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15q13.3 Recurrent Deletion

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Summary

Clinical characteristics

Individuals with the 15q13.3 recurrent deletion may have a wide range of clinical manifestations. The deletion itself may not lead to a clinically recognizable syndrome and a subset of persons with the recurrent deletion have no obvious clinical findings, implying that penetrance for the deletion is incomplete. A little over half of individuals diagnosed with this recurrent deletion have intellectual disability or developmental delay, mainly in the areas of speech acquisition and cognitive function. In the majority of individuals, cognitive impairment is mild. Other features reported in diagnosed individuals include epilepsy (in ~30%), mild hypotonia, and neuropsychiatric disorders (including autism spectrum disorder, attention-deficit/hyperactivity disorder, mood disorder, schizophrenia, and aggressive or self-injurious behavior). Congenital malformations are uncommon.

Diagnosis/testing

The diagnosis of the 15q13.3 recurrent deletion is established in a proband by the presence of a heterozygous recurrent 2.0-Mb deletion at the approximate position of 30.5-32.5 Mb in the reference genome (chr15:30366247-32929476 [GRCh37/hg19]) that includes deletion of 1.5 Mb of unique sequence as well as an additional 500 kb or more of segmental duplications.

Management

Treatment of manifestations: Epilepsy is treated with anti-seizure medication (ASM). The use of valproate has been successful in a number of affected individuals, while oxcarbazepine led to clinical worsening in one affected individual. However, a variety of ASMs may be used. Standard treatment for developmental delay / intellectual disability, neuropsychiatric disorders, congenital anomalies (cardiac and/or renal anomalies), refractive errors, strabismus, and chronic ear infections / glue ear.

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Surveillance: Monitor developmental progress / education needs at each visit. Assessment for anxiety, attention, aggressive/self-injurious behavior, and new neurologic manifestations (such as seizures) at each visit. Annual audiology evaluation in infancy and childhood (or as clinically indicated). Ophthalmology evaluation per treating ophthalmologist(s).

Genetic counseling

The 15q13.3 recurrent deletion is inherited in an autosomal dominant manner. Approximately 15% are *de novo* and approximately 85% are inherited. Offspring of an individual with this deletion have a 50% chance of inheriting the deletion. Although prenatal testing is technically feasible, it is not possible to reliably predict the phenotype based on the laboratory finding of the 15q13.3 recurrent deletion.

Diagnosis

No consensus clinical diagnostic criteria for the 15q13.3 recurrent deletion have been published.

Individuals with the 15q13.3 recurrent deletion may have a wide range of clinical manifestations. The deletion itself may not lead to a clinically recognizable syndrome and a subset of persons with the recurrent deletion have no obvious clinical findings, implying that penetrance for the deletion is incomplete.

Suggestive Findings

The 15q13.3 recurrent deletion **should be considered** in individuals with the following clinical findings and family history.

Clinical features

- Intellectual disability
- Speech delay
- Seizures
- Autism
- Schizophrenia
- Behavioral findings including poor attention span, hyperactivity, mood disorder, and aggressive and/or impulsive behavior

Some affected individuals have combinations of these findings, such as intellectual disability and seizures.

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of the 15q13.3 recurrent deletion **is established** in a proband by the presence of a heterozygous recurrent 2.0-Mb deletion at the approximate position of 30.5-32.5 Mb in the reference genome that includes deletion of 1.5 Mb of unique sequence as well as an additional 500 kb or more of segmental duplications (NCBI Genome Data Viewer) (see Table 1).

Note: (1) For the purposes of this chapter, the term "15q13.3 recurrent deletion" is defined as heterozygous and by the genomic coordinates provided in Table 1; it does not denote deletions outside of this region or biallelic deletions. (2) The phenotype of significantly larger or smaller heterozygous deletions within this region and of biallelic recurrent 15q13.3 deletions may be clinically distinct from the heterozygous recurrent 15q13.3 deletion (see Genetically Related Disorders).

Although several genes of interest (e.g., *CHRNA7* and *OTUD7A*) are within the 2.0-Mb deletion, no single gene has been associated with the disease findings (see Molecular Genetics for genes of interest in the deleted region).

Genomic testing methods that determine the copy number of sequences can include **chromosomal microarray (CMA)** or **targeted deletion analysis** by fluorescence in situ hybridization (FISH), quantitative PCR, or multiplex ligation-dependent probe amplification (MLPA). Note: The 15q13.3 deletion cannot be identified by routine analysis of G-banded chromosomes or other conventional cytogenetic banding techniques.

- **Chromosomal microarray (CMA)** using oligonucleotide arrays or SNP genotyping arrays can detect the common deletion in a proband. The ability to size the deletion depends on the type of microarray used and the density of probes in the 15q13.3 region.

  Note: (1) Most individuals with the 15q13.3 recurrent deletion are identified by CMA performed in the context of developmental delay, intellectual disability, or autism spectrum disorders. (2) Prior to 2008 some CMA platforms did not include coverage for this region and thus may not have detected the deletion.

- **Targeted deletion analysis.** FISH analysis, quantitative PCR, and MLPA may be used to test at-risk relatives of a proband known to have the 15q13.3 recurrent deletion.

  Note: (1) Targeted deletion testing by FISH, quantitative PCR, or MLPA is not appropriate for an individual in whom the deletion was not detected by CMA designed to target the 15q13.3 region. (2) It is not possible to size the deletion routinely by use of FISH, quantitative PCR, or MLPA.

Table 1. Genomic Testing Used in the 15q13.3 Recurrent Deletion

Deletion [1]	ClinGen ID [2]	Region Location [3, 4]	Method	Sensitivity	
				Proband	At-risk family members
~2.0-Mb heterozygous recurrent deletion at 15q13.3 (BP4-BP5) [5]	ISCA-37411	chr15:30366247-32929476 (GRCh37/hg19)	CMA [6]	100%	100%
			FISH, quantitative PCR, or MLPA	Not applicable [7]	100%

1. See Molecular Genetics for details of the deletion.
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. ClinGen still identifies chromosome anomalies by their original ISCA ID number.
3. Genomic coordinates represent the minimum deletion size associated with 15q13.3 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 15q13.3 recurrent deletion (see Genetically Related Disorders).
4. See Molecular Genetics for genes of interest included in the deleted region.
5. The deletion occurs between the recurrent breakpoint (BP) regions BP4 and BP5 (see Molecular Genetics).
6. CMA using oligonucleotide arrays or SNP genotyping arrays. CMA designs in current clinical use target the 15q13.3 region. Note: The 15q13.3 recurrent deletion may not have been detectable by older oligonucleotide or BAC platforms.
7. FISH, quantitative PCR, and MLPA are not appropriate as a diagnostic method for an individual in whom the 15q13.3 recurrent deletion was not detected by CMA designed to target this region.

Clinical Characteristics

Clinical Description

More than 200 individuals with an approximately 2.0-Mb heterozygous recurrent deletion at 15q13.3 have been reported [Lowther et al 2015, Pavone et al 2020]. The following description of the phenotypic features associated

with this condition is based on these reports. Note: To date, no clinically significant differences have been reported between individuals with deletions BP3-BP5 or BP3-BP4 compared to those with BP4-BP5. However, this chapter focuses specifically on those with the BP4-BP5 deletion [Pavone et al 2020], as this recurrent deletion accounts for about 94% of deletions in this recurrent deletion region [Lowther et al 2015].

Table 2. 15q13.3 Recurrent Deletion: Frequency of Select Features

Feature	% of Persons w/Feature [1]	Comment
Developmental delay / intellectual disability	~59%	Accounting for ascertainment [2]
Behavioral findings	~35% [3]	
Seizures/epilepsy	~30%	
Minor dysmorphic facial features	~16%	No specific areas of the face are consistently dysmorphic & no recognizable facial features have been reported [Pavone et al 2020].
Hypotonia	~14%	
Schizophrenia	~11%	
Autism spectrum disorder	~10%	
Mood disorders	~10%	
ADHD	~7%	

AHDH = attention-deficit/hyperactivity disorder

1. Derived from 125 known affected individuals specifically with BP4-BP5 deletions [Pavone et al 2020]. Percentages are also adjusted to correct for ascertainment bias. Data from affected individuals reported by Lowther et al [2015] are included in the Pavone et al [2020] report.

2. Individuals with developmental delay / intellectual disability are more likely to undergo advanced genetic testing, including chromosomal microarray analysis, than individuals without this finding [Ziats et al 2016].

3. Percentage of reported individuals with behavior problems ranges from 35% to 51%, although the report that found a high percentage of behavior problems excluded publications that contain fewer than three affected individuals and did not correct for ascertainment bias.

Intellectual disability and developmental delay. Accounting for ascertainment, intellectual disability or developmental delay has been observed in approximately 59% of individuals with the 15q13.3 recurrent deletion [Lowther et al 2015, Pavone et al 2020]. Developmental delays are mainly delays in speech acquisition and cognitive function rather than motor disability, although hypotonia can contribute to mild motor delays (see **Hypotonia**). In the majority of individuals, cognitive impairment is mild. However, a subset of individuals with moderate-to-severe disability have been reported [Ben-Shachar et al 2009, van Bon et al 2009, Lowther et al 2015]. In a small study of 18 individuals with 15q13.3 deletions (15 with the recurrent BP4-BP5 deletion and 3 others with larger deletions that included BP3-BP5) who underwent comprehensive IQ assessment, the average verbal and nonverbal subcomponents of the IQ test were 64.3 and 60.1, respectively [Ziats et al 2016], suggesting no significant difference between verbal and nonverbal IQ scores in affected individuals.

Some individuals with the 15q13.3 recurrent deletion have no discernible clinical features, including developmental or cognitive delays. However, data on 23,838 adult "controls" (individuals who did not undergo genetic testing for an indication of developmental concerns or other clinical features) detected no 15q13.3 deletions [Lowther et al 2015]. Another study reporting on a population-based sample (n=101,655) identified 25 such recurrent deletions (0.025%) [Stefansson et al 2014].

Epilepsy. About 30% of individuals with the 15q13.3 recurrent deletion are diagnosed with epilepsy [Lowther et al 2015, Pavone et al 2020]. Children commonly present with absence seizures that start in childhood, but this could be accompanied by atypical features such as persistence into adolescence, early onset, absence status epilepticus, and treatment resistance. More rare generalized seizure types (such as myoclonic absence and atonic

seizures in addition to focal with impaired awareness non-motor onset seizures) were also observed. EEG may show a mixture of generalized and focal findings. The presence of combined seizure types and EEG findings should be treated with caution, as some anti-seizure medications (ASMs) (i.e., specific sodium channel blockers such as oxcarbazepine) could potentially worsen seizures (see Management), although this requires further study. Valproate appeared effective, but more studies are needed to confirm the effectiveness of other ASMs and therapies [Whitney et al 2021].

Hypotonia. In general, hypotonia is mild and body muscular tone improves during childhood. Walking without support is often achieved between age 12 months and three years (average: 21.5 months). Hypotonia likely contributes to the delay in achievement of motor milestones reported in some individuals.

Neuroimaging. Brain MRI findings are not frequently observed or reported; they include rare reports of arachnoid cysts, cerebellar vermis hypoplasia, ventricular dilatation, corpus callosal agenesis, focal cortical dysplasia, and heterotopia. Other nonspecific findings such as mild prominence of extra cerebral spaces, focal volume loss, prominent cerebellar folia, and T_2 hyperintensities within the subcortical white matter have also been reported [Whitney et a 2021].

Neuropsychiatric disorders. Behavioral/psychiatric findings are present in about one third of individuals and mainly include autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), mood disorder, self-mutilation, and aggressive and/or impulsive behavior [Lowther et al 2015].

In three studies, the 15q13.3 recurrent deletion was enriched in cohorts of individuals with schizophrenia compared to controls [International Schizophrenia Consortium 2008, Stefansson et al 2008, Lowther et al 2015]. Accounting for ascertainment bias, schizophrenia may be present in 11% of adult individuals with the 15q13.3 recurrent deletion [Lowther et al 2015].

Facial features. No specific dysmorphic features have been observed. If present, dysmorphic features are nonspecific [Pavone et al 2020].

Rare features. Severe congenital malformations are uncommon.

- **Heart.** Structural congenital cardiac malformations are seen in a low number of individuals (3%) [Lowther et al 2015]. Hypercholesterolemia has been occasionally reported.
- **Ocular anomalies** have been reported in 6% of individuals [Pavone et al 2020], most frequently strabismus and astigmatism.
- **Hearing.** In general, children and adults have normal hearing. However, temporary hearing loss due to recurrent ear infections in infancy may occur.
- **Growth.** Abnormalities in growth may occur (both undergrowth and overgrowth), although most children grow normally.

Other. It is unclear if the following represent rare findings of the 15q13.3 recurrent deletion or chance co-occurrences that are unrelated [van Bon et al 2009, Lowther et al 2015, Pavone et al 2020]:

- **Gastrointestinal findings** including gastrointestinal reflux disease, hiatal hernia, and diverticulosis
- **Endocrine anomalies** such as hypothyroidism and insulin-resistant diabetes
- **Urogenital findings** such as renal cyst, urethral stricture, and nephrolithiasis
- **Placenta previa,** present of 1.6% in probands (i.e., ≤5x the standard population estimates). However, further studies including the investigation of possible confounding risk factors are needed to confirm this finding [Lowther et al 2015].

Genotype-Phenotype Correlations

No phenotype-genotype correlations are known; the phenotypic findings in individuals with the 15q13.3 recurrent deletion range from normal to significantly impaired.

Penetrance

The penetrance of the 15q13.3 recurrent deletion is incomplete and highly variable. In total, 80.5% of reported individuals with the recurrent deletion have at least one of the following neurodevelopmental or neuropsychiatric diagnoses [Lowther et al 2015]:

- Developmental delay / intellectual disability
- Speech delays/impairment
- Epilepsy
- Autism spectrum disorder
- Schizophrenia
- Mood disorder
- ADHD

Nomenclature

Owing to the lack of a recognizable phenotype in persons with the 15q13.3 recurrent deletion, it has not been described eponymously. Although the 15q13.3 region includes other segmental duplication breakpoints [Makoff & Flomen 2007, Shinawi et al 2009], the 15q13.3 recurrent deletion specifically refers to deletion of the 2.0-Mb region at the approximate position of 30.5-32.5 Mb in the reference genome (NCBI Genome Data Viewer).

Prevalence

The prevalence of the 15q13.3 recurrent deletion in the general population is estimated at 1:5,500 [Gillentine et al 2018].

Genetically Related Disorders

15q13.3 duplication. Reciprocal duplication in the 15q13.3 region has been observed in individuals with a range of neuropsychiatric phenotypes including intellectual disability, autism spectrum disorder, and attention-deficit/hyperactivity disorder (ADHD) [van Bon et al 2009, Szafranski et al 2010, Williams et al 2012]. These duplications have considerably lower penetrance than the reciprocal deletion. Smaller 15q13.3 duplications limited to *CHRNA7* have also been reported. However, many clinical labs are now interpreting the duplications that include only *CHRNA7* to be likely benign.

Due to the limited number of published cases reporting on other clinical features in addition to those used for ascertainment, the associated phenotype of the 15q13.3 duplication is still uncertain. Phenotypic features of reported individuals include intellectual disability, ADHD, behavior problems, autism spectrum disorders, hypotonia, obesity, and recurrent ear infections. No dysmorphic features, recurrent congenital anomalies, or epileptic seizures were noted. The duplication can either be *de novo* or inherited from an apparently unaffected parent. In a control cohort of 23,838 individuals, seven 15q13.3 reciprocal duplications were identified (0.029%) [Lowther et al 2015].

15q13.3 deletions that overlap the 2.0-Mb recurrent region. A few individuals with larger overlapping deletions (~4 Mb) have been reported [Sharp et al 2008, van Bon et al 2009, Lowther et al 2015, Pavone et al 2020]. There are also individuals who have a smaller (<700-kb) deletion nested within the 15q13.3 recurrent deletion region [Hoppman-Chaney et al 2013, Gillentine & Schaaf 2015, Lowther et al 2015]. These deletions

overlap *CHRNA7* only or *CHRNA7* and the first exon of *OTUD7A*. Individuals with these *CHRNA7* deletions have similar phenotypes to those with the larger BP4-BP5 and BP3-BP5 deletions [Gillentine & Schaaf 2015].

Homozygous 15q13.3 recurrent deletion. Biallelic 15q13.3 recurrent deletions (BP4-BP5) lead to a consistent phenotype including encephalopathy, hypotonia, intellectual disability, cortical vision impairment, optic nerve abnormality, epilepsy, and abnormal EEG findings [Simon et al 2019].

Differential Diagnosis

The differential diagnosis of the 15q13.3 recurrent deletion comprises an extensive and broad spectrum of disorders and includes any cause of intellectual disability / developmental delay, schizophrenia, autism spectrum disorders, and epilepsy without additional distinguishing clinical features. All chromosome anomalies and genes known to be associated with intellectual disability (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 15q13.3 recurrent deletion.

Management

No clinical practice guidelines for the 15q13.3 recurrent deletion have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with the 15q13.3 recurrent deletion, 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 the 15q13.3 Recurrent Deletion

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl ADHD &/or findings suggestive of ASD, schizophrenia, & mood disorders
Neurologic	Neurologic eval	Consider EEG & brain MRI if seizures are a concern.
Cardiovascular	Consider echocardiogram.	If there are concerning clinical signs &/or symptoms
Eyes	Ophthalmologic eval	To assess vision & strabismus
Hearing	Audiologic eval	Assess for hearing loss in those w/recurrent ear infections.
Genitourinary	Consider baseline renal ultrasound. [1]	To assess for renal anomalies & hydronephrosis
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of 15q13.3 recurrent deletion to facilitate medical & personal decision making

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder
1. It is unclear whether renal anomalies are a component of this condition. However, as the diagnosis is often made early in life, particularly in those with developmental delay, signs/symptoms of urinary findings may be lacking at the time of diagnosis. Baseline renal imaging, which is not invasive, is therefore left to the discretion of the treating physician.
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Ideally, treatment is tailored to the specific needs of the individual. Because of the high incidence of neurodevelopmental disability, referral to a clinical psychologist for neuropsychological and/or developmental assessment for treatment recommendations is suggested.

Additional management in healthy adults who have the 15q13.3 recurrent deletion is not necessary, although their medical care providers may benefit from being alerted to the possible increased risk for late-onset manifestations (e.g., schizophrenia).

Table 4. Treatment of Manifestations in Individuals with 15q13.3 Recurrent Deletion

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Psychiatric disorders	Standard treatment per psychologist/psychiatrist	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Use of valproate has been successful in some affected persons. [1] • Oxcarbazepine led to clinical worsening in 1 affected person. [1] • Ketogenic diet & cannabidiol have been tried in 1 person each, w/no efficacy. [1] • Education of parents/caregivers [2]
Congenital heart defects	Standard treatment per cardiologist	
Eyes	Standard treatment per ophthalmologist	Refractive errors, strabismus
Hearing	Grommets in recurrent glue ear & middle ear infections	
Renal anomalies / Hydronephrosis [3]	Standard treatment per urologist &/or nephrologist	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
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; OT = occupational therapy; PT = physical therapy
1. Whitney et al [2021]
2. 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.
3. It is unclear whether renal anomalies are a component of this condition. However, if renal anomalies are present, treatment is the same as for those in the general population.

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 and hearing 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.

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

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with the 15q13.3 Recurrent Deletion

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Psychiatric/ Behavioral	Behavioral assessment for anxiety, ADHD, ASD, & aggressive or self-injurious behavior	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures.	
Ophthalmologic involvement	Ophthalmologic eval	Per treating ophthalmologist(s)
Hearing	Audiologic eval	Annually in infancy & childhood or as clinically indicated
Family/ Community	Assess family need for social work support, care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder

Agents/Circumstances to Avoid

About 11% of individuals with the 15q13.3 recurrent deletion develop schizophrenia. The use of cannabis has been reported as a risk factor for development of schizophrenia. Although no studies have been performed on the possible additional risk of the use of cannabis by persons with the 15q13.3 recurrent deletion, discouraging the use of cannabis may be considered.

It is unclear if oxcarbazepine should be avoided. In at least one affected individual with seizures, oxcarbazepine led to clinical worsening [Whitney et al 2021]. However, this is only a single case.

Evaluation of Relatives at Risk

Using genomic testing that will detect the 15q13.3 recurrent deletion found in the proband, it is appropriate to evaluate the older and younger sibs of a proband in order to identify as early as possible those who would benefit from close assessment/monitoring of developmental milestones in childhood.

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 15q13.3 recurrent deletion is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 85% of individuals with a 15q13.3 recurrent deletion inherited the genetic alteration from a parent. The parent with the 15q13.3 recurrent deletion may be phenotypically normal or have features associated with the 15q13.3 recurrent deletion.
- The 15q13.3 recurrent deletion occurs *de novo* in approximately 15% of probands.
- Genomic testing that will detect the 15q13.3 recurrent deletion present in the proband is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the 15q13.3 recurrent deletion identified in the proband is not identified in either confirmed biological parent, the following possibilities should be considered:
  - The proband has a *de novo* deletion.
  - The proband inherited a deletion 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 sibs of a proband depends on the genetic status of the parents:

- If one of the parents has the 15q13.3 recurrent deletion identified in the proband, the risk to each sib of inheriting the deletion is 50%. It is not possible to predict the phenotype in sibs who inherit a 15q13.3 recurrent deletion because the penetrance of the deletion is incomplete and clinical manifestations are highly variable; phenotypic findings in individuals with the 15q13.3 recurrent deletion range from normal to significantly impaired.
- If the 15q13.3 recurrent deletion identified in the proband cannot be detected in either of the parents, the chance of recurrence 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 15q13.3 recurrent deletion has a 50% chance of inheriting the deletion; it is not possible to predict the phenotype in offspring who inherit the deletion.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the 15q13.3 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. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made 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 15q13.3 recurrent deletion.

Prenatal Testing and Preimplantation Genetic Testing

Pregnancies known to be at increased risk for the 15q13.3 recurrent deletion. Once a 15q13.3 recurrent deletion has been identified in a family member, prenatal and preimplantation genetic testing are possible.

Pregnancies not known to be at increased risk for the 15q13.3 recurrent deletion. CMA performed in a pregnancy for other indications (e.g., advanced maternal age) may detect the 15q13.3 recurrent deletion.

Note: Regardless of whether a pregnancy is known or not known to be at increased risk for the 15q13.3 recurrent deletion, the prenatal finding of a 15q13.3 recurrent deletion cannot be used to predict the phenotype (see Penetrance).

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.

- **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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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. 15q13.3 Recurrent Deletion: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ARHGAP11B	15q13.2	Inactive Rho GTPase-activating protein 11B		ARHGAP11B	ARHGAP11B
CHRNA7	15q13.3	Neuronal acetylcholine receptor subunit alpha-7		CHRNA7	CHRNA7
FAN1	15q13.3	Fanconi-associated nuclease 1		FAN1	FAN1
KLF13	15q13.3	Krueppel-like factor 13		KLF13	KLF13
OTUD7A	15q13.3	OTU domain-containing protein 7A		OTUD7A	OTUD7A
TRPM1	15q13.3	Transient receptor potential cation channel subfamily M member 1	TRPM1 @ LOVD	TRPM1	TRPM1

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 15q13.3 Recurrent Deletion (View All in OMIM)

118511	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, ALPHA POLYPEPTIDE 7; CHRNA7
605328	KRUPPEL-LIKE FACTOR 13; KLF13
612001	CHROMOSOME 15q13.3 DELETION SYNDROME
612024	OTU DOMAIN-CONTAINING PROTEIN 7A; OTUD7A

Molecular Pathogenesis

The proximal 15q region is characterized by a high density of low copy repeats [Bailey et al 2002, Makoff & Flomen 2007, Sharp et al 2008] and is therefore susceptible to several genomic rearrangements leading to partial aneuploidy. The breakpoints (BPs) of such rearrangements cluster in the low copy repeats. To date, six BPs have been characterized in the 15q11q14 region [Mignon-Ravix et al 2007]. The recurrent 2.0-Mb 15q13.3 deletion occurs between the breakpoints designated as BP4 and BP5 [Sharp et al 2008].

The 2.0-Mb deletion arises when the flanking low copy repeats are positioned in a direct orientation, most probably through a common inversion of the BP4-BP5 region, which generates a configuration predisposing to nonallelic homologous recombination [Sharp et al 2008].

Mechanism of disease causation. The 2.0-Mb microdeletion results in the loss of six known genes: *MTMR15*, *TRPM1*, *MTMR10*, *KLF13*, *OTUD7A*, and *CHRNA7*. How deletion of these genes results in the clinical findings of this condition is unknown; ongoing investigations may identify one or more genes as responsible for the phenotypic features.

Smaller 15q13.3 deletions overlapping only *CHRNA7* and the first exon of *OTUD7A* have been found in individuals with developmental delay, intellectual disability, autism spectrum disorders, epilepsy, and

schizophrenia (see Genetically Related Disorders), thus implicating one of those two genes as the likely cause of the neuropsychiatric manifestations of the 15q13.3 recurrent deletion. *CHRNA7* encodes a synaptic ion channel protein mediating neuronal signal transmission [Taske et al 2002, Hong et al 2004, Leonard & Freedman 2006, Iwata et al 2007]. No individuals with a pathogenic loss-of-function variant in *CHRNA7* have been reported to date. *OTUD7A* encodes a deubiquitinating enzyme localizing to dendritic spines in cortical neurons [Uddin et al 2018]. Loss-of-function pathogenic variants in *OTUD7A* have been reported in individuals with schizophrenia [Kozlova et al 2022]. A homozygous missense variant of *OTUD7A* was found in an individual with epileptic encephalopathy [Garret et al 2020], and biallelic loss of *OTUD7A* was reported in an individual with severe hypotonia, intellectual disability, and seizures [Suzuki et al 2021]. Neurologic phenotypes were also seen in an *Otud7a* knockout mouse [Garret et al 2020].

Chapter Notes

Revision History

- 17 November 2022 (ma) Comprehensive update posted live
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- 18 May 2010 (bvb) Original submission

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