



## MECP2 Disorders

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Created: October 3, 2001; Updated: September 19, 2019.

## Summary

### Clinical characteristics

The spectrum of *MECP2*-related phenotypes in females ranges from classic Rett syndrome to variant Rett syndrome with a broader clinical phenotype (either milder or more severe than classic Rett syndrome) to mild learning disabilities; the spectrum in males ranges from severe neonatal encephalopathy to pyramidal signs, parkinsonism, and macroorchidism (PPM-X) syndrome to severe syndromic/nonsyndromic intellectual disability.

- **Females:** Classic Rett syndrome, a progressive neurodevelopmental disorder primarily affecting girls, is characterized by apparently normal psychomotor development during the first six to 18 months of life, followed by a short period of developmental stagnation, then rapid regression in language and motor skills, followed by long-term stability. During the phase of rapid regression, repetitive, stereotypic hand movements replace purposeful hand use. Additional findings include fits of screaming and inconsolable crying, autistic features, panic-like attacks, bruxism, episodic apnea and/or hyperpnea, gait ataxia and apraxia, tremors, seizures, and acquired microcephaly.
- **Males:** Severe neonatal-onset encephalopathy, the most common phenotype in affected males, is characterized by a relentless clinical course that follows a metabolic-degenerative type of pattern, abnormal tone, involuntary movements, severe seizures, and breathing abnormalities. Death often occurs before age two years.

### Diagnosis/testing

The diagnosis of a *MECP2* disorder is established by molecular genetic testing in a female proband with suggestive findings and a heterozygous *MECP2* pathogenic variant, and in a male proband with suggestive findings and a hemizygous *MECP2* pathogenic variant.

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## Management

*Treatment of manifestations:* Treatment is mainly symptomatic and focuses on optimizing the individual's abilities using a multidisciplinary approach that should also include psychosocial support for family members. Risperidone may help in treating agitation; melatonin can ameliorate sleep disturbances. Treatment of seizures, constipation, gastroesophageal reflux, scoliosis, prolonged QTc, and spasticity per standard care.

*Surveillance:* Periodic evaluation by the multidisciplinary team; regular assessment of QTc for evidence of prolongation; regular assessment for scoliosis.

*Agents/circumstances to avoid:* Drugs known to prolong the QT interval.

## Genetic counseling

*MECP2* disorders are inherited in an X-linked manner. More than 99% are simplex cases (i.e., a single occurrence in a family), resulting from a *de novo* pathogenic variant or possibly from inheritance of the pathogenic variant from a parent who has germline mosaicism. Rarely, a *MECP2* variant may be inherited from a heterozygous mother in whom favorable skewing of X-chromosome inactivation results in minimal to no clinical findings. When the mother is a known heterozygote, the risk to her offspring of inheriting the *MECP2* variant is 50%. When the pathogenic *MECP2* variant has been identified in the family, heterozygote testing for at-risk female relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible. Because of the possibility of parental germline mosaicism, it is appropriate to offer prenatal diagnosis to couples who have had a child with a *MECP2* disorder regardless of whether the *MECP2* pathogenic variant has been detected in a parent.

## GeneReview Scope

<i>MECP2</i> Disorders: Included Phenotypes <sup>1, 2</sup>	
<b>Females</b>	<ul style="list-style-type: none"> <li>• <i>MECP2</i> classic Rett syndrome</li> <li>• Variant Rett syndrome</li> <li>• Mild learning disabilities</li> </ul>
<b>Males</b>	<ul style="list-style-type: none"> <li>• <i>MECP2</i>-related severe neonatal encephalopathy</li> <li>• Pyramidal signs, parkinsonism, and macroorchidism (PPM-X) syndrome</li> <li>• Syndromic/nonsyndromic intellectual disability</li> </ul>

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

2. Note: The allelic disorder *MECP2* duplication syndrome is not included in this *GeneReview*. See Genetically Related Disorders.

## Diagnosis

Note: Duplication of *MECP2* (ranging from 0.3 to 4 Mb and larger) is associated with the allelic disorder *MECP2* duplication syndrome and is not addressed in this *GeneReview*.

## Suggestive Findings in Females

A *MECP2* disorder **should be suspected/considered** in females with the following clinical findings suggestive of *MECP2* classic Rett syndrome or variant Rett syndrome (based on clinical diagnostic criteria published by Neul et al [2010] [[full text](#)] prior to the widespread availability of molecular genetic testing), or mild learning disabilities.

### Clinical findings of *MECP2* classic Rett syndrome and variant Rett syndrome

- Most distinguishing finding: A period of regression (range: ages 1-4 years) followed by recovery or stabilization (range: ages 2-10 years; mean: age 5 years)
- Main findings
  - Partial or complete loss of acquired purposeful hand skills
  - Partial or complete loss of acquired spoken language or language skill (e.g., babble)
  - Gait abnormalities: impaired (dyspraxic) or absence of ability
  - Stereotypic hand movements including hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms
- Supportive findings
  - Breathing disturbances when awake
  - Bruxism when awake
  - Impaired sleep pattern
  - Abnormal muscle tone
  - Peripheral vasomotor disturbances
  - Scoliosis/kyphosis
  - Growth restriction
  - Small, cold hands and feet
  - Inappropriate laughing/screaming spells
  - Diminished response to pain
  - Intense eye communication – "eye pointing"
- Exclusionary findings
  - Brain injury secondary to peri- or postnatal trauma, neurometabolic disease, or severe infection that causes neurologic problems
  - Grossly abnormal psychomotor development in the first six months of life, with early milestones not being met

**Clinical findings of MECP2 mild learning disability.** Typically mild and non-progressive. Note: Typically, females with mild learning disability are identified through molecular genetic testing following diagnosis of a first-degree relative (e.g., a more significantly affected brother or sister).

## Suggestive Findings in Males

MECP2 disorders should be considered in a male with severe neonatal encephalopathy; pyramidal signs, parkinsonism, and macroorchidism (PPM-X) syndrome; or syndromic/nonsyndromic intellectual disability.

### Clinical findings of MECP2 severe neonatal encephalopathy

- Microcephaly
- Relentless clinical course that follows a metabolic-degenerative type of pattern
- Abnormal tone
- Involuntary movements
- Severe seizures
- Breathing abnormalities (including central hypoventilation or respiratory insufficiency)

### Clinical findings of MECP2 severe intellectual disability (including PPM-X syndrome)

- Moderate-to-severe intellectual disability
- Resting tremor
- Slowness of movements
- Ataxia
- PPM-X syndrome: *pyramidal signs*, *parkinsonism*, and *macroorchidism*

- No seizures or microcephaly
- Usually normal brain MRI, EEG, EMG, and nerve conduction velocity studies

## Establishing the Diagnosis

**Female proband.** The diagnosis of a *MECP2* disorder **is usually established** in a female proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *MECP2* identified by molecular genetic testing (see Table 1).

**Male proband.** The diagnosis of a *MECP2* disorder **is established** in a male proband with suggestive findings and a hemizygous pathogenic (or likely pathogenic) variant in *MECP2* 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 hemizygous or heterozygous *MECP2* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (either single-gene, multigene panel) or **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *MECP2* disorders is broad, females with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas females and males with a phenotype indistinguishable from many other inherited disorders with intellectual disability and/or neonatal encephalopathy are more likely to be diagnosed using genomic testing (see Option 2).

### Option 1

When the clinical findings suggest the diagnosis of a *MECP2* disorder, molecular genetic testing approaches can include use of single-gene testing or a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *MECP2* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- Various **multigene panels** such as Rett/Angelman syndrome panels and more comprehensive childhood-onset epilepsy panels that include *MECP2* and other genes of interest (see Differential Diagnosis) are 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

## Option 2

When the phenotype overlaps with many other inherited disorders characterized by intellectual disability and/or neonatal encephalopathy, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is another option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 *MECP2* Disorders

Gene <sup>1</sup>	Method	Proportion of Pathogenic Variants <sup>2</sup> Identified by Method
<i>MECP2</i>	Sequence analysis <sup>3</sup>	90%-95% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	5%-10% <sup>6,7</sup>

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. 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](#).

4. Archer et al [2006], Philippe et al [2006]

5. 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 Hardwick et al [2007]) may not be detected by these methods.

6. The sizes of many reported disease-associated deletions are at the upper limits of detection by sequence analysis and the lower limits of detection by gene-targeted deletion/duplication analysis; therefore, the proportion of pathogenic variants detected by either method depends on the methods used by a laboratory.

7. Archer et al [2006], Pan et al [2006], Philippe et al [2006], Hardwick et al [2007], Zahorakova et al [2007]

## Clinical Characteristics

### Clinical Description

In females the spectrum of *MECP2*-related phenotypes ranges from classic Rett syndrome, to variant Rett syndrome (either milder or more severe than classic Rett syndrome), to mild learning disabilities. In males the spectrum ranges from severe neonatal encephalopathy, to pyramidal signs, parkinsonism, and macroorchidism (PPM-X) syndrome, to severe syndromic/nonsyndromic intellectual disability.

## MECP2 Disorders in Females

**Table 2.** Features of MECP2 Disorders in Females

Phenotype	Feature	% of Persons w/Feature
<b>MECP2 classic Rett syndrome</b>	Regression followed by recovery or stabilization	99%
	Deceleration of head growth	80%
	Gait abnormalities	99%
	Seizures	60%-80%
	Hand stereotypies & loss of purposeful hand skills	100% <sup>1</sup>
	Absence of speech; high-pitched crying	99%
	Cold extremities	99%
	Irregular breathing	99%
<b>Variant Rett syndrome</b>	Regression followed by recovery or stabilization	99%
	Gait abnormalities	80%-99%
	Sleep disturbances	80%-99%
	Seizures	6%-80%
	Hand stereotypies & loss of purposeful hand skills	97.3%
	Breathing irregularities	80%-99%
	Agitation	80%-99%

Gold et al [2018], Einspieler & Marschik [2019], Stallworth et al [2019]

1. Stallworth et al [2019]; 44% showed different patterns including hand wringing, washing, clapping, and tapping.

**MECP2 classic Rett syndrome.** Most individuals with classic Rett syndrome are female; however, males meeting the clinical criteria for classic Rett syndrome who have a 47,XXY karyotype [Hoffbuhr et al 2001, Leonard et al 2001, Schwartzman et al 2001] and postzygotic *MECP2* variants resulting in somatic mosaicism have been described [Clayton-Smith et al 2000, Topçu et al 2002].

Although early development is reportedly normal in children with classic Rett syndrome, parents – in retrospect – often identify subtle differences compared to unaffected sibs. Most (but not all) affected children have acquired microcephaly; stereotypic hand movements and breathing irregularities are seen in the majority.

**Variant Rett syndrome.** Females with variant Rett syndrome exhibit a broader spectrum of clinical features than those observed in classic Rett syndrome. At the more severe end of the spectrum, development is delayed from very early infancy; congenital hypotonia and infantile spasms are also seen. At the milder end of the spectrum, regression is less dramatic and intellectual disability is much less severe; some speech may be preserved.

**Mild learning disabilities.** In rare instances, females with a pathogenic *MECP2* variant may only exhibit mild learning disabilities or some autistic features, presumably as a consequence of favorable skewing of X-chromosome inactivation. When there is no regression phase and no characteristic hand stereotypies, the clinical course differs from that of classic and variant Rett syndrome.

## MECP2 Disorders in Males

**Table 3.** Features of MECP2 Disorders in Males

Phenotype	Feature	% of Persons w/Feature		
		Present	Absent	Not reported
MECP2-related severe neonatal encephalopathy <sup>1</sup>	Normal birth parameters	71%		29%
	Head growth deceleration / microcephaly	94%		5.8%
	Hypotonia &/or feeding difficulties in infancy	82.4%		17.6%
	Hypertonia of extremities	52.9%	11.8%	35.3%
	Movement disorder, e.g., myoclonus, tremors, & dystonia	58.8%	17.7%	23.5%
	Mild cerebral atrophy	18%	35%	47%
	Polymicrogyria	5.9%	23.5%	70.6%
	Poor head control	35%	12%	53%
	Seizures	58.8%	17.7%	23.5%
	Severe development delay	82.4%		17.6%
	Irregular breathing / sleep apnea	47.1%	29.4%	23.5%
	Gastroesophageal reflux	35.3%		64.7%
	EEG abnormality	88.2%	5.9%	5.9%
Pyramidal signs, parkinsonism, & macroorchidism (PPM-X syndrome) <sup>2</sup>	Psychosis	67.6%	10.8%	21.6%
	Pyramidal signs	46%	2.7%	51.3%
	Macroorchidism	19%		81%
	Intellectual disability	50%		50%
	Parkinsonism	2.7%		97.3%
	Progressive spasticity	67.6%		32.4%
	Delayed development	54%		46%
	Speech difficulties	50%		50%
	Seizures	2.7%		
	Bilateral juvenile cataract	2.7%		
	Scoliosis or kyphosis	10.8%		
	Large ears	8.1%		
	Movement disorders	32.4%		
	Apraxia	2.7%		36%
	Seizures	8.1%		91.9%
Dysmorphic features	5.4%		94.6%	

Table 3. continued from previous page.

Phenotype	Feature	% of Persons w/Feature		
		Present	Absent	Not reported
Syndromic/ nonsyndromic intellectual disability <sup>3</sup>	Severe intellectual disability	90%		10%
	Gait abnormalities	57%	7%	36%
	Facial dysmorphism	10%	3%	87%
	Behavioral problems	40%	3%	57%
	Autistic-like behavior	3%	53%	44%
	Seizures	20%	30%	50%
	Poor/absent language skills	47%	17%	36%
	Hypotonia	23%		77%
	Microcephaly	13%	23%	64%
	History of regression	17%	27%	56%
	Spasticity	33%	17%	50%
	Sleep disturbances	13%	10%	77%

1. Schüle et al [2008]

2. Lindsay et al [1996], Claes et al [1997], Gendrot et al [1999], Orrico et al [2000], Klauck et al [2002], Winnepeninckx et al [2002], Moog et al [2003], Psoni et al [2010]

3. Lubs et al [1999], Meloni et al [2000], Orrico et al [2000], Gomot et al [2003], Meins et al [2005], Van Esch et al [2005], Ramocki et al [2009]

**Severe neonatal-onset encephalopathy** is characterized by a relentless clinical course that follows a metabolic-degenerative type of pattern, abnormal tone, involuntary movements, severe seizures, and breathing abnormalities (including central hypoventilation or respiratory insufficiency) [Wan et al 1999, Villard et al 2000, Zeev et al 2002, Kankirawatana et al 2006]. Often, males with a severe neonatal encephalopathy die before age two years [Schanen et al 1998, Wan et al 1999].

The severe encephalopathy phenotype appears to be rare in females [Lugtenberg et al 2009].

**X-linked ID and PPM-X syndrome.** PPM-X syndrome, caused by the p.(Ala140Val) *MECP2* variant in males, is characterized by moderate-to-severe intellectual disability. Most have spasticity that may be progressive; some may have extrapyramidal movements. Episodic psychosis is seen in many but not all. Most affected males also have macroorchidism. Microcephaly is variable. See also Genotype-Phenotype Correlations.

## Genotype-Phenotype Correlations

Genotype-phenotype correlations are inconsistent, due in part to the pattern of X-chromosome inactivation (XCI); females who have a *MECP2* pathogenic variant and favorably skewed XCI may have mild or no manifestations [Wan et al 1999, Amir et al 2000, Cheadle et al 2000, Huppke et al 2000, Weaving et al 2003, Chae et al 2004, Schanen et al 2004, Charman et al 2005].

*MECP2* pathogenic variants with some residual function that are associated with milder phenotypes include the following:

- p.(Ala140Val). The phenotype is syndromic (PPM-X) intellectual disability in males and very mild cognitive impairment in females [Dotti et al 2002, Klauck et al 2002, Gomot et al 2003, Venkateswaran et al 2014, Lambert et al 2016, Sheikh et al 2016].



- p.(Arg133Cys). The phenotype is less severe than classic Rett syndrome in females; this variant can be present in affected males [Leonard et al 2003, Sheikh et al 2016].
- p.(Arg309Cys) is found in females and males with intellectual disability and some features of *MECP2* disorders, but not classic or variant Rett syndrome [Campos et al 2007, Schönewolf-Greulich et al 2016].

## Prevalence

The worldwide prevalence is 1:10,000-1:23,000 female births [Ellaway et al 1999, Armstrong et al 2010]. Reports of incidence are limited; available estimates range from 0.43-0.71:10,000 for females in France [Bienvenu et al 2006] to 0.586:10,000 for females in Serbia [Sarajlija et al 2015] and 1.09:10,000 for females in Australia [Laurvick et al 2006].

## Genetically Related (Allelic) Disorders

***MECP2* duplication syndrome** is characterized in affected males by infantile hypotonia, delayed psychomotor development leading to severe intellectual disability, poor speech development, progressive spasticity, recurrent respiratory infections, and seizures.

Duplications of *MECP2* ranging from 0.3 to 4 Mb and larger are found in all affected males.

The birth prevalence of *MECP2* duplication syndrome has been reported to be 0.65:100,000 for all live births and 1:100,000 for males in Australia with the median age at diagnosis of 23.5 months [Giudice-Nairn et al 2019].

## Differential Diagnosis

**Table 4.** Disorders to Consider in the Differential Diagnosis of *MECP2* Disorders

DiffDx Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/ <i>MECP2</i> Disorders	Distinguishing from <i>MECP2</i> Disorders
Angelman syndrome	Deficient expression or function of maternally inherited <i>UBE3A</i> allele	See footnote 1.	ID, severe speech impairment, gait ataxia &/or tremulousness of the limbs; microcephaly & seizures common; DD 1st noted at age ~6 mos	In classic Rett syndrome DD is not overtly evident in the 1st 6 mos.
Early infantile epileptic encephalopathy (See <a href="#">CDKL5 Deficiency Disorder.</a> )	<i>CDKL5</i>	XL	In females: early-onset severe seizures w/poor cognitive development; facial gestalt, cortical visual impairment; In males: severe-profound ID & early-onset intractable seizures <sup>2</sup>	Very early-onset seizures, facial dysmorphism, & cortical visual impairment are not generally seen in classic Rett syndrome.

Table 4. continued from previous page.

DiffDx Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/ <i>MECP2</i> Disorders	Distinguishing from <i>MECP2</i> Disorders
Rett syndrome, congenital variant (See <i>FOXP1</i> Syndrome.)	<i>FOXP1</i>	AD	Short normal period of development before onset of regression leading to severe ID, DD, postnatal microcephaly, agenesis of the corpus callosum, seizures, dyskinesia, & hypotonia <sup>3</sup>	Except for microcephaly, structural abnormalities are not usually seen on brain MRI.

AD = autosomal dominant; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. The risk to sibs of a proband depends on the genetic mechanism leading to the loss of *UBE3A* function: typically less than 1% risk for probands with a deletion or uniparental disomy (UPD), and as high as 50% for probands with an imprinting defect or a pathogenic variant of *UBE3A*.

2. Elia et al [2008]

3. Overlapping features and a similar facial appearance between individuals with *FOXP1* pathogenic variants has led to the suggestion that these individuals should be regarded as having *FOXP1* syndrome rather than a variant of Rett syndrome [Kortüm et al 2011].

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *MECP2* disorder, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 5.** Recommended Evaluations Following Initial Diagnosis in Individuals with a *MECP2* Disorder

System/Concern	Evaluation	Comment
<b>Constitutional</b>	Measurement of height, weight, & head circumference	
<b>Neurologic</b>	Neurologic eval	To incl brain MRI; consider EEG / video monitoring if seizures are a concern.
<b>Development</b>	Developmental assessment	<ul style="list-style-type: none"> <li>• Motor, adaptive, cognitive, &amp; speech-language eval</li> <li>• Eval for early intervention / special education</li> </ul>
<b>Psychiatric/ Behavioral</b>	Neuropsychiatric eval	In persons age >12 mos: screening for problems incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
<b>Musculoskeletal</b>	Orthopedics, physical medicine & rehab, PT/OT eval	To incl assessment of: <ul style="list-style-type: none"> <li>• Gross motor &amp; fine motor skills</li> <li>• Scoliosis</li> <li>• Mobility &amp; activities of daily living &amp; need for adaptive devices</li> <li>• Need for PT (to improve gross motor skills) &amp;/or OT (to improve fine motor skills)</li> </ul>
<b>Gastrointestinal/ Feeding</b>	Gastroenterology / nutrition / feeding team eval	To incl: <ul style="list-style-type: none"> <li>• Eval of aspiration risk &amp; nutritional status</li> <li>• History of constipation &amp; GERD</li> </ul> Consider need for gastric tube placement.
<b>Respiratory</b>	Overnight sleep studies	<ul style="list-style-type: none"> <li>• Analysis for abnormalities of breathing regularity</li> <li>• Noninvasive assessment of pulmonary gas exchange</li> </ul>

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
<b>Sleep disorder</b>	Breathing monitoring using portable polygraphic screening devices	To assess occurrence of apnea & hypopnea
<b>Cardiovascular</b>	Cardiac eval	To assess for prolonged QTc
<b>Osteopenia</b>	Bone densitometry	To assess for osteopenia
<b>Eyes</b>	Ophthalmologic eval	To assess for ↓ vision, abnormal ocular movement, strabismus
<b>Hearing</b>	Audiology eval	Assess for hearing loss
<b>ENT/Mouth</b>		
<b>Genitourinary</b>		
<b>Integument</b>	History & exam	↓ perfusion of hands & feet (possible autonomic abnormalities)
<b>Miscellaneous/ Other</b>	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family supports/ resources	Assess need for: <ul style="list-style-type: none"> <li>• Community or online resources, e.g., <a href="#">Parent to Parent</a>;</li> <li>• Social work involvement for parental support;</li> <li>• Home nursing referral.</li> </ul>

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease; OT = occupational therapy; PT = physical therapy

## Treatment of Manifestations

Treatment needs to be individualized following an assessment of the affected individual's clinical problems and needs.

Management is symptomatic and focuses on optimizing the individual's abilities using a multidisciplinary approach with input from a pediatric or adult specialist physician, dietician, occupational therapist, speech therapist, music therapist, dentist, and other medical subspecialists as needed.

Table 6. Treatment of Manifestations in Individuals with a MECP2 Disorder

Manifestation/ Concern	Treatment	Considerations/Other
<b>DD/ID</b>	See Developmental Delay / Intellectual Disability Management Issues.	
<b>Epilepsy</b>	Standardized treatment w/ASM by an experienced neurologist	<ul style="list-style-type: none"> <li>• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.</li> <li>• Education of parents/caregivers <sup>1</sup></li> </ul>
<b>Psychiatric/ Behavioral</b>	Risperidone (low dose) or selective serotonin uptake inhibitors have been somewhat successful in treating agitation.	
<b>Musculoskeletal</b>	Scoliosis	Per guidelines <sup>2</sup>
<b>Poor weight gain / Failure to thrive</b>	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; nutritional guidelines are available. <sup>3</sup>

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
<b>Spasticity</b>	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
<b>Sleep disorder</b>	Melatonin can ameliorate sleep disturbances.	Chloral hydrate, hydroxyzine, or diphenhydramine may be used w/melatonin.
<b>Abnormal vision &amp;/or strabismus</b>	Standard treatment(s) as recommended by ophthalmologist	Community vision services through early intervention or school district
<b>Central visual impairment</b>	No specific treatment; early intervention to help stimulate visual development	
<b>Hearing</b>	Hearing aids may be helpful; per otolaryngologist	Community hearing services through early intervention or school district
<b>Gastrointestinal</b>	<ul style="list-style-type: none"> <li>Constipation: stool softeners, prokinetics, osmotic agents, or laxatives as needed</li> <li>GERD: anti-reflux agents, smaller &amp; thickened feedings, &amp; positioning</li> </ul>	
<b>Cardiovascular</b>	Treatment for prolonged QTc	Under care of pediatric cardiologist
<b>Osteopenia</b>	Baseline densitometry; optimization of physical activity & calcium & vitamin D levels	Guidelines for management of bone health are available. <sup>4</sup>
<b>Family/ Community</b>	<ul style="list-style-type: none"> <li>Ensure appropriate social work involvement to connect families w/local resources, respite, &amp; support.</li> <li>Care coordination to manage multiple subspecialty appointments, equipment, medications, &amp; supplies</li> </ul>	<ul style="list-style-type: none"> <li>Ongoing assessment for need of palliative care involvement &amp;/or home nursing</li> <li>Consider involvement in adaptive sports or <a href="#">Special Olympics</a>.</li> </ul>

ASM = anti-seizure medication; DD = developmental delay; GERD = gastroesophageal reflux disease; ID = intellectual disability; 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](#).

2. Downs et al [2009]

3. Leonard et al [2013]

4. Jefferson et al [2016]

## 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 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 if 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 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 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.

## Motor Dysfunction

### Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox<sup>®</sup>, anti-parkinsonian medications, or orthopedic procedures.

**Fine motor dysfunction.** Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

**Oral motor dysfunction** should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically by an occupational or speech therapist) is recommended to improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

**Communication issues.** Consider evaluation for alternative means of communication (e.g., [augmentative and alternative communication](#) [AAC]) for individuals who have expressive language difficulties. An AAC evaluation

can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

## 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

Many of the clinical features in females with atypical Rett syndrome (Table 2) evolve with age and hence should be reassessed every six to 12 months.

**Table 7.** Recommended Surveillance for Individuals with a *MECP2* Disorder

System/Concern	Evaluation	Frequency
<b>Feeding</b>	<ul style="list-style-type: none"> <li>Measurement of growth parameters</li> <li>Eval of nutritional status &amp; safety of oral intake</li> </ul>	At each multidisciplinary clinic visit; at least annually
<b>Gastrointestinal</b>	Monitor for constipation.	
<b>Respiratory</b>	Monitor for evidence of aspiration, respiratory insufficiency.	
<b>Neurologic</b>	<ul style="list-style-type: none"> <li>Monitor those w/seizures as clinically indicated.</li> <li>Assess for new manifestations, e.g., seizures, changes in tone, movement disorders.</li> </ul>	
<b>Development</b>	Monitor developmental progress & educational needs.	
<b>Speech &amp; language</b>	Monitor communication skills.	
<b>Psychiatric/Behavioral</b>	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
<b>Musculoskeletal</b>	<ul style="list-style-type: none"> <li>Physical medicine, OT/PT assessment of mobility, self-help skills</li> <li>Monitor scoliosis.</li> </ul>	
<b>Cardiovascular</b>	Monitor for prolonged QTc.	
<b>Respiratory</b>	Apnea/hyperventilation	
<b>Miscellaneous/Other</b>	Assess family need for social work support (e.g., palliative/respite care, home nursing; other local resources) & care coordination.	

OT = occupational therapy; PT = physical therapy

## Agents/Circumstances to Avoid

Because individuals with *MECP2* disorders are at increased risk for life-threatening arrhythmias associated with a prolonged QT interval, avoidance of drugs known to prolong the QT interval, including the following, is recommended:

- Prokinetic agents (e.g., cisapride)
- Antipsychotics (e.g., thioridazine), tricyclic antidepressants (e.g., imipramine)
- Antiarrhythmics (e.g., quinidine, sotalol, amiodarone)
- Anesthetic agents (e.g., thiopental, succinylcholine)
- Antibiotics (e.g., erythromycin, ketoconazole)

See [CredibleMeds®](#) (free registration required) for a more extensive list of drugs to avoid.

## Evaluation of Relatives at Risk

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

## Therapies Under Investigation

A number of clinical trials are currently under way, including observational studies, studies focused on improvement of language and communication skills, and drug trials.

For details see [www.rettsyndrome.org](http://www.rettsyndrome.org).

Search [ClinicalTrials.gov](http://ClinicalTrials.gov) in the US and [EU Clinical Trials Register](http://EU Clinical Trials Register) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

## 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

MECP2 disorders are inherited in an X-linked manner.

## Risk to Family Members

### Parents of a proband

- Approximately 99.5% of affected individuals represent simplex cases (i.e., a single occurrence in the family).
- Female proband. *MECP2* molecular genetic testing is recommended for both parents.
- Male proband. *MECP2* molecular genetic testing is recommended for the mother. (Note: The father of an affected male will not have a *MECP2* disorder nor will he be hemizygous for the *MECP2* pathogenic variant; therefore, he does not require further evaluation/testing.)
- The mother of a proband who is found to be heterozygous for a *MECP2* variant may have favorably skewed X-chromosome inactivation that results in her being unaffected or mildly affected.
- If the *MECP2* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Maternal and paternal germline mosaicism have been reported [Amir et al 1999, Zeev et al 2002, Mari et al 2005].
  - Maternal germline mosaicism was reported in one of nine pregnancies [Mari et al 2005, Venâncio et al 2007].

- Paternal germline mosaicism was reported in five fathers of affected daughters from 21 families [Zhang et al 2019].

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

- If the mother of the proband has a *MECP2* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Females who inherit the pathogenic variant are at high risk of developing a *MECP2* disorder, although skewed X-chromosome inactivation may result in a variable phenotype.
  - Males who inherit the variant may have a severe neonatal encephalopathy or, if they survive the first year, will most likely have a severe intellectual disability syndrome.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *MECP2* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism [Amir et al 1999, Zeev et al 2002, Mari et al 2005, Venâncio et al 2007, Zhang et al 2019].

### Offspring of a proband

- Each child of a female proband with a *MECP2* disorder has a 50% chance of inheriting the *MECP2* pathogenic variant. Females with more severe *MECP2* disorders do not reproduce; mildly affected females have reproduced.
- Males with a *MECP2* disorder are not known to reproduce.

**Other family members.** The risk to other family members depends on the genetic status of the proband's mother: if the mother is affected or has a pathogenic *MECP2* variant, her family members may be at risk.

## Related Genetic Counseling Issues

**First-degree female relatives.** Once the pathogenic *MECP2* variant has been identified in a proband, it is appropriate to offer testing to all first-degree female relatives regardless of their clinical status. Apparently unaffected sisters of a female proband with a *MECP2* disorder may be heterozygous for the *MECP2* variant present in their sister but have few to no manifestations because of skewed X-chromosome inactivation. Genetic counseling should address this possibility as clinically unaffected sisters may be at risk of transmitting the pathogenic *MECP2* variant to their children.

### 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 mildly affected or are at risk of having a pathogenic *MECP2* variant.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

Once the *MECP2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Males with a *MECP2* variant who survive infancy will most likely



have severe intellectual disability. The phenotype in a female with a *MECP2* variant is difficult to predict and can range from apparently normal to severely affected.

Note: Because parental germline mosaicism for a *MECP2* pathogenic variant has been reported in multiple families, it is appropriate to offer prenatal testing to the parents of a child with a *MECP2* disorder whether or not the *MECP2* pathogenic variant has been identified in the leukocyte DNA of either parent.

## 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](#).*

- **AussieRett**  
Telethon Kids Institute  
Australia  
**Phone:** +61 419 956 946  
**Fax:** +61 8 6319 1761  
**Email:** [Helen.Leonard@telethonkids.org.au](mailto:Helen.Leonard@telethonkids.org.au)  
[Rett syndrome and Related Disorders](#)
- **International Rett Syndrome Foundation**  
**Phone:** 800-818-RETT (7388); 513-874-3020  
**Email:** [admin@rettsyndrome.org](mailto:admin@rettsyndrome.org)  
[rettsyndrome.org](http://rettsyndrome.org)
- **Medical Home Portal**  
[Rett Syndrome](#)
- **MedlinePlus**  
[Rett syndrome](#)
- **NCBI Genes and Disease**  
[Rett syndrome](#)
- **Rett New Zealand**  
New Zealand  
**Phone:** 04 475 9265  
**Email:** [rett.info@nzord.org.nz](mailto:rett.info@nzord.org.nz)  
[rettsyndrome.org.nz](http://rettsyndrome.org.nz)
- **Rett Syndrome Europe**  
**Email:** [info@rettsyndrome.eu](mailto:info@rettsyndrome.eu)  
[rettsyndrome.eu](http://rettsyndrome.eu)
- **Rett Syndrome Research Trust**  
**Phone:** 203-445-0041  
**Email:** [info@rsrt.org](mailto:info@rsrt.org)  
[reverserett.org](http://reverserett.org)
- **Rett UK**  
United Kingdom  
**Phone:** 01582 798911

**Email:** [info@rettuk.org](mailto:info@rettuk.org)  
[www.rettuk.org](http://www.rettuk.org)

## 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.** MECP2 Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<a href="#">MECP2</a>	Xq28	Methyl-CpG-binding protein 2	<a href="#">MECP2 @ LOVD</a> <a href="#">CCHMC - Human Genetics Mutation Database (MECP2)</a> <a href="#">RettBASE</a>	<a href="#">MECP2</a>	<a href="#">MECP2</a>

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 MECP2 Disorders ([View All in OMIM](#))

<a href="#">300005</a>	METHYL-CpG-BINDING PROTEIN 2; MECP2
<a href="#">300055</a>	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC 13; MRXS13
<a href="#">300496</a>	AUTISM, SUSCEPTIBILITY TO, X-LINKED 3; AUTSX3
<a href="#">300673</a>	ENCEPHALOPATHY, NEONATAL SEVERE, DUE TO MECP2 MUTATIONS
<a href="#">312750</a>	RETT SYNDROME; RTT

## Molecular Pathogenesis

Loss of the protein MeCP2 leads to epigenetic aberrations of chromatin, suggesting that MeCP2 deficiency could lead to loss of imprinting, thereby contributing to the pathogenesis of Rett syndrome [Horike et al 2005, Kaufmann et al 2005, Makedonski et al 2005].

The nuclear MeCP2 protein functional domains include:

- Methyl binding domain (MBD): binds specifically to DNA at symmetrically methylated CpGs within chromatin [Hansen et al 2010, Casas-Delucchi et al 2012]
- Transcription repression domain (TRD): responsible for recruiting other proteins that mediate transcription repression
- A-T hook domain: basic residues that bind A-T rich DNA [Baker et al 2013, Heckman et al 2014]
- WW domain: conserved C-terminal domain [Buschdorf & Stratling 2004]

It has also been shown that MeCP2 plays a role in gene splicing [Young et al 2005] and in long-range chromatin remodeling [Horike et al 2005], and may be a transcriptional activator [Chahrour et al 2008].

**Mechanism of disease causation.** Most pathogenic *MECP2* variants occur *de novo*. It has been suggested that pathogenic variants result in loss of protein function; some functional studies show that pathogenic *MECP2* variants affect the MBD or TRD domains of the abnormal protein, depending on the location of the variant [Kudo et al 2001, Kudo et al 2002, Kudo et al 2003].

**MECP2-specific laboratory technical considerations.** Two transcripts have been described:

- [NM\\_001110792.1](#): encodes *MECP2\_e1*, includes exons 1, 3, and 4 but not exon 2 (498 amino acids)

- [NM\\_004992.3](#): encodes *MECP2\_e2*, includes exons 2, 3, and 4 but not exon 1 (486 amino acids)

Although the isoforms are nearly identical, use of two alternative start codons creates alternative N-termini. The e1 transcript is much more highly expressed in brain than the e2 transcript [Kriaucionis & Bird 2004, Mnatzakanian et al 2004]. Of note:

- Exon 1 (*MECP2\_e1*): pathogenic variants in exon 1 are rare and include variants in the start codon (p.Met1?) and p.Ala2 as well as variant frameshift changes [Amir et al 2005, Evans et al 2005, Poirier et al 2005, Ravn et al 2005, Saxena et al 2006, Saunders et al 2009, Sheikh et al 2017].
- Exon 2 (*MECP2\_e2*): a pathogenic variant in the start codon (p.Met1?) has been reported in exon 2 [Gauthier et al 2005].

The majority of pathogenic variants occur in the region encoding the methyl binding domain (MBD, exons 3 and 4; amino acids 90-174 of the MeCP2 e2 isoform), affecting the ability of the MeCP2 protein to bind to target DNA. A number of highly recurrent nonsense variants are found in the transcriptional repression domain (TRD, exon 4; amino acids 219-322 of the MeCP2 e2 isoform) and beyond the TRD, a large number of frameshift variants delete the C-terminal end of the protein (3' end of exon 4).

**Table 8.** Notable *MECP2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
<a href="#">NM_004492.3</a> <a href="#">NP_004983.1</a>	c.473C>T	p.Thr158Met	Common, recurrent pathogenic variants [Miltenberger-Miltenyi & Laccone 2003, Archer et al 2006, Philippe et al 2006]
	c.502C>T	p.Arg168Ter	
	c.763C>T	p.Arg255Ter	
	c.808C>T	p.Arg270Ter	
	c.916C>T	p.Arg306Cys	
	c.397C>T	p.Arg133Cys	Milder phenotype in females is consistent w/in vitro functional studies showing that DNA binding is not impaired [Leonard et al 2003, Sheikh et al 2016].
	c.419C>T	p.Ala140Val	Nonclassic, variant Rett syndrome, observed in familial cases w/affected males [Dotti et al 2002, Klauck et al 2002, Gomot et al 2003, Venkateswaran et al 2014, Lambert et al 2016, Sheikh et al 2016]; heterozygous females may have mild ID & impaired speech acquisition [Klauck et al 2002, Lambert et al 2016].
	c.925C>T	p.Arg309Trp	Observed in females & males w/ID & some features of a <i>MECP2</i> disorder, but not classic or variant Rett syndrome [Campos et al 2007, Schönewolf-Greulich et al 2016]

ID = intellectual disability

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](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

## Chapter Notes

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## Revision History

- 19 September 2019 (bp) Comprehensive update posted live
- 28 June 2012 (me) Comprehensive update posted live
- 2 April 2009 (me) Comprehensive update posted live
- 15 August 2006 (me) Comprehensive update posted live
- 11 February 2004 (me) Comprehensive update posted live
- 3 October 2001 (me) Review posted live
- September 2000 (vb) Original submission

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