 49-year-old, the mother of Patients 12 and 13. She has normal intelligence and speech, hypotonia with unsteady gait, and feeding difficulties. She has a history of one febrile seizure at age 1 year. She has hirsutism on her chin, forehead and legs, and mild dysmorphic features.

2 | METHODS

For all patients, DES was performed with trios including the proband and both biological parents on genomic DNA isolated from blood. Diagnostically relevant alterations were confirmed by dideoxy sequencing. *SETD5* pathogenic or probably pathogenic alterations were found in 12/1 40 946 cases (0.0085%) with childhood onset IID/DD of cases tested at Ambry Genetics and GeneDx.

For Patients 1 to 6, DES was performed by Ambry Genetics Laboratory. Samples were prepared using either the SureSelect Target Enrichment System (Agilent Technologies, Santa Clara, California), SeqCap EZ VCRome 2.0 (Roche NimbleGen, Madison, Wisconsin), or the IDT xGen Exome Research Panel (Integrated DNA Technologies, Coralville, Iowa) and sequenced using paired-end 100- or 150-cycle chemistry on the Illumina HiSeq or NextSeq (Illumina, San Diego, California). Data annotation and interpretation were performed as previously reported.¹⁰

For Patients 7, 8 and 11, DES was performed at GeneDx Laboratory with methods as previously reported.¹¹

For Patients 9 and 10, DES was performed as a trio at Medical College of Wisconsin Laboratory via Transgenomic on an Illumina

sequencer with analysis using Carpe Novo software. Variants of interest were confirmed with dideoxy sequencing.

For patients 12, 13 and 14, WES was performed on the patients and their parents using the Roche NimbleGen EZ Exome System (Madison, Wisconsin). Sequencing was performed using paired-end 150-cycle chemistry (Illumina HiSeq 2000 platform; Illumina, San Diego, California). Reads were aligned to the reference genome (GRCh37/hg19) with the Burrows-Wheeler Aligner, and SNVs and small indels were identified with SAMtools. For each sample, SNVs and indels were called with the Genome Analysis Toolkit Unified Genotyper. Calls were annotated with VCFtools. Functional annotations were added with the Ensembl Variant Effect Predictor v. 2.8. Sequence quality criteria: alterations with a Phred-scaled quality score >40 and a mapping quality score >50 were investigated further. The underlying sequencing data were visually inspected using the Integrative Genomics Viewer. Only variants with MAF <1% in publicly available data sets were considered for downstream analyses. Alterations were Sanger confirmed.

Informed consent was obtained from all patients and family members undergoing sequencing. All research described in this case report was conducted in accordance with the World Medical Association Declaration of Helsinki. For Patients 1 to 11, clinical information presented herein was collected during the routine clinical care of a patient in the United States; thus in accordance with US law, this study is exempt from Institutional Research Board approval. For Patients 12 to 14, the family was part of a group of individuals or families investigated by WES for ID and developmental delay. The study was performed according to the documents of the National Bioethics Committee (Italy) and the guidelines established by the local IRB for clinical genetic investigations. All subjects participating in this study provided signed, written consent allowing for the publication of their clinical photographs and data. In the case of minors, signed written consent was provided by their parents or legal guardians.

3 | RESULTS

The genotypes of the alterations are presented in Figure 1. All sequence alterations are described in reference to RefSeq transcript NM_001080517.

Probably loss-of-function *SETD5* alterations were identified in all patients but one, including 4 frame shift alterations (Patients 1, 4, 8, 9 and 10), 2 alterations probably affecting splice function (Patients 2, 5, 6 and 11), and two nonsense alterations (patients 3 and 7). All alterations were de novo with the exception of one inherited alteration from an unaffected mother (Patient 10) and dizygotic twins with a mildly affected mother (Patients 12 to 14). For Patient 2, the alteration was also not present in 3 unaffected sisters and 2 unaffected brothers.

Summary of clinical characteristics of patients within this cohort and previously reported patients are presented in Table 1.

4 | DISCUSSION

We report 14 patients with 8 pathogenic alterations in *SETD5* with varying features. Two alterations in our cohort are recurrent de novo alterations previously identified.

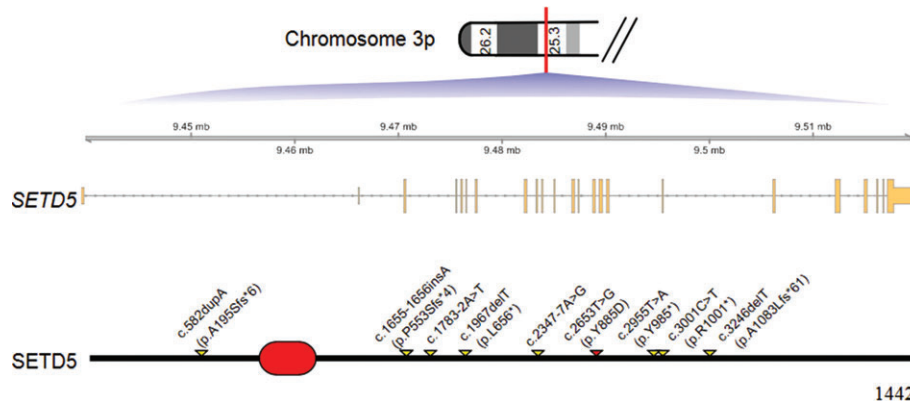


FIGURE 1 Genotypes of *SETD5* alterations

The de novo alteration p.R1001* identified in Patient 3 was previously reported in Grozeva et al.⁷ Similar to our patients, that case showed global developmental delay and abnormal philtrum, but also showed additional features such as nasal anomalies and unsteady gait. These cases showed the continued variability in phenotype, even within the same alteration.

In Patients 5, 6 and 11, DES independently identified the same heterozygous de novo splice alteration in *SETD5*, c.2347-7A>G. The alteration was previously reported in a patient who had West syndrome with early onset epilepsy at 7 months.¹² Kobayashi et al characterized the effect of this alteration on splicing and showed by both RT-PCR and sequencing that 6 base pairs are inserted due to the formation of a new splice acceptor site which results in a premature stop codon. They also show the mutant allele is subject to nonsense-mediated decay.

4.1.1 | Phenotype of patients with *SETD5* alterations in this cohort

Some form of delay (cognitive/motor and/or speech) is present in 93% of patients in this cohort and previously reported patients, with the majority having several forms of delay. Two carrier mothers of an affected proband are not cognitively affected, which has not been previously reported. Seventy percent of patients have reported feeding difficulties, hand anomalies such as polydactyly are present in 58% of patients. Behavioral/psychiatric abnormalities (including ASD) are present in 64% of patients in this cohort. Over half of the patients have hypotonia and unsteady gait (67% and 70%, respectively, of those in which these features were reported). Additional phenotypes in comparison to published cases are summarized in Table 1.

Craniofacial dysmorphism is present, including broad/low nasal bridge and or abnormal nasal shape (60%), long/smooth and/or prominent philtrum (42%), abnormal eyebrows (such as synophrys) (33%), and low set or malformed ears (25%). Dysmorphic features varied greatly in appearance and severity. Additional features present in this cohort include epicanthal folds, hirsutism, and a low posterior hairline. No genotype/phenotype correlation was apparent.

Our cohort contains two families in which the affected children inherited the *SETD5* alterations from their mothers who were not previously considered to be affected. One proband with cognitive delays, skeletal abnormalities, and hand anomalies had no dysmorphic features. Such cases show the wide variability in *SETD5*-related ID, and suggest

a possible protective effect in females. Of note, there are a few bona fide pathogenic mutations in the gnomAD population database (<http://gnomad.broadinstitute.org/gene/ENSG00000168137>); further studies could include an assessment of potential subclinical presentations in the corresponding subjects and determining if most of those are females. While the individuals reported in GnomAD are not expected to have early-onset severe disorder, due to the variability present in families, it is possible that this individual might be mildly affected. Without further analysis of this alteration variant in additional individuals, a potential female protective model cannot be ruled out.¹³

4.1.2 | Insight into the 3p25.3 deletion syndrome

SETD5 is among the genes deleted in patients with 3p25.3 deletion syndrome (OMIM_613 792) who present with ID and dysmorphic features.¹⁴ The variability of phenotype among patients with *SETD5* alterations adds to what is known about the genotype/phenotype correlations among the critical genes in the 3p25.3 deletion syndrome. *SETD5* has been concluded to be the main gene involved in the features of the deletion syndrome, while *BRPF1*, a gene also in the region has been implicated in more severe ID and ptosis and/or blepharophimosis, strabismus, short stature, and microcephaly.^{5,15} Interestingly, while most 3p25.3 deletion patients present with microcephaly, only one of the patients in our cohort has microcephaly and only one patient has been reported with microcephaly with a *SETD5* intragenic mutation suggesting that *SETD5* is not the gene involved with this feature in patients with the 3p25.3 deletion.

4.1.3 | Pathogenic mechanisms of the *SETD5* alterations

SETD5 is ubiquitously expressed in brain and contains a conserved domain of 130 amino acids that adopts a folded structure, with 2 signature motifs; ELxY/YDY and NHS/CxxPN (x is any amino acid).^{16–18} In humans, there are approximately 50 SET domain proteins that function primarily to transfer methyl groups from the cofactor S-adenosyl-L-methionine (SAM) to the lysine residues of histones impacting chromosome compaction, suggesting, the primary role of the SET domain proteins is to regulate the epigenetic state of chromatin.¹⁹ Studies in mice have showed that a number of SET domain genes are crucial for normal embryo development and survival.^{14,15,20,21} Furthermore, epigenetic regulation of chromatin is known to play a role in ID.²² The *SETD5* alterations presented here introduce premature termination codons into the transcript, and are expected to make the transcript an NMD target and result in haploinsufficiency. Notably,

TABLE 1 Summary of clinical characteristics of patients within this cohort and previously reported patients with *SETD5* alterations

Alteration details	Patient 1 (this report)	Patient 2 (this report)	Patient 3 (this report)	Patient 4 (this report)	Patient 5 (this report)	Patient 6 (this report)	Patient 7 (this report)	Patient 8 (this report)	Patient 9 (this report)	Patient 10 (this report, mother of Patient 9)
Genotype	c.1655_1656insA (p.P553Sfs*4)	c.1783-2A>T	c.3001C>T (p.R1001*)	c.582dupA (p.A195Sfs*6)	c.2347-7A>G	c.2347-7A>G	c.1967delT (p.L656*)	c.324delT (p. A1083Lfs*61)	c.1655_1656insA (p.P553Sfs*4)	c.1655_1656insA (p.P553Sfs*4)
Demographics										
Inheritance	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	Maternal	Unknown
Gender	Male	Male	Male	Female	Male	Male	Male	Male	Male	Female
Age at last exam	7 years	6 years	10 years	2 years	3 years	20 years	16 years	18 months	8 years	Adult
Growth										
Microcephaly	NR	None	None	None	NR	None	None	None	None	None
Development										
Growth retardation	NR	None	+	None	None	+	+	None	+	None
Motor delay	NR	+	+	+	+	NR	+	+	+	None
Speech delay	NR	+	+	+	+	NR	+	+	+	None
Cognitive delay	NR	+	+	+	+	+	+	+	+	None
Neurological and other findings										
Neuroimaging findings	NR	+	Normal	+	Normal	+	NR	+	+	Normal
Autism spectrum disorder/features	+	None	None	None	None	+	+	None	None	None
Other behavioral/psychiatric features										
ADHD	ADHD	None	Immature for age, fear of dogs, hyperactive	ADHD	None	ADHD	ADHD	+	+	None
Seizures	None	None	None	None	None	None	+	None	None	None
Unsteady gait	NR	NR	+	+	+	+	NR	NR	+	None
Hypotonia	NR	+	None	+	+	NR	None	+	+	None
Anomalies, system, and other findings										
Congenital heart defects	None	+	NR	NR	None	+	+	None	+	+
Feeding difficulties	NR	NR	NR	+	None	NR	+	+	+	None
Gastrointestinal or abdominal wall anomalies	NR	NR	NR	None	None	None	+	None	+	None
Scoliosis, kyphosis or lordosis	NR	None	+	None	None	NR	None	None	None	None
Leg length discrepancy	NR	NR	NR	None	NR	None	NR	None	None	None
Hyperextensibility	NR	+	NR	None	None	None	None	+	None	None
Genitourinary defects	NR	NR	NR	None	NR	None	NR	None	None	None
Minor anomalies	NR	None	Mild pectus excavatum, mildly enlarged tonsils	Ankle instability	None	Small corneas, tight heel cords broad gait, intention tremor.	Bilateral hearing loss, cutis marmorata, eczema	None	Dyskinesias (greatly improved with Diamox); dysarthria	Failure to thrive of unknown etiology

(Continues)

TABLE 1 (Continued)

	Patient 1 (this report)	Patient 2 (this report)	Patient 3 (this report)	Patient 4 (this report)	Patient 5 (this report)	Patient 6 (this report)	Patient 7 (this report)	Patient 8 (this report)	Patient 9 (this report)	Patient 10 (this report, mother of Patient 9)
Craniofacial and other dysmorphism	NR	NR	NR	None	NR	None	None	None	None	None
Triangular facies	NR	NR	NR	None	NR	None	None	None	None	+
Epicanthal folds	NR	NR	None	+	+	None	None	+	None	None
Low posterior hairline	NR	None	+	NR	None	None	NR	None	4	None
Synophrys, arched, or abnormal eyebrows	NR	NR	+	NR	None	NR	+	None	+	None
Ptosis	NR	NR	None	None	+	None	None	None	None	None
Palate anomalies	None	None	+	None	None	None	+	None	None	None
Long, smooth, or prominent philtrum	NR	+	+	+	+	None	+	+	None	None
Anteverted nares	NR	NR	NR	+	None	None	NR	None	+	None
Broad/low nasal bridge and/or abnormal shape	NR	NR	+	NR	+	None	+	+	None	None
Postaxial polydactyly	NR	None	None	None	None	None	None	None	+	+
Other hand anomalies	NR	+	+	None	None	None	+	+	None	None
Low set or malformed ears	NR	None	None	None	+	None	+	None	None	None
Palpebral fissures	NR	+	None	None	None	None	None	None	None	None
Long/smooth and/or prominent philtrum	NR	+	+	+	+	None	+	None	+	None
Micrognathia	NR	NR	NR	None	None	None	None	None	+	None
Other features		Branchial cleft	Flat occiput; narrow bitemporal diameter, midface hypoplasia, pattern aberrant scalp hair patterning; Dental crowding, course hair	Mild coarse face, hooded lids, web neck	Large head, right preauricular ear pit, port wine stain over the right cheek a short broad neck	Horizontal chin crease, accessory left upper tooth, widely spaced nipples, slight asymmetry of the chest wall				Natal tooth (single incisor) plagiocephaly, triangular- shaped face, midface hypoplasia, and hypertelorism

TABLE 1 (Continued)

Patient 10 (this report, mother of Patient 9)	Patient 11 (this report)	Patient 12 (this report)	Patient 13 (this report, fraternal twin of Patient 12)	Patient 14 (this report, mother of Patients 12 and 13)	Rauch et al ¹ (n = 1)	Grozeva et al ⁷ (n = 7)	Kuechler et al ⁴ (n = 2)	Kobayashi et al ¹² (n = 1)	Szczaluba et al ⁶ (family, n = 3)
c.1655,1656insA (p.P553Sfs*4)	c.2347-7A>G (IVS16-7A>G)	c.2955T>A (p.Y985*)	c.2955T>A (p.Y985*)	c.2955T>A (p.Y985*)	c.2302C>T (p.R768*)	a	c.2302C4T (p.Arg768*)	c.2347-7A>G (p.Arg783Lfs*)	c.2918C>G (p.S973*)
Unknown	de novo	Maternal	Maternal	Unknown	NR	de novo	de novo	de novo	Inherited
Female	Female	Male	Male	Female	Female	7 Males	2 Females	Male	3 Males
Adult	9 months	21 years	21 years	49 years	7 years	Varied	Varied	15	Varied
None	None	None	None	None	NR	0	0	NR	0
None	+	+	+	None	NR	0	0	NR	2
None	+	None	None	None	None	6	0	1	2
None	+	+	+	None	None	6	2	NR	1
None	+	+	+	None	+	7	2	NR	3
Normal	Normal	NR	NR	NR	NR	NR	0 (one not imaged)	None	NR
None	None	+	+	None	NR	2	0	NR	0
None	None	OCD	OCD	None	0	5	2	NR	0
None	None	None	None	None	NR	0	0	1	0
None	None	+	+	None	NR	2	NR	NR	1
None	+	+	+	None	NR	NR	0	NR	2
+	+	+	+	None	NR	2	0	NR	0
None	+	+	+	None	NR	5	NR	NR	2
None	NR	None	None	None	NR	5	0	NR	0
None	NR	+	+	+	NR	5	0	NR	0
None	None	None	None	None	NR	2	NR	NR	0
None	None	None	None	None	NR	NR	NR	NR	1
None	None	+	None	None	NR	2	NR	NR	2
Failure to thrive of unknown etiology	None	Inguinal hernia, pes planus	Pes Planus	Pes Planus	recurrent infections, strabismus, constipation	None	strabismus, ¹ myopia, astigmatism, ¹ recurrent infections ¹	NR	0
None	None	None	None	None	NR	3	0	NR	0
+	+	None	None	None	NR	NR	2	NR	2
None	None	None	None	None	NR	NR	NR	NR	0
None	None	None	None	None	NR	NR	NR	NR	0
None	NR	None	None	None	NR	5	0	NR	0
None	None	None	None	None	NR	1	0	NR	0
None	None	None	None	Mild	NR	2	NR	NR	0
None	None	None	None	None	NR	6	2	NR	1

(Continues)

TABLE 1 (Continued)

Patient 10 (this report, mother of Patient 9)	Patient 11 (this report)	Patient 12 (this report)	Patient 13 (this report, fraternal twin of Patient 12)	Patient 14 (this report, mother of Patients 12 and 13)	Rauch et al. ¹ (n = 1)	Grozeva et al. ⁷ (n = 7)	Kuechler et al. ⁴ (n = 2)	Kobayashi et al. ¹² (n = 1)	Szczaluba et al. ⁶ (family, n = 3))
None	+	None	None	None	NR	2	2	NR	0
None	NR	+	+	None	NR	7	2	NR	3
+	+	None	None	None	NR	1	0	NR	2
None	None	None	None	None	+	2	2	NR	NR
None	+	None	None	None	NR	5	1	NR	2
None	NR	None	None	None	NR	6	1	NR	0
None	NR	None	None	None	NR	5	2	NR	3
None	NR	None	None	None	NR	3	2	NR	3
Natal tooth (single incisor) plagiocephaly, triangular-shaped face, midface hypoplasia, and hypertelorism	Posteriorly rotated, ear pit on right ear lobe	Long and thin nose with short, broad neck	Long and thin nose with short, broad neck	Long and thin nose with short neck, hirsutism on chin forehead and legs	"Facial dysmorphism" details not reported	Sacral dimple, ¹ prominent forehead ²	Low anterior hairline ²	NR	NR

NR, not reported.

this does not cause microcephaly, as haploinsufficiency of other histone methyltransferases does, suggesting that SETD5 regulates distinct developmental pathways.

5 | CONCLUSION

Herein, we present 14 patients in this cohort and review 14 previously reported cases that have alterations in SETD5. Our data suggest that SETD5 mutations are a relatively frequent cause of ID, and the clinical spectrum characterization from patients identified via DES indicates that the phenotype of SETD5 appears more complex and variable than previously presented. The overall phenotype of developmental delay, behavioral/psychiatric issues, and variable hand and skeletal abnormalities remain consistent but facial features may be variable and thus difficult to diagnose clinically. Reduced penetrance or mild presentations were observed in some female carriers of SETD5 mutations, which have impacts on genetic counseling and family planning. Therefore, variable features and presentations need to be considered when evaluating a patient for SETD5 alterations.

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Conflict of interest

Z.P., K.F.H., C.M., I.P., R.H. and S.T. are employed by and receive a salary from Ambry Genetics. K.M., M.T.C., I.M.W., M.J.G. and R.W. are employed by and receive a salary from GeneDx. J.S.C. is a consultant to Invitae. Exome sequencing is a commercially available test. All other authors have nothing to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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