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3q29 Recurrent Deletion

Synonyms: 3q29 Deletion Syndrome, 3q29 Microdeletion Syndrome

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Summary

Clinical characteristics

3q29 recurrent deletion is characterized by neurodevelopmental and/or psychiatric manifestations including mild-to-moderate intellectual disability (ID), autism spectrum disorder (ASD), anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), executive function deficits, graphomotor weakness, and psychosis/schizophrenia. Age at onset for psychosis or prodrome can be younger than the typical age at onset in the general population. Neurodevelopmental and psychiatric conditions are responsible for the majority of the disability associated with the 3q29 deletion. Other common findings are failure to thrive and feeding problems in infancy that persist into childhood, gastrointestinal disorders (including constipation and gastroesophageal reflux disease [GERD]), ocular issues, dental anomalies, and congenital heart defects (especially patent ductus arteriosus). Structural anomalies of the posterior fossa may be seen on neuroimaging. To date more than 200 affected individuals have been identified.

Diagnosis/testing

The diagnosis of the 3q29 recurrent deletion is established by identification of a heterozygous 1.6-Mb deletion at the approximate position of chr3:195998129-197623129 in the reference genome (NCBI Build 38).

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Management

Treatment of manifestations: Early speech and language therapy to address speech delays; physical/occupational therapy as needed to address motor issues; individualized education program for school-age children; care by a child psychiatrist/psychologist as needed for neuropsychiatric disorders with transfer of care to an adult psychiatrist when appropriate; cognitive behavioral therapy to address social disability and/or anxiety; adaptive behavior as needed; applied behavioral analysis for ASD; medication as needed for anxiety, ADHD, or psychosis; standard treatment of seizures; feeding therapy and consideration of gastrostomy tube as needed; routine management of musculoskeletal issues, GERD, strabismus, dental issues, congenital heart defects, recurrent ear infections, and epistaxis; consider behavioral treatment for enuresis; implement healthy sleep hygiene; family support.

Surveillance: At each visit: monitor developmental progress, educational needs, growth, nutrition, and feeding; assess for seizures, gastrointestinal issues, otitis, enuresis, and/or sleep issues. Annual assessment for neuropsychiatric manifestations and scoliosis; annual ophthalmology examination; dental examination every six months.

Evaluation of relatives at risk: If one of the proband's parents has the 3q29 recurrent deletion, it is appropriate to test at-risk sibs of the proband in order to identify those who would benefit from close assessment/monitoring of developmental milestones (in children) and monitoring for neuropsychiatric manifestations (in children and adults).

Genetic counseling

3q29 recurrent deletion is an autosomal dominant disorder typically caused by a *de novo* deletion. If the proband represents a simplex case (i.e., a single affected family member) and neither parent has the 3q29 recurrent deletion or a balanced chromosome rearrangement, the recurrence risk to sibs is low (presumed to be <1%) but greater than that of the general population because of the possibility of parental mosaicism for the deletion. Each child of an individual with the 3q29 recurrent deletion has a 50% chance of inheriting the deletion. Once the 3q29 recurrent deletion has been identified in an affected family member, prenatal testing for a pregnancy at increased risk for the 3q29 recurrent deletion and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

The 3q29 recurrent deletion **should be considered** in individuals with the following clinical findings [Sanchez Russo et al 2021]:

- Developmental delay typically including speech and motor delays
- Intellectual disability; mild to moderate (34%), severe (<5%)
- Neuropsychiatric disorders including attention-deficit/hyperactivity disorder, anxiety disorders, and/or autism spectrum disorder (ASD)
- Failure to thrive and/or feeding problems in infancy that persist into childhood
- Gastrointestinal disorders including gastroesophageal reflux disease
- Ocular issues
- Dental anomalies
- Congenital heart defects, especially patent ductus arteriosus
- Subtle facial dysmorphology including a prominent forehead, prominent nasal tip, and thin vermilion of the upper lip [Mak et al 2021]

Of note, most individuals with the 3q29 recurrent deletion are identified by chromosomal microarray (CMA) analysis performed in the context of evaluation for developmental delay (DD), intellectual disability (ID), and/or ASD.

Establishing the Diagnosis

The diagnosis of the 3q29 recurrent deletion **is established** by identification of a heterozygous 1.6-Mb deletion at chromosome 3q29, typically by CMA.

For this *GeneReview*, the 3q29 recurrent deletion is defined as the presence of a recurrent 1.6-Mb deletion at the approximate position of chr3:195998129-197623129 in the reference genome (NCBI Build 38).

Note: (1) Since these deletions are recurrent and mediated by segmental duplications, the unique genetic sequence that is deleted is the same in all individuals with the deletion; however, the reported size of the deletion: (a) may be larger if adjacent segmental duplications are included in the size; and (b) may vary based on the design of the microarray used to detect it (see Molecular Pathogenesis). (2) The phenotype of significantly larger or smaller deletions within this region may be clinically distinct from the 3q29 recurrent deletion. (3) Although pathogenic variants in a single gene in the 3q29 region are not causative of the 3q29 recurrent deletion, several genes of interest have been identified (see Molecular Genetics).

Genomic testing methods that determine the copy number of sequences can include **CMA** or **targeted deletion analysis**. Note: The 3q29 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 3q29 region.

  Note: (1) Most individuals with a 3q29 recurrent deletion are identified by CMA performed in the context of evaluation for DD, ID, or ASD. (2) Prior to 2005 many CMA platforms did not include coverage for this region and thus may not have detected this deletion. This recurrent deletion was detected by early BAC arrays; at least 14 individuals with 3q29 deletion were identified with this technology [Ballif et al 2008].

- **Targeted deletion analysis.** FISH analysis, quantitative PCR, multiplex ligation-dependent probe amplification, or other targeted quantitative methods may be used to test relatives of a proband known to have the 3q29 recurrent deletion.

  Note: (1) Targeted deletion testing is not appropriate for an individual in whom the 3q29 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 the 3q29 Recurrent Deletion

Deletion [1]	Method	Sensitivity	
		Proband	At-risk family members
1.6-Mb heterozygous deletion at 3q29 • ISCN: seq[GRCh37] del(3)(q29) chr3:195,756,054-197,344,665 [2] • ISCA-37443	CMA [3]	100%	100%
	Targeted deletion analysis [4]	See footnote 5.	100% [6]

1. See Molecular Genetics for details of the deletion and genes of interest.
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). Genomic coordinates represent the minimum deletion size associated with the 3q29 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 3q29 recurrent deletion (see Genetically Related Disorders).
3. Chromosomal microarray analysis (CMA) using oligonucleotide or SNP arrays. CMA designs in current clinical use target the 3q29 region.
4. Targeted deletion analysis methods can include FISH, quantitative PCR, and multiplex ligation-dependent probe amplification (MLPA) as well as other targeted quantitative methods.
5. Not applicable. Targeted deletion analysis is not appropriate for an individual in whom the 3q29 recurrent deletion was not detected by CMA designed to target this region.
6. Targeted deletion analysis may be used to test at-risk relatives of a proband known to have the 3q29 recurrent deletion.

Clinical Characteristics

Clinical Description

3q29 recurrent deletion is characterized by neurodevelopmental and/or psychiatric manifestations. Other common findings are failure to thrive, feeding problems, gastrointestinal disorders, ocular issues, dental anomalies, and congenital heart defects. To date more than 200 affected individuals have been identified. The summary below is based on the comprehensive review of all reported individuals in Cox & Butler [2015], the self-reported findings in 44 individuals from the 3q29 Deletion Registry [Glassford et al 2016], and deep phenotyping of 32 individuals [Sanchez Russo et al 2021].

Table 2. 3q29 Recurrent Deletion: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
DD	70%-90%	Speech delay (60%), motor delay
ID	30%-40%	Mild to moderate (34%), severe (<5%)
ADHD	63%	
Anxiety disorders	40%	Generalized anxiety disorder, separation anxiety, social anxiety disorder, specific phobias
ASD	38%	
Executive function deficits	46%	
Graphomotor weakness	78%	
Psychosis/ Schizophrenia	>20%	%s based on a small sample of young persons still at risk for these manifestations; prevalence is likely higher.

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Musculoskeletal concerns	84%	Chest deformities (41%)
GI issues / Nutrition & feeding	>80%	Pediatric feeding disorder (60%), gastroesophageal reflux (50%), failure to thrive (44%), constipation (41%)
Ocular phenotypes	59%	Strabismus (28%)
Dental anomalies	41%	
Allergies	28%	
Congenital heart defects	25%	
Recurrent ear infections	22%	
Epistaxis	22%	May require surgical mgmt. Additional bleeding disorders have not been reported to date.
Enuresis	22%	Cause is unknown to date.
Sleep disturbance	31%	Reported in persons of all ages
Posterior fossa abnormalities on brain MRI	71%	Cerebellar vermis hypoplasia (33%), retrocerebellar arachnoid cyst (29%)

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; DD = developmental delay; GI = gastrointestinal; ID = intellectual disability

Developmental delay. Developmental milestones are delayed between six to twelve months.

Speech delay is reported in 60% of individuals. Speaking single words occurs at an average age of 23 months. Receptive language delay is reported in 33% and verbal apraxia (a motor speech disorder) is reported in 19%. Dysphasia/aphasia is reported in 10%. Only one of 44 individuals reported to have the 3q29 deletion is completely nonverbal [Glassford et al 2016].

Motor delay. Hypotonia is reported in 34% during the first year of life. Independent walking is usually achieved at age 20 months. Despite cerebellar anomalies observed on MRI, no pronounced ataxia or gait abnormalities are observed [Sanchez Russo et al 2021].

Cognitive issues. Children with the 3q29 deletion show a range of intellectual ability, with approximately 34% having mild-to-moderate intellectual disability (ID). Fewer than 5% have severe ID. IQ measures reveal a wide differential between subtest scores, with on average a 14-point absolute difference between verbal and nonverbal IQ subtest scores. Although speech delay is common in individuals with the 3q29 recurrent deletion, among individuals age six years and older, 61% have a verbal subtest score that is higher than their nonverbal subtest score (see medRxiv). Sixty-six percent of children with the 3q29 recurrent deletion have IQ scores within the normal range; however, these individuals may have substantial neurodevelopmental and psychiatric disability that is not captured by IQ measures.

Neuropsychiatric disorders

- ASD (38%). Individuals with the 3q29 recurrent deletion without a diagnosis of autism may exhibit social disability [Pollak et al 2019].
- Anxiety disorder (40%)
- Schizophrenia (at least 20%) [Mulle et al 2010, Mulle 2015, Sanchez Russo et al 2021]

- ADHD (63%)
- Bipolar disorder (5%)

Individuals with the 3q29 recurrent deletion may exhibit more than one neuropsychiatric disorder. For example, roughly 50% of individuals with the 3q29 deletion and ASD also report an anxiety disorder.

The age at onset for psychosis or prodrome can be younger than the typical age at onset in the general population. Early-onset psychosis was reported in one boy age five years [Sagar et al 2013] and one girl age ten years with the 3q29 deletion [Quintero-Rivera et al 2010]. Murphy et al [2020] reported attenuated psychosis syndrome in a boy age eight years. The average age of onset for schizophrenia and psychosis in the general population is 20-25 years.

Executive function deficits. Executive function, or the higher-order cognitive processes that regulate planning, decision making, and goal-oriented behavior, are substantially impaired in nearly half of individuals with the 3q29 recurrent deletion.

Graphomotor weakness. Graphomotor skills, or the skills required for writing and other fine-motor tasks, are substantially impaired in most individuals with the 3q29 recurrent deletion and can lead to difficulties in language learning and literacy. If not recognized, graphomotor weakness will present challenges in educational settings.

Seizures occur in 13% of reported individuals and are generally mild and respond to standard anti-seizure treatment. Seizures may be atonic (3%), febrile (6%), nocturnal (3%), or unspecified (3%).

Musculoskeletal anomalies include chest deformities such as pectus excavatum (25%) and pectus carinatum (9%). There is elevated prevalence of scoliosis (6%). Lower-extremity anomalies are reported in 72%, including abnormal toes (28%), medial rotation of the medial malleolus (31%), and pes planus (31%). Upper-extremity anomalies are reported in 47%, such as long, thin fingers (25%) and abnormal palmar creases (9%).

Gastrointestinal issues. Pediatric feeding problems are present in 60% and failure to thrive in 44%, sometimes necessitating feeding by gastrostomy tube (see medRxiv). Additional gastrointestinal issues include gastroesophageal reflux disease (50%), chronic constipation (41%), dysphagia (12%), hiatal hernia (5%), and chronic diarrhea (5%).

Ocular anomalies include astigmatism, hypermetropia, myopia, and strabismus. Strabismus is present in 28% of individuals with the 3q29 deletion; of these, approximately 30% require surgical correction.

Dental anomalies include dental caries (24%), weak tooth enamel (19%), enamel hypoplasia (10%), and missing teeth (5%). Abnormal dental spacing is also reported with crowded teeth (24%), widely spaced teeth (17%), and diastema between the central incisors (12%). Abnormally large teeth in reported in 10%, and abnormally small teeth in 7%.

Allergies include seasonal allergies (16%) and food allergies (13%). Rarely, individuals report drug allergies (3%). Immunoglobulin (Ig) deficiencies including IgA deficiency (3%) and IgG deficiency (3%) have been reported.

Congenital heart defects include patent ductus arteriosus (12%), ventricular septal defect (5%), and pulmonary valvar stenosis (5%).

Craniofacial features. Systematic characterization of craniofacial features on a cohort of 31 individuals with the 3q29 recurrent deletion showed a subtle but seemingly non-random pattern of craniofacial findings [Mak et al 2021]. Dysmorphic features were seen in the vast majority of individuals. The most common findings included prominent forehead and wide nose in almost half of individuals, prominent nasal tip in approximately 35%, and thin vermilion of the upper lip in approximately 25% of individuals. Other common findings include low-

hanging columella (23%), prominent nasal bridge (23%), and incisor macrodontia (23%). Phenotyping technology (Face2gene), successfully differentiated between an individual with the 3q29 deletion and a control individual 87.3% of the time (p-value of 0.006).

Genotype-Phenotype Correlations

No genotype-phenotype correlations for the 3q29 recurrent deletion are known.

Penetrance

Penetrance for the 3q29 recurrent deletion is not known. Reports of the deletion having been inherited from an unaffected parent suggest that while penetrance is high, it is likely not 100%. However, in reports of inherited 3q29 deletion, transmitting parents are rarely assessed for neurodevelopmental and psychiatric phenotypes. One transmitting parent who was assessed with a comprehensive phenotyping protocol was found to have schizoaffective disorder, ADHD, panic disorder, social anxiety disorder, clinically significant deficits in executive function, and significant delays in adaptive behavior – all previously undiagnosed. This individual had an average IQ score of 94 [Murphy et al 2020].

Prevalence

The approximate prevalence is 1:30,000-1:40,000, based on (1) a large population-based study in Iceland in which three of 101,655 individuals tested had the 3q29 recurrent deletion [Stefansson et al 2014] and (2) prevalence in the UK Biobank, in which five individuals with the 3q29 recurrent deletion were identified in a population-based cohort of 152,728 individuals [Kendall et al 2017]. Prevalence in other populations is not known.

Genetically Related Disorders

At least 50 individuals with **recurrent 3q29 duplication** have been reported in the literature. Ballif et al [2008] summarized manifestations in eight individuals and found that at least half had intellectual disability, microcephaly, and obesity. A more recent study described 31 individuals with the 3q29 duplication; feeding problems (55%), failure to gain weight (42%), and hypotonia (39%) were common in infancy. Later in childhood, phenotypes that emerge include learning problems (71%), seizures (26%), anxiety disorders (32%), and autism spectrum disorder (39%) [Pollak et al 2020].

Differential Diagnosis

The differential diagnosis of the 3q29 recurrent deletion is broad due to the variable spectrum and presence of relatively common abnormal phenotypes that occur in affected individuals including developmental delay, learning problems, and neuropsychiatric disorders. All manifestations of the 3q29 recurrent deletion can also be seen in individuals with other genomic disorders.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with the 3q29 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 3q29 Recurrent Deletion

System	Evaluation	Comment
Neuro-developmental	Eval by developmental pediatrician &/or clinical psychologist	• Eval for developmental needs & early intervention (e.g., PT, speech-language therapy, cognitive behavioral therapy for social skills training) • Eval of fine motor function (e.g., OT) • Eval for ASD, cognitive ability, & for executive function deficits
Psychiatric	Eval by child/adult psychiatrist	Eval for anxiety disorders, ADHD, & emerging features of prodrome/psychosis
Neurologic	• Eval for seizures if indicated • Eval of muscle tone • Brain MRI to identify posterior fossa anomalies	Referral to neurologist as needed
Musculo-skeletal	Clinical exam for chest anomalies, flat feet, & scoliosis	Referral to orthopedist as needed
GI/Nutrition	• Assess growth & feeding • Assess for signs/symptoms of GER, constipation, &/or chronic diarrhea	
Ocular	Ophthalmology exam	To assess vision, evaluate for refractive errors, & identify strabismus
Dental	Dental eval for abnormal enamel & tooth shape & number	Initial pediatric dental eval by age 1 yr
Cardiovascular	Eval by cardiologist & echocardiogram for congenital heart disease	
Ears, nose throat	• Otolaryngology eval • Audiology eval	Eval for recurrent ear infections &/or epistaxis as needed
Renal	Assess for enuresis.	
Pulmonary & sleep	• Assess for sleep issues. • Polysomnography as needed	Referral to pulmonologist / sleep clinic as needed
Allergy & immunology	• Allergy testing as needed • Assess for food allergies.	Referral to specialist as needed
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of 3q29 deletion to facilitate medical & personal decision making

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; GER = gastroesophageal reflux; GI = gastrointestinal; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with 3q29 Recurrent Deletion

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	• Early speech & language therapy to address speech delays • PT/OT as necessary to address fine & gross motor delays • IEP for school-age children	

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Neuropsychiatric disorders	• Care by a child psychiatrist for anxiety disorder &/or other neuropsychiatric manifestations w/transfer of care to adult psychiatrist when appropriate • Cognitive behavioral therapy for social disability &/or anxiety • Adaptive behavior (e.g., social skills training) • Applied behavioral analysis or other treatment for manifestations of ASD • Medication as necessary for anxiety disorder, ADHD, or psychosis	Because of the risk of psychosis assoc w/ 3q29 deletion, cautious use of stimulant treatment for ADHD, w/explicit monitoring for emerging psychosis, is recommended. Medications less likely to drive frank psychotic symptoms (e.g., bupropion, atomoxetine) could be considered as alternatives to amphetamines or methylphenidate.
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Musculoskeletal issues	Treatment per orthopedist	
Poor weight gain / FTT	Feeding therapy (incl nutrition assessment) w/pediatric feeding specialist or behavioral pediatric psychologist	Consider gastrostomy tube for severe feeding problems & continued FTT.
GER	Age-specific treatment for reflux per gastroenterologist incl testing for food allergies	
Bowel dysfunction	• Behavioral &/or medical treatment of constipation (stool softeners, prokinetics, osmotic agents, or laxatives) if persistent • Consider referral to gastroenterologist.	
Strabismus	Treatment per ophthalmologist	May require patching or surgery
Dental anomalies/ caries	May require: • More frequent dental exams & cleanings • Assistance w/daily brushing & flossing	
Cardiac anomalies	Management per cardiologist &/or cardiothoracic surgeon	
Ear infections	Standard medical &/or surgical management as recommended by otolaryngologist	
Epistaxis	Standard treatment as recommended by otolaryngologist	
Enuresis	• Consider eval for enuresis if persistent. • Consider behavioral interventions incl alarm techniques if indicated. • Assess for medications that could contribute to enuresis.	
Sleep issues	• Recommendations for implementing healthy sleep hygiene habits • Referral to pulmonologist/sleep clinic as needed	

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.	Consider involvement in adaptive sports or Special Olympics.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; ASM = anti-seizure medication; DD/ID = developmental delay / intellectual disability; FTT = failure to thrive; GER = gastroesophageal reflux; IEP = individualized education program; 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 5. Recommended Surveillance for Individuals with 3q29 Recurrent Deletion

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit throughout early childhood
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attentional difficulties, & emerging symptoms of schizophrenia prodrome or psychosis	Annual evals; more often if symptoms begin to emerge or medication is necessary
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new seizures.	At each visit
Scoliosis	Clinical exam for scoliosis	Annually throughout childhood
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Gastrointestinal	Monitor for gastroesophageal reflux, constipation, & chronic diarrhea	
Vision / Ocular issues	Ophthalmology exam & vision screening for refractive errors & strabismus	As recommended by ophthalmologist
Dental anomalies	Eval w/pediatric dentist throughout childhood for abnormal enamel, tooth shape & number	Every 6 mos or more frequently as recommended by pediatric dentist
Ears, nose, throat	Assess for recurrent otitis & epistasis.	At each visit
Enuresis	Assess for enuresis.	
Pulmonary & sleep	Assess for sleep issues.	
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

Evaluation of Relatives at Risk

If genomic testing detects the 3q29 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 in order to identify those who would benefit from close assessment/monitoring of developmental milestones (in children) and monitoring for neuropsychiatric manifestations (in children and adults).

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 3q29 recurrent deletion is an autosomal dominant disorder typically caused by a *de novo* deletion.

Risk to Family Members

Parents of a proband

- Although most deletions are *de novo*, inherited deletions have been reported [Cox & Butler 2015]. Of the 28 families with the 3q29 recurrent deletion in which parents have undergone genomic testing, the deletion was confirmed to be inherited in two families (7%).
- Evaluation of the parents by genomic testing that will detect the 3q29 recurrent deletion present in the proband is recommended to confirm their genetic status and to allow reliable recurrence risk counseling. (Note: A parent who has a 3q29 recurrent deletion may have only mild manifestations of the disorder or have phenotypes that go undetected because appropriate evaluations have not been conducted.) Testing for a balanced chromosome rearrangement in the parents is also recommended.
- If neither parent has the 3q29 recurrent deletion identified in the proband or a balanced chromosome rearrangement, the following possibilities should be considered:
    - The proband has a *de novo* deletion.
    - The proband inherited the deletion from a parent with germline (or somatic and germline) mosaicism. Somatic/germline mosaicism was reported in one father of a proband with the 3q29 recurrent deletion [Petrin et al 2011].

      Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a deletion that is present in the germ cells only.

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

- If the proband represents a simplex case (i.e., a single affected family member) and neither parent has the 3q29 recurrent deletion or a balanced chromosome rearrangement, the recurrence risk to sibs is low (presumed to be <1%) but greater than that of the general population because of the possibility of parental germline mosaicism for the deletion.
- If one of the parents has the 3q29 recurrent deletion, the risk to each sib of inheriting the deletion is 50%. However, it is not possible to reliably predict the phenotype in a sib who inherits the deletion, as the phenotypic spectrum associated with the 3q29 recurrent deletion can vary widely among family members [Digilio et al 2009, Li et al 2009, Murphy et al 2020].

- If one of the parents has a balanced chromosome rearrangement, the risk to sibs of having the 3q29 recurrent deletion is increased and depends on the specific chromosome rearrangement and the possibility of other variables.

Offspring of a proband. Each child of an individual with the 3q29 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 parents: if a parent has the 3q29 recurrent deletion or a balanced chromosome rearrangement, the parent's family members may also have the deletion or the chromosome rearrangement.

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 3q29 recurrent deletion. Note: If a parent is known to have a balanced chromosome rearrangement, genetic counseling should also address reproductive risks associated with balanced chromosome rearrangements.

Prenatal Testing and Preimplantation Genetic Testing

Pregnancies known to be at increased risk for the 3q29 recurrent deletion. Once the 3q29 recurrent deletion has been identified in an affected family member, prenatal testing for a pregnancy at increased risk for the 3q29 recurrent deletion and preimplantation genetic testing are possible.

Prenatal testing or preimplantation genetic testing using genomic testing that will detect the 3q29 recurrent deletion found in the proband may be offered when:

- A parent has the 3q29 recurrent deletion;
- The parents do not have the recurrent deletion but have had a child with the 3q29 recurrent deletion. In this instance, the recurrence risk associated with the possibility of parental germline mosaicism or other predisposing genetic mechanisms is probably slightly greater than that of the general population (though still presumed to be <1%).

Pregnancies not known to be at increased risk for 3q29 recurrent deletion. CMA performed in a pregnancy not known to be at increased risk may detect the 3q29 recurrent deletion.

Note: Regardless of whether a pregnancy is known or not known to be at increased risk for the 3q29 recurrent deletion, prenatal test results cannot reliably predict the phenotype.

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

Resources

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

- **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
- **3q29 Deletion Registry**
  Rutgers University
  Robert Wood Johnson School of Medicine
  679 Hoes Lane West
  Piscataway NJ 08854
  Phone: 848-445-9866
  Email: Jennifer.mulle@rutgers.edu
  Join The 3q29 Registry

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. 3q29 Recurrent Deletion: Genes and Databases

Gene	Chromosome Locus	Protein	ClinVar
Unknown	3q29	Not applicable	

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for 3q29 Recurrent Deletion (View All in OMIM)

609425	CHROMOSOME 3q29 DELETION SYNDROME

Molecular Pathogenesis

Deletion mechanism. Deletion breakpoints are usually found in low-copy repeats (LCRs) that flank the 3q29 recurrent deletion region. Nonallelic homologous recombination (NAHR) occurs when LCRs flanking the region misalign during meiosis followed by unequal crossing over between the LCRs. This process can produce gametes with the recurrent deletion or the reciprocal recurrent duplication. Breakpoints of the 3q29 recurrent deletion lie within the flanking LCRs, suggesting that the deletion arises through NAHR.

Genes of interest in this region. It is not currently known which of the genes in the region is responsible for the phenotype. However, there are several genes of interest: *DLG1* and *PAK2* are of interest for the neurodevelopmental and psychiatric phenotypes. It is hypothesized that 3q29 deletion phenotypes result from the loss of multiple genes (i.e., loss of both *DLG1* and *PAK2*). A mouse model of the 3q29 deletion has deficits in learning, memory, and social behaviors [Rutkowski et al 2021]. Mouse models with loss of *DLG1* alone [Rutkowski et al 2021] or *PAK2* alone [Wang et al 2018] do not fully recapitulate the 3q29 deletion phenotype.

- *DLG1* plays a role in trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors to the neuronal membrane.
- *PAK2* is involved in mediating molecular processes such as neuron migration, outgrowth, and spine morphogenesis, and also controls neuronal differentiation.

Chapter Notes

Author Notes

The 3q29 Project (sites.rutgers.edu/mulle), a large interdisciplinary collaboration led by PI Jennifer Mulle, is devoted to understanding the phenotypic spectrum, natural history, and molecular mechanism of 3q29 deletion syndrome. For information about ongoing research studies, contact Dr Mulle at jennifer.mulle@rutgers.edu.

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