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17q12 Recurrent Duplication

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Summary

Clinical characteristics

The 17q12 recurrent duplication is characterized by intellectual abilities ranging from normal to severe disability and other variable clinical manifestations. Speech delay is common, and most affected individuals have some degree of hypotonia and gross motor delay. Behavioral and psychiatric conditions reported in some affected individuals include autism spectrum disorder, schizophrenia, and behavioral abnormalities (aggression and self-injury). Seizures are present in 75%. Additional common findings include microcephaly, ocular abnormalities, and endocrine abnormalities. Short stature and renal and cardiac abnormalities are also reported in some individuals. Penetrance is incomplete and clinical findings are variable.

Diagnosis/testing

The diagnosis is established in a proband by detection of the 1.4-megabase heterozygous recurrent duplication at chromosome 17q12 by chromosomal microarray testing or other genomic methods.

Management

Treatment of manifestations: Those with developmental delays, cognitive disability, and/or behavioral issues should be evaluated by a neurodevelopmental pediatrician or clinical psychologist/psychiatrist. Seizures should be managed by a neurologist using standard practice. Feeding therapy as needed. Individuals with vision, endocrine, cardiac, and/or renal abnormalities should be managed by the appropriate specialist.

Surveillance: Regular assessment of psychomotor development is recommended for all children with the 17q12 recurrent duplication as well as psychological evaluation in both affected children and adults. Monitor for new-onset seizures, growth and nutritional assessment, and assessment of family needs at each visit.

Evaluation of relatives at risk: Presymptomatic diagnosis and treatment is warranted in at-risk relatives to identify as early as possible those who would benefit from close assessment/monitoring of developmental milestones in childhood or psychological assessment/intervention through adulthood.

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Genetic counseling

The 17q12 recurrent duplication is inherited in an autosomal dominant manner, with approximately 10% of duplications occurring *de novo* and approximately 90% inherited from a parent who is often minimally affected or phenotypically normal. Prenatal testing for an at-risk pregnancy requires prior identification of the duplication in an affected family member. Interpretation of results from prenatal testing is challenging given the inherent difficulty in accurately predicting the phenotype.

Diagnosis

Suggestive Findings

The 17q12 recurrent duplication **should be suspected** in individuals with the following:

- Intellectual disability
- Developmental delays
- Seizures
- Ocular anomalies and/or vision problems
- Cardiac malformations
- Renal malformations
- Gastrointestinal abnormalities (e.g., duodenal obstruction)

Establishing the Diagnosis

The diagnosis of the 17q12 recurrent duplication **is established** in a proband by detection of the 1.4-Mb heterozygous duplication at chromosome 17q12 (see Table 1 and Molecular Genetics).

For this *GeneReview*, the 17q12 recurrent duplication is defined as the presence of a recurrent 1.4-Mb heterozygous duplication at the approximate position of chr17:36459259-37832869 in the reference genome (NCBI Build GRCh38/hg38).

Note: The phenotype of significantly larger or smaller duplications or deletions within this region may be clinically distinct from the 17q12 recurrent duplication (see Genetically Related Disorders).

For information on the 15 known genes within the 17q12 region see Molecular Genetics.

Genomic testing methods that determine the copy number of sequences can include **chromosomal microarray (CMA)** or **targeted deletion analysis**.

Note: The 17q12 recurrent duplication is **submicroscopic** and cannot be identified by routine analysis of G-banded chromosomes or other conventional cytogenetic banding techniques.

- **CMA** using oligonucleotide or SNP arrays can detect the recurrent duplication in a proband. The ability to size the duplication depends on the type of microarray used and the density of probes in the 17q12 region.

  Note: (1) Most individuals with the 17q12 recurrent duplication are identified by CMA performed in the context of developmental delay, intellectual disability, and/or autism spectrum disorders. (2) Prior to 2008, many CMA platforms did not include coverage for this region and thus may not have detected this duplication.

- **Targeted duplication analysis.** FISH analysis, quantitative PCR (qPCR), multiplex ligation-dependent probe amplification (MLPA), or other targeted quantitative methods may be used to test relatives of a proband who is known to have the 17q12 recurrent duplication.

Note: (1) Targeted duplication testing is not appropriate for an individual in whom the 17q12 recurrent duplication was not detected by CMA designed to target this region. (2) It is not possible to size the duplication routinely by use of targeted methods.

Table 1. Genomic Testing Used in the 17q12 Recurrent Duplication

Duplication [1]	Method	Sensitivity	
		Proband	At-risk family members
1.4-Mb heterozygous duplication at 17q12 ISCN: seq[GRCh38] del(17)(q12) chr17:36,459,259-37,832,869 del [2] ClinGen ID: ISCA-37432	CMA [3]	100%	100%
	Targeted duplication analysis [4]	NA [5]	Up to 100% [6]

NA = not applicable

1. See Molecular Genetics for details of the duplication and genes of interest included in the region.

2. Standardized clinical annotation and interpretation for genomic variants from the Clinical Genome Resource (ClinGen) project (formerly the International Standards for Cytogenomic Arrays (ISCA) Consortium). The region is identified in dbVar (www.ncbi.nlm.nih.gov/dbvar) as nsv491563. Genomic coordinates represent the minimum duplication size associated with the 17q12 recurrent duplication as designated by ClinGen. Duplication coordinates may vary slightly based on array design used by the testing laboratory. Note that the size of the duplication as calculated from these genomic positions may differ from the expected duplication size due to the presence of segmental duplications near breakpoints. The phenotype of significantly larger or smaller duplications within this region may be clinically distinct from that of the recurrent 17q12 duplication (see Genetically Related Disorders).

3. Chromosomal microarray analysis (CMA) using oligonucleotide or SNP arrays. CMA designs in current clinical use target the 17q12 region. Note: The 17q12 recurrent duplication may not have been detectable by older oligonucleotide or BAC platforms.

4. Targeted duplication analysis methods can include FISH, quantitative PCR (qPCR), and multiplex ligation-dependent probe amplification (MLPA) as well as other targeted quantitative methods.

5. Targeted duplication analysis is not appropriate for an individual in whom the 17q12 recurrent duplication was not detected by CMA designed to target this region.

6. Targeted duplication analysis may be used to test at-risk relatives of a proband known to have the 17q12 recurrent duplication.

Clinical Characteristics

Clinical Description

To date, published reports include 86 individuals with the 17q12 recurrent duplication, along with some phenotypic data [Sharp et al 2006, Mefford et al 2007, Mencarelli et al 2008, Nagamani et al 2010, Faguer et al 2011, Brandt et al 2012, Bierhals et al 2013, Girirajan et al 2013, Hardies et al 2013, Smigiel et al 2014, Casey et al 2015, Mitchell et al 2015, Rasmussen et al 2016, Kamath et al 2018, Kotalova et al 2018, Zhang et al 2021, Zhou et al 2021]. Individuals found to have this rare duplication were typically referred for testing because of intellectual disability and/or developmental delays, and occasionally because of multiple congenital anomalies. The 17q12 recurrent duplication likely also has reduced penetrance and variable expressivity since it is inherited in most instances from a parent with findings reported to be minimally abnormal or normal.

Table 2. Frequency of Phenotypic Features in 86 Reported Individuals with 17q12 Recurrent Duplication

Phenotypic Feature	% of Persons with Feature
Intellectual disability	71%
Speech delay	65%
Gross motor delay	49%
OFC <5th centile	41%
Behavioral abnormalities	62%
Seizures/epilepsy	36%
Hypotonia	73%

Table 2. continued from previous page.

Phenotypic Feature	% of Persons with Feature
Other neurologic abnormalities	85%
Height <5th centile	22%
Ophthalmologic abnormalities	28%
Weight <5th centile	21%
Endocrine abnormalities	26%
Weight >95th centile	13%
Cardiac abnormalities	14%
Renal abnormalities	20%
Height >95th centile	6%

Based on Mitchell et al [2015] and two cases published subsequently by Bertini et al [2015], Rasmussen et al [2016], Kamath et al [2018], Zhou et al [2021]

Developmental delay (DD) and intellectual disability (ID). Intellectual abilities range from normal to severe ID. The majority of affected individuals (71%) are reported to have delays or ID. However, the true incidence may be lower given variable expressivity and the ascertainment bias that is present due to the fact that most individuals who are found to have the 17q12 duplication are referred because of DD or ID. Speech delay is common (65%). Most affected individuals (49%-73%) have some degree of hypotonia and gross motor delay.

Behavioral and psychiatric conditions reported in a subset of affected individuals are autism spectrum disorder, schizophrenia, and behavioral abnormalities (including aggression, self-injurious behaviors, and compulsive disorders).

Seizures are reported in 36% of affected individuals.

Brain MRI occasionally reveals abnormalities including focal cortical dysplasia, agenesis of the corpus callosum, periventricular leukomalacia, and schizencephaly.

Microcephaly is reported in approximately 40% of individuals.

Eye and/or vision abnormalities including strabismus, astigmatism, amblyopia, cataract, coloboma, and microphthalmia occur in up to 28% of individuals.

Growth is variable. Both short (22%) and tall (6%) stature have been reported. Prenatal detection of short femur and humerus was reported in one fetus.

Endocrine abnormalities, reported in 26% of individuals, are variable and include diabetes insipidus, type 2 diabetes, growth hormone deficiency, hypoglycemia, hyponatremia and hyperkalemia, and pseudohypoaldosteronism.

Cardiac. The most common reported congenital heart defect is a small ventricular septal defect.

Renal abnormalities, present in approximately 20% of individuals, include horseshoe kidney, renal cysts, and hypoplastic kidneys.

Facial features. No specific dysmorphic features have been consistently observed. If present, dysmorphic features are nonspecific.

Other

- Tracheoesophageal fistula has been reported in three individuals.

- Duodenal atresia has been reported in three individuals.

Penetrance

The penetrance of the 17q12 recurrent duplication has not been established. Although an estimated penetrance of approximately 21% has been proposed [Rosenfeld et al 2013], the majority of 17q12 recurrent duplications are inherited from a parent who is often minimally affected or phenotypically normal, making the true penetrance difficult to ascertain.

Prevalence

In four studies of apparently unaffected controls, the 17q12 recurrent duplication was present in 1:2443 individuals [International Schizophrenia Consortium 2008, Itsara et al 2009, Shaikh et al 2009, Moreno-De-Luca et al 2010]. In a population study of 101,655 individuals from Iceland, the prevalence was 1:2,675 [Stefansson et al 2014].

In two different studies of individuals with intellectual disability, developmental delay or autism, the 17q12 recurrent duplication was reported in 5:2,034 (0.25%) individuals [Mitchell et al 2015] and 21:15,749 (0.13%) [Moreno-De-Luca et al 2010]; however, the frequency is much lower when accounting for all samples submitted in a clinical laboratory setting (19:22,231 [0.085%]) [Mitchell et al 2015].

In a cohort of individuals with schizophrenia, the 17q12 recurrent duplication was identified in 4:4,719 (0.08%) individuals [Szatkiewicz et al 2014].

Genetically Related Disorders

17q12 recurrent deletion syndrome. Reciprocal deletion of the same 17q12 region is characterized by variable combinations of the three following findings: structural or functional abnormalities of the kidney and urinary tract, maturity-onset diabetes of the young type 5 (MODY5), and neurodevelopmental or neuropsychiatric disorders (e.g., developmental delay, intellectual disability, autism spectrum disorder, schizophrenia, anxiety, bipolar disorder). The 17q12 recurrent deletion is inherited in an autosomal dominant manner, with approximately 75% of deletions occurring *de novo* and approximately 25% inherited from a parent. The deletion is highly penetrant but expressivity is variable.

Differential Diagnosis

The differential diagnosis of the 17q12 recurrent duplication is broad due to the clinical variability and the presence of relatively common abnormal phenotypes that occur in affected individuals including developmental delay, intellectual disability (ID), epilepsy, behavioral abnormalities, and microcephaly. All chromosome anomalies and genes known to be associated with ID (see OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series) should be included in the differential diagnosis of the 17q12 recurrent duplication.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with the 17q12 recurrent duplication, 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 17q12 Recurrent Duplication

System/Concern	Evaluation	Comment
Constitutional	Growth assessment	
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	In persons age >12 mos: screen for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD.
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern.
Gastrointestinal/ Feeding	Consultation w/gastroenterologist &/or feeding team for GI concerns, suspected dysphagia, or feeding difficulties	
Eyes	Ophthalmologic eval	To assess for ↓ vision, abnormal ocular movement, strabismus
Endocrine	Assess for growth issues, dehydration, & signs/ symptoms of diabetes or electrolyte disturbances.	
Cardiovascular	Echocardiogram	
Renal	Kidney ultrasound exam	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of 17q12 recurrent duplication in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; GI = gastrointestinal; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with 17q12 Recurrent Duplication

Manifestation/Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Psychiatric/ behavioral disorders		
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Poor weight gain / Failure to thrive	Feeding therapy	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Abnormal vision &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	Community vision services through early intervention or school district

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Central visual impairment	No specific treatment; early intervention to stimulate visual development	
Endocrine	Treatment per endocrinologist	
Cardiac anomalies	Treatment per cardiologist	
Renal anomalies	Treatment per nephrologist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; DD/ID = developmental delay / intellectual disability
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.

- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US 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

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

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 5. Recommended Surveillance for Individuals with 17q12 Recurrent Duplication

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Psychiatric/ Behavioral	Assessment for anxiety, attention, & aggressive or self-injurious behavior	
Neurologic	• Assess for new seizures. • Monitor those w/seizures as clinically indicated.	
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Eyes	Ophthalmology exam	Frequency as recommended by ophthalmologist
Endocrine	Monitor for signs/symptoms of endocrinologic disorders; evaluate as needed.	At each visit
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

Evaluation of Relatives at Risk

Consider genomic testing of sibs of a proband who is known to have the 17q12 recurrent duplication in order to refer sibs with a duplication promptly for close assessment/monitoring of developmental milestones in childhood and psychological issues through adulthood.

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.

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

The 17q12 recurrent duplication is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 90% of individuals with a 17q12 recurrent duplication inherited the genetic alteration from a parent. In many instances, the parent with the 17q12 recurrent duplication is phenotypically normal or minimally affected; in parents with features associated with the 17q12 recurrent duplication, reported manifestations range from mild cognitive impairment to learning difficulties, seizures, and mental illness.
- The 17q12 recurrent duplication is *de novo* in approximately 10% of probands.
- Genomic testing that will detect the 17q12 recurrent duplication present in the proband is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the 17q12 recurrent duplication identified in the proband is not identified in either confirmed biological parent, the following possibilities should be considered:
  - The proband has a *de novo* duplication.
  - The proband inherited a duplication from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.

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

- If one of the parents has the 17q12 recurrent duplication identified in the proband, the risk to each sib of inheriting the duplication is 50%. It is not possible to predict the phenotype in sibs who inherit a 17q12 recurrent duplication because a wide spectrum of manifestations may be observed in family members with the duplication, ranging from no or mild cognitive impairment to learning difficulties, seizures, and mental illness.
- If the 17q12 recurrent duplication identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is low (<1%) but greater than that of the general population because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with the 17q12 recurrent duplication has a 50% chance of inheriting the duplication; it is not possible to predict the phenotype in offspring who inherit the duplication.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the 17q12 recurrent duplication, the parent's family members may also have the duplication.

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 optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are at risk of having a child with a 17q12 recurrent duplication.

Prenatal Testing and Preimplantation Genetic Testing

Pregnancies known to be at increased risk for the 17q12 recurrent duplication. Once a 17q12 recurrent duplication has been identified in a family member, prenatal and preimplantation genetic testing are possible.

Pregnancies not known to be at increased risk for the 17q12 recurrent duplication. CMA performed in a pregnancy for other indications (e.g., advanced maternal age) may detect the recurrent 17q12 duplication.

Note: Regardless of whether a pregnancy is known or not known to be at increased risk for the 17q12 recurrent duplication, the prenatal finding of a 17q12 recurrent duplication cannot be used to predict the phenotype.

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.

- **17q12 Foundation**

  Email: chromosome17q12@gmail.com

  www.chromo17q12.org

- **Chromosome Disorder Outreach Inc.**
  Phone: 561-395-4252
  Email: info@chromodisorder.org
  chromodisorder.org
- **Unique: Understanding Rare Chromosome and Gene Disorders**
  United Kingdom
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  rarechromo.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. 17q12 Recurrent Duplication: Genes and Databases

Gene	Chromosome Locus	Protein	ClinVar
Not applicable	17q12	Not applicable	

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 17q12 Recurrent Duplication (View All in OMIM)

614526	CHROMOSOME 17q12 DUPLICATION SYNDROME

Molecular Pathogenesis

Duplication mechanism. The 17q12 recurrent duplication region is flanked by segmental duplications (low copy repeats) and is therefore susceptible to nonallelic homologous recombination (NAHR) [Sharp et al 2006]. The breakpoints of the recurrent duplication lie within the segmental duplication regions.

Genes of interest in this region. The 1.4-Mb 17q12 recurrent duplication contains 15 unique genes (*AATF*, *ACACA*, *C17orf78*, *DDX52*, *DHRS11*, *DUSP14*, *GGNBP2*, *HNF1B*, *LHX1*, *MRM1*, *MYO19*, *PIGW*, *SYNRG*, *TADA2A*, and *ZNHIT3*). It is not known which gene(s) may be responsible for the phenotypic features seen in individuals with the 17q12 recurrent duplication.

Pathogenic variants in (or deletion of) *HNF1B* are associated with renal cysts and diabetes syndrome, and pathogenic variants in *LHX1* have been described in individuals with müllerian aplasia / Mayer-Rokitansky-Küster-Hauser syndrome. However, whether or how pathogenic variants in these genes contribute to phenotypes associated with the 17q12 recurrent duplication is unknown.

Chapter Notes

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- 13 January 2022 (aa) Revision: percentage of probands with duplications occurring *de novo* corrected to 10% in Genetic Counseling
- 29 April 2021 (sw) Comprehensive update posted live
- 25 February 2016 (bp) Review posted live
- 5 October 2015 (jh) Original submission

References

Literature Cited

Bertini V, Orsini A, Bonuccelli A, Cambi F, Del Pistoia M, Vannozzi I, Toschi B, Saggese G, Simi P, Valetto A. 17q12 Microduplications: A challenge for clinicians. Am J Med Genet Part A. 2015;167A:674–6. PubMed PMID: 25691423.

Bierhals T, Maddukuri SB, Kutsche K, Girisha KM. Expanding the phenotype associated with 17q12 duplication: case report and review of the literature. Am J Med Genet A. 2013;161A:352–9. PubMed PMID: 23307502.

Brandt T, Desai K, Grodberg D, Mehta L, Cohen N, Tryfon A, Kolevzon A, Soorya L, Buxbaum JD, Edelmann L. Complex autism spectrum disorder in a patient with a 17q12 microduplication. Am J Med Genet A. 2012;158A:1170–7. PubMed PMID: 22488896.

Casey JP, Goggin P, McDaid J, White M, Ennis S, Betts DR, Lucas JS, Elnazir B, Lynch SA. A case report of primary ciliary dyskinesia, laterality defects and developmental delay caused by the co-existence of a single gene and chromosome disorder. BMC Med Genet. 2015;16:45. PubMed PMID: 26123568.

Faguer S, Chassaing N, Bandin F, Prouheze C, Arveiler B, Rooryck C, Nogier MB, Chauveau D, Calvas P, Decramer S. A 17q12 chromosomal duplication associated with renal disease and esophageal atresia. Eur J Med Genet. 2011;54:e437–40. PubMed PMID: 21540130.

Girirajan S, Dennis MY, Baker C, Malig M, Coe BP, Campbell CD, Mark K, Vu TH, Alkan C, Cheng Z, Biesecker LG, Bernier R, Eichler EE. Refinement and discovery of new hotspots of copy-number variation associated with autism spectrum disorder. Am J Hum Genet. 2013;92:221–37. PubMed PMID: 23375656.

Hardies K, Weckhuysen S, Peeters E, Holmgren P, Van Esch H, De Jonghe P, Van Paesschen W, Suls A. Duplications of 17q12 can cause familial fever-related epilepsy syndromes. Neurology. 2013;81:1434–40. PubMed PMID: 24049133.

International Schizophrenia Consortium. Rare chromosomal deletions and duplications increase risk of schizophrenia. Nature. 2008;455:237–41. PubMed PMID: 18668038.

Itsara A, Cooper GM, Baker C, Girirajan S, Li J, Absher D, Krauss RM, Myers RM, Ridker PM, Chasman DI, Mefford H, Ying P, Nickerson DA, Eichler EE. Population analysis of large copy number variants and hotspots of human genetic disease. Am J Hum Genet. 2009;84:148–61. PubMed PMID: 19166990.

Kamath A, Linden SC, Evans FM, Hall J, Jose SF, Spillane SA, Hardie ADR, Morgan SM, Pilz DT. Chromosome 17q12 duplications: further delineation of the range of psychiatric and clinical phenotypes. Am J Med Genet B Neuropsychiatr Genet. 2018;177:520–8. PubMed PMID: 30134084.

Kotalova R, Dusatkova P, Drabova J, Elblova L, Dedic T, Cinek O, Lebl J, Pruhova S. Choledochal cyst with 17q12 chromosomal duplication. Ann Hum Genet. 2018;82:48–51. PubMed PMID: 28940454.

Mefford HC, Clauin S, Sharp AJ, Moller RS, Ullmann R, Kapur R, Pinkel D, Cooper GM, Ventura M, Ropers HH, Tommerup N, Eichler EE, Bellanne-Chantelot C. Recurrent reciprocal genomic rearrangements of 17q12 are associated with renal disease, diabetes, and epilepsy. Am J Hum Genet. 2007;81:1057–69. PubMed PMID: 17924346.

Mencarelli MA, Katzaki E, Papa FT, Sampieri K, Caselli R, Uliana V, Pollazzon M, Canitano R, Mostardini R, Grosso S, Longo I, Ariani F, Meloni I, Hayek J, Balestri P, Mari F, Renieri A. Private inherited microdeletion/microduplications: implications in clinical practice. Eur J Med Genet. 2008;51:409–16. PubMed PMID: 18657637.

Mitchell E, Douglas A, Kjaegaard S, Callewaert B, Vanlander A, Janssens S, Lawson Yuen A, Skinner C, Failla P, Alberti A, Avola E, Fichera M, Kibaek M, Digilio MC, Hannibal MC, Den Hollander NS, Bizzarri V, Renieri A, Mencarelli MA, Fitzgerald T, Piazzolla S, Van Oudenhove E, Romano C, Schwartz C, Eichler EE, Slavotinek A, Escobar L, Rajan D, Crolla J, Carter N, Hodge JC, Mefford HC. Recurrent duplications of 17q12 associated with variable phenotypes. Am J Med Genet A. 2015;167A:3038–45. PubMed PMID: 26420380.

Moreno-De-Luca D, Mulle JG, Kaminsky EB, Sanders SJ, Myers SM, Adam MP, Pakula AT, Eisenhauer NJ, Uhas K, Weik L, Guy L, Care ME, Morel CF, Boni C, Salbert BA, Chandrareddy A, Demmer LA, Chow EW, Surti U, Aradhya S, Pickering DL, Golden DM, Sanger WG, Aston E, Brothman AR, Gliem TJ, Thorland EC, Ackley T, Iyer R, Huang S, Barber JC, Crolla JA, Warren ST, Martin CL, Ledbetter DH, et al. Deletion 17q12 is a recurrent copy number variant that confers high risk of autism and schizophrenia. Am J Hum Genet. 2010;87:618–30. PubMed PMID: 21055719.

Nagamani SC, Erez A, Shen J, Li C, Roeder E, Cox S, Karaviti L, Pearson M, Kang SH, Sahoo T, Lalani SR, Stankiewicz P, Sutton VR, Cheung SW. Clinical spectrum associated with recurrent genomic rearrangements in chromosome 17q12. Eur J Hum Genet. 2010;18:278–84. PubMed PMID: 19844256.

Rasmussen M, Vestergaard EM, Graakjaer J, Petkov Y, Bache I, Fagerberg C, Kibaek M, Svaneby D, Petersen OB, Brasch-Andersen C, Sunde L. 17q12 deletion and duplication syndrome in Denmark-A clinical cohort of 38 patients and review of the literature. Am J Med Genet A. 2016;170:2934–42. PubMed PMID: 27409573.

Rosenfeld JA, Coe BP, Eichler EE, Cuckle H, Shaffer LG. Estimates of penetrance for recurrent pathogenic copy-number variations. Genet Med. 2013;15:478–81. PubMed PMID: 23258348.

Shaikh TH, Gai X, Perin JC, Glessner JT, Xie H, Murphy K, O'hara R, Casalunovo T, Conlin LK, D'arcy M, Frackelton EC, Geiger EA, Haldeman-Englert C, Imielinski M, Kim CE, Medne L, Annaiah K, Bradfield JP, Dabaghyan E, Eckert A, Onyiah CC, Ostapenko S, Otieno FG, Santa E, Shaner JL, Skraban R, Smith RM, Elia J, Goldmuntz E, Spinner NB, Zackai EH, Chiavacci RM, Grundmeier R, Rappaport EF, Grant SF, White PS, Hakonarson H. High-resolution mapping and analysis of copy number variations in the human genome: a data resource for clinical and research applications. Genome Res. 2009;19:1682–90. PubMed PMID: 19592680.

Sharp AJ, Hansen S, Selzer RR, Cheng Z, Regan R, Hurst JA, Stewart H, Price SM, Blair E, Hennekam RC, Fitzpatrick CA, Segraves R, Richmond TA, Guiver C, Albertson DG, Pinkel D, Eis PS, Schwartz S, Knight SJ, Eichler EE. Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome. Nat Genet. 2006;38:1038–42. PubMed PMID: 16906162.

Smigiel R, Marcelis C, Patkowski D, De Leeuw N, Bednarczyk D, Barg E, Mascianica K, Maria Sasiadek M, Brunner H. Oesophageal atresia with tracheoesophageal fistula and anal atresia in a patient with a de novo microduplication in 17q12. Eur J Med Genet. 2014;57:40–3. PubMed PMID: 24239950.

Stefansson H, Meyer-Lindenberg A, Steinberg S, Magnusdottir B, Morgen K, Arnarsdottir S, Bjornsdottir G, Walters GB, Jonsdottir GA, Doyle OM, Tost H, Grimm O, Kristjansdottir S, Snorrason H, Davidsdottir SR, Gudmundsson LJ, Jonsson GF, Stefansdottir B, Helgadottir I, Haraldsson M, Jonsdottir B, Thygesen JH, Schwarz AJ, Didriksen M, Stensbøl TB, Brammer M, Kapur S, Halldorsson JG, Hreidarsson S, Saemundsen E, Sigurdsson E, Stefansson K. CNVs conferring risk of autism or schizophrenia affect cognition in controls. Nature. 2014;505:361–6. PubMed PMID: 24352232.

Szatkiewicz JP, O'Dushlaine C, Chen G, Chambert K, Moran JL, Neale BM, Fromer M, Ruderfer D, Akterin S, Bergen SE, Kähler A, Magnusson PK, Kim Y, Crowley JJ, Rees E, Kirov G, O'Donovan MC, Owen MJ,

Walters J, Scolnick E, Sklar P, Purcell S, Hultman CM, McCarroll SA, Sullivan PF. Copy number variation in schizophrenia in Sweden. Mol Psychiatry. 2014;19:762–73. PubMed PMID: 24776740.

Zhang W, Lei T, Fu F, Deng Q, Li R, Wang D, Yang X, Li D, Liao C. Microarray analysis in fetuses with duodenal obstruction: It is not just trisomy 21. Prenat Diagn. 2021;41:316–22. PubMed PMID: 33000500.

Zhou CX, Zhu XY, Zhu YJ, Gu LL, He LL, Liu W, Yang Y, Wu X, Duan HL, Ru T, Li J. Prenatal features of 17q12 microdeletion and microduplication syndromes: A retrospective case series. Taiwan J Obstet Gynecol. 2021;60:232–7. PubMed PMID: 33678321.

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