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PPP2R5D-Related Neurodevelopmental Disorder

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Summary

Clinical characteristics

PPP2R5D-related neurodevelopmental disorder is characterized by mild to severe neurodevelopmental delay. Pronounced hypotonia with delay in gross motor skills is common. Onset of independent walking varies widely and ataxia is reported. All reported individuals have speech impairment, with a wide range of abilities. Autism spectrum disorder is reported in six individuals. Macrocephaly is common. Seizures and ophthalmologic abnormalities are reported in fewer than half of individuals. Additional anomalies include skeletal, endocrine, and cardiac malformations, each reported in a few individuals. To date, 23 individuals with *PPP2R5D*-related neurodevelopmental disorder have been reported.

Diagnosis

The diagnosis of *PPP2R5D*-related neurodevelopmental disorder is established in a proband by identification of a heterozygous pathogenic variant in *PPP2R5D* on molecular genetic testing.

Management

Treatment of manifestations: Standard treatment for seizures, visual impairment, and developmental delays.

Surveillance: Monitor for seizures, vision issues, developmental progress, and educational needs.

Genetic counseling

PPP2R5D-related neurodevelopmental disorder is inherited in an autosomal dominant manner. All probands reported to date with *PPP2R5D*-related neurodevelopmental disorder whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo PPP2R5D* pathogenic variant. Risk to future pregnancies is presumed to be low, as the proband most likely has a *de novo PPP2R5D* pathogenic variant; however, given the

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theoretic possibility of parental germline mosaicism, recurrence risk to sibs is estimated at 1%, and thus prenatal and preimplantation genetic testing may be considered.

Diagnosis

Formal diagnostic criteria for *PPP2R5D*-related neurodevelopmental disorder have not been established.

Suggestive Findings

PPP2R5D-related neurodevelopmental disorder **should be considered** in individuals presenting with the following clinical and brain MRI findings.

Clinical findings

- Macrocephaly
- Generalized hypotonia of infancy
- Mild-to-profound developmental delays or intellectual disability
- Autism spectrum disorder
- Epilepsy (reported seizure types: generalized tonic-clonic, multifocal, complex partial, and generalized epileptic spasms)

Brain MRI findings

- Megalencephaly
- Nonspecific MRI findings include: hydrocephalus (2 individuals), mild-to-moderate ventricular dilatation (4 individuals), small or dysplastic corpus callosum (2), cavum septum pellucidum (1), cavum septum pellucidum et vergae (1), and white matter abnormalities (1) [Houge et al 2015, Shang et al 2016].

Establishing the Diagnosis

The diagnosis of *PPP2R5D*-related neurodevelopmental disorder **is established** in a proband by identification of a heterozygous pathogenic variant in *PPP2R5D* by molecular genetic testing (see Table 1).

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *PPP2R5D* -related neurodevelopmental disorder is nonspecific and indistinguishable from many other inherited disorders, it is most likely to be diagnosed by either a multigene panel (see Option 1) or genomic testing (see Option 2).

Option 1

An **intellectual disability, macrocephaly, or epilepsy multigene panel** that includes *PPP2R5D* 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*. Of note, given the rarity of *PPP2R5D*-related neurodevelopmental disorder and the recent identification of the condition, most panels for intellectual disability may not include this gene. (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, and/or other non-sequencing-based tests (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 diagnosis of *PPP2R5D*-related neurodevelopmental disorder has not been considered, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **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 *PPP2R5D*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
PPP2R5D	Sequence analysis [3]	23/23 (100%) [4]
	Gene-targeted deletion/duplication analysis [5]	0/23 (0%) None reported

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Houge et al [2015], Loveday et al [2015], Shang et al [2016], Yeung et al [2017]
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.

Clinical Characteristics

Clinical Description

To date 23 individuals with *PPP2R5D*-related neurodevelopmental disorder have been reported [Houge et al 2015, Loveday et al 2015, Shang et al 2016, Yeung et al 2017]. Affected individuals range in age from 22 months to 53 years. Developmental delay and/or mild-to-severe intellectual disability has been reported in all individuals. Published clinical information is currently limited; it is likely that understanding of the phenotypic spectrum will evolve as additional affected individuals are identified.

The following are the most common clinical features of *PPP2R5D*-related neurodevelopmental disorder.

Psychosocial and cognitive development. All individuals reported to date have had developmental delay and/or intellectual disability. Developmental milestones are consistently delayed.

Although children were reported to have pronounced hypotonia, feeding difficulties were not reported as a major issue for most children. Gastric reflux was reported in one affected child [Houge et al 2015].

The age at which individuals walk independently varied widely – from age 18 months to nine years, with some individuals still unable to walk at age ten years. Six individuals were reported to walk with an ataxic gait [Houge et al 2015, Shang et al 2016].

All reported individuals had speech impairment, with a wide range of abilities. Seven individuals, ranging in age from two to 53 years, remained nonverbal. Eleven individuals were able to use words, although this ranged from two words with poor articulation at age ten years to 100-200 words and the ability to form short sentences at age

15 years. All individuals with *PPP2R5D*-related neurodevelopmental disorder have had issues with language development [Yeung et al 2017].

Evaluations for autism spectrum disorder (ASD) were done in eight children with *PPP2R5D*-related disorder. ASD was diagnosed in six of the eight children evaluated and suspected in one child who met some but not all of the DSM-IV criteria for ASD [Shang et al 2016, Yeung et al 2017]. Four children displayed behavioral issues such as tantrums, aggressiveness, trouble adjusting to new situations, and problems with impulse control [Shang et al 2016].

Macrocephaly/megalencephaly. Macrocephaly was reported in 18 of 23 individuals. Megalencephaly was specifically mentioned in two individuals. Head occipitofrontal circumference ranged from >2 to >3.8 SD above the mean in affected individuals. Congenital macrocephaly was reported in one individual [Loveday et al 2015]. The onset of macrocephaly has not been reported in most other affected individuals.

Hypotonia was reported in 17 individuals. Onset and severity were not reported.

Seizures have been reported in six individuals. Seizure types observed include generalized tonic-clonic, multifocal, complex partial, and generalized epileptic spasms. The age of onset ranged from four days to four years. Both individuals reported with megalencephaly also had epilepsy [Yeung et al 2017]. Further, two affected individuals with epilepsy were described to have mild ventricular dilatation [Houge et al 2015] and one individual with complex partial seizures had cavum septum pellucidum (a nonspecific finding) on brain imaging [Shang et al 2016].

Ophthalmologic abnormalities such as strabismus, astigmatism, esotropia, rotational nystagmus, ptosis, and myopia were reported in seven of the 18 individuals assessed [Houge et al 2015, Shang et al 2016]. One individual had cataracts at age 53 years [Houge et al 2015].

Dysmorphic facial features. Many individuals have dysmorphic facial features including hypertelorism, downslanting palpebral fissures, frontal bossing, and a long, hypotonic face. Midface hypoplasia, low-set ears, and plagiocephaly have also been reported. Two affected individuals with heights 2 SD above the mean were reported. However, dysmorphic features are mild, nonspecific, and vary widely among individuals reviewed.

Other

- **Skeletal** abnormalities observed in seven individuals include scoliosis, hip dysplasia, camptodactyly of the fourth toe, and middle 2/3 and 3/4 finger syndactyly [Houge et al 2015, Loveday et al 2015, Shang et al 2016].
- **Endocrine** abnormalities such as short stature (<3rd percentile) were observed in three individuals [Houge et al 2015, Shang et al 2016]. One individual had hypoglycemia and another was diagnosed with failure to thrive [Houge et al 2015, Shang et al 2016]. Age of onset of these conditions was unknown.
- **Cardiac.** Two individuals had significant cardiac abnormalities with atrial and ventricular septal defects and a bicuspid aortic valve in one individual and ventricular septal defect and patent foramen ovale in the other.
- **Genital anomalies.** One individual had hypospadias.

Genotype-Phenotype Correlations

There are no clear genotype-phenotype correlations as only 23 affected individuals have been reported to date.

Penetrance

There is no evidence of reduced penetrance; the majority of the reported pathogenic variants (22/23) are confirmed *de novo*. Parental results were not available for one affected individual.

Prevalence

The prevalence of *PPP2R5D*-related neurodevelopmental disorder is unknown. To date, 23 individuals with *PPP2R5D*-related neurodevelopmental disorder have been reported.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PPP2R5D*.

Contiguous gene deletions and duplication of 6p21.1 that include *PPP2R5D* are reported in public databases as being associated with disease (decipher.sanger.ac.uk):

- A duplication including part of *PPP2R5D* has been reported in a child with developmental delays.
- Deletions including all of *PPP2R5D* have been reported in two children with overlapping phenotypes. Clinical features available for one child included developmental delay, prominent forehead, low-set ears, and a depressed nasal bridge; an additional child had delayed speech and language development, downslanted palpebral fissures, hydrocephalus, intellectual disability, and muscular hypotonia.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of *PPP2R5D*-Related Neurodevelopmental Disorder

Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/*PPP2R5D*-related ND	Distinguishing from *PPP2R5D*-related ND
PTEN hamartoma tumor syndrome	*PTEN*	AD	• Macrocephaly • Autism • DD	• Hamartomatous overgrowths of multiple tissues • ↑ cancer predisposition
MTOR-related disorders (e.g., Smith-Kingsmore syndrome; OMIM 616638)	*MTOR*	AD	• Megalencephaly • ID • ASD • Hypotonia	• Cortical brain malformations (polymicrogyria, focal cortical dysplasia) • Pigmentary abnormalities of the skin
Sotos syndrome	*NSD1*	AD	• Megalencephaly • ID	• Somatic overgrowth • Characteristic facial features • Additional congenital anomalies (e.g., cardiac, skeletal)
Megalencephaly-capillary malformation syndrome (see *PIK3CA*-Related Segmental Overgrowth)	*PIK3CA*	AD	• ID • Autistic features • Seizures • Hypotonia • Megalencephaly	• Vascular malformations • Somatic overgrowth (that can be focal) • Lymphatic abnormalities • Digital abnormalities (syndactyly, polydactyly) • Cortical brain malformations (incl polymicrogyria) • Hydrocephalus
Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome	*PIK3R2* *AKT3* *CCND2*	AD	• ID • Autistic features • Seizures • Hypotonia • Megalencephaly	• Cortical brain malformations (incl polymicrogyria) • Hydrocephalus • Polydactyly

Table 2. continued from previous page.

Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/*PPP2R5D*-related ND	Distinguishing from *PPP2R5D*-related ND
16p11.2 deletion syndrome	See footnote 1.	AD	• ID • Autistic features • Seizures • Hypotonia	Obesity in adolescence & later in life
Kleefstra syndrome	*EHMT1*	AD	• ID • Hypotonia • Seizures • Autistic-like features	• Obesity • Distinct dysmorphic features

AD = autosomal dominant; ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; ND = neurodevelopmental disorder

1. The 16p11.2 recurrent deletion involves the loss of one chromosome segment harboring 25 annotated genes or transcripts [Kumar et al 2008, Marshall et al 2008, Weiss et al 2008]. The recurrent deletion is flanked by segmental duplications that contain four additional genes.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *PPP2R5D*-related neurodevelopmental disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *PPP2R5D*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Comment
Gastrointestinal/ Feeding	Nutrition eval if feeding difficulties present	Incl feeding assessment related to hypotonia & eval for gastroesophageal reflux.
Neurologic	Neurologic eval	Incl EEG if seizures are suspected.
Psychiatric/ Behavioral	Neuropsychiatric eval	Screen individuals age >12 mos for behavior concerns &/or traits suggestive of ASD.
Eyes	Ophthalmologic eval & vision assessment	
Cardiac	Full cardiac eval if audible murmurs present	True prevalence of cardiac malformation in this syndrome not yet known
Miscellaneous/ Other	Developmental assessment	Incl motor, speech/language eval, general cognitive, & vocational skills.
	Consultation w/clinical geneticist &/or genetic counselor	

ASD = autism spectrum disorder

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *PPP2R5D*-Related Neurodevelopmental Disorder

Manifestation/ Concern	Treatment	Considerations/Other
Seizures	Standardized treatment w/ASM by experienced neurologist	Many different ASMs may be effective; none has been demonstrated effective specifically for this disorder.
	Education of parents regarding common seizure presentations	For information on non-medical interventions & coping strategies for parents or caregivers of children diagnosed w/ epilepsy, see Epilepsy Foundation Toolbox.
Abnormal vision &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	

ASM = anti-seizure medication

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. In the US, early intervention is a federally funded program available in all states.

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.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion of transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

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.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- 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.

- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

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. Assuming that the individual is safe to eat by mouth, feeding therapy, typically from an occupational or speech therapist, is recommended for affected individuals who have difficulty feeding as a result of poor oral motor control.

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

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 is 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 5. Recommended Surveillance for Individuals with *PPP2R5D*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Frequency
Neurologic	Monitor those w/seizures	As clinically indicated
Psychiatric	Behavior assessment for anxiety, attention, & aggressive or self-injurious behavior	As clinically indicated
Eyes	Ophthalmologic eval	At time of diagnosis & subsequently as needed depending on findings
Miscellaneous/ Other	Monitor developmental progress & educational needs	As clinically indicated

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

PPP2R5D-related neurodevelopmental disorder is inherited in an autosomal dominant manner and is typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- All probands reported to date with *PPP2R5D*-related neurodevelopmental disorder whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo PPP2R5D* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *PPP2R5D* pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism. Although theoretically possible, no instances of germline mosaicism have been reported to date.
- Theoretically, if the parent is the individual in whom the *PPP2R5D* pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents. If the *PPP2R5D* pathogenic variant found in the proband 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].

Offspring of a proband. To date, individuals with *PPP2R5D*-related neurodevelopmental disorder are not known to have reproduced.

Other family members. Given that all probands with *PPP2R5D*-related neurodevelopmental disorder reported to date have the disorder as a result of a *de novo PPP2R5D* pathogenic variant, the risk to other family members is presumed to be low.

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo PPP2R5D* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal testing and preimplantation genetic testing may be considered.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather

than early diagnosis. While most centers would consider use of prenatal testing to be a personal choice, 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.

- **Jordan's Guardian Angels**
  1121 L Street
  Suite 100
  Sacramento 95814
  Email: info@jordansguardianangels.org
  www.jordansguardianangels.org
- **Simons Searchlight**
  PPP2R5D

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. PPP2R5D-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
PPP2R5D	6p21.1	Serine/threonine-protein phosphatase 2A 56 kDa regulatory subunit delta isoform	PPP2R5D	PPP2R5D

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 PPP2R5D-Related Neurodevelopmental Disorder (View All in OMIM)

601646	PROTEIN PHOSPHATASE 2, REGULATORY SUBUNIT B (B56), DELTA; PPP2R5D
616355	HOUGE-JANSSENS SYNDROME 1; HJS1

Molecular Pathogenesis

PPP2R5D is a member of the PP2A family of phosphatases with critical roles in development, including neurodevelopment.

Gene structure. *PPP2R5D* comprises 16 exons. Three isoforms are described by alternative splicing.

See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. All known pathogenic variants to date are missense variants. Four variants (p.Glu197Lys, p.Glu198Lys, p.Glu200Lys, and p.Glu420Lys) alter a highly conserved negatively charged glutamic acid to a positively charged lysine, and are predicted to affect protein structure. Of these, p.Glu198Lys has been frequently encountered, identified in 48% (11/23) of individuals with *PPP2R5D*-related disorder. With the exception of variant p.Pro53Ser, pathogenic variants showed deficient holoenzyme formation in HEK293 cells [Houge et al 2015]; p.Pro53Ser has been associated with a different phenotype including microcephaly and short stature.

No affected individuals with an isolated whole-gene or intragenic deletion or duplication of *PPP2R5D* have been reported, although contiguous gene deletions and duplication of 6p21.1 are reported in public databases as being associated with disease (see Genetically Related Disorders; decipher.sanger.ac.uk).

Table 6. *PPP2R5D* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.157C>T	p.Pro53Ser	NM_006245.3 NP_006236.1
c.589G>A	p.Glu197Lys	
c.592G>A	p.Glu198Lys	
c.598G>A	p.Glu200Lys	
c.602C>G	p.Pro201Arg	
c.619T>A	p.Trp207Arg	
c.1258G>A	p.Glu420Lys	

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.

Normal gene product. *PPP2R5D* encodes a 602-amino acid protein B56δ, a subunit of the serine/threonine-protein phosphatase 2A (PP2A). The PP2A complex is composed of three subunits: a scaffolding subunit A, a regulatory subunit B, and a catalytic domain C. B56δ is one of the isoforms of subunit B and is highly expressed in the brain. This protein is thought to be involved in cell growth, chromatin remodeling, and transcriptional regulation. There is evidence that PP2A-B56δ holoenzyme interacts with PI3K/AKT growth regulatory cascade [Loveday et al 2015].

Abnormal gene product. The p.Glu198Lys and p.Glu200Lys disease-associated variants disrupt PP2A subunit binding and impair dephosphorylation of specific substrates [Houge et al 2015]. The p.Glu420Lys variant is positioned near an active site of the catalytic subunit and is likely to disrupt holoenzyme formation or substrate recognition [Shang et al 2016]. A dominant-negative effect is proposed, supported by biochemical evidence of B56δ-dependent PP2A dysregulation [Houge et al 2015]; however, large 6p21.1-deletion phenotypes are suggestive of a loss-of-function mechanism.

Chapter Notes

Author Notes

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