NLM Citation: Newman WG, Friedman TB, Conway GS, et al. Perrault Syndrome. 2014 Sep 25 [Updated 2018 Sep 6]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Perrault Syndrome

William G Newman, MD, PhD,[1] Thomas B Friedman, PhD,[2] Gerard S Conway, MD,[3] and Leigh AM Demain, PhD[1]

Created: September 25, 2014; Updated: September 6, 2018.

Summary

Clinical characteristics

Perrault syndrome is characterized by sensorineural hearing loss (SNHL) in males and females and ovarian dysfunction in females. SNHL is bilateral and ranges from profound with prelingual (congenital) onset to moderate with early-childhood onset. When onset is in early childhood, hearing loss can be progressive. Ovarian dysfunction ranges from gonadal dysgenesis (absent or streak gonads) manifesting as primary amenorrhea to primary ovarian insufficiency (POI) defined as cessation of menses before age 40 years. Fertility in affected males is reported as normal (although the number of reported males is limited). Neurologic features described in some individuals with Perrault syndrome include learning difficulties and developmental delay, cerebellar ataxia, and motor and sensory peripheral neuropathy.

Diagnosis/testing

The diagnosis of Perrault syndrome is based on the clinical findings of SNHL in men and women and ovarian dysfunction in women with a 46,XX karyotype. The diagnosis is confirmed by the presence of biallelic pathogenic variants in one of six genes (*CLPP*, *ERAL1*, *HARS2*, *HSD17B4*, *LARS2*, or *TWNK*); however, in approximately 60% of individuals with Perrault syndrome identified to date, a molecular diagnosis cannot be established.

Management

Treatment of manifestations: Hearing loss should be assessed and treated by a multidisciplinary team including an audiologist and otolaryngologist. Possible interventions for those with hearing loss include special educational resources, hearing aids, vibrotactile devices, and cochlear implantation. Cochlear implantation is an option for children older than 12 months with severe-to-profound hearing loss. Primary amenorrhea is treated

Author Affiliations: 1 Manchester Centre for Genomic Medicine, University of Manchester and Manchester University NHS Foundation Trust, Manchester, United Kingdom; Email: william.newman@manchester.ac.uk; Email: leigh.demain@manchester.ac.uk. 2 Laboratory of Molecular Genetics, National Institute on Deafness and Other Communication Disorders, NIH, John David Porter Neuroscience Research Center, NIH, Bethesda, Maryland; Email: friedman@nidcd.nih.gov. 3 Institute for Women's Health, University College London, London, United Kingdom; Email: g.conway@ucl.ac.uk.

in adolescents in collaboration with a pediatric endocrinologist in the usual manner, first to induce puberty and then to mimic the menstrual cycle and maintain bone health. Assisted reproduction through in vitro fertilization using donor eggs is a consideration for women with gonadal dysgenesis; oocyte cryopreservation can be considered in women at risk for POI.

Surveillance: Routine audiologic assessments when hearing loss is mild to moderate; no follow up or audiologic assessments when hearing loss is profound. For children with hearing impairment: monitor development

For women with primary amenorrhea: during induction of puberty, follow up every three months for staging of pubertal development and adjustment of estrogen dose. For women on maintenance estrogen replacement therapy: annual follow up as well as assessment of bone density approximately every five years.

Agents/circumstances to avoid: Avoid: ototoxic medication (e.g., aminoglycosides) if alternative medications are available; exposure to loud noise, which can exacerbate hearing loss.

Evaluation of relatives at risk: It is appropriate to evaluate the older and younger sibs of a proband in order to identify as early as possible those who would benefit from early interventions (e.g., in young children with profound hearing loss; estrogen replacement to facilitate pubertal development in females with ovarian involvement; and potential oocyte cryopreservation if POI is an issue).

Genetic counseling

Perrault syndrome is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. When the pathogenic variants in the family are known, carrier testing for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible.

Diagnosis

No formal diagnostic criteria have been published for Perrault syndrome.

Suggestive Findings

Perrault syndrome **should be suspected** in individuals with the following clinical findings and family history.

Clinical findings

- **Sensorineural hearing loss (SNHL) in men and women.** SNHL is bilateral and ranges in severity from moderate with early-childhood onset to profound with prelingual (congenital) onset. The hearing threshold increase can be variable. When presenting in early childhood, hearing loss can be progressive.
    - SNHL may be apparent from birth in infants who fail neonatal screening tests.
    - In older children SNHL can be demonstrated on an audiogram, which will show similar hearing thresholds for both bone and air conduction.
- **Ovarian dysfunction in women with a 46,XX karyotype.** The spectrum of ovarian dysfunction extends across a continuum from primary ovarian insufficiency (POI) to ovarian dysgenesis.
    - POI is defined as cessation of menses before age 40 years, with raised levels of follicle stimulating hormone (FSH) and reduced serum estrogen concentration.
    - Ovarian dysgenesis is a developmental disorder characterized by loss of germ and supportive cells (e.g., granulosa and theca cells, respectively) in the gonads. The ovaries are dysplastic, streak, or absent. Serum concentration of estrogen is decreased with a consequent elevation in serum concentration of the two gonadotropins, lutenizing hormone (LH) and follicle stimulating hormone

(FSH) (i.e., with hypergonadotropic hypogonadism). The uterus is rudimentary and prepubertal on ultrasound examination.

Family history is consistent with autosomal recessive inheritance including the possibility of parental consanguinity.

Establishing the Diagnosis

The diagnosis of Perrault syndrome **is established**:

- Either by clinical findings, family history, and exclusion of other possible diagnoses with findings similar to Perrault syndrome (see Differential Diagnosis);
- Or by identification of biallelic pathogenic variants in one of the six associated genes (see Table 1) in a person with Suggestive Findings.

Clinical Findings and Family History

- **SNHL** that is bilateral and ranges in severity from moderate with early-childhood onset to profound with prelingual (congenital) onset
- **Ovarian dysfunction** in women with a 46,XX karyotype

Note: Sensorineural hearing loss is usually the initial manifestation of Perrault syndrome. The diagnosis will not be considered, based on clinical findings alone, in males who do not have an affected sister. The initial diagnosis will not be made in females based on clinical findings alone until delayed pubertal development is noted, usually in the teenage years.

Molecular Genetic Testing

The diagnosis of Perrault syndrome is molecularly confirmed by the presence of biallelic pathogenic (or likely pathogenic) variants in one of six genes: *CLPP*, *ERAL1*, *HARS2*, *HSD17B4*, *LARS2*, and *TWNK* (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 biallelic variants of uncertain significance (or of one known pathogenic variant and one variant of uncertain significance) in one of the genes in Table 1 does not establish or rule out the diagnosis. (3) To date biallelic pathogenic variants in these six genes do not account for all individuals with clinically confirmed Perrault syndrome (see Table 1) [Demain et al 2017].

Due to the heterogeneous nature of this disorder, molecular genetic testing approaches can include **gene-targeted testing** (through a multigene panel) or **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved).

- **A multigene panel** that includes *CLPP*, *ERAL1*, *HARS2*, *HSD17B4*, *LARS2*, and *TWNK* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

- **Comprehensive genomic testing** is the best option when the diagnosis of Perrault syndrome has not been considered because an individual has atypical phenotypic features. **Exome sequencing** is the most commonly used genomic testing method; **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 Perrault Syndrome

Gene [1, 2]	Proportion of Perrault Syndrome Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Identified by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
CLPP	7/42	7/7	None reported
ERAL1	3/42	3/3	None reported
HARS2	3/42	3/3	None reported
HSD17B4	3/42	3/3	None reported
LARS2	8/42	8/8	None reported
TWNK	5/42	5/5	None reported
Unknown [6]	13/42	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. 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.
6. When multigene panel testing that includes most/all of the known genes is used, approximately 60% of individuals with Perrault syndrome have not had pathogenic variants [Lerat et al 2016, Demain et al 2017]. Failure to detect pathogenic variants in one of these genes suggests either the presence of a variant in a gene region not sequenced (e.g., enhancer, promoter, intron), pathogenic variants in an as-yet-unidentified gene, or inaccurate clinical diagnosis (see Differential Diagnosis).

Clinical Characteristics

Clinical Description

Perrault syndrome is characterized by sensorineural hearing loss (SNHL) in males and females and ovarian dysfunction in females.

Significant inter- and intrafamilial phenotypic variability has been observed [Jenkinson et al 2012]. Of note, the variable age of onset and degree of deafness do not depend on the sex of the affected individual.

SNHL is bilateral and ranges from profound with prelingual (congenital) onset to moderate with early-childhood onset. When onset is in early childhood, hearing loss can be progressive. There is no evidence of impaired vestibular function.

Affected females have gonadal dysfunction. Although the ovarian findings in Perrault syndrome were originally described as primary ovarian failure due to absent or streak gonads, subsequent reports identified a spectrum of ovarian dysfunction ranging from gonadal dysgenesis presenting as primary amenorrhea (also known as primary ovarian failure) to primary ovarian insufficiency (POI) (presenting as secondary amenorrhea) which is defined as cessation of menses before age 40 years. One woman with Perrault syndrome had children prior to the onset of ovarian insufficiency [Jenkinson et al 2013].

Fertility in affected males is usually reported as normal, although the number of reported affected males is limited. Males with variants in *CLPP* have been noted to be azoospermic [Demain et al 2017].

Other features. Some individuals have been reported to have additional clinical features. No consistent pattern has been observed with these additional features, which have been reported in more than one individual [Jenkinson et al 2012].

Neurologic features are present in some individuals with Perrault syndrome. Members of families with *CLPP*-related Perrault syndrome and *LARS2*-related Perrault syndrome have been reported with or without neurologic features [Jenkinson et al 2013, Pierce et al 2013, Kosaki et al 2018]:

- Learning difficulties and developmental delay [Jenkinson et al 2012, Lerat et al 2016, Demain et al 2017]
- Cerebellar ataxia [Jenkinson et al 2012, Lerat et al 2016, Demain et al 2017]
- Motor and sensory peripheral neuropathy [Jenkinson et al 2012, Lerat et al 2016, Demain et al 2017]

Skeletal features reported in some individuals include high-arched palate, positive thumb and wrist signs, and marfanoid habitus [Zerkaoui et al 2017]

Phenotype Correlations by Gene

Sensorineural hearing loss (SNHL) in Perrault syndrome resulting from biallelic pathogenic variants in *ERAL1*, *HARS2*, *HSD17B4*, or *LARS2* can be congenital and profound or progressive with varying degrees of severity; onset is usually in early childhood and a range of frequencies are affected.

***CLPP*.** In families reported to date with biallelic *CLPP* pathogenic variants, SNHL is severe to profound with congenital or early childhood onset [Jenkinson et al 2013, Ahmed et al 2015, Lerat et al 2016, Demain et al 2017].

***TWNK*.** All individuals reported to date with biallelic *TWNK* variants have had associated neurologic features including ataxia and peripheral neuropathy [Morino et al 2014, Lerat et al 2016, Demain et al 2017, Ołdak et al 2017].

Genotype-Phenotype Correlations

Low-frequency SNHL resulting in an upsloping audiogram has been associated with the *LARS2* pathogenic variant c.1565C>A in either the homozygous state or in a heterozygous state in *trans* to another pathogenic *LARS2* variant. Other variants in *LARS2* have not been associated with low-frequency SNHL [Pierce et al 2013, Demain et al 2017].

Nomenclature

Perrault syndrome has also been referred to as ovarian dysgenesis with sensorineural deafness or XX gonadal dysgenesis with deafness.

Prevalence

Perrault syndrome is rare; approximately 100 affected individuals have been reported to date [Lerat et al 2016]. However, underascertainment is likely as males without an affected sister will be diagnosed with nonsyndromic deafness rather than Perrault syndrome. For example, the authors are aware of males with SNHL and prepubertal girls with SNHL with variants in Perrault syndrome-related genes.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *ERAL1* or *HARS2.* Other phenotypes associated with germline pathogenic variants in *CLPP*, *HSD17B4*, *LARS2*, and *TWNK* are summarized in Table 2.

Table 2. Allelic Disorders

Gene	Disorder	Reference
CLPP	Sensorineural hearing loss, epilepsy, & leukoencephalopathy	Theunissen et al [2016]
HSD17B4	D-bifunctional protein deficiency	van Grunsven et al [1999]
LARS2	Lethal infantile multisystem failure	Riley et al [2016]
TWNK	Infantile-onset spinocerebellar ataxia	Morino et al [2014]
	Mitochondrial DNA maintenance defect presenting w/ encephalohepatopathy	Mitochondrial DNA Maintenance Defects Overview
	Mitochondrial DNA maintenance defect presenting w/ ophthalmoplegia	

Differential Diagnosis

For individuals with a clinical diagnosis of Perrault syndrome in whom a molecular basis has not been identified, other causes of sensorineural hearing loss and ovarian dysfunction need to be excluded before a clinical diagnosis of Perrault syndrome can made with confidence.

Sensorineural hearing loss (SNHL) is genetically heterogeneous. See Genetic Hearing Loss Overview for a detailed differential diagnosis.

XX gonadal dysgenesis and primary ovarian insufficiency are genetically heterogeneous.

- **XX gonadal dysgenesis.** For individuals with primary ovarian failure, defined by primary amenorrhea with low estrogen and raised gonadotropins, Turner syndrome (45, X) or other abnormalities of the X chromosome should be excluded by karyotype analysis or chromosomal microarray (also known as array CGH). Hearing loss is present in approximately 50% of women with Turner syndrome [King et al 2007], but tends to be mild to moderate at higher frequencies [Oliveira et al 2013].
    - Testing of genes in which pathogenic variants have been reported to cause ovarian dysgenesis (including *BMP15, FSHR, MCM9*, *PSMC3IP*, and *SOHLH1*) is appropriate (OMIM PS233300).
    - Other causes of primary ovarian failure include 17α-hydroxylase deficiency and 17,20-lysase deficiency (OMIM 202110); which can be excluded by measurement of 11-deoxycorticosterone and androstenedione levels.
- **Primary ovarian insufficiency (POI).** Multiple genetic causes of POI are known. Analysis of a limited number of genes is available by routine clinical testing.
    - Premutation carriers of an expanded *FMR1* allele are at increased risk for ovarian insufficiency; see *FMR1*-Related Disorders.
    - Many females with BPES (*b*lepharophimosis, *p*tosis, *e*picanthus inversus *s*yndrome), caused by pathogenic variants or deletions of *FOXL2*, have POI. BPES can be distinguished from Perrault syndrome by the presence of marked blepharophimosis and ptosis in BPES.
    - Ovarian antibodies are increased in polyglandular autoimmune syndrome type 1 (OMIM 240300) and type 2 (OMIM 269200).

SNHL and POI

- *RMND1*-associated mitochondrial disease, which has a wide phenotypic range including SNHL, hypotonia, developmental delay, lactic acidemia, and renal dysfunction [Ng et al 2016] can present with features consistent with a diagnosis of Perrault syndrome [Demain et al 2018].
- The authors described a novel and likely rare cause of Perrault syndrome in a female who did not have pathogenic variants in any of the known Perrault syndrome-related genes [Faridi et al 2017]. She manifested SNHL and POI as a result of inheriting homozygous pathogenic variants in each of two distinct unlinked genes: *CLDN14* and *SGO2*. *CLDN14* is a well-known cause of autosomal recessive SNHL. Her POI was attributed to inactivating variants in *SGO2*, a gene not known to cause any human disorder but essential for meiosis and strongly implicated in infertility by studies in murine models. The variants of both *CLDN14* and *SGO2* were segregating in her multigenerational family; her parents were documented to be heterozygous for variants in both genes. Although relatives either manifested SNHL or were heterozygous for the *CLDN14* variant, she was the only female who had both SNHL and POI.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Perrault syndrome, 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 Perrault Syndrome

System/Concern	Evaluation	Comment
ENT [1]	Audiologic assessment	To define the degree & frequency range of hearing impairment by audiometry & physiologic tests (summarized in Genetic Hearing Loss Overview)
Neurologic [1]	Neurologic assessment	Determine if ataxia, peripheral neuropathy, &/or learning disability is present.
Endocrine [2]	Serum estrogen & gonadotropin (LH & FSH) concentrations	In women w/relatively intact ovarian function, serum anti-müllerian hormone concentrations may provide evidence of incipient ovarian failure. [3]
	Pelvic imaging	Ultrasound scan or magnetic resonance imaging to define the presence of ovaries & antral follicle count
Miscellaneous/ Other [1]	Consultation w/clinical geneticist &/or genetic counselor	

1. Men and women
2. Women only
3. De Vos et al [2010]

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Perrault Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Hearing loss	Possible interventions: • Hearing aids • Vibrotactile devices • Cochlear implantation [1]	• Assessment & treatment by multidisciplinary team incl: audiologist, otolaryngologist, speech therapist • Provide for any special educational needs. • Early intervention in young children w/profound hearing loss improves cognitive & language development.

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Ovarian insufficiency	In adolescents presenting w/primary amenorrhea, induction of puberty w/ incremental doses of estrogen	• In consultation w/pediatric endocrinologist • If puberty is complete, administer cyclic estrogen & progesterone to mimic menstrual cycle & trigger withdrawal bleeding. • Estrogen replacement therapy (if no contraindications) until age ≥50 yrs to ↓ risks of cardiovascular disease & osteoporosis
	Assisted reproduction through in vitro fertilization	• For women w/gonadal dysgenesis: consider assisted reproduction through in vitro fertilization using donor eggs. • For women at risk for ovarian insufficiency: consider oocyte cryopreservation if ovarian function is sufficiently well preserved to allow for successful harvesting of oocytes. • Consider use of donor eggs. • Before considering pregnancy, assess uterine size.

1. Cochlear implantation can be considered in children age >12 months with severe-to-profound hearing loss.

Surveillance

Table 5. Recommended Surveillance for Individuals with Perrault Syndrome

System/Concern	Evaluation	Frequency
Hearing	• Routine audiologic assessment for possible progressive hearing impairment • Audiologic surveillance not required for persons w/profound hearing loss	Annually
Musculoskeletal	Assess bone density in women on maintenance estrogen replacement therapy.	Every ~5 yrs
Endocrine	• Before puberty: clinical staging of puberty • During induction of puberty: adjustment of estrogen dose	Every 3 mos
	Women on maintenance estrogen replacement therapy: assessment of withdrawal bleeding & well being	Annually

Agents/Circumstances to Avoid

For individuals with hearing loss, avoid:

- Ototoxic medication such as aminoglycosides if alternatives are available;
- Exposure to loud noise, which may contribute to deterioration of hearing.

Evaluation of Relatives at Risk

It is appropriate to evaluate the older and younger sibs of a proband in order to identify as early as possible those who would benefit from early interventions (e.g., in young children with profound hearing loss, estrogen replacement to facilitate pubertal development in females with ovarian involvement, and potential oocyte cryopreservation if primary ovarian insufficiency is an issue). See Treatment of Manifestations.

- If the pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variants in the family are not known, screening of sibs should include audiologic assessment in males and females and baseline measurements of serum LH and FSH in females.

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 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

Perrault syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one Perrault syndrome-related pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The unaffected offspring of an individual with Perrault syndrome are obligate heterozygotes (carriers) for a pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a Perrault syndrome-related pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the pathogenic variants causing Perrault syndrome in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The increased risk for primary ovarian insufficiency and infertility in females with Perrault syndrome should be addressed when discussing family planning.
- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

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 biallelic *CLPP*, *ERAL1*, *HARS2*, *HSD17B4*, *LARS2*, or *TWNK* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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.

- **Action on Hearing Loss**
  United Kingdom
  Phone: 44 020 7296 8000; 0808 808 0123
  Email: informationline@hearingloss.org.uk
  www.actiononhearingloss.org.uk

- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)
  Fax: 202-337-8314
  Email: info@agbell.org
  Listening and Spoken Language Knowledge Center

- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org

- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org

- **RESOLVE: The National Infertility Association**
  Phone: 703-556-7172
  Email: info@resolve.org
  resolve.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. Perrault Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CLPP	19p13.3	ATP-dependent Clp protease proteolytic subunit, mitochondrial		CLPP	CLPP
ERAL1	17q11.2	GTPase Era, mitochondrial		ERAL1	ERAL1
HARS2	5q31.3	Histidine--tRNA ligase, mitochondrial		HARS2	HARS2
HSD17B4	5q23.1	Peroxisomal multifunctional enzyme type 2	HSD17B4 database	HSD17B4	HSD17B4
LARS2	3p21.31	Leucine--tRNA ligase, mitochondrial		LARS2	LARS2
TWNK	10q24.31	Twinkle mtDNA helicase		TWNK	TWNK

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 Perrault Syndrome (View All in OMIM)

233400	PERRAULT SYNDROME 1; PRLTS1
600783	HISTIDYL-tRNA SYNTHETASE 2; HARS2
601119	CASEINOLYTIC MITOCHONDRIAL MATRIX PEPTIDASE PROTEOLYTIC SUBUNIT; CLPP
601860	17-@BETA-HYDROXYSTEROID DEHYDROGENASE IV; HSD17B4
604544	LEUCYL-tRNA SYNTHETASE 2; LARS2
606075	TWINKLE mtDNA HELICASE; TWNK
607435	ERA G-PROTEIN-LIKE 1; ERAL1
614129	PERRAULT SYNDROME 3; PRLTS3
614926	PERRAULT SYNDROME 2; PRLTS2
615300	PERRAULT SYNDROME 4; PRLTS4
616138	PERRAULT SYNDROME 5; PRLTS5
617565	PERRAULT SYNDROME 6; PRLTS6

Molecular Pathogenesis

To date biallelic pathogenic variants in one of six genes – *CLPP, ERAL1, HARS2, HSD17B4, LARS2*, and *TWNK* – are known to cause Perrault syndrome. However, many cases of Perrault syndrome are not molecularly defined.

CLPP and *ERAL1* have roles in the formation of the mitochondrial ribosome; *HARS2* and *LARS2* are important for the translation of mitochondrial proteins; and *TWNK* maintains mitochondrial DNA. It is likely that defects of mitochondrial translation and protein homeostasis in the inner ear and ovary underlie the pathogenesis of Perrault syndrome.

CLPP

Gene structure. *CLPP* is predicted to generate four protein-coding transcripts. The longest transcript of 1194 bp (NM_006012.2) has six exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Initially three unrelated families – all of Pakistani ethnicity – were reported [Jenkinson et al 2013]. Affected individuals in each family were homozygous for the pathogenic variant c.433A>C, c.440G>C, or c.270+4A>G. Fewer than ten additional families from across the world have subsequently been reported, with biallelic missense variants. Six of ten *CLPP* pathogenic missense variants localized to a region of *CLPP* from amino acid residue 142 to 162, with a cluster around residues 144-147 [Demain et al 2017].

Theunissen et al [2016] reported three affected individuals who were compound heterozygous for at least one loss-of-function *CLPP* pathogenic variant and had more severe phenotypes (see Table 6).

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

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.270+4A>G		NM_006012.2 NP_006003.1
c.433A>C	p.Thr145Pro	
c.440G>C	p.Cys147Ser	

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. *CLPP* encodes ATP-dependent Clp protease proteolytic subunit, mitochondrial. The longest transcript encodes the longest isoform of CLPP with 277 amino acids (NP_006003.1).

Abnormal gene product. Crystal-structure modeling suggests that many of the pathogenic missense variants would alter the structure of the CLPP barrel chamber that captures unfolded or misfolded proteins and exposes them to proteolysis [Jenkinson et al 2013].

ERAL1

Gene structure. *ERAL1* is predicted to generate three protein-coding transcripts. The longest transcript of 1923 bp (NM_005702.3) is generated from ten exons. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Three families from a genetically isolated population of Dutch ancestry have been reported [Chatzispyrou et al 2017]. All affected individuals were homozygous for the missense variant c.707A>T.

Table 7. *ERAL1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.707A>T	p.Asn236Ile	NM_005702.2 NP_005693.1

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. *ERAL1* encodes GTPase Era, mitochondrial, an ERA-like protein 1 chaperone of mitochondrial 12s rRNA, which is essential for assembly of the mitochondrial 28s ribosomal subunit. The longest coding isoform of ERAL1 comprises 437 amino acids (NP_001304914).

Abnormal gene product. The c.707A>T variant is predicted to interfere with GTP binding in ERAL1 and, therefore, its interaction with mitochondrial 12S RNA. Affected individuals had reduced levels of mitochondrial 12S rRNA and of the 28S mitochondrial subunit.

HARS2

Gene structure. *HARS2* is predicted to be expressed as a number of transcript variants. The longest transcript of 2515 bp (NM_012208.3) is generated from 13 exons.

For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Three families with Perrault syndrome with pathogenic missense variants in *HARS2* have been reported. Two unrelated Moroccan families were reported with both affected individuals homozygous for c.1010A>G, which is suspected to be a founder variant due to shared haplotypes between affected individuals [Lerat et al 2016]. In a single family of European descent affected individuals were compound heterozygotes for c.598C>G and c.1102G>T [Pierce et al 2011].

Table 8. *HARS2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.598C>G [1]	p.Leu200Val [1]	NM_012208.3 NP_036340.1
c.1102G>T	p.Val368Leu	
c.1010A>G	p.Tyr337Cys	

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.
1. Created an alternate splice site leading to deletion of 12 codons [Pierce et al 2011]

Normal gene product. *HARS2* encodes probable histidine--tRNA ligase, mitochondrial. Variable protein-coding isoforms of HARS2 have been reported. The canonic transcript variant NM_012208.3 encodes the 506 amino acids of the isoform NP_036340.1.

Abnormal gene product. The pathogenic variants in *HARS2* reduced the aminoacylation activity of HARS2 [Pierce et al 2011].

HSD17B4

Gene structure. *HSD17B4* is predicted to encode multiple protein-coding transcripts. The canonic transcript comprises 2710 bp encoded by 24 exons (NM_000414.3). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Three families with Perrault syndrome with pathogenic missense variants in *HSD17B4* have been reported. Two affected sisters were compound heterozygotes for a nonsense and a missense variant, c.1704T>A and c.650A>G, respectively [Pierce et al 2010]. A single individual with PS was reported as compound heterozygous for the variants *HSD17B4* c.46G>A and c.244G>T [Demain et al 2017]. Affected individuals of a family were homozygous for the variant c.298G>T [Chen et al 2017]. The variant c.46G>A is associated with D-bifunctional protein deficiency [Demain et al 2017] (see Table 9, footnote 1).

Table 9. *HSD17B4* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.46G>A [1]	p.Gly16Ser	NM_000414.3 NP_000405.1
c.244G>T	p.Val82Phe	
c.298G>T	p.Ala100Ser	
c.650A>G	p.Tyr217Cys	
c.1704T>A	p.Tyr568Ter	

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.
1. The most common pathogenic variant causing D-bifunctional protein deficiency (see Table 2)

Normal gene product. *HSD17B4* encodes the peroxisomal multifunctional enzyme type 2 protein (HSD17B4), also known as bifunctional enzyme, hydroxysteroid (17-beta) dehydrogenase 4 and D-bifunctional protein (DBP). It is involved in fatty acid beta-oxidation and steroid metabolism. The canonic isoform (NP_000405.1) has 736 amino acid residues.

Abnormal gene product. The *HSD17B4* pathogenic missense variants in individuals with PS are predicted to destabilize the dehydrogenase domain of DBP or interrupt co-factor binding [Pierce et al 2010, Demain et al 2017]. Biallelic loss-of-function or pathogenic missense variants in *HSD17B4* may cause the allelic disorder D-bifunctional protein deficiency (see Table 2), which is more severe than Perrault syndrome and usually fatal in childhood. The variants associated with Perrault syndrome are thought to be less deleterious than those causing D-bifunctional protein deficiency, thus resulting in the milder phenotype.

LARS2

Gene structure. The longest *LARS2* transcript of 4203 bp (NM_015340.3) is generated from 21 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. A number of individuals with biallelic pathogenic variants in *LARS2* have been reported. Initially two individuals with Perrault syndrome were reported [Pierce et al 2013]: one with a homozygous pathogenic missense variant c.1565C>A, and another with a compound heterozygous frameshift variant c.1077delT and missense variant c.1886C>T (Table 10). The transversion c.1565C>A has been identified as a homozygous variant in two additional families and as a compound heterozygous variant in *trans* to c.351G>C in another family [Demain et al 2017, Zerkaoui et al 2017]. All four families with the variant c.1565C>A had low-frequency SNHL. The variant c.1886C>T has been reported in a second family in *trans* to the variant c.1358G>A. In a single family biallelic compound heterozygous variants in *LARS2* c.880G>A and c.1556C>T were associated with a neurologic phenotype.

Table 10. *LARS2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
c.351G>C	p.Met117Ile	NM_015340.3 NP_056155.1
c.880G>A	p.Glu294Lys	
c.1077delT	p.Ile360PhefsTer15 (Ile360fsTer)	
c.1358G>A	p.Arg453Gln	
c.1556C>T	p.Thr519Met	
c.1565C>A	p.Thr522Asn [2]	
c.1886C>T	p.Thr629Met	

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.
1. Variant designation that does not conform to current naming conventions
2. See Genotype-Phenotype Correlations.

Normal gene product. *LARS2* encodes mitochondrial leucyl-tRNA synthetase 2. The longest coding isoform of LARS2 is 903 amino acids (NP_056155.1).

Abnormal gene product. The p.Thr522Asn variant occurs in a catalytic domain and has been shown to reduce the aminoacylation activity of *LARS2* ninefold [Riley et al 2016]. Many of the other reported variants also lie in the catalytic domain and are predicted to reduce aminoacylation activity. The p.Thr629Met variant is in a site adjacent to a conserved catalytic loop [Pierce et al 2013].

TWNK

Gene structure. The longest *TWNK* transcript and major splice variant (NM_021830.4) comprises five exons and encodes the protein isoform twinkle (also known as isoform A).

Transcript variant NM_001163812.1 is a minor splice variant that encodes the distinct protein isoform known as twinky (also known as isoform B). This transcript results from the use of a downstream exon 4 splice-donor site and leads to a 43-bp insertion between the regular exon 4 - exon 5 sequence, which causes a premature stop codon [Spelbrink et al 2001]. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Biallelic variants in *TWNK* associated with Perrault syndrome were initially reported in affected individuals of two unrelated families who were compound heterozygotes for c.[1172G>A];[1754A>G] and c.[1321T>G];[1519G>A] [Morino et al 2014]. Additional affected individuals and variants have been reported, including c.1196A>G, which was reported in two unrelated families in *trans* to the variants c.968G>A [Demain et al 2017] and c.1802G>A [Ołdak et al 2017]. A family was also reported to be homozygous for the variant c. 793C>T. To date all affected individuals have reported neurologic features [Demain et al 2017, Ołdak et al 2017].

Table 11. *TWNK* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1172G>A	p.Arg391His	NM_021830.4 NP_068602.2
c.1754A>G	p.Asn585Ser	
c.1321T>G	p.Trp441Gly	
c.1519G>A	p.Val507Ile	
c.968G>A	p.Arg323Gln	
c.1196A>G	p.Asn399Ser	
c.1802G>A	p.Arg601Gln	
c. 793C>T	p.Arg265Cys	

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. *TWNK* encodes two splicing isoforms, twinkle and twinkie. Twinkle (NP_001157284.1) comprises 684 amino acids and forms hexamer complexes. Twinky (NP_068602.2) comprises 582 amino acids, shares the first 578 amino acids with twinkle, and terminates with four alternative amino acids. Twinkle is the mitochondrial DNA replicative helicase and localizes to mitochondrial nucleosomes. Twinkle contains three functional domains: a 3-prime helicase region, required for mtDNA replication; a linker region involved in hexamer formation; and a 5-primase domain. Twinkie has a mitochondrial localization and its function is currently unknown [Spelbrink et al 2001].

Abnormal gene product. Most of the pathogenic variants associated with Perrault syndrome are located in the linker and helicase domains of twinkle. Variants located in the linker region have been predicted to interfere with hexamer formation. Variants in the helicase region are predicted to affect the helicase function or interaction of subunits within the hexamer complex [Morino et al 2014, Demain et al 2017, Ołdak et al 2017].

Chapter Notes

Author Notes

Bill Newman is Professor of Translational Genomic Medicine at the University of Manchester. His main interests are in applying new technologies in clinical practice, the characterization of rare diseases, and pharmacogenetics. Web: www.research.manchester.ac.uk/en/persons/william.newman

Tom Friedman is Chief of the Laboratory of Molecular Genetics at the NIDCD/NIH. His goal is to identify and study the functions of genes associated with syndromic and nonsyndromic forms of deafness.

Gerard Conway is Professor of Reproductive Endocrinology at the Institute of Women's Health, University College London, UK. His clinical research interests are in the fields of reproductive endocrinology and disorders of development.

Leigh Demain is a Research Associate at the University of Manchester. Her research focuses on the genetic and molecular causes of Perrault syndrome.

Acknowledgments

Prof Newman's work is supported by Action on Hearing Loss. Prof Friedman is supported by the Intramural Program of the NIDCD.

Revision History

- 6 September 2018 (bp) Comprehensive update posted live
- 25 September 2014 (me) Review posted live
- 10 March 2014 (wn) Original submission

References

Literature Cited

Ahmed S, Jelani M, Alrayes N, Mohamoud HS, Almramhi MM, Anshasi W, Ahmed NA, Wang J, Nasir J, Al-Aama JY. Exome analysis identified a novel missense mutation in the CLPP gene in a consanguineous Saudi family expanding the clinical spectrum of Perrault syndrome type-3. J Neurol Sci. 2015;353:149–54. PubMed PMID: 25956234.

Chatzispyrou IA, Alders M, Guerrero-Castillo S, Zapata Perez R, Haagmans MA, Mouchiroud L, Koster J, Ofman R, Baas F, Waterham HR, Spelbrink JN, Auwerx J, Mannens MM, Houtkooper RH, Plomp AS. A homozygous missense mutation in ERAL1, encoding a mitochondrial rRNA chaperone, causes Perrault syndrome. Hum Mol Genet. 2017;26:2541–50. PubMed PMID: 28449065.

Chen K, Yang K, Luo SS, Chen C, Wang Y, Wang YX, Li DK, Yang YJ, Tang YL, Liu FT, Wang J, Wu JJ, Sun YM. A homozygous missense variant in HSD17B4 identified in a consanguineous Chinese Han family with type II Perrault syndrome. BMC Med Genet. 2017;18:91. PubMed PMID: 28830375.

Demain LA, Urquhart JE, O'Sullivan J, Williams SG, Bhaskar SS, Jenkinson EM, Lourenco CM, Heiberg A, Pearce SH, Shalev SA, Yue WW, Mackinnon S, Munro KJ, Newbury-Ecob R, Becker K, Kim MJ, O'Keefe RT, Newman WG. Expanding the genotypic spectrum of Perrault syndrome. Clin Genet. 2017;91:302–12. PubMed PMID: 26970254.

Demain LAM, Antunes D, O'Sullivan J, Bhaskhar SS, O'Keefe RT, Newman WG. A known pathogenic variant in the essential mitochondrial translation gene RMND1 causes a Perrault-like syndrome with renal defects. Clin Genet. 2018;94:276–7. PubMed PMID: 29671881.

De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. Lancet. 2010;376:911–21. PubMed PMID: 20708256.

Faridi R, Rehman AU, Morell RJ, Friedman PL, Demain L, Zahra S, Khan AA, Tohlob D, Assir MZ, Beaman G, Khan SN, Newman WG, Riazuddin S, Friedman TB. Mutations of SGO2 and CLDN14 collectively cause coincidental Perrault syndrome. Clin Genet. 2017;91:328–32. PubMed PMID: 27629923.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Jenkinson EM, Clayton-Smith J, Mehta S, Bennett C, Reardon W, Green A, Pearce SH, De Michele G, Conway GS, Cilliers D, Moreton N, Davis JR, Trump D, Newman WG. Perrault syndrome: further evidence for genetic heterogeneity. J Neurol. 2012;259:974–6. PubMed PMID: 22037954.

Jenkinson EM, Rehman AU, Walsh T, Clayton-Smith J, Lee K, Morell RJ, Drummond MC, Khan SN, Naeem MA, Rauf B, Billington N, Schultz JM, Urquhart JE, Lee MK, Berry A, Hanley NA, Mehta S, Cilliers D, Clayton PE, Kingston H, Smith MJ, Warner TT, Black GC, Trump D, Davis JR, Ahmad W, Leal SM, Riazuddin S, King MC, Friedman TB, Newman WG, et al. Perrault syndrome is caused by recessive mutations in CLPP, encoding a mitochondrial ATP-dependent chambered protease. Am J Hum Genet. 2013;92:605–13. PubMed PMID: 23541340.

King KA, Makishima T, Zalewski CK, Bakalov VK, Griffith AJ, Bondy CA, Brewer CC. Analysis of auditory phenotype and karyotype in 200 females with Turner syndrome. Ear Hear. 2007;28:831–41. PubMed PMID: 17982369.

Kosaki R, Horikawa R, Fujii E, Kosaki K. Biallelic mutations in LARS2 can cause Perrault syndrome type 2 with neurologic symptoms. Am J Med Genet A. 2018;176:404–8. PubMed PMID: 29205794.

Lerat J, Jonard L, Loundon N, Christin-Maitre S, Lacombe D, Goizet C, Rouzier C, Van Maldergem L, Gherbi S, Garabedian EN, Bonnefont JP, Touraine P, Mosnier I, Munnich A, Denoyelle F, Marlin S. An application of NGS for molecular investigations in Perrault syndrome: study of 14 families and review of the literature. Hum Mutat. 2016;37:1354–62. PubMed PMID: 27650058.

Morino H, Pierce SB, Matsuda Y, Walsh T, Ohsawa R, Newby M, Hiraki-Kamon K, Kuramochi M, Lee MK, Klevit RE, Martin A, Maruyama H, King MC, Kawakami H. Mutations in Twinkle primase-helicase cause Perrault syndrome with neurologic features. Neurology. 2014;83:2054–61. PubMed PMID: 25355836.

Ng YS, Alston CL, Diodato D, Morris AA, Ulrick N, Kmoch S, Houstek J, Martinelli D, Haghighi A, Atiq M, Gamero MA, Garcia-Martinez E, Kratochvilova H, Santra S, Brown RM, Brown GK, Ragge N, Monavari A, Pysden K, Ravn K, Casey JP, Khan A, Chakrapani A, Vassallo G, Simons C, McKeever K, O'Sullivan S, Childs AM, Ostergaard E, Vanderver A, Goldstein A, Vogt J, Taylor RW, McFarland R. The clinical, biochemical and genetic features associated with RMND1-related mitochondrial disease. J Med Genet. 2016;53:768–75. PubMed PMID: 27412952.

Ołdak M, Oziębło D, Pollak A, Stępniak I, Lazniewski M, Lechowicz U, Kochanek K, Furmanek M, Tacikowska G, Plewczynski D, Wolak T, Płoski R, Skarżyński H. Novel neuro-audiological findings and further evidence for TWNK involvement in Perrault syndrome. J Transl Med. 2017;15:25. PubMed PMID: 28178980.

Oliveira CS, Ribeiro FM, Lago R, Alves C. Audiological abnormalities in patients with turner syndrome. Am J Audiol. 2013;22:226–32. PubMed PMID: 23824435.

Pierce SB, Chisholm KM, Lynch ED, Lee MK, Walsh T, Opitz JM, Li W, Klevit RE, King MC. Mutations in mitochondrial histidyl tRNA synthetase HARS2 cause ovarian dysgenesis and sensorineural hearing loss of Perrault syndrome. Proc Natl Acad Sci USA. 2011;108:6543–8. PubMed PMID: 21464306.

Pierce SB, Gersak K, Michaelson-Cohen R, Walsh T, Lee MK, Malach D, Klevit RE, King MC, Levy-Lahad E. Mutations in LARS2, encoding mitochondrial leucyl-tRNA synthetase, lead to premature ovarian failure and hearing loss in Perrault syndrome. Am J Hum Genet. 2013;92:614–20. PubMed PMID: 23541342.

Pierce SB, Walsh T, Chisholm KM, Lee MK, Thornton AM, Fiumara A, Opitz JM, Levy-Lahad E, Klevit RE, King MC. Mutations in the DBP-deficiency protein HSD17B4 cause ovarian dysgenesis, hearing loss, and ataxia of Perrault Syndrome. Am J Hum Genet. 2010;87:282–8. PubMed PMID: 20673864.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Riley LG, Rudinger-Thirion J, Schmitz-Abe K, Thorburn DR, Davis RL, Teo J, Arbuckle S, Cooper ST, Campagna DR, Frugier M, Markianos K, Sue CM, Fleming MD, Christodoulou J. LARS2 variants associated with hydrops, lactic acidosis, sideroblastic anemia, and multisystem failure. JIMD Rep. 2016;28:49–57. PubMed PMID: 26537577.

Spelbrink JN, Li FY, Tiranti V, Nikali K, Yuan QP, Tariq M, Wanrooij S, Garrido N, Comi G, Morandi L, Santoro L, Toscano A, Fabrizi GM, Somer H, Croxen R, Beeson D, Poulton J, Suomalainen A, Jacobs HT, Zeviani M, Larsson C. Human mitochondrial DNA deletions associated with mutations in the gene encoding Twinkle, a phage T7 gene 4-like protein localized in mitochondria. Nat Genet. 2001;28:223–31. PubMed PMID: 11431692.

Theunissen TE, Szklarczyk R, Gerards M, Hellebrekers DM, Mulder-Den Hartog EN, Vanoevelen J, Kamps R, de Koning B, Rutledge SL, Schmitt-Mechelke T, van Berkel CG, van der Knaap MS, de Coo IF, Smeets HJ.

Specific MRI abnormalities reveal severe Perrault syndrome due to CLPP defects. Front Neurol. 2016;7:203. PubMed PMID: 27899912.

van Grunsven EG, van Berkel E, Mooijer PA, Watkins PA, Moser HW, Suzuki Y, Jiang LL, Hashimoto T, Hoefler G, Adamski J, Wanders RJ. Peroxisomal bifunctional protein deficiency revisited: resolution of its true enzymatic and molecular basis. Am J Hum Genet. 1999;64:99–107. PubMed PMID: 9915948.

Zerkaoui M, Demain LAM, Cherkaoui Jaouad I, Ratbi I, Amjoud K, Urquhart JE, O'Sullivan J, Newman WG, Sefiani A. Marfanoid habitus is a nonspecific feature of Perrault syndrome. Clin Dysmorphol. 2017;26:200–4. PubMed PMID: 28832386.

License