COLD SPRING HARBOR
Molecular Case Studies

MINI-REVIEW

Clinical features of PPP2 syndrome type R5D (Jordan's syndrome) to support standardization of care

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Abstract PPP2 syndrome type R5D, or Jordan's syndrome, is a neurodevelopmental disorder caused by pathogenic missense variants in *PPP2R5D*, a β-subunit of the Protein Phosphatase 2A (PP2A). The condition is characterized by global developmental delays, seizures, macrocephaly, ophthalmological abnormalities, hypotonia, attention disorder, social and sensory challenges often associated with autism, disordered sleep, and feeding difficulties. Among affected individuals, there is a broad spectrum of severity, and each person only has a subset of all associated symptoms. Some, but not all, of the clinical variability is due to differences in the *PPP2R5D* genotype. These suggested clinical care guidelines for the evaluation and treatment of individuals with PPP2 syndrome type R5D are based on data from 100 individuals reported in the literature and from an ongoing natural history study. As more data are available, particularly for adults and regarding treatment response, we anticipate that revisions to these guidelines will be made.

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Ontology terms: attention deficit hyperactivity disorder; autism; delayed fine motor development; delayed gross motor development; intellectual disability; moderate; macrocephaly at birth; moderate global developmental delay; postnatal macrocephaly; sleep disturbance

Published by Cold Spring Harbor Laboratory Press

doi:10.1101/mcs.a006285

INTRODUCTION

PPP2 syndrome type R5D (Jordan's syndrome [JS]) is characterized by neurodevelopmental delay and intellectual disability and/or neurobehavioral challenges, caused by heterozygous pathogenic variants in the *PPP2R5D* gene that are usually de novo (OMIM #616355 Intellectual developmental disorder, autosomal dominant, MRD35). Pathogenic variants in *PPP2R5D* are recurrent de novo missense variants that are all located in the substrate binding pocket and likely change the substrate specificity for the phosphatase. There is a single genetic condition associated with *PPP2R5D* to date. The condition was first recognized in 2015 (Houge et al. 2015). Distinctive clinical features include macrocephaly, a protruding forehead, hypotonia, speech delay, gross motor delay, behavioral challenges, and epilepsy (Biswas et al. 2019). Less frequently, individuals have ophthalmologic, skeletal, cardiac, and genital malformations. The condition has been variously referred to as PPP2R5D-related disorder, PPP2A-related (neuro)developmental disorder, and intellectual developmental disorder, autosomal dominant 35. Given the technical complexity of these names, the families of individuals with the condition commonly refer to the condition as Jordan's syndrome, named after one of the first individuals identified with the condition. We suggest using the term PPP2 syndrome type R5D (Jordan's syndrome) to facilitate bidirectional communication between the patient community and the medical/scientific community. Here, we will use PPP2 syndrome type R5D.

PPP2R5D is a Ser/Thr-specific protein phosphatase, 2A (PP2A). PP2A phosphatases are multisubunit enzymes, encoded by 19 human genes; *PPP2R5D* is one of three of these genes

currently known to cause neurodevelopmental disorders (along with *PPP2R1A* and *PPP2CA*) (Fitzgerald et al. 2015). *PPP2R5D* encodes the regulatory PP2A B56δ subunit. PP2A with protein phosphatase 1 (PP1) accounts for more than 90% of all Ser/Thr dephosphorylation in different tissues (Biswas et al. 2019). The PP2A regulatory B-type subunits give rise to tissue and cell specific expression, localization, and specificity to PP2A complexes and are therefore critical to PP2A regulation (Lambrecht et al. 2013). The B56δ is highly expressed in the brain, and the holoenzyme plays a critical role in neuronal function (Sandal et al. 2021).

PP2A-mediated dephosphorylation plays an important role in learning and memory, and dysfunction has been associated with Alzheimer's disease and Parkinson's-like symptoms (Biswas et al. 2019). PP2A is essential for regulation of many functions such as gene transcription, cell division, and growth (Eichhorn et al. 2009). De novo mutations in *PPP2R5D* alter PP2A–PPP2R5D holoenzyme activity (Shang et al. 2016). In addition to the neurological manifestations, mutations in the family of B56δ, B56γ, and B56δ subunits have resulted in overgrowth disorder (Loveday et al. 2015).

The diagnosis of PPP2 syndrome type R5D is made with a sequencing-based genetic test such as whole-exome sequencing or testing for a panel of genes associated with neurodevelopmental disorders or seizures. Most pathogenic/likely pathogenic mutations are recurrent de novo missense variants (see a summary of the identified variants in Fig. 1) (Oyama et al. 2022). Interpretation of novel variants benefit from parental testing to determine if they are de novo. For parents of a child with a de novo variant, the recurrence risk to have another child with JS is ~1% because of the theoretical possibility of parental germline mosaicism. Prenatal testing is available in future pregnancies (Rahbari et al. 2016). Referral to a genetic counselor is recommended to discuss recurrence risk and reproductive options.

Here, we aim to further describe the manifestations of PPP2 syndrome type R5D by age, to aid physicians in treating individuals with PPP2 syndrome type R5D. Regardless of age, at the first visit after a PPP2 syndrome type R5D diagnosis has been made, it is recommended that the genetics of PPP2 syndrome type R5D is explained to the family. Clinicians may introduce the family-to-family support groups to help parents learn about the condition.

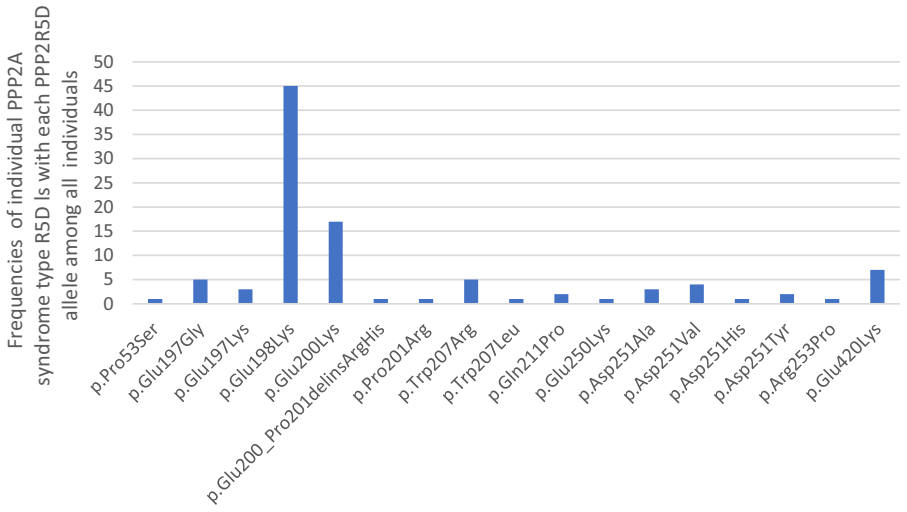

Figure 1. Frequencies of individual *PPP2R5D* variants among 100 individuals with pathogenic *PPP2R5D* variants. Distribution of *PPP2R5D* variants: 100 individuals with pathogenic variants in the *PPP2R5D* gene, the regulatory PP2A B56δ subunit (Oyama et al. 2022). The B-type subunit confers substrate specificity, and all pathogenic variants are clustered in the binding site of the phosphatase (Oyama et al. 2022).

EXPECTED ISSUES BY AGE AND CORRESPONDING THERAPIES AND EVALUATIONS RECOMMENDED

Prenatal

Although to our knowledge PPP2 syndrome type R5D has not yet been diagnosed prenatally, head circumference is predicted to be increased and there is no hydrocephalus. Increased head circumference may be an indication for prenatal genetic testing. The prenatal course is otherwise expected to be uncomplicated, but parents may elect to deliver at a hospital with neonatal intensive care in case the infant needs additional support.

Infancy

Many infants with PPP2 syndrome type R5D are transferred to the neonatal intensive care unit after birth mostly because of challenges related to hypotonia. In one study of 72 individuals with PPP2 syndrome type R5D, 75% of participants exhibited hypotonia (Mirzaa et al. 2019).

Development

Referral to a developmental pediatrician is recommended to help monitor the infant's development and recommend therapies and treatments. For example, infants with hypotonia may be referred to early intervention for physical therapy, occupational therapy, and later speech therapy.

Neurology

If macrocephaly is observed in the infant, magnetic resonance imaging (MRI) is unlikely to identify any structural anomalies (hydrocephalus) that require intervention (shunt). Head growth should be monitored with imaging reserved for significant increases in head circumference. Macrocephaly was present in 66.7% of individuals with PPP2 syndrome type R5D (Mirzaa et al. 2019).

Even if the infant has not been observed to have a seizure, a baseline electroencephalogram (EEG) is recommended, as many individuals (45.8%) with PPP2 syndrome type R5D have seizures at some point (Mirzaa et al. 2019).

Feeding and Gastrointestinal Abnormalities

A feeding and swallowing assessment may be necessary if the infant is not latching onto the breast, feeds slowly, or is not gaining weight. Feeding therapy and nutritional support may help identify the right nipple/bottle and formula for feeding, help with transition to solid food, and decide when a feeding tube is necessary. Approximately 19.4% of infants with PPP2 syndrome type R5D experienced failure to thrive (Mirzaa et al. 2019). Gastroesophageal reflux disease (GERD) is common (27.8% of individuals with PPP2 syndrome type R5D) and individuals often benefit from medications (Mirzaa et al. 2019). Although this frequency of GERD is similar to typically developing infants, infants with PPP2 syndrome type R5D have more severe GERD and require medication (Singendonk et al. 2019).

Toddler and Preschool Age

Development

Developmental milestones should be continually monitored by the pediatrician and/or developmental pediatrician/neurologist. Early intervention is thought to improve develop-

mental outcomes. Once the child is preschool-aged, parents or guardians should work with the school to develop an individualized education plan (IEP), so all the child's needs may be addressed and therapies given at school. Toilet training is delayed, and behavioral approaches and positive reinforcement strategies used for children with special needs can be beneficial (Luxem and Christophersen 1994). Expected issues and therapies/evaluations needed to address them are discussed below.

Gross Motor Delays, Low Endurance, Hypotonia

Physical therapy and orthotics (such as ankle–foot orthotics) are recommended. Age of walking varies from 18 mo to 9 yr old. Rarely do individuals never achieve independent walking. In one study of 11 individuals with PPP2 syndrome type R5D, five individuals achieved independent walking between 6 and 9 years old (Houge et al. 2015). Two individuals (ages 2 and 10 years old) had not yet achieved walking (Houge et al. 2015). Four individuals achieved walking between 1.5 and 2.2 years old (Houge et al. 2015).

Fine Motor Delays

Fine motor delays are one of the less significantly affected areas in patients with PPP2 syndrome type R5D (Oyama et al. 2022). Occupational therapy can be helpful (Mirzaa et al. 2019).

Speech Delays

Speech delays are universal. Age of talking varies greatly as well as verbal abilities, with some individuals remaining nonverbal. Some individuals achieve verbal fluency, whereas others achieve only a few words, and with a wide spectrum of abilities. However, regardless of language eventually achieved, all individuals with PPP2 syndrome type R5D experience speech delay (Biswas et al. 2019). Speech therapy, alternative communication methods including signing and communication devices, and social exposure groups can all be helpful.

Autism

Some children with PPP2 syndrome type R5D have autism, whereas others may have some autistic features such as sensory difficulties, especially with touch. Interventions such as applied behavior analysis may be useful (Shang et al. 2016; Mirzaa et al. 2019).

Seizures

Seizures can begin at any age (mean age of onset is 2.3 yr, with onset ranging from birth to 17.8 yr) and include almost all seizure types including tonic, simple partial, petit mal, myoclonic, infantile spasms, grand mal, complex partial, and atonic drop attacks (Oyama et al. 2022). Severity of seizures can range from 200 episodes per day to a single lifetime seizure (Oyama et al. 2022). The most common reported genetic mutation concurring with seizures is the p.Glu198Lys variant (Oyama et al. 2022). If there is concern of possible seizures, an EEG should be performed. Seizures can frequently be treated with a single medication. There is no single best medication to treat seizures and, in some cases, ketogenic diets have also been helpful.

Feeding Difficulties

Feeding difficulties are common and may continue beyond infancy. Oral motor/feeding therapy, diet adjustment, and/or a feeding tube may be necessary depending on severity (Oyama et al. 2022).

Gastrointestinal Abnormalities

Constipation and/or diarrhea (23.6%) are common. Many have food sensitivities, such as gluten and dairy sensitivity. Dietary adjustments and an elimination diet may be helpful in consultation with a gastroenterologist (Oyama et al. 2022).

Ophthalmological Abnormalities

Baseline evaluation with a pediatric ophthalmologist: glasses, corrective surgery, or vision therapy. In a study of 72 individuals with PPP2 syndrome type R5D, 27.8% of participants had strabismus and 16.7% of participants had astigmatism (Oyama et al. 2022).

Cardiac Abnormalities

The frequency of cardiac abnormalities is, as one source reports, two of 23 individuals had cardiac abnormalities; yet there have begun to be more reports of cardiac abnormalities among the family community of affected individuals.

Genitourinary Malformations

Some males with PPP2 syndrome type R5D have undescended testes and require orchiopexy if the testes do not descend by age 3. One male with PPP2 syndrome type R5D had hypospadias (Mirzaa et al. 2019).

Dental Issues

Difficulty with oral hygiene due to oral sensitivities may lead to tooth decay and caries. Seeing a pediatric dentist who treats children with special needs can be helpful and fluoride treatment and sealants are frequently recommended (Shang et al. 2016).

Sleep

Many individuals with PPP2 syndrome type R5D have difficulty falling or staying asleep, and 19% of individuals take a medication to aid with sleep. Melatonin can be helpful in falling asleep.

School Age

Expected issues and therapies/evaluations needed to address them are listed below.

PPP2 Syndrome Type R5D Attention

All individuals with PPP2 syndrome type R5D have learning disabilities and/or attention deficit hyperactivity disorder (ADHD). ADHD medication can improve focus and reduce hyperactivity. One study reported that of 72 individuals with PPP2 syndrome type R5D, of the 6 to 18 year olds sampled, 29% met clinical diagnosis for ADHD (Oyama et al. 2022).

Behavioral Issues

Anxiety and obsessive compulsion disorder have been noted, and medication can improve these symptoms. Consistency helps to prevent anxiety. In 24 children with PPP2 syndrome type R5D aged 2–5 yr, 4.2% were borderline for a clinical diagnosis of anxiety on the Child Behavioral Checklist (Oyama et al. 2022). In 14 children with PPP2 syndrome type R5D aged 6–18 yr, 14% were borderline for a clinical diagnosis of anxiety on the Child Behavioral Checklist (Oyama et al. 2022).

Individualized educational programs are recommended to ensure all necessary supports are in place to maximize learning.

Physical therapy should continue to support gross motor development and coordination (Mirzaa et al. 2019).

Scoliosis

Orthopedic evaluation is useful to assess the need for orthotics and to treat scoliosis, ideally before surgery is required. In one study of 16 patients with PPP2 syndrome type R5D, four patients were reported to have scoliosis (Houge et al. 2015).

Early Adolescence

Expected issues and therapies/evaluations needed to address them are listed below.

Puberty

Precocious puberty has been observed in PPP2 syndrome type R5D and is benign in etiology. Females with PPP2 syndrome type R5D can have irregular menses.

Late Adolescence and Adulthood

Expected issues and therapies/evaluations needed to address them are listed below.

Parkinsonism

Special attention should be paid to tremors and cognitive decline over time in adults, often starting in the 30s. PPP2 syndrome type R5D has been associated with early-onset parkinsonism and seems to respond to medications used to treat parkinson's disease. Currently, levodopa treatment has led to improvement in PPP2 syndrome type R5D associated atypical parkinsonism movements (Kim et al. 2020; Hetzelt et al. 2021). Hand tremor has been noted as early as adolescence. Initially it does not interfere with function. Consultation with a neurologist specialized in Parkinson's disease and movement disorders will help assess utility of levodopa (Hetzelt et al. 2021).

It is important to note that data on adults with PPP2 syndrome type R5D are limited. Thus, recommendations for adults are still evolving. It is likely that there are many more adults living with PPP2 syndrome type R5D who are undiagnosed because of the need for genetic testing to make the diagnosis that only recently became available.

In the United States, many people with PPP2 syndrome type R5D qualify to attend school and receive services until age 21. Afterward, they may transition to day programs, or in some cases hold a job. Periods of transition can be difficult for individuals with PPP2 syndrome type R5D, and stepwise transition is optimal.

SUMMARY

Here, we propose a standard of care for the treatment of PPP2 syndrome type R5D. These recommendations have been established based on a relatively small ($n = 100$) number of patients. As more patients are diagnosed, and the longitudinal data becomes more robust, it is expected that these recommendations will evolve.

ADDITIONAL INFORMATION

Competing Interest Statement

Dr. Wendy Chung is a member of the board of directors of Prime Medicine.

Referees

Chris Gunter
Anonymous

Acknowledgments

We thank Jordan's Guardian Angels for supporting this work on PPP2 syndrome type R5D or Jordan's syndrome.

Funding

This work was supported by the Office of Statewide Health Planning and Development, State of California: SB 840, year 2018; SB 129 #44, year 2021.

REFERENCES

Biswas D, Cary W, Nolta JA. 2019. PPP2R5D-related intellectual disability and neurodevelopmental delay: a review of the current understanding of the genetics and biochemical basis of the disorder. *Int J Mol Sci* **21:** 1286. doi:10.3390/ijms21041286

Eichhorn PJA, Creyghton MP, Bernards R. 2009. Protein phosphatase 2A regulatory subunits and cancer. *Biochim Biophys Acta* **1795:** 1–15. doi:10.1016/j.bbcan.2008.05.005

Fitzgerald TW, Gerety SS, Jones WD, van Kogelenberg M, King DA, McRae J, Morley KI, Parthiban V, Al-Turki S, Ambridge K, et al. 2015. Large-scale discovery of novel genetic causes of developmental disorders. *Nature* **519:** 223–228. doi:10.1038/nature14135

Hetzelt KLML, Kerling F, Kraus C, Rauch C, Thiel CT, Winterholler M, Reis A, Zweier C. 2021. Early-onset parkinsonism in PPP2R5D -related neurodevelopmental disorder. *Eur J Med Genet* **64:** 104123. doi:10.1016/j.ejmg.2020.104123

Houge G, Haesen D, Vissers LELM, Mehta S, Parker MJ, Wright M, Vogt J, McKee S, Tolmie JL, Cordeiro N, et al. 2015. B56δ-related protein phosphatase 2A dysfunction identified in patients with intellectual disability. *J Clin Invest* **125:** 3051–3062. doi:10.1172/JCI79860

Kim CY, Wirth T, Hubsch C, Németh AH, Okur V, Anheim M, Drouot N, Tranchant C, Rudolf G, Chelly J, et al. 2020. Early-onset parkinsonism is a manifestation of the *PPP2R5D* p.E200K mutation. *Ann Neurol* **88:** 1028–1033. doi:10.1002/ana.25863

Lambrecht C, Haesen D, Sents W, Ivanova E, Janssens V, Structure JV. 2013. Structure, regulation, and pharmacological modulation of PP2A phosphatases. *Methods Mol Biol* **1053:** 283–305. doi:10.1007/978-1-62703-562-0_17

Loveday C, Tatton-Brown K, Clarke M, Westwood I, Renwick A, Ramsay E, Nemeth A, Campbell J, Joss S, Gardner M, et al. 2015. Mutations in the PP2A regulatory subunit B family genes PPP2R5B, PPP2R5C and *PPP2R5D* cause human overgrowth. *Hum Mol Genet* **28:** 1578. doi:10.1093/hmg/ddy424

Luxem M, Christophersen E. 1994. Behavioral toilet training in early childhood: research, practice, and implications. *J Dev Behav Pediatr* **15:** 370–378. doi:10.1097/00004703-199410000-00009

Mirzaa G, Foss K, Nattakom M, Chung WK. 2019. *PPP2R5D*-related neurodevelopmental disorder. 2019 Jan 24. In *GeneReviews® 1993–2023 [Internet]* (ed. Adam MP, Mirzaa GM, Pagon RA, et al.). University of Washington, Seattle. https://www.ncbi.nlm.nih.gov/books/NBK536360/

Oyama N, Vaneynde P, Reynhout S, Pao EM, Timms A, Fan X, Foss K, Derua R, Janssens V, Chung W, et al. 2022. Clinical, neuroimaging and molecular characteristics of *PPP2R5D*-related neurodevelopmental disorders: an expanded series with functional characterisation and genotype–phenotype analysis. *J Med Genet* **60:** 511–522. doi:10.1136/jmg-2022-108713

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, et al. 2016. Timing, rates and spectra of human germline mutation. *Nat Genet* **48:** 126–133. doi:10.1038/ng.3469

Sandal P, Jong CJ, Merrill RA, Song J, Strack S. 2021. Protein phosphatase 2A: structure, function and role in neurodevelopmental disorders. *J Cell Sci* **134:** jcs248187. doi:10.1242/jcs.248187

Shang L, Henderson LB, Cho MT, Petrey DS, Fong CT, Haude KM, Shur N, Lundberg J, Hauser N, Carmichael J, et al. 2016. *De novo* missense variants in *PPP2R5D* are associated with intellectual disability, macrocephaly, hypotonia, and autism. *Neurogenetics* **17:** 43–49. doi:10.1007/s10048-015-0466-9

Singendonk M, Goudswaard E, Langendam M, van Wijk M, van Etten-Jamaludin F, Benninga M, Tabbers M. 2019. Prevalence of gastroesophageal reflux disease symptoms in infants and children: a systematic review. *J Pediatr Gastroenterol Nutr* **68:** 811–817.

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Cold Spring Harb Mol Case Stud 2023, **9:** a006285 originally published online June 20, 2023
Access the most recent version at doi:10.1101/mcs.a006285