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SETD2 Neurodevelopmental Disorders

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Summary

Clinical description

SETD2 neurodevelopmental disorders (*SETD2*-NDDs) represent a clinical spectrum that most commonly includes various degrees of intellectual disability and behavioral findings (most typically an autism spectrum disorder), macrocephaly with or without ventriculomegaly, brain malformations (including Chiari I malformation and syringomyelia), and obesity with generalized overgrowth and advanced bone age. A specific, somewhat different phenotype (denoted *SETD2*-NDD with multiple congenital anomalies [MCA]) has been reported in association with a particular pathogenic variant, c.5218C>T (p.Arg1740Trp), which leads to a higher frequency of multiple congenital anomalies compared to those without this genetic change. Individuals with *SETD2*-NDD with MCA may have microcephaly, congenital heart malformations, urogenital anomalies, eye findings (specifically Coats disease of the retina), severe failure to thrive, hypotonia, hyponatremia, respiratory issues (tracheomalacia, frequent aspiration, hypoventilation), epilepsy, profound intellectual disability with limited-to-no speech, and distinctive craniofacial features.

Diagnosis/testing

The diagnosis of a *SETD2*-NDD is established in a proband with suggestive findings and a heterozygous pathogenic variant in *SETD2* identified by molecular genetic testing.

Management

Treatment of manifestations:

- ***SETD2*-NDD with or without macrocephaly/overgrowth.** Nutritional management of obesity to include diet/exercise; consideration of growth hormone therapy in those with poor growth; standard treatment for developmental delay / autistic features, seizures, hypothyroidism, precocious puberty, hypotonia/ hypermobility, scoliosis, refractive error / strabismus, hearing loss, congenital heart defects, and cryptorchidism.

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- ***SETD2*-NDD with MCA.** Feeding therapy to include consideration of a gastrostomy tube; supplemental oxygen therapy with consideration of tracheostomy in those with tracheomalacia/hypoventilation; sodium supplementation for those with hyponatremia; standard treatment for developmental delay, seizures, joint contractures, sensorineural/conductive hearing loss, Coats disease of the retina, congenital heart defects, cryptorchidism, dysplastic kidneys, and skeletal anomalies.

Surveillance:

- ***SETD2*-NDD with or without macrocephaly/overgrowth.** Monitor for psychiatric symptoms, seizures, changes in tone, movement disorders, and developmental progress at each clinic visit; weight checks at home for obesity prevention starting in the second year of life; annual thyroid-stimulating hormone and free T4; clinical evaluation for precocious puberty and scoliosis at each visit during childhood; annual (or as clinically indicated) ophthalmology and audiology evaluations.
- ***SETD2*-NDD with MCA.** Monitor for appropriate growth, evidence of aspiration, respiratory sufficiency, seizures, changes in tone, movement disorders, and developmental progress at each clinic visit; electrolyte panel to include sodium level to assess for hyponatremia at each visit during infancy; annual (or as clinically indicated) ophthalmology and audiology evaluations.

Genetic counseling

SETD2-NDDs are inherited in an autosomal dominant manner, although most affected individuals represent simplex cases (i.e., a single occurrence in a family). To date, transmission of a *SETD2* pathogenic variant from a parent to a child has been reported in one family. If a parent of the proband is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Each child of an individual with a *SETD2*-NDD has a 50% chance of inheriting the *SETD2* pathogenic variant. Once the *SETD2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

GeneReview Scope

***SETD2* Neurodevelopmental Disorders: Included Phenotypes**

GeneReviews Designation	Abbreviations / Other Designations
SETD2 neurodevelopmental disorder with or without macrocephaly/overgrowth	• *SETD2*-NDD with macrocephaly/overgrowth, also referred to as Luscan-Lumish syndrome or Sotos-like syndrome • *SETD2*-NDD with normal growth without MCA
SETD2 neurodevelopmental disorder with multiple congenital anomalies (MCA)	*SETD2*-NDD with MCA

For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

No consensus clinical diagnostic criteria for *SETD2* neurodevelopmental disorders (*SETD2*-NDDs) have been published. *SETD2*-NDD represents a clinical spectrum with the most common well-defined phenotype being *SETD2*-NDD with macrocephaly/overgrowth, although not everyone has overgrowth; a specific, somewhat different phenotype has been reported in association with a particular pathogenic variant, c.5218C>T (p.Arg1740Trp), which leads to a higher frequency of multiple congenital anomalies (MCA) compared to those without this genetic change (see *GeneReview* Scope). This chapter covers both of these recognized phenotypes.

Suggestive Findings

***SETD2*-NDD with or without macrocephaly/overgrowth can be considered** in individuals with the following nonspecific findings:

- **Macrocephaly** with or without ventriculomegaly (Figure 1)
- **Brain malformations** including Chiari I malformation and/or syringomyelia
- **Developmental delay,** especially in the area of speech and language development
- **Intellectual disability,** usually moderate (ranging from mild to severe)
- **Behavioral difficulties** including autism spectrum disorder and/or outbursts of aggression
- **Overgrowth,** although some affected individuals have growth that falls within the normal range

***SETD2*-NDD with multiple congenital anomalies (MCA) can be suspected** in individuals with the following specific findings [Rabin et al 2020]:

- **Microcephaly** with head size often normal at birth and microcephaly developing in infancy
- **Brain malformations** including the triad of hypoplasia of the corpus callosum, pons, and cerebellum (Figure 2)
- **Profound intellectual disability** with no speech and no independent ambulation
- **Severe failure to thrive** in infancy typically accompanied by hypotonia and associated respiratory and feeding difficulties
- **Multiple congenital anomalies**
  - Congenital heart defects
  - Urogenital anomalies
  - Ophthalmologic findings including **Coats disease of the retina** characterized by telangiectatic, tortuous, and sometimes leaky retinal vessels
- **Distinctive craniofacial features** (Figure 3) including:
  - Low anterior hairline
  - Biparietal narrowing
  - Flat face with maxillary hypoplasia
  - Arched eyebrows
  - Widely spaced eyes
  - Short palpebral fissures
  - Wide nasal bridge
  - Short nose with anteverted nares
  - Broad nasal tip with low-hanging columella
  - Micrognathia with mandibular hypoplasia

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of a *SETD2*-NDD **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *SETD2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *SETD2* variant of uncertain significance does not establish or rule out the diagnosis.

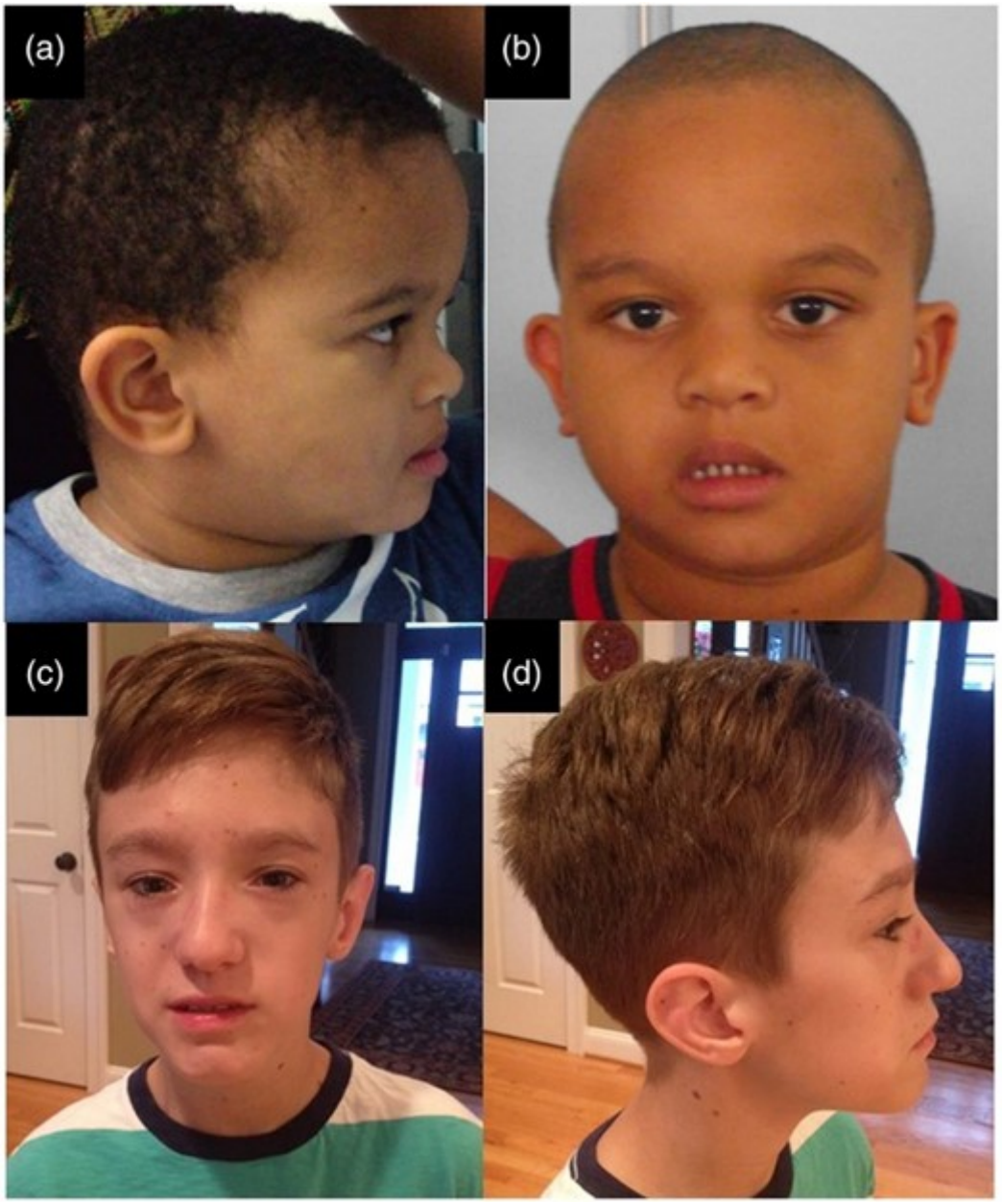

Figure 1. Clinical features of individuals with *SETD2*-NDD with macrocephaly/overgrowth syndrome

a & b. Lateral and frontal views of an affected individual; note the prominent forehead with high frontal hairline, frontal bossing, and low-set ears

c & d. Frontal and lateral views of an unrelated affected individual showing relative macrocephaly, long face, tall forehead and pointed chin, posteriorly rotated ears, and malar flattening

Reprinted with permission from Marzin et al [2019]

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings of *SETD2*-NDD with MCA described in Suggestive Findings could be diagnosed using single-gene testing (see Option 1), whereas those in whom the diagnosis of a *SETD2*-NDD has not been considered are more likely to be diagnosed using a multigene panel or genomic testing (see Option 2).

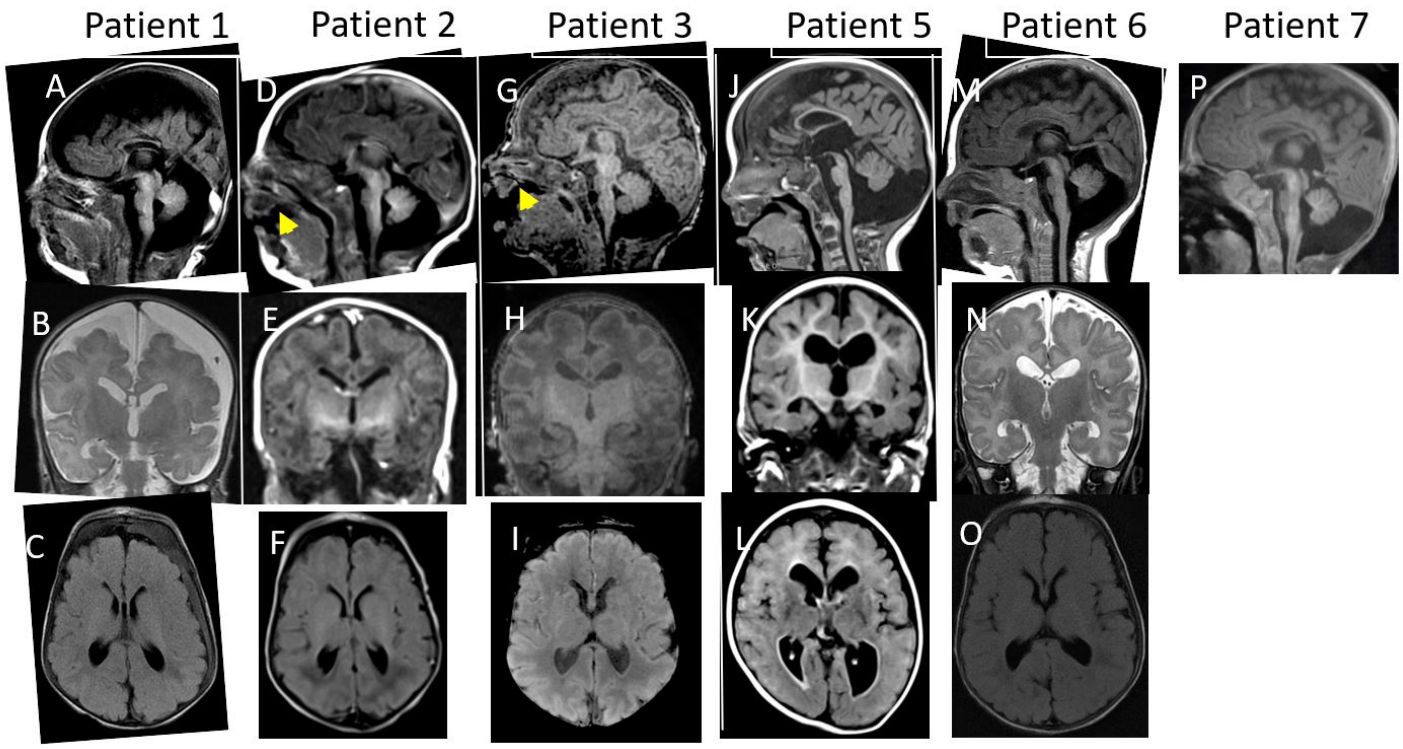

Figure 2. Magnetic resonance images of six individuals who are heterozygous for a recurrent p.Arg1740Trp pathogenic variant in *SETD2*. Sagittal T_1-weighted images (A, D, G, J, M, P), coronal T_2- (B, N) and T_1- (E, H, K) weighted images, and axial FLAIR images (C, F, I, L, O) are provided.

Patient 1 (A-C); male age six weeks

Patient 2 (D-F): male age four days

Patient 3 (G-I): newborn female

Patient 5 (J-L): female age six years

Patient 6 (M-O): male age four years

Patient 7 (P): male age two months

All affected individuals have low craniofacial ratios (corresponding to clinical microcephaly), as well as a foreshortened and thin corpus callosum (A, D, G, J, M, P). Thinning of the corpus callosum in A, D, G, and P could be due to a combination of callosal hypogenesis and unmyelinated state of white matter during the first few weeks of life. There is subtle overhanging appearance of the terminal portions of the frontal horns of the lateral ventricles relative to the striatum (best seen on coronal B and E). Gyri are somewhat simplified and sulci are shallow (C, F, I, and L). All affected individuals have cystic enlargement of the posterior fossa (mega cisterna magna) and prominent supracerebellar cisterns (A, D, G, and M). Slightly upturned hippocampi can be appreciated on coronal images (particularly in B, H, K, and N). Patient 1 has prominent convexity extra-axial spaces with left more than right subdural hemorrhage, which may be related to birth trauma. A cleft palate can be seen in D and G (small arrows). Patient 5 has white matter volume loss (K, L), with enlargement of the third and lateral ventricles. Patients 5, 6, and 7 have probable persistent Blake pouch cyst (J, N, P). Patients 3, 5, and 6 (G, J, M) demonstrate abnormality of anteroposterior midbrain-hindbrain patterning.

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Option 1

Single-gene testing. Sequence analysis of *SETD2* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Typically, if no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Figure 3. Facial appearance of individuals with *SETD2*-NDD with multiple congenital anomalies

Patient 2 at age seven years (A); at age ten years (B-C)

Patient 4 in infancy (D-E)

Patient 5 in infancy (F-G); as a toddler (H-I)

Patient 6 as a toddler (J)

Patient 7 at age two weeks (K)

Patient 8 at age two years (L); at age 12 years (M)

Patient 10 at age five weeks (N-O)

Common facial features include widely spaced eyes, micrognathia, small upturned nose, biparietal narrowing, small forehead, microcephaly, flat face, short palpebral fissures, arched eyebrows, strabismus, broad nasal bridge and tip of the nose with low hanging columella, maxillary and mandibular hypoplasia, and slightly forward facing ears.

Reprinted from Rabin et al [2020]

Option 2

An overgrowth/macrocephaly or autism / intellectual disability multigene panel that includes *SETD2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the

testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *SETD2* Neurodevelopmental Disorders

Gene [1]	Method	Proportion of Pathogenic Variants [2, 3] Identified by Method
SETD2	Sequence analysis [4]	30/30 [5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Several additional individuals with contiguous gene deletions in the 3p21.31 region (not included in these calculations) have been reported (see Genetically Related Disorders) [Lovrecic et al 2016].
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. O'Roak et al [2012a], O'Roak et al [2012b], Luscan et al [2014], Lumish et al [2015], Marzin et al [2019], Rabin et al [2020]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Lovrecic et al [2016]) may not be detected by these methods.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Epigenetic Signature Analysis / Methylation Array

A distinctive epigenetic signature (disorder-specific genome-wide changes in DNA methylation profiles) in peripheral blood leukocytes has been identified in individuals with *SETD2*-NDD syndrome [Levy et al 2021]. Epigenetic signature analysis of a peripheral blood sample or DNA banked from a blood sample can therefore be considered to clarify the diagnosis in individuals with: (1) suggestive findings of *SETD2*-NDD syndrome but in whom no pathogenic variant in *SETD2* has been identified via sequence analysis or genomic testing; or (2) suggestive findings of *SETD2*-NDD syndrome and a *SETD2* variant of uncertain clinical significance identified by molecular genetic testing. For an introduction to epigenetic signature analysis click here.

Clinical Characteristics

Clinical Description

To date, 30 individuals have been reported with a *SETD2* pathogenic variant, excluding those who have deletions of the 3p21.31 region that includes *SETD2* and other adjacent genes (see Genetically Related Disorders) [O'Roak

et al 2012a, O'Roak et al 2012b, Luscan et al 2014, Lumish et al 2015, Tlemsani et al 2016, van Rij et al 2018, Marzin et al 2019, Rabin et al 2020, Suda et al 2021].

***SETD2* neurodevelopmental disorder (*SETD2*-NDD) with macrocephaly/overgrowth,** the most common phenotype, can also include developmental delay / intellectual disability, obesity, advanced bone age, and behavioral findings (most typically an autism spectrum disorder). This spectrum also includes three individuals (2 male and 1 female) with a heterozygous c.5219G>A (p.Arg1740Gln) pathogenic *SETD2* variant who have normal growth (see Genotype-Phenotype Correlations).

***SETD2*-NDD with multiple congenital anomalies (MCA)** presents with microcephaly, brain malformations, profound intellectual disability, severe failure to thrive, and multiple congenital anomalies including congenital heart defects, urogenital anomalies, and ophthalmic findings such as Coats disease of the retina. These individuals have a c.5218C>T (p.Arg1740Trp) pathogenic *SETD2* variant (see Genotype-Phenotype Correlations).

Table 2. *SETD2* Neurodevelopmental Disorders: Phenotypes by Selected Distinguishing Features

Feature	*SETD2*-NDD with or without Macrocephaly/Overgrowth [1]	*SETD2*-NDD with MCA (c.5218C>T pathogenic variant)
# of reported persons	18	12
Macrocephaly (incl relative macrocephaly)	12/17	0
Intellectual disability	14/18 (typically in moderate range)	12/12 (typically in profound range)
Overgrowth &/or obesity	9/18	0
Advanced bone age	5/6 examined	1/1 person examined
Autism spectrum disorder	10/13	0
Microcephaly	0	12/12 [2]
Failure to thrive in infancy [3]	0	12/12
Hypotonia	5/8	12/12
Seizures	3/18	7/12
Brain malformations	7/11 examined	12/12
Ophthalmologic	4/6 examined	10/10 examined
Hearing loss (conductive or mixed)	1/2 examined	7/9
Skeletal abnormalities	5/7	12/12
Congenital heart defects	1/3 reported	11/12
Urogenital anomalies	2/2 reported	11/12

Data from O'Roak et al [2012a], O'Roak et al [2012b], Luscan et al [2014], Lumish et al [2015], Tlemsani et al [2016], van Rij et al [2018], Marzin et al [2019], Rabin et al [2020], Suda et al [2021]
MCA = multiple congenital anomalies; NDD = neurodevelopmental disorder
1. This column also includes those individuals with a heterozygous c.5219G>A (p.Arg1740Gln) pathogenic variant in *SETD2*.
2. Two individuals had prenatal-onset microcephaly, but all eventually developed microcephaly.
3. Typically accompanied by respiratory and feeding difficulties

SETD2-NDD with or without Macrocephaly/Overgrowth

Growth parameters are typically normal at birth; however, macrocephaly can be observed at birth. Obesity and tall stature usually become apparent in childhood, although stature may normalize with age. A subset of individuals have normal growth parameters throughout their lives, although height tends to be above the 50th

centile (see Genotype-Phenotype Correlations). Bone age is frequently advanced [Marzin et al 2019; Author, personal observation].

Developmental delay (DD) and intellectual disability (ID) range from severe disability to normal intelligence with behavioral issues. Most affected individuals have cognitive impairment that falls within the moderate range, with two individuals having severe ID and several having mild ID. Developmental delays are usually apparent early in life, with speech being the most severely affected.

Other neurologic features

- Hypotonia may be present. This typically does not require feeding therapy or supplemental tube feeds, as seen with *SETD2*-NDD with MCA.
- Epilepsy has been rarely described.
  - Generalized tonic-clonic seizures occurred in one individual at age ten years, but the affected individual remained seizure free on lamotrigine monotherapy for at least three years [Lumish et al 2015].
  - Another individual experienced one seizure at age three years, and a third individual experienced several seizures that did not recur after ventriculoperitoneal shunt placement [O'Roak et al 2012a, Marzin et al 2019].

Neuroimaging may identify Chiari I malformation, syringomyelia, hydrocephaly, ventriculomegaly, and Dandy-Walker malformation.

Behavioral findings can include autism spectrum disorder, attention-deficit disorder, aggressive outbursts, self-mutilating behaviors, frustration intolerance, anxiety, hyperphagia, and stereotypies.

Endocrinologic findings may include the following [Marzin et al 2019; Author, personal observation]:

- Precocious puberty
- Polycystic ovarian syndrome
- Hypothyroidism
- Growth hormone deficiency

Sensory impairment

- Hearing loss is uncommon but has been observed. It is more commonly seen in those with the *SETD2* pathogenic variant c.5218C>T.
- Strabismus has been observed; cortical visual impairment and optic nerve hypoplasia have been described but are uncommon.

Other associated features that may be present:

- Recurrent infections, including recurrent otitis media, sinus infections, and/or respiratory infections
- Gastroesophageal reflux disease
- Constipation
- Congenital heart defects
- Sleep apnea (type not well described in the literature)
- Hirsutism
- Scoliosis
- Large- and small-joint hypermobility
- Cryptorchidism
- Nevi

SETD2-NDD with MCA

Prenatal complications include preterm labor. Brain malformation may be apparent in the third trimester. Cardiac and kidney anomalies are also sometimes detected prenatally. Polyhydramnios and maternal preeclampsia are also common.

Growth

- **Microcephaly** can have prenatal onset (2/9) or develop by early infancy. Microcephaly is usually progressive and at least 2.5 standard deviations (SD) below the mean, with head circumference reported to be up to 5.5 SD below the mean.
- **Severe failure to thrive** is noted in infancy and is frequently accompanied by hypotonia, which contributes to feeding issues.
  - All affected individuals had normal weight and length at birth.
  - Weight usually remains below the 50th centile in infancy and childhood, whereas height is more variable.

Feeding issues. Most affected individuals require nasogastric tube feedings, which may be transitioned to gastrostomy tube for long-term nutritional support, particularly in those with frequent aspiration (see **Respiratory issues**).

Cleft palate with Pierre Robin sequence is common, observed in 10/12 individuals, and may contribute to both feeding and breathing issues.

Respiratory issues include tracheomalacia, frequent aspiration, hypoventilation, desaturations, and sleep apnea (both obstructive and central). Three of 12 affected individuals required tracheostomy; one affected individual without a tracheostomy required oxygen support at night, and another used CPAP at night.

Developmental delay and intellectual disability is severe to profound in all affected individuals. All affected individuals reported are nonverbal and nonambulatory. Two were able to take a few steps in late childhood and some were able to sit independently. No regression of developmental skills and no behavioral concerns have been reported.

Epilepsy. Seizures typically have onset in infancy and are usually difficult to control. Types of seizures observed include migrating focal seizures; infantile spasms; and apneic, absence, and generalized myoclonic seizures.

One individual had medically intractable seizures until treatment with phenobarbital and a ketogenic/modified Atkin's diet. Another had better seizure control while taking cannabidiol (CBD) oil.

Neuroimaging. Brain malformations have been identified in all individuals who have undergone brain imaging and are strikingly similar.

- A triad of findings include hypoplasia of the corpus callosum, pons, and cerebellum.
- Shallow sulci, ventriculomegaly, and mega cisterna magna can also be observed.

Sensory impairment

- **Hearing loss** of a conductive or mixed nature was reported to range from mild to severe; some affected individuals wear hearing aids for support. Some have had tympanostomy tubes placed due to middle ear effusion.
- **Coats disease of the retina** is reported in 8/10 individuals with telangiectatic vessels of the eyes. Additional ophthalmic abnormalities include optic nerve hypoplasia, glaucoma, and/or cataracts. Onset of ophthalmic abnormalities, including Coats disease, is typically in infancy.

Other associated features

- **Congenital heart defects** may include ventricular septal defect, atrial septal defect, patent ductus arteriosus, tetralogy of Fallot, double outlet right ventricle, pulmonary stenosis, persistent left superior vena cava, dysplastic pulmonary valve, pulmonary artery hypoplasia, hypoplastic aortic valve, transverse arch hypoplasia, and coarctation of the aorta. The majority of affected individuals have multiple congenital heart defects.
- **Urogenital anomalies** may include dilated or duplicated collecting system and multicystic dysplastic kidneys.
  - One affected individual with multicystic dysplastic kidneys developed end-stage kidney disease.
  - All males reported have cryptorchidism; micropenis and shawl scrotum have also been reported in some.
  - Two females have anteriorly placed anus, and one also has a short vagina, absent cervix, and absent midline müllerian structures.
- **Endocrinologic findings**
  - Hyponatremia is common in infancy, observed in 8/12 affected individuals.

    The hyponatremia was initially concerning for the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, but hyponatremia ultimately resolved with sodium supplementation.
  - Additional endocrine abnormalities have been observed including acquired hypothyroidism and hypothalamic hamartoma in one affected individual each.
- **Skeletal abnormalities** are observed in all individuals. These include:
  - Hip dysplasia
  - Contractures of digits, knees, and/or elbows
  - Thoracic dysplasia
  - Craniosynostosis involving sagittal and metopic sutures
  - Neuromuscular scoliosis
  - Abnormalities of the hands and feet
    - Brachydactyly
    - Camptodactyly
    - Syndactyly
    - Proximally implanted triphalangeal thumbs
    - Broad proximally implanted halluces
    - Hypoplastic distal phalanges and nails
    - Rocker bottom feet
    - Small hands and feet
    - Persistent fetal fingertip pads
- **Malignancy.** Osteosarcoma was diagnosed in two individuals, age 12 and 15 years [personal communication with Francis Sansbury, MB, PhD, All Wales Medical Genomics Service and John A Bernat, MD, PhD, University of Iowa Division of Medical Genetics and Genomics].

Genotype-Phenotype Correlations

***SETD2*-NDD with normal growth and without macrocephaly.** The c.5219G>A (p.Arg1740Gln) variant is the only *SETD2* pathogenic variant known to be associated with this phenotype (see Molecular Genetics). Features of the three individuals with this finding include the following:

- **Growth.** Head circumference may drift toward the lower end of normal, but not within the microcephalic range.

- **Developmental delay and intellectual disability.** All three developed some speech by age two years.
- **Behavioral problems.** Autism spectrum disorder was not observed. One individual has anxiety, executive functioning impairment, and slow processing speed.
- **Other associated features** (each reported in 1 individual):
  - Strabismus
  - Myopia
  - Laryngomalacia
  - Constipation

***SETD2*-NDD with MCA.** The c.5218C>T (p.Arg1740Trp) variant is the only *SETD2* pathogenic variant known to be associated with this phenotype (see Table 2 and Molecular Genetics).

Prevalence

SETD2-NDDs appear to be very rare. Fewer than 40 affected individuals have been reported in the medical literature to date.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with a heterozygous germline pathogenic variant in *SETD2*.

Deletion of 3p21.31. Deletions of this chromosomal region are rare, although one report of a male age seven years with a deletion of 3p21.31 including *SETD2* and 28 other genes has been published [Lovrecic et al 2016]. This individual had many features that overlapped with *SETD2*-NDD with macrocephaly/overgrowth (Figure 4).

Sporadic tumors (including clear cell renal cell cancer, primary central nervous system tumors, leukemia) occurring as single tumors in the absence of any other findings of *SETD2* neurodevelopmental disorders frequently contain somatic variants in *SETD2* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

Because the phenotypic features associated with *SETD2* neurodevelopmental disorder (*SETD2*-NDD) without macrocephaly/overgrowth or multiple congenital anomalies (MCA) are not sufficient to diagnose this condition, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series. For the differential diagnosis of *SETD2*-NDD with macrocephaly/overgrowth, see Table 3. For the differential diagnosis of *SETD2*-NDD with MCA, see Table 4.

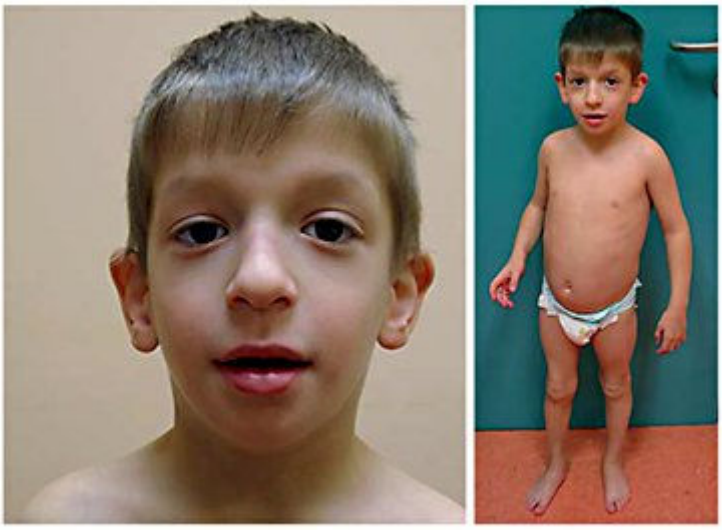

Figure 4. Craniofacial characteristics in an individual with a 3p21.31 deletion. A long face, downslanted palpebral fissures, broad nasal tip, deep philtrum, and low-set, dysmorphic ears are shown.

Reprinted with permission from Lovrecic et al [2016]

Table 3. Differential Diagnosis of *SETD2*-NDD with Macrocephaly/Overgrowth

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*SETD2*-NDD w/macrocephaly/ overgrowth	Distinguishing from *SETD2*-NDD w/macrocephaly/ overgrowth
FMR1	Fragile X syndrome (See *FMR1* Disorders.)	XL	Macrocephaly, ID	Macroorchidism, joint laxity
NSD1	Sotos syndrome	AD	Macrocephaly, overgrowth, ID	Pointed chin, small mouth, everted lower lip
NFIX	*NFIX*-related Malan syndrome			
Mutation or deletion of imprinted genes w/in chromosome 11p15.5 region: *ICR1* *KCNQ1OT1* *CDKN1C*	Beckwith-Wiedemann syndrome	AD [1]	Generalized overgrowth, DD	Macroglossia, hypoglycemia, coarse facies, hepatomegaly, ear lobe creases
RNF125	Tenorio syndrome (OMIM 616260)	AD	Macrocephaly, overgrowth, ID	Macroglossia, hypoglycemia
DICER1	GLOW syndrome (See *DICER1* Tumor Predisposition.)	AD	Macrocephaly, overgrowth, ID	Lung cysts, Wilms tumor
HERC1	MDFPMR (OMIM 617011)	AR	Macrocephaly, overgrowth, ID	Large ears, asthenic adult habitus
PIK3CA	Megalencephaly-capillary malformation-polymicrogyria syndrome (See *PIK3CA*-Related Overgrowth Spectrum.)	Somatic	Macrocephaly, overgrowth, ID	Capillary malformations, polymicrogyria, hemihyperplasia
PTEN	*PTEN* hamartoma tumor syndrome	AD	Macrocephaly, autism	Hamartomata, tumors

Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*SETD2*-NDD w/macrocephaly/ overgrowth	Distinguishing from *SETD2*-NDD w/macrocephaly/ overgrowth
TET3	Beck-Fahrner syndrome	AD AR	Macrocephaly, overgrowth, ID	Elongated myopathic facies; short stature & microcephaly in some
FIBP	Thauvin-Robinet-Faivre syndrome (OMIM 617107)	AR	Macrocephaly, overgrowth, ID	Macroglossia, large hands & feet, kidney & urinary tract malformations
SUZ12	Imagawa-Matsumoto syndrome (OMIM 618786)	AD	Macrocephaly, overgrowth, ID	Skeletal abnormalities
HRAS	Costello syndrome	AD	Macrocephaly, ID	Fetal overgrowth w/postnatal short stature, coarse facial features, loose redundant skin
EED	Cohen-Gibson syndrome (See *EED*-Related Overgrowth.)	AD	Macrocephaly, overgrowth, ID	Large long ears, skeletal abnormalities
GPC3	Simpson-Golabi-Behmel syndrome	XL	Macrocephaly, overgrowth, ID	Coarse facies; hearing loss; large liver, spleen, & kidneys; skeletal anomalies
SHANK3 or deletion of 22q13.33	Phelan-McDermid syndrome	AD	Macrocephaly, overgrowth, ID	Large fleshy hands, ptosis
EZH2	Weaver syndrome (See *EZH2*-Related Overgrowth.)	AD	Macrocephaly, overgrowth, ID	Large bifrontal diameter, flat occiput, skeletal anomalies

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MDFPMR = macrocephaly, dysmorphic facies, and psychomotor retardation; NDD = neurodevelopmental disorder; XL = X-linked

1. Most instances of Beckwith-Wiedemann syndrome are due to methylation abnormalities that are not heritable. A subset of affected persons have a pathogenic variant that is heritable, most commonly in an autosomal dominant manner.

Table 4. Differential Diagnosis of *SETD2*-NDD with Multiple Congenital Anomalies

Gene	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*SETD2*-NDD w/MCA	Distinguishing from *SETD2*-NDD w/MCA
DHCR7	Smith-Lemli-Opitz syndrome	AR	Microcephaly, FTT, cardiac & genital abnormalities, seizures, ID	Coats disease of the eye, brain malformations
SON	Zhu-Tokita-Takenouchi-Kim syndrome (OMIM 617140)	AD	FTT, cerebellar hypoplasia, cardiac & kidney abnormalities, seizures, ID	Coats disease of the eye, microcephaly, hearing loss

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; FTT = failure to thrive; ID = intellectual disability; MCA = multiple congenital anomalies; MOI = mode of inheritance; NDD = neurodevelopmental disorder

Management

No clinical practice guidelines for *SETD2* neurodevelopmental disorders have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SETD2* neurodevelopmental disorders (*SETD2*-NDD), the evaluations summarized in Table 5 (*SETD2*-NDD w/or w/o macrocephaly/overgrowth) and Table 6 (*SETD2*-NDD w/MCA) – if not performed as part of the evaluation that led to the diagnosis – are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis: *SETD2*-NDD with or without Macrocephaly/Overgrowth

System/Concern	Evaluation	Comment
Constitutional	Measurement of height, weight, head circumference	To assess for overgrowth &/or obesity
Development	Developmental assessment	• Incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	Persons age >12 mos: screen for concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Neurologic	Neurologic eval	• Incl brain MRI • Consider EEG if seizures are a concern.
Endocrinologic	TSH & free T4	To screen for hypothyroidism
	Screening for growth hormone deficiency	In those w/suggestive signs/symptoms, incl poor growth velocity
	Clinical eval for signs & symptoms of precocious puberty	Consider referral to endocrinologist in those w/suggestive features
Musculoskeletal	Orthopedics / physical medicine & rehab / PT/OT eval	Incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Eyes	Ophthalmologic exam	Incl assessment of visual acuity & strabismus
Hearing	Audiologic eval	Assess for sensorineural &/or conductive hearing loss.
Cardiovascular	Echocardiogram	To assess for structural heart defects
Genitourinary	Physical exam for cryptorchidism in males	Consult w/urologist as needed.
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *SETD2*-NDD to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; TSH = thyroid stimulating hormone

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Table 6. Recommended Evaluations Following Initial Diagnosis: *SETD2*-NDD with Multiple Congenital Anomalies (c.5218C>T Pathogenic Variant)

System/Concern	Evaluation	Comment
Constitutional	Measurement of height, weight, head circumference	To assess for FTT in infants
Gastrointestinal	Gastroenterology / nutrition / feeding team eval	• Incl eval of aspiration risk & nutritional status. • Consider eval for gastrostomy tube placement in those w/ dysphagia &/or aspiration risk.
Respiratory	Assess for signs & symptoms of hypoventilation &/or tracheomalacia.	Consider referral to pulmonologist.
Development	Developmental assessment	• Incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurologic	Neurologic eval	• Incl brain MRI • Consider EEG if seizures are a concern.
Hearing	Audiologic eval	Assess for sensorineural &/or conductive hearing loss.
Eyes	Ophthalmologic exam	Incl assessment of visual acuity, slit lamp exam (for cataracts), fundus exam (for optic nerve hypoplasia, retinal telangiectasia, retinal detachment)
Cardiovascular	Echocardiogram	For congenital heart defects
Genitourinary	Physical exam for cryptorchidism in males	Consider referral to urologist.
	Kidney ultrasound exam	Consider referral to urologist &/or nephrologist as needed.
Endocrinologic	Electrolyte panel [1]	• To assess for hyponatremia • If present, consider eval for SIADH. [2]
	TSH & free T4	To assess for hypothyroidism
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	Incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, kyphoscoliosis • Mobility, ADL, need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Genetic counseling	By genetics professionals [3]	To inform affected persons & their families re nature, MOI, & implications of *SETD2*-NDD to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADL = activities of daily living; FTT= failure to thrive; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; TSH = thyroid stimulating hormone; SIADH = syndrome of inappropriate antidiuretic hormone

1. To include sodium, potassium, chloride, and bicarbonate at a minimum

2. To date, SIADH has not been found in those with hyponatremia who have undergone evaluation.

3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 7 and Table 8 summarize the recommended treatment for individuals with *SETD2*-NDD with or without macrocephaly/overgrowth and those with *SETD2*-NDD with MCA, respectively.

Table 7. Treatment of Manifestations: *SETD2*-NDD with or without Macrocephaly/Overgrowth

Manifestation/ Concern	Treatment	Considerations/Other
Obesity	Diet & exercise	Consider nutrition consultation.
Developmental Delay	See Developmental Delay / Intellectual Disability Management Issues.	
Autism spectrum disorder	See Social/Behavioral Concerns.	
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Hypothyroidism	Standard treatment per endocrinologist	
Growth hormone deficiency	Growth hormone therapy	Per endocrinologist
Precocious puberty	Standard treatment per endocrinologist	Depending on age, hormonal suppression may be considered.
Hypotonia / Joint hypermobility	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid positional scoliosis & falls	Consider need for positioning & mobility devices, disability parking placard.
Scoliosis	Standard treatment per orthopedist	
Strabismus / Refractive error	Standard treatment per ophthalmologist	
Hearing loss	Hearing aids may be helpful; per otolaryngologist & audiologist.	Community hearing services through early intervention or school district
Congenital heart defect	Standard treatment per cardiologist	
Cryptorchidism	Standard treatment per urologist	
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Table 8. Treatment of Manifestations: *SETD2*-NDD with Multiple Congenital Anomalies (c.5218C>T Pathogenic Variant)

Manifestation/ Concern	Treatment	Considerations/Other
Feeding difficulties	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia

Table 8. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Tracheomalacia/ Hypoventilation	Consider tracheostomy in those w/significant issues.	Neonates often benefit from a high level of care, such as admission to a Level IV neonatal intensive care unit.
	Supplemental oxygen	As needed to support oxygen saturations; may be needed particularly during sleep
Developmental Delay	See Developmental Delay / Intellectual Disability Management Issues.	
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • In refractory cases, a ketogenic diet may be trialed. • Education of parents/caregivers [1]
Joint contractures	Orthopedics / physical medicine & rehab / PT & OT	Consider need for positioning & mobility devices, disability parking placard.
Sensorineural hearing loss	Hearing aids may be helpful; per otolaryngologist & audiologist	Community hearing services through early intervention or school district
Conductive hearing loss	Standard treatment by otolaryngologist	May incl consideration of tympanostomy tubes
Coats disease / Low visual acuity / Glaucoma &/or cataracts	Per treating ophthalmologist	Laser photocoagulation & cryotherapy for Coats disease
	Per low vision specialist	Incl community & school services for visually impaired students
Congenital heart defect	Standard treatment per cardiologist	Conservative or surgical approaches according to specific heart defect & overall health status of patient
Cryptorchidism	Standard treatment per urologist	
Dysplastic kidneys	Standard treatment per neurologist	Kidney replacement therapy for end-stage kidney disease
Hyponatremia	Sodium supplementation	After eval for syndrome of SIADH has excluded this diagnosis [2]
Skeletal abnormalities	Orthopedic & rehab eval	Orthotics & splints &/or surgery as needed
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy; SIADH = syndrome of inappropriate antidiuretic hormone

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

2. To date, SIADH has not been found in those with hyponatremia who have undergone evaluation.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
    - An IEP provides specially designed instruction and related services to children who qualify.
    - IEP services will be reviewed annually to determine whether any changes are needed.
    - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
    - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
    - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 9 and Table 10 summarize the recommended surveillance for individuals with *SETD2*-NDD with or without macrocephaly/overgrowth and those with *SETD2*-NDD with MCA, respectively.

Table 9. Recommended Surveillance for Individuals with *SETD2*-NDD with or without Macrocephaly/Overgrowth

System/Concern	Evaluation	Frequency
Constitutional	Measurement of growth parameters	Monthly weight checks at home for obesity prevention starting in 2nd yr of life
Developmental delay	Monitor developmental progress & educational needs.	At each visit
Psychiatric/ Behavioral	Monitor for anxiety, attention, & aggressive or self-injurious behavior.	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures, changes in tone, mvmt disorders.	
Endocrinologic	TSH & free T4	Annually or as clinically indicated
	Clinical eval for signs & symptoms of precocious puberty	At each visit during childhood
Musculoskeletal	Clinical eval for scoliosis	At each visit in childhood until completion of puberty
Eyes	Ophthalmologic eval	Annually or as clinically indicated
Hearing	Audiologic eval	
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

Table 10. Recommended Surveillance for Individuals with *SETD2*-NDD with Multiple Congenital Anomalies (c.5218C>T Pathogenic Variant)

System/Concern	Evaluation	Frequency
Constitutional	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	
Developmental delay	Monitor developmental progress, educational needs.	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures, changes in tone, movement disorders.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Hearing	Audiologic eval	Annually or as clinically indicated
Eyes	Ophthalmologic eval	
Endocrinologic	Electrolyte panel to incl sodium level to assess for hyponatremia	At each visit during infancy
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

SETD2 neurodevelopmental disorders (*SETD2*-NDDs) are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- An individual diagnosed with a *SETD2*-NDD may have the disorder as the result of a *SETD2* pathogenic variant inherited from a parent. To date, transmission of a *SETD2* pathogenic variant from a parent to a child has been reported in one family; it is unknown whether the heterozygous parent had features of a *SETD2*-NDD [O'Roak et al 2012a].
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the *SETD2* pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
    - The proband has a *de novo SETD2* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
    - The proband inherited a *SETD2* pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Mosaicism for a *SETD2* pathogenic variant has been observed in one individual. This individual was mildly affected and presented with hearing loss, Chiari malformation, epilepsy, hypoglycemia, and normal intelligence [R Rabin, personal communication]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

      * A parent with somatic and germline mosaicism for a *SETD2* pathogenic variant may be mildly/minimally affected.
- The family history of some individuals diagnosed with *SETD2*-NDD may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, an apparently

negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. The penetrance of *SETD2*-NDD in a sib who inherits a familial pathogenic variant and the likelihood of intrafamilial clinical variability are unknown.
- If the proband has a known *SETD2* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *SETD2* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for a *SETD2*-NDD because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with a *SETD2*-NDD has a 50% chance of inheriting the *SETD2* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *SETD2* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SETD2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Luscan-Lumish SETD2 Support**
  Email: support@luscan-lumish.org
  www.luscan-lumish.org
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org

- **Autism Society**
  Phone: 800-328-8476
  Email: info@autism-society.org
  autismsociety.org
- **National Center on Birth Defects and Developmental Disabilities (NCBDDD)**
  Phone: 800-232-4636 (toll-free); 888-232-6348 (TTY)
  www.cdc.gov/ncbddd

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. SETD2 Neurodevelopmental Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SETD2	3p21.31	Histone-lysine N-methyltransferase SETD2	SETD2 @ LOVD	SETD2	SETD2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for SETD2 Neurodevelopmental Disorders (View All in OMIM)

612778	SET DOMAIN-CONTAINING PROTEIN 2; SETD2
616831	LUSCAN-LUMISH SYNDROME; LLS
620155	RABIN-PAPPAS SYNDROME; RAPAS
620157	INTELLECTUAL DEVELOPMENTAL DISORDER, AUTOSOMAL DOMINANT 70; MRD70

Molecular Pathogenesis

SETD2 codes for a histone methyltransferase that trimethylates the lysine at position 36 of histone H3 (H3K36me3) [Edmunds et al 2008]. Deficiency of the SETD2 protein has been associated with loss of H3K36me3 and abnormal DNA methylation [Xu et al 2019]. SETD2 is a dual-function methyltransferase for histones and microtubules and plays an important role in transcriptional regulation, genomic stability, and cytoskeletal functions [Zhou et al 2011, Park et al 2016, McDaniel & Strahl 2017].

Loss-of-function variants in *SETD2* lead to hypomethylation of H3 at K36, which has been associated with overgrowth [Weinberg et al 2019]. Evidence from hypermethylation of polycomb-regulated regions [Heyn et al 2019] and association with microcephalic dwarfism points to possible loss of function associated with the variant c.5218C>T (p.Arg1740Trp) in *SETD2* neurodevelopmental disorder with multiple congenital anomalies.

Mechanism of disease causation. Loss of function

Table 11. Notable *SETD2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_014159.7 NP_054878.5	c.5218C>T	p.Arg1740Trp	Only variant known to be assoc w/*SETD2*-NDD w/MCA [Rabin et al 2020]
	c.5219G>A	p.Arg1740Gln	Only variant known to be assoc w/*SETD2*-NDD w/normal growth & w/o macrocephaly [Rabin et al 2020]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
MCA = multiple congenital anomalies

Cancer and Benign Tumors

SETD2 is a tumor suppressor gene. Somatic variants have been detected in a variety of cancers, including clear cell renal cell, gastrointestinal, lung, pancreatic, and osteosarcoma [Li et al 2016, Chen et al 2020]. Somatic variants are also described in primary central nervous system tumors [Viaene at al 2018] and leukemia [Skucha et al 2019].

Chapter Notes

Author Notes

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- 30 December 2021 (ma) Review posted live
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