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NLM Citation: Mitchel MW, Moreno-De-Luca D, Myers SM, et al. 17q12 Recurrent Deletion Syndrome. 2016 Dec 8 [Updated 2020 Oct 15]. 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/

17q12 Recurrent Deletion Syndrome

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Created: December 8, 2016; Updated: October 15, 2020.

Summary

Clinical characteristics

The 17q12 recurrent deletion syndrome 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, and bipolar disorder). Using a method of data analysis that avoids ascertainment bias, the authors determined that multicystic kidneys and other structural and functional kidney anomalies occur in 85% to 90% of affected individuals, MODY5 in approximately 40%, and some degree of developmental delay or learning disability in approximately 50%. MODY5 is most often diagnosed before age 25 years (range: age 10-50 years).

Diagnosis/testing

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

Management

Treatment of manifestations: Treatment of kidney anomalies, neurodevelopmental and neuropsychiatric disorders, MODY5, genital tract abnormalities, liver abnormalities, eye abnormalities, congenital heart defects, seizures and sensorineural hearing loss should follow standard practice.

Surveillance: Kidneys and urinary tract: In the absence of known structural abnormalities, kidney and bladder ultrasound examination 12 months after establishing the diagnosis, then every 2-3 years in childhood/adolescence, then every 3-5 years in adulthood; presence of an abnormality may warrant more frequent monitoring. Annual monitoring of kidney function in individuals with abnormalities detected on kidney

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ultrasound examination; more frequent monitoring may be advised in those taking potentially nephrotoxic medications and/or known to have impaired kidney function. Routine monitoring of neurodevelopment through early childhood; full neuropsychological evaluation for children who experience difficulty with school. HbA1C annually to monitor for MODY5; self-monitoring by individuals and their families for clinical signs and symptoms of diabetes mellitus, such as polydipsia and polyuria. Consider reevaluation for uterine and vaginal abnormalities related to müllerian duct aplasia in pubertal females with primary amenorrhea. Consider annual hepatic function panel (or comprehensive metabolic panel), GGT, and lipid panel. Annual ophthalmologic evaluation during early childhood. Monitor those with seizures as clinically indicated. Hearing screening throughout childhood.

Agents/circumstances to avoid: Because kidney transplantation increases the risk for post-transplant diabetes mellitus, an immunosuppressive regimen that avoids tacrolimus and mammalian target of rapamycin (mTOR) inhibitors and reduces corticosteroid exposure may benefit those without preexisting diabetes mellitus. Nephrotoxic and hepatotoxic drugs should be avoided by individuals with kidney or liver abnormalities. For individuals with mental health conditions such as autism, schizophrenia, or bipolar disorder, careful consideration of antipsychotic agents that may lead to weight gain is recommended, as this potential increase has been associated with metabolic syndrome and the later development of diabetes mellitus, for which people with 17q12 deletions are at baseline increased risk. Likewise, the use of mood stabilizers that affect kidney function in the long term, such as lithium, should be carefully considered in the setting of potential underlying anatomic and functional abnormalities in people with 17q12 deletions.

Evaluation of relatives at risk: If one of the proband's parents has the 17q12 recurrent deletion, it is appropriate to test older and younger sibs of the proband and other relatives at risk in order to identify those who would benefit from close assessment/monitoring for evidence of genitourinary structural or functional defects, MODY5, and developmental delays / intellectual disability.

Genetic counseling

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. If the 17q12 recurrent deletion identified in the proband is not found in one of the parents, the risk to sibs is presumed to be lower than 1% (but slightly greater than that of the general population because of the theoretic possibility of parental germline mosaicism for the deletion). Offspring of an individual with the 17q12 recurrent deletion have a 50% chance of inheriting the deletion. Prenatal testing and preimplantation genetic testing using genomic testing that will detect the 17q12 recurrent deletion are possible.

Diagnosis

Suggestive Findings

17q12 recurrent deletion syndrome **should be suspected** in individuals with any of the following clinical and laboratory findings.

Clinical findings

- **Kidney abnormalities**
  - Congenital abnormalities of the kidney and urinary tract (CAKUT), including the following:
    - Abnormalities on prenatal imaging including hyperechogenicity or poor corticomedullary differentiation
    - Abnormalities of kidney parenchyma including hypoplasia, dysplasia, multicystic dysplastic kidney (MCDK), or agenesis

        - Fusion anomalies (e.g., horseshoe kidney)
        - Collecting system abnormalities, including duplicated collecting systems, ureteropelvic junction obstruction, isolated hydronephrosis, or hydroureter
    - Tubulointerstitial disease, characterized by reduced urine concentrating ability with bland urinary sediment, absent-to-minimal albuminuria/proteinuria, hyperuricemia, hypomagnesemia, hypokalemia, and tubulointerstitial fibrosis on kidney histology. In some cases, hypomagnesemia is the initial and predominant symptom of kidney disease [van der Made et al 2015].
- **Maturity-onset diabetes of the young (MODY),** a type of monogenic diabetes resulting from beta-cell dysfunction
- **Neurodevelopmental or neuropsychiatric disorders** (e.g., developmental delay, intellectual disability, autism spectrum disorder, schizophrenia, anxiety, and bipolar disorder)
- **Müllerian aplasia / Mayer-Rokitansky-Küster-Hauser syndrome** in females

Note: The combination of kidney or urogenital anomalies with MODY has been referred to as renal cysts and diabetes (RCAD) syndrome.

Laboratory findings. The 17q12 recurrent deletion syndrome should be suspected in individuals with a deletion of *HNF1B* identified on gene-targeted deletion/duplication analysis (i.e., testing that detects deletion of *HNF1B,* but cannot reliably detect the diagnostic recurrent 17q12 deletion), as virtually all whole-gene deletions have been found to be the 17q12 recurrent deletion [Laffargue et al 2015].

Note that identification of an intragenic *HNF1B* pathogenic variant on sequence analysis establishes the diagnosis of an *HNF1B*-related disorder (see Genetically Related Disorders) and excludes the diagnosis of the 17q12 recurrent deletion syndrome.

Establishing the Diagnosis

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

For this *GeneReview*, the 17q12 recurrent deletion is defined as the presence of a recurrent 1.4-Mb deletion at the approximate position of 36458167-37854616 in the reference genome (NCBI Build GRCh38/hg38).

ISCN nomenclature for this deletion is: seq[GRCh37] del(17)(q12) chr17:g. 36,458,167-37,854,616del. Note: Since this deletion is recurrent and mediated by segmental duplications, the unique genetic sequence that is deleted is the same in all individuals with the syndrome; however, the reported size of the deletion may: (1) be larger if adjacent segmental duplications are included in the size and (2) vary based on the design of the microarray used to detect it.

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

Genomic testing methods that determine the copy number of sequences can include **chromosomal microarray** (CMA), **exome sequencing with CNV calling**, **genome sequencing**, or **targeted deletion analysis**. Note: The 17q12 recurrent deletion 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 deletion in a proband. The ability to size the deletion depends on the type of microarray used and the density of probes in the 17q12 region.

Note: (1) Most individuals with the 17q12 recurrent deletion are identified by CMA performed in the context of evaluation for developmental delay, intellectual disability, or autism spectrum disorder. (2) Prior to 2007, many CMA platforms did not include coverage for this region and thus may not have detected this deletion.

Exome and genome sequencing analyses are next-generation sequencing technologies that generate DNA sequence either for all coding regions (exome) or the entire genome. Copy number variant-calling algorithms need to be utilized to detect the 17q12 recurrent deletion.

Targeted deletion 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 deletion. Virtually all whole-gene deletions of *HNF1B* identified by gene-targeted deletion/duplication analysis have been shown to include the entire 17q12 recurrent deletion region [Laffargue et al 2015], which can be confirmed using CMA.

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

Table 1. Genomic Testing Used in 17q12 Recurrent Deletion Syndrome

Deletion [1]	Method	Sensitivity	
		Proband	At-risk family members
1.4-Mb heterozygous deletion at 17q12 ISCN: seq[GRCh38] del(17)(q12) chr17:g. 36,458,167-37,854,616del [2] ClinGen ID: ISCA-37432	CMA [3]	100%	100%
	Exome & genome sequencing [4]	100%	100%
	Targeted deletion analysis [5]	NA [6]	100% [7]

1. See Molecular Genetics for details of the deletion and genes of interest included in the region.
2. Standardized ISCN 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 deletion size associated with the 17q12 recurrent deletion as designated by ClinGen. Deletion coordinates may vary slightly based on array design used by the testing laboratory. Note that the size of the deletion as calculated from these genomic positions may differ from the expected deletion size due to the presence of segmental duplications near breakpoints. The phenotype of significantly larger or smaller deletions within this region may be clinically distinct from the recurrent 17q12 deletion (see Genetically Related Disorders).
3. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 17q12 region. Note: The 17q12 recurrent deletion may not have been detectable by older oligonucleotide or BAC platforms.
4. Copy number variant-calling algorithms need to be utilized to detect the 17q12 recurrent deletion.
5. Targeted deletion analysis methods can include FISH, quantitative PCR (qPCR), and multiplex ligation-dependent probe amplification (MLPA), as well as other targeted quantitative methods.
6. Targeted deletion analysis is not appropriate for an individual in whom the 17q12 recurrent deletion was not detected by CMA designed to target this region.
7. Targeted deletion analysis may be used to test at-risk relatives of a proband known to have the 17q12 recurrent deletion.

Evaluating at-risk relatives. FISH, qPCR, or other quantitative methods of targeted deletion analysis can be used to identify the 17q12 recurrent deletion in at-risk relatives of the proband. Testing of parental samples is important in determining recurrence risk (see Genetic Counseling).

Clinical Characteristics

Clinical Description

The 17q12 recurrent deletion syndrome is characterized by variable combinations of the following three most common findings: kidney abnormalities including congenital abnormalities of the kidney and urinary tract (CAKUT) and tubulointerstitial disease, maturity-onset diabetes of the young (MODY), and

neurodevelopmental/neuropsychiatric disorders (e.g., developmental delay, intellectual disability, autism spectrum disorder, schizophrenia, anxiety, and bipolar disorder).

To calculate the frequency rates for these features reported in 17q12 recurrent deletion syndrome, the authors reviewed phenotypic information for 282 individuals on whom sufficiently detailed phenotypic information was reported in 42 studies (Table 2) using the following criteria:

- To minimize ascertainment bias, studies involving disease-specific cohorts were not included in the prevalence calculations of that particular phenotypic manifestation (e.g., kidney anomalies).
- Individuals with *HNF1B* pathogenic sequence variants were not included; however, individuals with whole-gene *HNF1B* deletions were included, as virtually all whole-gene deletions have been found to be the 17q12 recurrent deletion [Laffargue et al 2015].

Table 2. 17q12 Recurrent Deletion Syndrome: Frequency of Select Features

Frequency	Features
Most common (>50%)	• Kidney structural or functional defects • Neurodevelopmental/neuropsychiatric disorders • Mild dysmorphic features • Hyperparathyroidism
Common (25%-50%)	• Maturity-onset diabetes of the young type 5 • Female & male genital abnormalities • Structural & functional liver abnormalities • Eye abnormalities • Structural &exocrine abnormalities of the pancreas • Nonspecific structural brain findings • Prematurity
Less common (<25%)	• Congenital cardiac anomalies • Musculoskeletal features • Other gastrointestinal features • Seizures

Clinical data summarized from 42 studies, including 282 individuals in whom the 17q12 recurrent deletion was identified [Bellanné-Chantelot et al 2005, Faguer et al 2007, Mefford et al 2007, Cheroki et al 2008, Edghill et al 2008, Bernardini et al 2009, Raile et al 2009, Loirat et al 2010, Moreno-De-Luca et al 2010, Nagamani et al 2010, Oram et al 2010, Kasperavičiūtė et al 2011, Nik-Zainal et al 2011, Dixit et al 2012, George et al 2012, Grozeva et al 2012, Hendrix et al 2012, Hinkes et al 2012, Sanna-Cherchi et al 2012, Ferrè et al 2013, Palumbo et al 2014, Quintero-Rivera et al 2014, Roberts et al 2014, Stefansson et al 2014, Goumy et al 2015, Laffargue et al 2015, Verbitsky et al 2015, Rasmussen et al 2016, Dubois-Laforgue et al 2017a, Madariaga et al 2018, Roehlen et al 2018, Stiles et al 2018, Dotto et al 2019, Li et al 2019, Okorn et al 2019, Vasileiou et al 2019, Bustamante et al 2020, Du et al 2020, Kołbuc et al 2020, Lim et al 2020, Sztromwasser et al 2020, Berberich et al 2021]

Most Common Features (>50%)

Kidney disease. Structural kidney abnormalities and unspecified chronic kidney disease have been described in 257 individuals (Table 2). Cystic dysplastic kidneys and other structural kidney anomalies are reported in 130/148 (88%) individuals who were *not* ascertained through cohorts with kidney disease, making this feature the most commonly reported manifestation of the 17q12 recurrent deletion syndrome.

Cystic dysplasia is the most common kidney finding; other kidney and urinary tract abnormalities include poor cortico-medullary differentiation, collecting system abnormalities (duplicated collecting system, hydronephrosis, pyelectasis, vesicoureteral reflux, dilated ureter), single kidney (due to unilateral agenesis or involution of a cystic dysplastic kidney), and horseshoe kidney.

Individuals may also present with tubulointerstitial disease, which is characterized by reduced urine concentrating ability, bland urinary sediment, absent-to-minimal albuminuria/proteinuria, hyperuricemia, hypomagnesemia, hypokalemia, and slowly progressive kidney disease; interstitial fibrosis and tubular atrophy

are seen on biopsy (although biopsy is not routinely indicated) [Eckardt et al 2015, Verhave et al 2016]. Of note, autosomal dominant tubulointerstitial kidney disease (ADTKD) caused by *HNF1B* haploinsufficiency (frequently due to 17q12 deletion) is designated ADTKD-*HNF1B* [Eckardt et al 2015].

Tubular wasting of magnesium resulting in hypomagnesemia is common and can be the initial and predominant manifestation of kidney disease in individuals with *HNF1B* haploinsufficiency, including those with the 17q12 recurrent deletion [Clissold et al 2015, Raaijmakers et al 2015, van der Made et al 2015]. Hypomagnesemia is reported in 36/81 (44%) individuals with 17q12 recurrent deletion and can be severe [Ferrè et al 2013, Madariaga et al 2018, Dotto et al 2019, Li et al 2019, Okorn et al 2019, Berberich et al 2021]. Some studies suggest that hypomagnesemia may be underdiagnosed among children with *HNF1B*-related disorders, including 17q12 recurrent deletion [Kołbuc et al 2020]. Tubular magnesium wasting can be diagnosed through an elevated fractional excretion of magnesium (FEMg >2%) in individuals with normal kidney function.

The spectrum of severity and range in age of detection of *HNF1B*-associated kidney disease are broad, including prenatal severe kidney failure, slow progression to end-stage kidney disease (ESKD) in adulthood, and normal kidney function never requiring kidney replacement therapy [Madariaga et al 2013, Clissold et al 2015, Verhave et al 2016]. While initial evidence suggested that the cause of *HNF1B* haploinsufficiency – 17q12 deletion, a *HNF1B* missense variant, or a *HNF1B* truncating variant (nonsense, frameshift, or splice site) – did not predict the type and severity of kidney involvement [Raaijmakers et al 2015], more recent evidence indicates that intragenic *HNF1B* pathogenic variants may be associated with worse kidney function and higher risk of progression to ESKD compared to 17q12 deletions [Dubois-Laforgue et al 2017b, Clissold et al 2018]. The reason for this finding is unknown, but the authors speculate a possible dominant-negative effect of certain *HNF1B* variants resulting in a more severe phenotype, or a protective effect conferred by the loss of one or more genes in the 17q12 recurrent deletion region.

Progression to ESKD in childhood appears to be uncommon among individuals with *HNF1B* haploinsufficiency, including those with the 17q12 recurrent deletion [Bockenhauer & Jaureguiberry 2016]. In a large retrospective cohort study, progression to ESKD was less common among adults with 17q12 deletion at follow-up (51%) compared with those with *HNF1B* intragenic mutations (78%) [Dubois-Laforgue et al 2017b].

Neurodevelopmental/neuropsychiatric disorders. Several studies have identified an increased risk for neurodevelopmental and neuropsychiatric disorders, such as developmental delay, intellectual disability (mild to severe), autism spectrum disorder (ASD), and schizophrenia [Moreno-De-Luca et al 2010, Lalière et al 2020].

In a case-control study, Moreno-De-Luca et al [2010] identified the following number of individuals with the 17q12 recurrent deletion:

- Eighteen of 15,749 individuals referred for developmental delay, intellectual disability, and/or ASD. Detailed phenotypic information for nine individuals revealed six with anxiety and/or phobias, one of whom was diagnosed with bipolar disorder. Because the 17q12 recurrent deletion was not detected in 4,519 controls, the authors concluded that the deletion confers a high risk for developmental brain disorders.
- Four of 6,340 individuals from two large schizophrenia cohorts. Because the 17q12 recurrent deletion was not detected in 43,076 controls, the authors concluded that deletion also confers a high risk for schizophrenia.

Overall, about half (37/79) of individuals with the 17q12 recurrent deletion are reported to have some degree of learning disability, although phenotypic information about cognitive skills was limited in most studies. Speech and motor delay are common findings, reported in 78% and 68% of individuals, respectively. While not routinely assessed, autism or autistic features are described in 9% of individuals ascertained for other clinical findings [Raile et al 2009, Loirat et al 2010, Dixit et al 2012, Palumbo et al 2014, Roberts et al 2014, Goumy et al 2015, Laffargue et al 2015, Rasmussen et al 2016, Li et al 2019, Vasileiou et al 2019, Lim et al 2020]. Learning

difficulties, when noted, are most often described as mild. One study found that only 14/110 (12.7%) children with the 17q12 recurrent deletion required special school placement, which the researchers used as a proxy for severe neuropsychiatric disorder [Lalière et al 2020].

Some studies suggest that genes other than *HNF1B* in the 17q12 region could be responsible for neurodevelopmental and neuropsychiatric features, although evidence is mixed. One study found that individuals with the recurrent 17q12 deletion, but not an *HNF1B* intragenic pathogenic variant, exhibited neurodevelopmental disorders, psychopathology, and autistic traits [Clissold et al 2016]; however, other studies have found that both groups of *HNF1B*-related disorders are associated with an increased risk of intellectual disability [Dubois-Laforgue et al 2017a, Lalière et al 2020]. While haploinsufficiency of *HNF1B* alone may not be sufficient to result in the cognitive and behavioral features associated with the 17q12 recurrent deletion, the role of *HNF1B* in neurologic impairment cannot be ruled out.

Dysmorphic features. Subtle but highly variable dysmorphic features are described for most individuals for whom this information is available. The most commonly described features include high forehead, frontal bossing, depressed nasal bridge, deep-set eyes, full cheeks, downslanting palpebral fissures, high palate, and high-arched eyebrows [Moreno-De-Luca et al 2010, Laffargue et al 2015, Rasmussen et al 2016, Roehlen et al 2018, Vasileiou et al 2019].

Hypoplastic nails, 2-3 finger/toe syndactyly, and clinodactyly of the fifth finger are also frequently reported [Moreno-De-Luca et al 2010, Kasperavičiūtė et al 2011, Palumbo et al 2014].

Hyperparathyroidism. Nineteen of 36 (53%) individuals who had parathyroid hormone plasma levels tested were found to have hyperparathyroidism [Ferrè et al 2013, Li et al 2019, Kołbuc et al 2020, Lim et al 2020, Berberich et al 2021]. Furthermore, one study reported transient neonatal hypercalcemia and hypophosphatemia, the combination of which is suggestive of hyperparathyroidism, although PTH levels were not specifically measured to confirm [Dixit et al 2012]. Another study demonstrated that *HNF1B* is expressed in the parathyroid gland and acts as a transcriptional repressor of *PTH* [Ferrè et al 2013]. Additionally, this study found that PTH levels remained increased even after kidney transplantation and normalized magnesium levels in some individuals. Although hyperparathyroidism is persistent in 20%-50% of individuals who are post-transplant independent of genetics, the authors concluded that the weight of the evidence suggests that *HNF1B* haploinsufficiency causes hyperparathyroidism independent of associated kidney failure.

Common Features (25%-50%)

Maturity-onset diabetes of the young type 5 (MODY5) is most often diagnosed before age 25 years (range: 10-50 years) [Bellanné-Chantelot et al 2005].

Overt diabetes mellitus and abnormal blood glucose levels and/or insulin response are reported in 49/125 (39%) individuals with the 17q12 recurrent deletion *not* ascertained from cohorts with diabetes mellitus; however, this is almost certainly an underestimate of the lifetime prevalence, since many individuals described in the literature are children and young adults who may not yet have developed manifestations of diabetes. When cohorts with diabetes mellitus are considered, prevalence of MODY5 among individuals with the 17q12 recurrent deletion is 50%.

While many individuals with 17q12 deletion with MODY5 have some residual insulin secretion at the time of diagnosis, one study found that 79% required insulin therapy by ten-year follow up [Dubois-Laforgue et al 2017b].

Genital abnormalities. About one third of females and one quarter of males have genital abnormalities.

In females, the most commonly reported finding is partial or complete absence of the upper part of the vagina, cervix, and uterus, often referred to as müllerian aplasia or Mayer-Rokitansky-Küster-Hauser syndrome

[Bernardini et al 2009]. Other reported uterine abnormalities include bicornuate uterus, uterus didelphys, hypoplastic uterus, and ovarian cysts [Oram et al 2010, Stiles et al 2018, Vasileiou et al 2019].

In males, genital abnormalities include cryptorchidism, shawl scrotum, phimosis, urethral stenosis or obstruction, hypospadias, and epydidimary cysts [Nagamani et al 2010, Madariaga et al 2018, Lim et al 2020].

Structural and functional abnormalities of the liver. Elevated liver enzymes were reported in 64/133 (48%) individuals in cohorts ascertained for kidney involvement, diabetes mellitus, and uterine malformations [Rasmussen et al 2016, Dubois-Laforgue et al 2017a, Okorn et al 2019]. Liver involvement ranges from asymptomatic elevation of hepatic transaminase enzyme levels to neonatal and adult-onset cholestasis [Kotalova et al 2015, Pinon et al 2019]. Neonatal cholestasis with paucity of interlobular bile ducts and variable periportal fibrosis has also been reported in several infants with 17q12 recurrent deletion, including one who required portoenterostomy and one who developed hepatocellular carcinoma requiring liver transplantation [Pinon et al 2019]. Additional reported liver abnormalities include choledochal and common bile duct cysts, hepatomegaly, and steatohepatitis [Roehlen et al 2018, Lim et al 2020]. One study reported an even higher frequency of abnormal liver function tests (71%) in a large cohort that included both intragenic *HNF1B* variants and 17q12 deletions [Dubois-Laforgue et al 2017b]. While the study's authors did not differentiate between genotypes, no statistically significant genotype/phenotype correlations were reported, suggesting that elevated LFTs may be even more common (>50%).

Eye abnormalities. Fifteen of 37 (41%) reported individuals had eye findings that included strabismus [Vasileiou et al 2019], horizontal nystagmus [Cheroki et al 2008], posterior embryotoxon [Dixit et al 2012], hypermetropia [Moreno-De-Luca et al 2010], cataracts [Nagamani et al 2010], and coloboma [Raile et al 2009].

Structural and exocrine abnormalities of the pancreas. About one third (32/105) of individuals with imaging results were found to have some morphologic abnormality of the pancreas, most often hypoplasia, atrophy, and/or agenesis of the body and tail [Madariaga et al 2018, Roehlen et al 2018, Dotto et al 2019, Kołbuc et al 2020].

One retrospective cohort study involving both 17q12 deletions and *HNF1B* sequence variants found pancreatic exocrine insufficiency in 29/38 cases (76%) and structural pancreatic abnormalities in 62% of 95 individuals who had imaging [Dubois-Laforgue et al 2017b]. The study's authors did not differentiate between the groups of individuals, but reported no significant genotype/phenotype differences for this feature. Most other studies did not measure fecal elastase, but those that did reported a lower frequency of pancreatic exocrine insufficiency (2 of 8 cases) [Raile et al 2009, Quintero-Rivera et al 2014, Roehlen et al 2018].

Prematurity. Among 16 studies that reported premature birth (gestational age <37 weeks), 13 of 47 individuals (28%) were affected.

Nonspecific structural brain findings. No systematic neuroimaging studies of cohorts with 17q12 recurrent deletion syndrome have been published. Among publications describing neuroimaging findings, structural brain anomalies were reported in eight of 31 (26%) individuals. These abnormalities, which appeared to be nonspecific and to vary widely, included the following:

- Ventricular dilatation [Vasileiou et al 2019]
- Mild cerebellar atrophy [Kasperavičiūtė et al 2011]
- Abnormal signal intensity of subcortical white matter [Moreno-De-Luca et al 2010]
- Atrophy of the hippocampus [Nagamani et al 2010]

Less Common Features (<25%)

Congenital cardiac anomalies. Congenital heart defects are reported in nine of 45 (20%) individuals, ranging from mild to severe. Cardiac anomalies include right heart failure with tricuspid valve insufficiency, increased

aortic root size, aortic insufficiency, coarctation of the aorta, ventricular septal defect, transposition of the great arteries, pulmonary valve defect, tricuspid regurgitation, and patent ductus arteriosus [Hinkes et al 2012, Palumbo et al 2014, Roberts et al 2014, Vasileiou et al 2019, Du et al 2020].

Musculoskeletal. Nine of 39 (23%) individuals were reported to have short stature. Other musculoskeletal differences include joint laxity (5 persons), long/slender hands and feet (4), pectus deformity (3), fifth finger clinodactyly (3), single transverse palmar crease (1), and hip dysplasia (1).

Other gastrointestinal features. Gastroesophageal reflux disease was reported in three individuals [Moreno-De-Luca et al 2010, Goumy et al 2015, Rasmussen et al 2016]. One individual had duodenal atresia [Quintero-Rivera et al 2014] and two had esophageal abnormalities, including hiatus hernia caused by a short esophagus and dysphagia [Rasmussen et al 2016].

Seizures. Seven out of 50 cases (14%) reported seizure activity, including febrile seizures [Moreno-De-Luca et al 2010], partial complex seizures [Nagamani et al 2010], and mesial temporal lobe epilepsy requiring lobectomy [Kasperavičiūtė et al 2011].

Case Reports

Other reported physical findings include hypotonia (6 persons), prenatal oligohydramnios (4), macrocephaly (4), sensorineural hearing loss (3), deep vein thrombosis/vascular calcifications (2) and congenital diaphragmatic hernia (2).

Intrafamilial Variability

While the recurrent 17q12 deletion most often occurs *de novo*, there have been several reports of familial inheritance [Moreno-De-Luca et al 2010, George et al 2012, Quintero-Rivera et al 2014, Dotto et al 2019, Okorn et al 2019, Kołbuc et al 2020]. Although the size of the deletion did not differ between parents and children in these reports, significant variability in clinical presentation has been reported both between and within phenotype categories.

Penetrance

The 17q12 recurrent deletion is highly pathogenic and penetrant, but expressivity is variable.

Because population-based studies with evaluation of all individuals with a 17q12 recurrent deletion are lacking, the exact penetrance is unknown both for individual phenotypic categories (e.g., kidney anomalies, neurodevelopmental disorders, diabetes) and for the presence of **any** associated pathologic phenotype (e.g., kidney anomaly OR neurodevelopmental disorder OR diabetes).

However, high pathogenicity and penetrance is supported by several lines of evidence:

- High rate of structural kidney anomalies among individuals who were **not** ascertained as part of kidney disease cohorts (130/148; 88%) (Table 2)
- Preliminary evidence suggesting a high rate of neurodevelopmental and neuropsychiatric disorders among individuals who were **not** ascertained as part of NDD/NPD cohorts (3/4; 75%) [Martin et al 2020]
- Very low frequency of the deletion in control populations (e.g., none in ~48,000 controls in one study [Moreno-De-Luca et al 2010])
- High *de novo* ratio (percentage of cases that are *de novo*) [Kirov et al 2014]

These studies suggest that penetrance is virtually 100%, with missing data and variable expressivity accounting for the very rare presence of the 17q12 deletion in control populations.

Nomenclature

In 1997, heterozygous pathogenic variants in *HNF1B* were described as a cause of MODY in one family [Horikawa et al 1997]; shortly thereafter the same family was found to have kidney involvement [Iwasaki et al 1998]. In 2001, the combination of congenital anomalies of the kidney and urinary tract and MODY5 became known as "renal cysts and diabetes (RCAD) syndrome" [Bingham et al 2001].

Prevalence

The reported prevalence of the 17q12 recurrent deletion in large populations not selected on the basis of disease ranges from 0.002% (1:50,000) to 0.007% (1:14,000) – 0.002% in healthy European volunteers (UK Biobank; n = ~421K), 0.004% in a US health care system-based population (DiscovEHR; n = ~90K), and 0.007% in a large Icelandic control sample (deCODE; n = ~101K) [Martin et al 2020]. A higher prevalence estimate of 0.025% (1:4,000) was described in a population-based pregnancy cohort study of 12,252 mother-father-newborn trios [Smajlagić et al 2021].

Among individuals undergoing clinical postnatal chromosomal microarray analysis, the prevalence of the 17q12 recurrent deletion is much higher: approximately 0.1% (1:1000) [Moreno-De-Luca et al 2010, Rosenfeld et al 2013, Kirov et al 2014, Rasmussen et al 2016]. The main indications for clinical CMA in these studies were neurodevelopmental disorders (global developmental delay, intellectual disability, ASD) and congenital malformations.

It may be useful to consider the estimated prevalence of the 17q12 recurrent deletion in certain clinical populations:

- Congenital anomalies of the kidney. 1.9% (~1:53); when considering CAKUT more broadly, 0.8% (~1:123) have 17q12 deletion [Verbitsky et al 2019].
- Chronic kidney disease. 0.03%-2.2% (~1:3000 - 1:46) [Lata et al 2018, Connaughton et al 2019, Groopman et al 2019]
- Neurodevelopmental disorders. 0.09% (~1:1,150) [Kirov et al 2014]
- Schizophrenia. 0.036% (~1:2,800) [Kirov et al 2014]
- Müllerian aplasia. 3%-6% (~1:33 - 1:17) [Nik-Zainal et al 2011, Williams et al 2017]. Among women with both uterine and kidney anomalies, 18% (~1:6) had a 17q12 deletion or pathogenic *HNF1B* sequence variant [Oram et al 2010].

Genetically Related Disorders

The phenotype of significantly larger or smaller deletions within this region may be clinically distinct from the 17q12 recurrent deletion syndrome.

17q12 recurrent duplication. The recurrent reciprocal duplication of the 17q12 region is defined as the presence of a recurrent 1.4-Mb duplication at the approximate position of chr17: 34,815,072-36,192,492 in the reference genome (NCBI Build GRCh37/hg19). The 17q12 recurrent duplication encompasses the same genes as the 17q12 recurrent deletion. Although there are several genes of interest (e.g., *ACACA*, *LHX1*, and *HNF1B*) within the 1.4-Mb recurrent duplication, no single gene has been identified as causative of the phenotype.

The 17q12 recurrent duplication is inherited in an autosomal dominant manner, with approximately 10% of duplications occurring *de novo* and 90% inherited from a parent. Since the majority of 17q12 recurrent microduplications are inherited from a parent with minimally abnormal or reportedly normal findings, the 17q12 recurrent duplication likely has a smaller effect size compared to the deletion, resulting in reduced penetrance and highly variable expressivity. Since the initial description of 17q12 recurrent duplication [Sharp et

al 2006], studies including approximately 50 individuals with some phenotypic data have been published. Clinical features observed in these individuals include the following:

- Intellectual disability or developmental delays, including speech and motor delay. While the majority of probands referred for genetic testing were reported to have delays or intellectual disability, many had inherited the duplication from a parent with average cognitive ability.
- Seizures (25% of affected individuals)
- Eye or vision problems (≤33%)
- Cardiac and kidney anomalies (not common)
- Other neurodevelopmental and psychiatric conditions (e.g., autism spectrum disorder, schizophrenia, and behavioral abnormalities)

Differential Diagnosis

Kidney anomalies. The differential diagnosis of kidney cysts is age dependent (see Table 3).

Table 3. Genetic Disorders with Kidney Cysts in the Differential Diagnosis of 17q12 Recurrent Deletion Syndrome

Gene(s)	Disorder	MOI	Kidney Phenotype	Extrarenal Phenotype
DNAJB11 *GANAB* *PKD1* *PKD2*	ADPKD	AD	Numerous bilateral cysts; kidney enlargement; hypertension; nephrolithiasis; progressive CKD, w/ESKD in mid- to late-adulthood. *DNAJB11*- & *GANAB*-assoc disease have milder phenotypes w/normal-sized kidneys, smaller cysts, & less progression to ESKD.	Liver cysts; intracranial aneurysms; cardiac valve abnormalities; diverticular disease; hernias
ALG8 *GANAB* [1] *LRP5* *PRKCSH* *SEC63* *SEC61B* [2]	ADPLD (OMIM PS174050)	AD	Few cysts occasionally reported	Polycystic liver disease
MUC1	ADTKD-*MUC1* (previously known as MCKD1)	AD	Tubulointerstitial disease; few small corticomedullary cysts in 50%; normal or small-sized kidneys; CKD, highly variable progression to ESKD	Hyperuricemia, gout
REN	ADTKD-*REN* (previously known as FJHN2)	AD	Tubulointerstitial disease, cysts, slowly progressive CKD	Anemia, hyperuricemia, gout
SEC61A1	ADTKD-*SEC61A1* [3] (also referred to as FJHN4)	AD	Bilateral small cysts in 50%; normal or small-sized kidneys; CKD	IUGR, congenital anemia
UMOD	ADTKD-*UMOD* (previously known as FJHN1 or MCKD2)	AD	Tubulointerstitial disease; normal or small kidneys; few unilateral or bilateral cysts in 1/3; variable progression of CKD to ESKD	Hyperuricemia, gout
JAG1 *NOTCH2*	Alagille syndrome	AD	Renal dysplasia, renal tubular acidosis, CAKUT	Cholestatic liver disease, cardiac anomalies, characteristic facies, skeletal anomalies, ophthalmic anomalies

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Kidney Phenotype	Extrarenal Phenotype
PKHD1 (*DZIP1L*) [4]	ARPKD	AR	Enlarged, hyperechogenic kidneys in utero; multiple small bilateral cysts in childhood; ESKD in 1st decade in 50%	Congenital hepatic fibrosis, Caroli syndrome, pulmonary hypoplasia, prenatal oligoanhydramnios
EYA1 *SIX1* *SIX5*	Branchiootorenal spectrum disorder	AD	Renal agenesis, hypoplasia, or dysplasia; ureteropelvic junction obstruction; calyceal cyst/ diverticulum; calyectasis, pelviectasis, hydronephrosis, VUR	Ear abnormalities (deafness, outer ear anomalies, middle ear anomalies, preauriular pits); 2nd branchial arch anomalies (sinus tract, cyst)
BICC1	Cystic renal dysplasia, susceptibility to (OMIM 601331)	AD	Cystic renal dysplasia, VUR	None
BMPER	Diaphanospondylo-dysostosis (OMIM 608022)	AR	Nephroblastomatosis w/cystic kidneys	Skeletal anomalies (small chest, abnormal vertebral segmentation, & posterior rib gaps); craniofacial anomalies (ocular hypertelorism, epicanthal folds, depressed nasal bridge w/short nose, & low-set ears)
PMM2	HIPKD [5]	AR	Antenatal or childhood onset enlarged hyperechogenic kidneys w/multiple cysts; variable progression of CKD to ESKD from infancy to early adulthood	Infantile hyperinsulinemic hypoglycemia; liver cysts
CEP290 *INVS* *IQCB1* *NPHP1* *NPHP3* *NPHP4* *TMEM67* (≥19 genes) [6]	Nephronophthisis	AR	Corticomedullary cysts; normal or small-sized kidneys (but often moderately enlarged in infantile onset type); urinary concentrating & sodium reabsorption defect; progressive CKD	Nephronophthisis may be isolated or part of a syndrome, such as Joubert, Bardet-Biedl, Jeune, Meckel-Gruber, Senior-Loken, Leber congenital amaurosis, Cogan, or COACH.
OFD1	Oral-facial-digital syndrome type I	XL	Polycystic kidneys in women; progressive kidney dysfunction in adulthood	Cleft palate, dental anomalies, facial dysmorphology, digital anomalies, ID
PAX2	Renal coloboma syndrome (See *PAX2*-Related Disorder.)	AD	Hypoplasia, hypodysplasia, multicystic dysplastic kidney, VUR, other CAKUT, FSGS, uric acid nephrolithiasis	Optic nerve dysplasia, retinal coloboma, other eye malformations
TSC1 *TSC2*	Tuberous sclerosis complex	AD	Multiple & bilateral cysts & angiomyolipomas, oncocytomas, renal cell carcinoma	Cortical tubers, astrocytomas; epilepsy, ID; cutaneous angiofibromas, hypopigmented patches; retinal hamartoma; cardiac rhabdomyoma; pulmonary LAM;
VHL	von Hippel-Lindau syndrome	AD	Bilateral cysts, renal cell carcinoma	retinal hemangiomas; hemangioblastomas of the cerebellum, spine, retina; pheochromocytoma; pancreatic neuroendocrine tumors

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Kidney Phenotype	Extrarenal Phenotype
CRB2	Ventriculomegaly w/cystic kidney disease (OMIM 219730)	AR	Microscopic renal tubular cysts	Dilated cerebral ventricles, postaxial polydactyly, ventricular septal defect

Adapted from: Cornec-Le Gall et al [2019]; Lanktree et al [2019]; Armstrong & Thomas [2019]; Polycystic Kidney Disease, Autosomal Dominant; Polycystic Kidney Disease, Autosomal Recessive; and Nephronophthisis
AD = autosomal dominant; ADPKD = autosomal dominant polycystic kidney disease; ADPLD = autosomal dominant polycystic liver disease; ADTKD = autosomal dominant tubulointerstitial kidney disease; AR = autosomal recessive; ARPKD = autosomal recessive polycystic kidney disease; CAKUT = congenital anomalies of the kidney and urinary tract; CKD = chronic kidney disease; COACH = cerebellar vermis hypo/aplasia, oligophrenia, ataxia, coloboma, and hepatic fibrosis; ESKD = end-stage kidney disease; FJHN = familial juvenile hyperuricemic nephropathy; FSGS = focal segmental glomerulonephritis; HIPKD = hyperinsulinemia with hypoglycemia and polycystic kidney disease; ID = intellectual disability; IUGR = intrauterine growth restriction; LAM = lymphangioleiomyomatosis; MCKD = medullary cystic kidney disease; MOI = mode of inheritance; VUR = vesicoureteric reflux
1. Porath et al [2016]
2. Besse et al [2017]
3. Bolar et al [2016]
4. DZIP1L has not yet been definitively proven to be a second locus for ARPKD (see ARPKD).
5. Soares et al [2020]
6. Listed genes represent the most common genetic causes of nephronophthisis; for other genes associated with this phenotype, see Nephronophthisis.

The differential diagnosis of kidney cysts also includes, in children: idiopathic cystic dysplasia and obstructive dysplasia; and in adults: acquired kidney cysts (related to chronic kidney disease and/or dialysis) or simple cortical cysts [Clissold et al 2015].

Maturity-Onset Diabetes of the Young (MODY) is a group of inherited disorders of non-autoimmune diabetes mellitus which usually present in adolescence or young adulthood (typically age <35 years). MODY is generally inherited in an autosomal dominant manner.

The clinical findings are either:

- An atypical type 2 diabetes-like condition that occurs in the absence of the usual predisposing factors (obesity, hypertension, dyslipidemia, and acanthosis nigricans); OR
- An atypical type 1 diabetes-like condition that occurs in the absence of the usual clinical and laboratory manifestations (islet cell autoantibodies, persistence of measurable C-peptide levels, and diabetic ketoacidosis) [American Diabetes Association 2010, Fajans & Bell 2011, Carroll & Murphy 2013].

Table 4. Maturity-Onset Diabetes of the Young (MODY): Genes and Associated Clinical Features

Gene	Locus	Clinical Features
ABCC8	MODY12	Similar to *HNF1A*- & *HNF4A*-MODY
APPL1	MODY14	Overweight/obesity in some
BLK	MODY11	Overweight/obesity in some
CEL	MODY8	Pancreatic atrophy → exocrine pancreatic insufficiency. Fibrosis & lipomatosis → diabetes.
GCK	MODY2	Stable, mild fasting hyperglycemia at birth. Typically asymptomatic; diagnosis often incidental.
HNF1A	MODY3	Transient neonatal hyperinsulinemic hypoglycemia in some. Progressive insulin secretory defect. OGTT frequently needed to make an early diagnosis. Renal glycosuria.
HNF1B	MODY5	IUGR, kidney anomalies, urogenital tract anomalies, pancreatic hypoplasia
HNF4A	MODY1	Birth weight >800 g above normal. Transient neonatal hyperinsulinemic hypoglycemia common. Progressive insulin secretory defect.
INS	MODY10	

Table 4. continued from previous page.

Gene	Locus	Clinical Features
KCNJ11	MODY13	Similar to *HNF1A*-MODY & *HNF4A*-MODY
KLF11	MODY7	
NEUROD1	MODY6	Overweight/obesity in some
PAX4	MODY9	
PDX1	MODY4	Overweight/obesity in some

Adapted from the MODY Overview.
IUGR = intrauterine growth restriction; OGTT = oral glucose tolerance test

Other genetic causes of müllerian aplasia. Six percent of women in a large cohort with müllerian aplasia had the 17q12 recurrent deletion; an additional 8% had other recurrent copy number variants, including the 16p11.2 recurrent deletion and the distal 22q11.2 recurrent deletion [Nik-Zainal et al 2011]. Additional case reports of women with uterine malformations have identified intragenic pathogenic variants in *LHX1*, a gene found within the recurrent 17q12 deletion region that encodes a transcription factor required for the formation of müllerian ducts [Ledig et al 2012, Sandbacka et al 2013].

Other genetic causes of neurodevelopmental or neuropsychiatric disorders. The differential diagnosis for developmental delay, intellectual disability, schizophrenia, and autism spectrum disorder includes hundreds of known copy number and single-nucleotide variants and is too broad for discussion here. See OMIM Phenotypic Series:

- Autosomal Dominant Intellectual Developmental Disorder
- Autosomal Recessive Intellectual Developmental Disorder
- Nonsyndromic X-Linked Intellectual Developmental Disorder
- Syndromic X-Linked Intellectual Developmental Disorder
- Susceptibility to Autism

Management

No clinical practice guidelines for 17q12 recurrent deletion syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with the 17q12 recurrent deletion syndrome, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with 17q12 Recurrent Deletion Syndrome

System/Concern	Evaluation	Comment
Kidney structural or functional defects	Blood pressure; kidney & bladder ultrasound examination; serum BUN, creatinine, electrolytes (incl calcium, Mg, phosphorus) & uric acid; urine protein, Mg, & creatinine; consultation w/nephrologist	Random urine Mg/creatinine is needed to calculate fractional excretion of Mg. ↑ FEMg (>2%) is diagnostic of tubular Mg wasting in those w/ normal kidney function.
Neurodevelopmental/ neuropsychiatric disorders	Assessment of speech & language; cognitive, motor, & social development; perceptual anomalies; mood; behavior	

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Maturity-onset diabetes of the young type 5	Fasting glucose & hemoglobin A1C levels; consultation w/ endocrinologist	
Genital tract abnormalities	• Males: clinical exam • Females: pelvic ultrasound exam & gynecologic exam to evaluate for possible müllerian abnormalities	
Liver abnormalities	Liver function tests (hepatic function panel, GGT)	
Eye abnormalities	Ophthalmologic exam	
Congenital heart defects	Clinical assessment; consultation w/cardiologist & echocardiography if warranted	
Seizures	Neurology consultation if seizures are suspected clinically	
Sensorineural hearing loss	Audiologic eval	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of 17q12 recurrent deletion syndrome 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; • Home psychotherapy or behavioral support.	

GGT = gamma-glutamyl transferase; Mg = magnesium; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Treatment is symptomatic and depends on an individual's specific needs.

Table 6. Treatment of Manifestations in Individuals with 17q12 Recurrent Deletion Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Kidney disease	Treatment should follow standard practice. Established guidelines for the management of chronic kidney disease, incl that related to CAKUT or ADTKD, are available for children & adults [KDIGO CKD Work Group 2013].	• Some persons have normal kidney function; others may progress to ESKD & require dialysis or kidney transplantation. • Mg depletion is common & often requires replacement. Oral Mg supplements in organic salt forms (e.g., aspartate, citrate, gluconate) may be more bioavailable than inorganic salt forms (e.g., oxide, sulfate, glycerophosphate) [NIH 2018] • In those developing ESKD, transplantation is a good option, as kidney disease is not expected to recur. For those who also have diabetes mellitus, simultaneous pancreas & kidney transplantation has been successful & should be considered [Poitou et al 2012].
Neurodevelopmental/ neuropsychiatric disorders	• Provide specialized instruction, OT, PT, & speech/behavioral therapies if indicated. • Treatment of developmental disabilities involves a multimodal approach to educational needs, social & recreational activities, & assoc impairments incl behavior problems & coexisting diagnoses. • Management of ASD should follow AAP [Hyman et al 2020] & AACAP [Volkmar et al 2014] guidelines. • Psychiatric consultation & therapy for those w/mental health concerns incl mood disorders, anxiety, &/or psychosis. The AACAP has published guidelines for assessment & treatment of psychiatric disorders in children & adolescents w/ID [Siegel et al 2020].	Early identification & intervention for neurodevelopmental or neuropsychiatric disorders is important for optimal outcomes.
Maturity-onset diabetes of the young type 5	Treatment should follow standard practice.	Initial response to oral antihyperglycemic agents is common, but clinical course tends to be progressive, & most ultimately require treatment w/insulin [Dubois-Laforgue et al 2017b].
Genital tract abnormalities	• Nonsurgical & surgical intervention may be considered for those w/genital tract anomalies, incl müllerian agenesis. • All individuals w/müllerian agenesis should be offered counseling & encouraged to connect w/peer support groups.	Primary vaginal dilation is successful for >90%-96% of persons w/müllerian agenesis [Committee on Adolescent Health Care 2018]
Liver abnormalities	Standard treatment(s) as recommended by gastroenterologist.	A minority of persons w/neonatal cholestasis have required surgical intervention [Kotalova et al 2015, Pinon et al 2019].
Eye abnormalities	Standard treatment(s) as recommended by ophthalmologist, incl refractory eye exam & corrective lenses as needed	

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Congenital heart defects	Medical & surgical management per cardiologist & cardiothoracic surgery	
Seizures	Standardized treatment w/ASMs by experienced neurologist	• Many ASMs may be effective (none demonstrated effective specifically for this disorder). • Education of parents/caregivers [1]
Sensorineural hearing loss	Hearing aids may be helpful; per audiologist.	Community hearing services through early intervention or school district

AACAP = American Academy of Child & Adolescent Psychiatrists; AAP = American Academy of Pediatrics; ADTKD = autosomal dominant tubulointerstitial kidney disease; ASD = autism spectrum disorder; ASM = anti-seizure medication; ESKD = end-stage kidney disease; OT = occupational therapy; PT = physical therapy

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.

Surveillance

Table 7. Recommended Surveillance for Individuals with 17q12 Recurrent Deletion Syndrome

System/Concern	Evaluation	Frequency
Kidney structure/ function	Kidney & bladder ultrasound exam to monitor for kidney cysts or other structural abnormalities	In those without known structural defects, 12 months after establishing the diagnosis, then every 2-3 years in childhood/adolescence and every 3-5 years in adulthood. If an abnormality is detected, more frequent ultrasound examinations may be warranted
	Monitoring of: • Blood pressure • Kidney function • Serum concentration of Mg, potassium, uric acid • Urine protein:creatinine ratio • Urine Mg & creatinine	Periodic, preferably under guidance of nephrologist. Annual or more frequent monitoring may be advised for those who: • Have lab findings suggestive of kidney disease, • Are taking potentially nephrotoxic medications (e.g., NSAIDs) • Have genitourinary structural abnormalities [Verbitsky et al 2015]
Neurodevelopment	• Monitor developmental progress & educational needs. • A full psychoeducational eval incl assessment of speech, cognitive, social/emotional, adaptive, & motor skills is indicated for children who experience difficulty w/school or behavioral challenges. • Surveillance for autism symptoms in early childhood & prodromal psychotic symptoms in teenage years is warranted (although autism & schizophrenia occur less frequently than intellectual & learning disabilities).	At each visit

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Maturity-onset diabetes of the young type 5	HgbA1C	Annually
	Individuals & families should be educated on how to monitor for clinical signs/symptoms of diabetes mellitus (e.g., polyuria, polydipsia, weight loss [sometimes w/ polyphagia], fatigue, nausea, vomiting, blurred vision) in order to promote early diagnosis & treatment.	Referral to endocrinologist as indicated depending on clinical manifestations
Genital tract abnormalities	Consider reevaluation for uterine & vaginal abnormalities related to müllerian duct aplasia in pubertal females w/ primary amenorrhea.	Rudimentary müllerian structures are commonly found on MRI. On US, these rudimentary structures are difficult to interpret & may be particularly misleading before puberty [Committee on Adolescent Health Care 2018].
Liver abnormalities	Hepatic function panel (or comprehensive metabolic panel) & GGT. Consider lipid panel given case reports of hepatic steatosis. Ultrasound may be indicated if labs are abnormal.	Periodic; consider annually w/kidney function tests & electrolytes as described above.
Eyes	Ophthalmologic eval	Annually during early childhood
Neurology	Monitor those w/seizures as clinically indicated.	
Hearing	Hearing screening	Throughout childhood, per established guildelines of Bright Futures/American Academy of Pediatrics [Hagan et al 2017]

GGT = gamma-glutamyl transferase; NSAIDs = nonsteroidal anti-inflammatory drugs; US = ultrasound

Agents/Circumstances to Avoid

Individuals with *HNF1B*-associated kidney disease (including the 17q12 recurrent deletion) who develop ESKD and require kidney transplantation are at increased risk for developing post-transplant diabetes mellitus; therefore, use of an immunosuppressive regimen that avoids tacrolimus and mammalian target of rapamycin (mTOR) inhibitors and reduces corticosteroid exposure may be beneficial, including for those who do not have preexisting diabetes [Zuber et al 2009, Faguer et al 2011, Clissold et al 2015].

Nephrotoxic drugs (e.g., NSAIDs) should be avoided by those with kidney abnormalities. Hepatotoxic medications and alcohol should be avoided by those with liver abnormalities.

For individuals with mental health conditions such as autism, schizophrenia, or bipolar disorder, the authors recommend careful consideration of antipsychotic agents that may lead to weight gain, as this potential increase has been associated with metabolic syndrome and the later development of diabetes mellitus, for which people with 17q12 deletions are at baseline increased risk. Likewise, the use of mood stabilizers that affect kidney function in the long term, such as lithium, should be carefully considered in the setting of potential underlying anatomic and functional abnormalities in people with 17q12 deletions. These recommedations stem from empirically grounded clinical reasoning based on the underlying phenotypes associated with 17q12 deletions, as large studies assessing the efficacy of these interventions have not yet been performed.

Evaluation of Relatives at Risk

If genomic testing detects the 17q12 recurrent deletion in one of the proband's parents, it is appropriate to clarify the genetic status of older and younger sibs of the proband and other relatives at risk in order to identify those who would benefit from close assessment/monitoring for evidence of kidney structural or functional defects, maturity-onset diabetes of the young, and developmental delays / intellectual disability.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- Most studies examining the 17q12 recurrent deletion have not reported whether or not the parents were tested; therefore, inheritance status is often unknown or the data are limited. However, in 70 individuals with the deletion from 18 studies for which this information is available, the deletion was *de novo* in 51 (73%) and inherited in 19 (27%).
- Evaluation of the parents by genomic testing to determine if they have the 17q12 recurrent deletion present in the proband is recommended. Because features range in severity, it is possible for parents who are mildly affected to be unaware of any clinical manifestations (diabetes and kidney problems may not be evident until adulthood). See Clinical Characteristics, Intrafamilial Variability.

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

- If the 17q12 recurrent deletion identified in the proband is not identified in a parent, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism for the deletion.
- If one of the parents has the 17q12 recurrent deletion, the risk to each sib of inheriting the deletion is 50%. However, it is not possible to reliably predict the full phenotypic expression in a sib who inherits the deletion because significant intrafamilial variability may be observed (see Clinical Characteristics, Intrafamilial Variability).

Offspring of a proband. Each child of an individual with the 17q12 recurrent deletion has a 50% chance of inheriting the deletion.

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

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 the 17q12 recurrent deletion syndrome.

Prenatal Testing and Preimplantation Genetic Testing

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

Prenatal testing or preimplantation genetic testing using genomic testing that will detect the 17q12 recurrent deletion may be offered when:

- A parent has the 17q12 recurrent deletion;
- Neither parent has the 17q12 recurrent deletion but the couple is concerned about a recurrence in subsequent pregnancies after having had a child with the 17q12 recurrent deletion based on the theoretic possibility of parental germline mosaicism or other predisposing genetic mechanisms (presumed to be ~1%).

Pregnancies not known to be at increased risk for the 17q12 recurrent deletion. Prenatal CMA performed in follow up to indications other than a positive family history (e.g., fetal kidney anomalies detected on ultrasound examination) may detect the 17q12 recurrent deletion [Hendrix et al 2012, Wapner et al 2012]. There is a high correlation between fetal hyperechogenic kidneys and the 17q12 deletion [Jing et al 2019, Wan et al 2019, Cai et al 2020] prompting several authors to recommend genetic testing for the 17q12 recurrent deletion when hyperechogenic kidneys of unknown cause are detected prenatally [Jones et al 2015, Jing et al 2019].

Note: Regardless of whether the pregnancy is known or not known to be at increased risk for the 17q12 recurrent deletion syndrome, prenatal test results cannot reliably predict the phenotype (see Clinical Characteristics, Intrafamilial Variability).

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
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org
  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 Deletion Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HNF1B	17q12	Hepatocyte nuclear factor 1-beta	HNF1B database	HNF1B	HNF1B

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 Deletion Syndrome (View All in OMIM)

137920	RENAL CYSTS AND DIABETES SYNDROME; RCAD
189907	HNF1 HOMEOBOX B; HNF1B
614527	CHROMOSOME 17q12 DELETION SYNDROME

Molecular Pathogenesis

The 17q12 deletion is recurrent, meaning that it involves the same unique genomic sequence. The 17q12 region is considered a hot spot for copy number variants, as it has specific molecular features (known as segmental duplications) that predispose to these events [Mefford et al 2007, Moreno-De-Luca et al 2010].

Deletion mechanism. The 17q12 genomic region involved in the recurrent 17q12 deletion is flanked on each side by segmental duplications, which are highly repetitive segments of genomic material. Since these segmental duplications have a high degree of homology to one another, they can misalign during meiosis and give rise to deletions and duplications of the intervening genomic interval. This process, called nonallelic homologous recombination, accounts for the absence of the same unique genomic region in individuals with 17q12 recurrent deletion [Sharp et al 2006, Moreno-De-Luca et al 2010].

Genes of interest in this region. Genes within the 17q12 recurrent deletion region include *AATF*, *ACACA*, *C17orf78*, *DDX52*, *DHRS11*, *DUSP14*, *GGNBP2*, *HNF1B*, *LHX1*, *MRM1*, *MYO19*, *PIGW*, *SYNRG*, *TADA2A*, and *ZNHIT3*.

Three genes are of particular interest with respect to phenotypes associated with the 17q12 recurrent deletion:

- ***HNF1B.*** *HNF1B* haploinsufficiency has been established as the cause of the kidney, urogenital, and endocrine abnormalities that occur as part of the 17q12 recurrent deletion syndrome. Heterozygous pathogenic sequence variants in *HNF1B* cause renal cysts and diabetes (RCAD) syndrome, which is characterized by the combination of congenital anomalies of the kidney and urinary tract (CAKUT) and maturity-onset diabetes of the young type 5 (MODY5) [Bingham et al 2001]. While other genes in the 17q12 recurrent deletion region likely account for most of the neurodevelopmental features associated with the syndrome, isolated sequence variants within *HNF1B* have also been associated with an increased

risk for learning problems, albeit at a lesser frequency [Clissold et al 2016, Dubois-Laforgue et al 2017a, Lalière et al 2020]. Thus, more research is needed to define the role of *HNF1B* in the human brain.

- ***LHX1.*** Heterozygous *LHX1* likely pathogenic variants have been identified in females with müllerian aplasia / Mayer-Rokitansky-Küster-Hauser syndrome, though inheritance information was not available [Ledig et al 2011, Ledig et al 2012, Sandbacka et al 2013]. Because of its role in neural development, *LHX1* may also contribute to the neurodevelopmental manifestations observed in the 17q12 recurrent deletion syndrome [Moreno-De-Luca et al 2010, Nagamani et al 2010].
- ***ACACA*** encodes acetyl-CoA carboxylase 1, involved in lipogenesis in adipose tissue. There has been speculation that haploinsufficiency of *ACACA* may contribute to the leaner phenotype and decreased risk of diabetic glomerular disease in individuals with the 17q12 recurrent deletion compared to those with *HNF1B* sequence variants [Dubois-Laforgue et al 2017b].

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Acknowledgments

This work was funded in part by the National Institute for Mental Health of the National Institutes of Health under awards RO1MH074090 (to DHL and CLM), RO1MH107431 (to CLM), K23MH120376 (to DMD), and grants from the Simons Foundation (SFARI# 215355 to CLM and SFARI# 240413 to DHL). The authors would also like to thank all of the individuals and families with 17q12 deletions for their participation in these research studies.

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Revision History

- 15 October 2020 (sw) Comprehensive update posted live
- 8 December 2016 (bp) Review posted live
- 10 August 2015 (mm) Original submission

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