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RERE-Related Disorders

Synonym: Neurodevelopmental Disorder with or without Anomalies of the Brain, Eye, or Heart (NEDBEH)

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Summary

Clinical characteristics

RERE-related disorders are characterized by neurodevelopmental problems with or without structural anomalies of the eyes, heart, kidneys, and genitourinary tract and mild sensorineural hearing loss. Hypotonia and feeding problems are common among affected individuals. Developmental delay and intellectual disability range from mild to profound. Behavior problems may include attention-deficit/hyperactivity disorder, self-injurious behavior, and autism spectrum disorder. A variety of eye anomalies (coloboma, optic nerve anomalies, microphthalmia, and/or Peter's anomaly) and vision issues (myopia, anisometropia, astigmatism, exotropia, esotropia) have been reported. Congenital heart defects, most commonly septal defects, have also been described. Genitourinary abnormalities include vesicoureteral reflux, and cryptorchidism and hypospadias in males. Sensorineural hearing loss can be unilateral or bilateral.

Diagnosis/testing

The diagnosis of *RERE*-related disorders is established in a proband by identification of a heterozygous pathogenic variant in *RERE* by molecular genetic testing.

Management

Treatment of manifestations: Feeding difficulties may require the use of feeding therapy and/or thickened liquids; in severe cases, a nasogastric or gastrostomy tube may be considered. Seizure disorders, abnormal vision and/or strabismus, hearing loss, congenital heart defects, gastroesophageal reflux, genitourinary anomalies, scoliosis, congenital hip dysplasia, developmental delay, and behavioral problems are treated in the standard manner.

Surveillance: At least annual monitoring of developmental progress / educational needs and for scoliosis (until growth is complete). Annual (or as clinically indicated) ophthalmologic and audiologic evaluations. Routine

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follow up with a cardiologist and a urologist, as indicated for those who have anomalies involving these organ systems. Monitoring of seizure activity and behavioral issues as needed.

Genetic counseling

RERE-related disorders are inherited in an autosomal dominant manner and are typically caused by a *de novo* pathogenic variant. If the *RERE* pathogenic variant identified in the proband is not identified in one of the parents, the risk to sibs is low (~1%) but greater than that of the general population because of the possibility of parental germline mosaicism for the pathogenic variant. Once the *RERE* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

No clinical diagnostic criteria have been published.

Suggestive Findings

RERE-related disorders **should be considered** in individuals presenting with the following clinical and brain MRI findings.

Clinical findings. Mild-to-profound developmental delay, intellectual disability, and/or autism spectrum disorder; AND any of the following features presenting in infancy or childhood:

- Behavioral issues, including attention-deficit/hyperactivity disorder and self-injurious behavior
- Generalized hypotonia of infancy
- Infant feeding difficulties
- Eye/vision problems:
  - Structural eye defects (coloboma, optic nerve atrophy/hypoplasia, micropthalmia, and/or Peter's anomaly)
  - Vision issues (myopia, anisometropia, astigmatism, exotropia, esotropia, and/or ptosis)
- Sensorineural hearing loss
- Congenital heart defects, especially septal defects
- Epilepsy
- Genitourinary anomalies including vesicoureteral reflux, hypospadias, and cryptorchidism
- Choanal atresia

Brain MRI findings. Brain MRI may be normal or may reveal a range of related abnormalities including diminished white matter volume, abnormalities of or thin corpus callosum, and ventriculomegaly.

Establishing the Diagnosis

The diagnosis of *RERE*-related disorders **is established** in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *RERE* by molecular genetic testing (see Table 1).

Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability typically begins with chromosomal microarray analysis (CMA). If CMA is not diagnostic, the next step is

typically either a multigene panel or exome sequencing. Note: Single-gene testing (sequence analysis of *RERE*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *RERE*) that cannot be detected by sequence analysis.
- **An intellectual disability (ID) multigene panel** that includes *RERE* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA 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 *RERE*-related disorders, some 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, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **Exome sequencing,** which does not require the clinician to determine which gene is likely involved, yields results similar to an ID multigene panel but has two advantages: (1) a multigene panel may not include all rare genes recently identified as causing ID; and (2) exome sequencing may be able to detect pathogenic variants in genes which – for technical reasons – do not sequence well.

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

Table 1. Molecular Genetic Testing Used in *RERE*-Related Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
RERE	Sequence analysis [3]	18/19 [4]
	Gene-targeted deletion/duplication analysis [5]	1/19 [6, 7]

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. Fregeau et al [2016], Jordan et al [2018]
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 with a larger 1p36 deletion) may not be detected by these methods.
6. Although a 317-kb deletion encompassing exons 1-10 was detected by chromosomal microarray analysis (CMA) [Jordan et al 2018], the detection rate of gene-targeted deletion/duplication analysis is not known.
7. CMA uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *RERE*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 1p36 region. CMA designs in current clinical use target the 1p36 region.

Clinical Characteristics

Clinical Description

RERE-related disorders are characterized by neurodevelopmental problems with or without structural anomalies of the eyes, heart, kidneys, and genitourinary tract and sensorineural hearing loss.

To date, 19 individuals have been identified with a pathogenic variant in *RERE* [Fregeau et al 2016, Jordan et al 2018]. The following description of the phenotypic features associated with this condition is based on these reported cases.

Developmental delay (DD) and intellectual disability (ID) have been documented in most individuals with *RERE*-related disorders and can vary from mild to profound. Some affected individuals may have normal early developmental milestones.

Other neurodevelopmental features including hypotonia and feeding problems (which may be caused by brain stem or cranial nerve abnormalities) are common among affected individuals.

Behavioral problems are often noted and can include attention-deficit/hyperactivity disorder, self-injurious behavior, and autism spectrum disorder.

Sensory impairments are common.

- 6/19 (~30%) of affected individuals have structural **eye anomalies** (see Suggestive Findings). Both iris and chorioretinal colobomas have been described, although none of the reported individuals to date are blind. Other eye/vision problems such as myopia, anisometropia, astigmatism, exotropia, esotropia, and ptosis have also been documented.
- 4/19 (~20%) of affected individuals have sensorineural **hearing loss.** Hearing loss has been described as mild and can be unilateral or bilateral. One affected individual had progressive hearing loss that became severe, but it is unclear if this is typical.

Congenital heart defects are seen in 8/19 (~40%) of affected individuals, with ventricular septal defects being particularly common.

Epilepsy has been diagnosed in 2/19 (~10%) of affected individuals. Given the small numbers, it is not yet known if there is a predominant seizure type.

Neuroimaging reveals central nervous system anomalies in 13/19 (approximately 70%) of affected individuals. Typical findings include diminished white matter volume, abnormalities of or thin corpus callosum, and ventriculomegaly (see Suggestive Findings).

Other associated features

- **Gastrointestinal problems,** especially gastroesophageal reflux disease, is present in a minority of affected individuals. Some affected individuals have poor suck and swallow without true dysphagia. One person required tube feeding as an infant.
- **Genitourinary abnormalities** including vesicoureteral reflux, and cryptorchidism and hypospadias in males
- **Musculoskeletal features** including congenital hip dysplasia (2/19 individuals; approximately 10%) and scoliosis without vertebral anomalies (3/19 individuals; ~15%). Some affected individuals are still very young, so the true incidence of scoliosis may be higher than reported.
- **Facial features.** No specific dysmorphic features have been observed. If present, dysmorphic features are nonspecific.

- **Choanal atresia** has been identified only in individuals with the c.4313_4318dupTCCACC, p.(Leu1438_His1439dup) pathogenic variant (see Genotype/Phenotype Correlations).
- Cranial nerve dysfunction has been identified in one affected individual.

Prognosis. It is unknown if life span in *RERE*-related disorders is abnormal. Two reported individuals are alive in their early twenties [Jordan et al 2018], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

In general, pathogenic missense variants affecting the atrophin-1 domain of RERE are associated with an increased risk of structural eye defects, congenital heart defects, genitourinary anomalies, and sensorineural hearing loss when compared with loss-of-function variants [Jordan et al 2018]. This suggests that some changes in this domain may represent dominant negative alleles.

The c.4313_4318dupTCCACC, p.(Leu1438_His1439dup) variant is associated with a unique phenotypic presentation that includes many features commonly seen in individuals with CHARGE syndrome including coloboma, choanal atresia, congenital heart defects, growth deficiency, genitourinary anomalies, and DD/ID.

Prevalence

The prevalence of this condition is unknown. Approximately 19 individuals with *RERE*-related disorders have been identified and published in the literature [Fregeau et al 2016, Jordan et al 2018].

Genetically Related (Allelic) Disorders

1p36 deletion syndrome (OMIM 607872)**.** *RERE* is located in the proximal critical region for the 1p36 deletion syndrome. It is likely that RERE haploinsufficiency contributes to many of the phenotypic features associated with proximal 1p36 deletions (see Differential Diagnosis).

Differential Diagnosis

Because the phenotypic features associated with *RERE*-related disorders are not sufficient to diagnose this condition, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Table 2. Disorders to Consider in the Differential Diagnosis of *RERE*-Related Disorders

Disorder	Gene / Genetic Mechanism	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/*RERE*-related disorders	Distinguishing from *RERE*-related disorders
CHARGE syndrome	*CHD7*	AD	• Colobomata, congenital heart defects, choanal atresia, ear anomalies, & genitourinary anomalies • Neurocognitive defects • Hearing loss • Growth deficiencies • Cranial nerve dysfunction or anomaly	• Semicircular canal defects • Tracheoesophageal fistula

Table 2. continued from previous page.

Disorder	Gene / Genetic Mechanism	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/*RERE*-related disorders	Distinguishing from *RERE*-related disorders
1p36 deletion syndrome (OMIM 607872)	Deletion of 1p36	See footnote 1.	• Central nervous system anomalies, ophthalmologic abnormalities, congenital heart defects, & renal & genitourinary anomalies • Neurocognitive abnormalities • Hearing loss	• Typical dysmorphic features (straight eyebrows, deeply set eyes, midface retrusion, wide & depressed nasal bridge, long philtrum, pointed chin, epicanthal folds, posteriorly rotated & low-set ears) • Late-closing anterior fontanelle

AD = autosomal dominant; MOI = mode of inheritance
1. Risks to family members depend on the mechanism of origin of the deletion.

Management

Evaluations Following Initial Diagnosis

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

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *RERE*-Related Disorders

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	May incl EEG & brain MRI, as clinically indicated
Psychiatric/ Behavioral	Neuropsychiatric eval	Screen individuals age >12 mos for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
	Developmental assessment	Incl evaluation of motor, speech/language, general cognitive, & vocational skills.
Eyes	Ophthalmologic eval	To assess for structural eye anomalies & vision problems
Hearing	Audiologic eval	To assess for sensorineural hearing loss
Cardiovascular	Echocardiogram	For eval of congenital heart defects
Gastrointestinal/ Feeding	Assessment for signs & symptoms of GERD	
	Clinical assessment for sucking/swallowing difficulties	Consider swallow study.
Genitourinary	Renal ultrasound	There should be a high index of suspicion for vesicoureteral reflux, which is best evaluated using a VCUG.
	Assessment for cryptorchidism & hypospadias in males	Refer to urologist as indicated.
Musculoskeletal	Clinical eval for congenital hip dysplasia in infants	Consider a hip ultrasound & referral to orthopedist.
	Physical exam for signs of scoliosis	Consider referral to orthopedist if severe.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; EEG = electroencephalogram; GERD = gastroesophageal reflux disease; MRI = magnetic resonance imaging; VCUG = voiding cystourethrogram

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *RERE*-Related Disorders

Manifestation/Concern	Treatment	Considerations/Other
Seizures [1]	Standard treatment w/ASMs by experienced neurologist	Many different ASMs may be effective; none has been demonstrated effective specifically for this disorder.
Abnormal vision &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	
Hearing loss	Standard therapy, which may incl hearing aids	See Hereditary Hearing Loss and Deafness Overview.
Congenital heart defects	Standard treatment(s) as recommended by cardiologist	
Gastroesophageal reflux	Standard treatment(s)	
Feeding difficulties	Consider feeding therapy &/or use of thickened liquids.	Eval by gastroenterologist &/or feeding specialist
	Nasogastric or gastrostomy tube may be required if feeding difficulties fail to resolve.	
Genitourinary anomalies & vesicoureteral reflux	Standard treatment(s) as recommended by urologist	
Scoliosis & congenital hip dysplasia	Standard treatment(s) as recommended by orthopedist	

ASM = anti-seizure medication

1. Education of parents regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy & My Child Toolkit.

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 about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can assist 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) for individuals who have expressive language difficulties, particularly those for whom this is a motor deficit.

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 *RERE*-Related Disorders

System/Concern	Evaluation	Frequency
Neurodevelopment	Monitor developmental progress & educational needs.	At least annually
Neurologic	Monitor those w/seizures as clinically indicated.	As needed
Psychiatric	Behavioral assessment for anxiety, attention, or self-injurious behavior	

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Eyes	Ophthalmologic eval	Annually or as clinically indicated
Hearing	Audiologic eval	
Cardiovascular	Routine follow up w/cardiologist	As indicated for individuals w/congenital heart defects
Genitourinary	Routine follow up w/urologist	As clinically indicated for those w/genitourinary issues
Musculoskeletal	Clinical assessment for scoliosis	At least annually, until growth is complete

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

RERE-related disorders are inherited in an autosomal dominant manner and are typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- All probands reported to date with *RERE*-related disorders whose parents have undergone molecular genetic testing have the disorder as a result of a *de novoRERE* pathogenic variant.
- Theoretically, if the parent is the individual in whom the *RERE* pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected. Therefore, molecular genetic testing should be considered in cases where the parents appear clinically asymptomatic.
- If the *RERE* pathogenic variant found in the proband cannot be detected in the 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.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents: if the *RERE* 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. No individuals with an *RERE*-related disorder have been reported to have had children. However, many are not yet of reproductive age and there is no reason to assume that reproduction would not be biologically possible.

Other family members. Given that all probands with an *RERE*-related disorder reported to date have the disorder as a result of a *de novo RERE* 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 RERE* 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 and preimplantation genetic testing may be considered.

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

Resources

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

- **National Library of Medicine Genetics Home Reference**
  Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.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. RERE-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
RERE	1p36.23	Arginine-glutamic acid dipeptide repeats protein	RERE	RERE

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 RERE-Related Disorders (View All in OMIM)

605226	ARGININE-GLUTAMIC ACID DIPEPTIDE REPEATS; RERE
616975	NEURODEVELOPMENTAL DISORDER WITH OR WITHOUT ANOMALIES OF THE BRAIN, EYE, OR HEART; NEDBEH

Molecular Pathogenesis

RERE is a nuclear receptor coregulator that functions in protein complexes to both positively and negatively modulate the transcription of target genes.

Gene structure. *RERE*, previously called the arginine-glutamic dipeptide repeats encoding gene (NM_012102.3), contains 22 coding exons and two noncoding exons. Alternative transcripts and splice isoforms have been identified.

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

Pathogenic variants. A large percentage of the pathogenic variants reported in *RERE* are missense variants in the histidine-rich region of the 21-amino acid atrophin-1 domain (p.His1425_p.1445Pro). The amino acid sequence in this region is highly conserved, but the functional significance of this domain is currently unknown.

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

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.4313_4318dupTCCACC	p.Leu1438_His1439dup	NM_012102.3 NP_036234.3

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. *RERE* encodes the 1,566-amino acid protein RERE, which has a predicted molecular weight of 172 kd and contains BAH-MTA, ELM2, SANT, ZnF_GATA, and atrophin-1 domains. Within the atrophin-1 domain, there are two arginine-glutamic acid dipeptide repeat regions. RERE protein has previously been known as atrophin 1-associated protein, atrophin-related protein, and atrophin 2.

Abnormal gene product. Loss-of-function variants in *RERE* are likely to cause disease by haploinsufficiency. Missense variants may also cause disease by generating a nonfunctioning protein; however, some evidence suggests that they may produce an abnormal protein product that functions in a dominant negative fashion [Jordan et al 2018].

Chapter Notes

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References

Literature Cited

Fregeau B, Kim BJ, Hernández-García A, Jordan VK, Cho MT, Schnur RE, Monaghan KG, Juusola J, Rosenfeld JA, Bhoj E, Zackai EH, Sacharow S, Barañano K, Bosch DGM, de Vries BBA, Lindstrom K, Schroeder A, James P, Kulch P, Lalani SR, van Haelst MM, van Gassen KLI, van Binsbergen E, Barkovich AJ, Scott DA, Sherr EH. De novo mutations of RERE cause a genetic syndrome with features that overlap those associated with proximal 1p36 deletions. Am J Hum Genet. 2016;98:963–70. PubMed PMID: 27087320.

Jordan VK, Fregeau B, Ge X, Giordano J, Wapner RJ, Balci TB, Carter MT, Bernat JA, Moccia AN, Srivastava A, Martin DM, Bielas SL, Pappas J, Svoboda MD, Rio M, Boddaert N, Cantagrel V, Lewis AM, Scaglia F, Kohler JN, Bernstein JA, Dries AM, Rosenfeld JA, DeFilippo C, Thorson W, Yang Y, Sherr EH, Bi W, Scott DA. Genotype-phenotype correlations in individuals with pathogenic RERE variants. Hum Mutat. 2018;39:666–75. PubMed PMID: 29330883.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

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