U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Guo R, Haldeman-Englert CR. 1q21.1 Recurrent Deletion. 2011 Feb 24 [Updated 2024 Feb 1]. 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/

1q21.1 Recurrent Deletion

Rose Guo, DO[1] and Chad R Haldeman-Englert, MD[2]

Created: February 24, 2011; Updated: February 1, 2024.

Summary

Clinical characteristics

The 1q21.1 recurrent deletion itself does not lead to a clinically recognizable syndrome, as some persons with the deletion have no obvious clinical findings. Others have variable findings that most commonly include mildly dysmorphic but nonspecific facial features (>75%), mild intellectual disability or learning disabilities (25%), microcephaly (43%), and eye abnormalities (26%). Other findings can include cardiac defects, genitourinary anomalies, skeletal malformations, joint laxity, and seizures (~23%). Psychiatric and behavioral abnormalities can include autism spectrum disorder, attention-deficit/hyperactivity disorder, and sleep disturbances. Sensorineural hearing loss and recurrent infections /otitis media are rare.

Diagnosis/testing

The diagnosis of the 1q21.1 recurrent deletion is established by the detection of the recurrent distal heterozygous deletion between BP3 and BP4 at the approximate position of chr1:147105904-147917509 in the reference genome (NCBI Build 38).

Management

Treatment of manifestations: Feeding therapy to address poor growth, with a low threshold for a clinical feeding evaluation and/or radiographic swallowing study when there are clinical signs or symptoms of dysphagia. Standard treatment for gastroparesis, constipation, gastroesophageal reflux disease, developmental delay / intellectual disability, eye anomalies/refractive error, congenital heart disease, epilepsy, tremors/tics, hernia, cryptorchidism, skeletal anomalies, and hearing loss.

Surveillance: At each visit: measure growth parameters; monitor for constipation; assessment for anxiety, ADHD, and behavioral problems; monitor for developmental progress and educational needs; monitor those with seizures as clinically indicated; assess for new manifestations, such as seizures, tremors, or tics; and assess motility and self-help skills. At least annually or as clinically indicated: ophthalmology evaluation and audiology evaluation.

Author Affiliations: 1 Cone Health, Greensboro, North Carolina; Email: rose.guo@conehealth.com. 2 Mission Fullerton Genetics Center, Asheville, North Carolina; Email: chad.haldemanenglert@hcahealthcare.com.

Genetic counseling

The 1q21.1 recurrent deletion is inherited in an autosomal dominant manner. Between 18% and 35% of deletions occur *de novo*. The deletion can be inherited from either parent; a parent with the deletion may show a normal phenotype or an abnormal phenotype that is similar to but usually less severe than that of the parent's child. Each child of an individual with the 1q21.1 recurrent deletion has a 50% chance of inheriting the deletion; it is not possible to predict the phenotype in offspring who inherit the deletion. Recurrence risk for future pregnancies for parents who do not have the deletion is low (probably <1%) but greater than that of the general population because of the possibility of germline mosaicism.

Diagnosis

The breakpoints of the distal 1q21.1 recurrent deletion described in this *GeneReview* are between BP3 and BP4 [Mefford et al 2008]; these are sometimes referred to as class I deletions. Because of the variability of the phenotypic features, the diagnosis of the 1q21.1 recurrent deletion is often made following chromosomal microarray analysis (CMA) or through genomic testing, such as exome analysis.

Suggestive Findings

The 1q21.1 recurrent deletion **should be considered** in probands with the following clinical features:

- Hypotonia
- Developmental delays
- Intellectual disability (ID), typically in the mild-to-moderate range, although not all individuals with this deletion have ID
- Microcephaly
- Poor growth
- Neurobehavioral/psychiatric manifestations, such as behavioral outbursts, attention-deficit/hyperactivity disorder, aggression, sleep disturbances, or autism spectrum disorder
- Seizures
- Ophthalmologic involvement, such as strabismus or nystagmus
- Hearing impairment
- Joint laxity
- Mild but nonspecific dysmorphic facial features (See Clinical Description.)

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Because not all individuals with this deletion will have discernable clinical features, absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of the 1q21.1 recurrent deletion is established by detection of the recurrent distal 0.8-Mb heterozygous deletion at the approximate position of chr1:147105904-147917509 in the reference genome (NCBI Build 38).

Note: (1) The phenotype of significantly larger or smaller deletions within this region may be clinically distinct from the 1q21.1 recurrent deletion (see Molecular Genetics). (2) For features of the reciprocal 1q21.1 duplication (defined as between BP3-BP4), see Genetically Related Disorders.

Although several genes of interest (*PRKAB2*, *FMO5*, *CHD1L*, *BCL9*, *ACP6*, *GJA5*, *GJA8*) are within the distal 0.8-Mb recurrent deletion [Yoon & Mao 2021], no single gene has been identified to be causative of the overall

phenotype of this recurrent deletion syndrome (see Molecular Genetics for genes of interest in the deleted region).

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 1q21.1 region.

Note: (1) The 1q21.1 recurrent deletion cannot be identified by routine analysis of G-banded chromosomes or other conventional cytogenetic banding techniques. (2) Most individuals with the 1q21.1 recurrent deletion are identified by CMA performed in the context of developmental delay, intellectual disability, or autism spectrum disorders. (3) Prior to 2008 many CMA platforms did not include coverage of the 1q21.1 region and thus may not have detected this deletion.

Table 1. Molecular Genetic Testing Used to Detect the 1q21.1 Recurrent Deletion

Deletion [1]	Region Location [2, 3]	Method	Sensitivity	
			Proband	At-risk family members
~0.8-Mb heterozygous deletion at 1q21.1	GRCh38/hg38 chr1:147105904-147917509	CMA [4]	100%	100%
		Targeted deletion analysis [5]	Not applicable [5]	100%

1. See Molecular Genetics for details of the deletion.
2. Genomic coordinates represent the minimum deletion size associated with the 1q21.1 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. Previous reports have used various size ranges for this recurrent deletion, with the most common sizes used being 1.2 Mb and 1.35 Mb. However, these estimates likely include some of the flanking segmental duplication regions and are not specific to the unique DNA sequence [Mefford et al 2008, Brunetti-Pierri et al 2008, Bernier et al 2016, Bourgois et al 2023]. Therefore, these various size estimates (0.8 Mb, 1.2 Mb, and 1.35 Mb) should be considered the same from a clinical standpoint. The phenotype of significantly larger or smaller deletions within this region may be clinically distinct from the 1q21.1 recurrent deletion (see Genetically Related Disorders).
3. See Molecular Genetics for genes of interest included in this region.
4. Chromosome microarray analysis (CMA) using oligonucleotide arrays or SNP genotyping arrays. CMA designs in current clinical use target the 1q21.1 region. Note: The 1q21.1 recurrent deletion may not have been detectable by older oligonucleotide or BAC platforms.
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. Targeted deletion analysis is not appropriate for an individual in whom the 1q21.1 recurrent deletion was not detected by CMA designed to target this region.

Clinical Characteristics

Clinical Description

Individuals with the 1q21.1 recurrent deletion (BP3-BP4) have a wide range of clinical manifestations, ranging from unaffected to severely affected. The most common findings include developmental delay and mild but nonspecific dysmorphic facies. There is not a clinically recognizable syndrome, as a subset of persons with the deletion do not have obvious clinical findings.

Clinical information from reports involving 102 probands with the 1q21.1 recurrent deletion is summarized in Table 2 [Brunetti-Pierri et al 2008, Mefford et al 2008, Bernier et al 2016, Edwards et al 2021, Bourgois et al 2023].

Table 2. Select Features Present in Individuals with the 1q21.1 Recurrent Deletion

Frequency	Select Features [1]
>75%	Nonspecific mild dysmorphic facial features
50%-75%	• Mild-to-moderate developmental delay (includes speech & motor delays) • Gastrointestinal abnormalities
25%-50%	• Eye abnormalities • Intellectual disability • Microcephaly • Short stature • Musculoskeletal abnormalities
10%-25%	• Attention-deficit/hyperactivity disorder • Cardiac abnormalities • Genitourinary abnormalities • Poor growth • Hypotonia • Seizures
<10%	• Autism spectrum disorder / autistic features • Brain malformations • Sensorineural deafness • Frequent/recurrent infections

1. Clinical data shown is summarized from 102 probands with the 1q21.1 recurrent deletion [Mefford et al 2008, Brunetti-Pierri et al 2008, Bernier et al 2016, Edwards et al 2021, Bourgois et al 2023]. Note: Not all individuals in these studies were assessed for every feature listed in the table.

Facial features. Dysmorphic craniofacial features are a common finding but are highly variable and therefore not easily recognizable nor characteristic. The facial features may include frontal bossing; thin eyebrows; deep-set eyes; epicanthal folds; prominent, large, and/or wide nasal bridge with bulbous tip; long philtrum; and highly arched palate.

Growth. Microcephaly is described in 43% of individuals with the 1q21.1 recurrent deletion. This is more common in females than males. Short stature and poor growth may also be seen. While approximately 19% of individuals were described as having dysphagia, a definite etiology for poor growth (such as growth hormone deficiency) has not been determined [Edwards et al 2021] (see also **Gastrointestinal issues** in the following text).

Developmental delay (DD) and intellectual disability (ID). The majority of individuals with the 1q21.1 recurrent deletion have developmental delay.

- Most delays are mild and may involve specific areas, particularly gross motor delay, or be global, involving all areas of development.
- Some may also have generalized learning disabilities throughout life.
- Mild intellectual disability and learning disabilities are seen in approximately 25% of affected individuals.

Ophthalmologic involvement is present in about one third of individuals and may include strabismus, nystagmus, nasolacrimal duct obstruction, chorioretinal and iris colobomas, microphthalmia, hypermetropia, Duane anomaly, and various types of cataracts (e.g., congenital, nuclear pulverulent) [Edwards et al 2021].

Neurobehavioral/psychiatric manifestations. Psychiatric and behavioral abnormalities that may be present include autism spectrum disorders, attention-deficit/hyperactivity disorder (ADHD), anxiety and mood disorders, sleep disturbances, and self-injurious behaviors. In addition, distal 1q21.1 deletions have been identified in 0.2%-0.6% of persons with schizophrenia [International Schizophrenia Consortium 2008, Stefansson et al 2008, Walsh et al 2008, Rees et al 2014].

Cardiac anomalies. Several reported individuals with the 1q21.1 recurrent deletion have cardiac defects [Digilio et al 2013, Edwards et al 2021], which may include:

- Patent ductus arteriosus
- Truncus arteriosus
- Ventricular and atrial septal defects
- Tetralogy of Fallot
- Bicuspid aortic valve
- Dilatation of ascending aorta, with no further information on whether this is progressive or static
- Aortic insufficiency
- Coarctation of the aorta
- Interrupted aortic arch
- Supravalvular aortic stenosis
- Anomalous origin of the right coronary artery
- Pulmonary valve stenosis
- Transposition of the great vessels
- Rhythm abnormalities (sinus bradycardia, prolonged QT interval). Of note, one individual with long QT syndrome was also found to have a pathogenic *KCNH2* variant.

Females are more likely to have a cardiac anomaly.

Neurologic. Most affected individuals have a normal neurologic physical examination, but hypotonia and tremors are fairly common features.

- **Seizures** (e.g., tonic-clonic, absence) are seen in approximately 23% of individuals and often begin during the first year of life.
- **Brain malformations** that have been described range from structural anomalies (including agenesis of the corpus callosum) to migrational anomalies. Hydrocephalus has also been reported.

Genitourinary anomalies include vesicoureteral reflux, hydronephrosis, renal asymmetry, unilateral renal agenesis, inguinal hernia, and cryptorchidism. Two individuals with the deletion had Mayer-Rokitansky-Kuster-Hauser syndrome [Chen et al 2015].

Gastrointestinal issues include chronic constipation, dysphagia, gastroesophageal reflux, and poor gastric emptying/gastroparesis. Some affected individuals required G-tube for feeding difficulty [Edwards et al 2021].

Skeletal malformations are variable and include:

- Craniosynostosis (one report of metopic synostosis specifically)
- Scoliosis, ranging from mild to severe (requiring spinal hardware)
- Joint laxity
- Brachydactyly with or without short distal phalanges
- Broad thumbs
- Clinodactyly of the fifth finger
- Clubfoot
- Small feet
- Pes planus
- Broad or duplicated/bifid great toes
- Overlapping or syndactyly of the toes
- Polydactyly of the hands or feet

Hearing impairment. Sensorineural hearing loss has been reported in at least five individuals, with an additional six individuals having mild-to-profound hearing loss, though conductive/sensorineural/mixed is not specified.

Recurrent infections have been reported in a minority of affected individuals and may include frequent otitis media [Bourgois et al 2023].

Genotype-Phenotype Correlations

No genotype-phenotype correlations are observed in those with the 1q21.1 recurrent deletion.

Penetrance

Little information is available regarding penetrance of the 1q21.1 recurrent deletion. Similar to several other recurrent deletions (e.g., 16p11.2, 15q13.3), the 1q21.1 recurrent deletion can be inherited from a parent with minimally abnormal or completely normal clinical findings. In addition, several relatives of probands (e.g., sibs, cousins) with the same 1q21.1 deletion have a normal phenotype or only mild manifestations [Christiansen et al 2004; Shaffer et al 2006; Brunetti-Pierri et al 2008; Mefford et al 2008; Bernier et al 2016; Authors, personal observation]. This suggests that the 1q21.1 recurrent deletion has reduced penetrance and variable expressivity.

Prevalence

The frequency of the 1q21.1 recurrent deletion is approximately 0.2% (46/22,563) of individuals with developmental delays, intellectual disabilities, and/or congenital anomalies evaluated by chromosomal microarray [Brunetti-Pierri et al 2008, Mefford et al 2008, Rosenfeld et al 2013]. The estimated prevalence for 1q21.1 deletions in the general population is 0.01% (1/6,882) [Gillentine et al 2018].

Genetically Related (Allelic) Disorders

Duplication of distal 1q21.1. At least 47 individuals with reciprocal duplications of the 1q21.1 recurrent deletion (defined by breakpoints at BP3-BP4; see Molecular Genetics) have been reported [Brunetti-Pierri et al 2008, Mefford et al 2008, Bernier et al 2016, Bourgois et al 2023]; their occurrence is less frequent than the recurrent distal deletion based on these reports (aggregate total frequency of duplication vs deletion of cohorts studied by chromosomal microarray for developmental delay, intellectual disability, or congenital anomalies: 0.12% vs 0.2%).

Features seen in individuals with this duplication may include hypotonia, macrocephaly, prominent forehead, widely spaced eyes, tremor, learning or developmental delay, intellectual disability, attention-deficit/hyperactivity disorder (ADHD), and autistic features or autism spectrum disorder.

The duplications can be inherited from a parent or occur *de novo*. Reduced penetrance and variable expressivity are commonly present.

Deletions of varying size. See Molecular Genetics for information about significantly larger or smaller deletions in this region.

Differential Diagnosis

The differential diagnosis of the 1q21.1 recurrent deletion is broad due to the nonspecific, variable spectrum and the presence of relatively common abnormal phenotypes that occur in affected individuals, including developmental delay, learning problems, and neuropsychiatric disorders. All manifestations of the 1q21.1 recurrent deletion can also be seen in individuals with other genomic disorders.

Dual molecular diagnoses (i.e., two distinct pathogenic genetic alterations identified at separate loci) have been reported in multiple individuals with the 1q21.1 recurrent deletion and may explain features that are more severe or atypical compared to findings seen in most individuals with the 1q21.1 recurrent deletion [Qiao et al 2017, Edwards et al 2021, Bourgois et al 2023]. For individuals with comparatively severe/atypical phenotypes found to have a 1q21.1 recurrent deletion inherited from an unaffected parent, additional genetic testing (such as exome sequencing) can be considered to assess the possibility of a second contributing genetic alteration.

Management

No clinical practice guidelines for the 1q21.1 recurrent deletion have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with the 1q21.1 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 of the 1q21.1 Recurrent Deletion

System/Concern	Evaluation	Comment
Constitutional	Measurement of weight, length, & head circumference	To assess for growth restriction &/or microcephaly
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Eyes	Ophthalmologic eval	To assess for best corrected visual acuity, strabismus, & more complex findings (e.g., cataract, colobomas, Duane anomaly) that may require referral for subspecialty care
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
Cardiac	Cardiac eval, which may incl echocardiogram & EKG	To assess for structural cardiac anomalies & aortic root size, rhythm abnormalities
Neurologic	Neurologic eval	• Consider brain MRI for those w/microcephaly, macrocephaly, or seizures. • Consider EEG if seizures are a concern. • Consider referral to neurologist for those w/hypotonia, seizures, tics, or tremors.
Genitourinary	Renal ultrasound	To assess for renal anomalies
	Physical exam	To assess for hernias & cryptorchidism in males
	Consider pelvic ultrasound.	To assess for müllerian anomalies in females of pubertal age or older
Gastrointestinal	Gastrointestinal eval	To assess for constipation, dysphagia, gastroesophageal reflux, gastroparesis
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Clubfoot & scoliosis • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Hearing	Audiologic eval	To assess for hearing loss

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of the 1q21 recurrent deletion to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine 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; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for the 1q21.1 recurrent deletion. Supportive care to improve quality of life, maximize function, and reduce complications is recommended (see Table 4).

Table 4. Treatment of Manifestations in Individuals with the 1q21.1 Recurrent Deletion

Manifestation/Concern	Treatment	Considerations/Other
Poor growth / Feeding difficulty	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Gastroparesis/ Constipation/ GERD	Standard treatment per gastroenterologist	Aripiprazole improved gastroparesis in 1 person. [1]
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Eye anomalies / Refractive error	Ophthalmologist	Refractive errors, strabismus
	Ophthalmic subspecialist	More complex findings (e.g., cataract, colobomas)
Congenital heart defects / Aortic root dilatation / Arrhythmias	Standard treatment per cardiologist	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [2]
Tremors/Tics	Standard treatment per neurologist	
Hernia/Cryptorchidism	Standard treatment per urologist	
Clubfoot/Scoliosis	Standard treatment per orthopedist	
Hearing	Hearing aids may be helpful per otolaryngologist	Community hearing services through early intervention or school district
Family/Community	Ensure appropriate social work involvement to connect families w/local resources & support.	Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; GERD = gastroesophageal reflux disease; OT = occupational therapy; PT = physical therapy
1. Rabinowitz et al [2018]
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.

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.

Motor Dysfunction

Gross motor dysfunction. Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

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

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

Neurobehavioral/Psychiatric 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.

Surveillance

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

Table 5. Recommended Surveillance in Individuals with the 1q21 Recurrent Deletion

System/Concern	Evaluation	Frequency
Growth	Measurement of growth parameters	At each visit
Gastrointestinal	Monitor for constipation.	
Development	Monitor developmental progress & educational needs.	
Neurobehavioral/ Psychiatric	Assessment for anxiety, ADHD, ASD, & behavioral problems	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, tremors, & tics.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Family/Community	Assess family need for social work support, care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	
Eyes	Ophthalmology eval	At least annually in childhood, or as clinically indicated
Hearing	Audiology eval	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

Using genomic testing that will detect the 1q21.1 recurrent deletion found in the proband, it is appropriate to evaluate the 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.

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 known to have the1q21.1 recurrent deletion.

Note: (1) Targeted deletion testing is not appropriate for an individual in whom the 1q21.1 recurrent deletion was not detected by chromosomal microarray designed to target this region. (2) It is not possible to size the deletion routinely by use of targeted methods.

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 1q21.1 recurrent deletion is inherited in an autosomal dominant manner.

The recurrent deletion can be inherited from either parent, and it does not appear that the phenotypic severity varies with the parent of origin.

Risk to Family Members

Parents of a proband

- Many individuals with the 1q21.1 recurrent deletion inherited the deletion from a parent. A parent with the recurrent deletion may show an abnormal phenotype similar to their child but in general is less severely affected. In approximately 25% of instances in which the recurrent deletion is inherited, the parent has a normal phenotype.
  - Mefford et al [2008] found that in 50% (7/14) of the probands for whom parental testing was possible, a parent also had the recurrent deletion.
  - In another study [Brunetti-Pierri et al 2008], 82% (9/11) of the probands for whom parental testing was possible had inherited the deletion.
- Edwards et al [2021] identified a *de novo* rate of 35% (8/23) in probands for whom parental testing data were available.
- Genomic testing that will detect the 1q21.1 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 1q21.1 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 and will not detect a deletion that is present in the germ cells only.
- The family history of some individuals diagnosed with the 1q21.1 recurrent deletion may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the 1q21.1 recurrent deletion.

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

- If one of the parents has the 1q21.1 recurrent deletion, the risk to each sib of inheriting the deletion is 50%. Because studies suggest that the 1q21.1 recurrent deletion is associated with variable expressivity and reduced penetrance, it is not possible to reliably predict the phenotype in a sib who inherits the deletion.
- If the 1q21.1 recurrent deletion identified in the proband cannot be detected in either of the parents, the recurrence risk to sibs is low (<1%) but greater than that of the general population because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with the 1q21.1 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 1q21.1 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 have or are at risk of having a child with the 1q21.1 recurrent deletion.

Prenatal Testing and Preimplantation Genetic Testing

Pregnancies known to be at increased risk for the 1q21.1 recurrent deletion. Once a 1q21.1 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 1q21.1 recurrent deletion. Chromosomal microarray performed in a pregnancy not known to be at increased risk may detect the recurrent deletion.

Note: Regardless of whether a pregnancy is known or not known to be at increased risk for the 1q21.1 recurrent deletion, the prenatal finding of a 1q21.1 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.

- **MedlinePlus**
  1q21.1 microdeletion
- **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
- **Simons Searchlight Registry**
  Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.
  Phone: 855-329-5638
  Fax: 570-214-7327
  Email: coordinator@simonssearchlight.org
  simonssearchlight.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. 1q21.1 Recurrent Microdeletion: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GJA5	1q21.2	Gap junction alpha-5 protein	GJA5 database	GJA5	GJA5
GJA8	1q21.2	Gap junction alpha-8 protein	GJA8 @ LOVD	GJA8	GJA8
Not applicable	1q21.1	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 1q21.1 Recurrent Microdeletion (View All in OMIM)

121013	GAP JUNCTION PROTEIN, ALPHA-5; GJA5
600897	GAP JUNCTION PROTEIN, ALPHA-8; GJA8

Table B. continued from previous page.

612474	CHROMOSOME 1q21.1 DELETION SYNDROME, 1.35-MB

Molecular Pathogenesis

Deletion Mechanism

Similar to other genomic disorders (e.g., deletions and reciprocal duplications of 22q11.2, 7q11.2, 15q11q13, 15q13.3, 16p11.2, 17q21.31), the breakpoints of the 1q21.1 recurrent deletion commonly occur within flanking segmental duplications. In all reported cases, the flanking segmental duplications in direct orientation share a high degree of sequence homology, predisposing these regions to rearrangements by nonallelic homologous recombination (NAHR). NAHR occurs from misalignment of and subsequent recombination between the flanking segmental duplications. The result is a recurrent deletion and a recurrent microduplication of the unique sequences between the flanking segments, which is at least 0.8 Mb of the 1q21.1 region [Emanuel & Shaikh 2001, Lupski & Stankiewicz 2005].

In the 1q21.1 region, there are four copies of segmental duplications in direct orientation, each with high sequence identity. These noncontiguous segmental duplication elements are termed BP1, BP2, BP3, and BP4, so named because they are recombination breakpoint (BP) hotspots for deletion and duplication of sequences between the BP elements [Mefford et al 2008].

The breakpoints of the distal 1q21.1 recurrent deletion described in this *GeneReview* are between BP3 and BP4 [Mefford et al 2008]; these are sometimes referred to as class I or "distal" deletions (the coordinates referenced in this chapter are from ClinGen).

A smaller, more proximal deletion occurring between BP2 and BP3 has been associated with thrombocytopenia absent radius (TAR) syndrome.

A third type of deletion, sometimes called a class II deletion, occurs between BP2 and BP4. This approximately 2-Mb deletion involves the chromosomal regions of both the TAR syndrome-associated deletion and the 0.8-Mb distal 1q21.1 deletion (the subject of this *GeneReview*) [Velinov & Dolzhanskaya 2010]. The features are variable, but they are similar to those of the 1q21.1 recurrent deletion, including dysmorphic features, developmental delays, and cardiac and genitourinary abnormalities.

Genes of Interest in this Region

Although several genes of interest (*PRKAB2*, *FMO5*, *CHD1L*, B*CL9*, *ACP6*, *GJA5*, *GJA8*) are within the 1q21.1 recurrent deletion, no single gene has been identified to be causative of the overall phenotype of this recurrent deletion syndrome. Haploinsufficiency of one or more of the deleted genes likely contributes to the phenotypes associated with pathogenic variants in these genes.

- ***PRKAB2.*** Harvard et al [2011] showed decreased protein levels of *CHD1L* and *PRKAB2* in lymphoblastoid cell lines from persons with the 1q21.1 recurrent deletion. Defects in chromatin remodeling and decreased AMP kinase function were found during functional analysis. Nagy et al [2018] showed that decreased AMP kinase signaling may contribute to the increased risk of developing mental disorders and sleep disturbances in individuals with the 1q21.1 deletion. Wagh et al [2021] identified *PRKAB2* as a differentially expressed gene in a cohort of individuals with schizophrenia.
- ***CHD1L.*** Heterozygous and biallelic pathogenic variants have been identified in persons with congenital anomalies of the kidneys and urinary tract [Hwang et al 2014, Chen et al 2019]. Girirajan et al [2013] identified copy number variants involving *CHD1L* in individuals with autism.
- ***BCL9.*** Li et al [2011] demonstrated that common pathogenic variants in *BCL9* confer risk for schizophrenia and may also be associated with bipolar disorder and major depressive disorder in the

Chinese Han population. A heterozygous pathogenic variant has also been identified in a person with a left ventricular outflow tract abnormality [Zaidi et al 2013].

- ***GJA5.*** Heterozygous pathogenic variants or deletions have been identified in persons with atrial fibrillation [Gollob et al 2006], structural cardiac defects [Christiansen et al 2004, Soemedi et al 2012, Guida et al 2013], and essential hypertension [Wang et al 2023].
- ***GJA8.*** Heterozygous pathogenic variants have been identified in persons with various types of cataracts [Mackay et al 2014, Ceroni et al 2019], microphthalmia [Huang et al 2015, Ceroni et al 2019], glaucoma [Huang et al 2015], and other developmental eye disorders [Prokudin et al 2014, Ceroni et al 2019].

Pathophysiology

Chapman et al [2022] showed that, after neuronal differentiation, neural progenitor cells that contain the 1q21.1 deletion or reciprocal duplication display altered morphology, synaptic density, and dysregulated cortical layer identity in comparison to controls cells. In addition, there was differential expression of calcium channels. The authors found that the neurons could be pharmacologically modulated by targeting Ca^{2+} channel activity, which may be a potential target for therapeutic intervention.

A mouse model for the 1q21.1 deletion has been established, showing shortened head-to-tail length, altered dopamine transmission, and increased response to stimulant medication [Nielsen et al 2017].

Chapter Notes

Author Notes

Baylor Genetics is conducting data collection on individuals with 1q21.1 distal deletions. Interested parties should contact precisiongenome@bcm.edu.

Author History

Rose Guo, DO (2024-present)
Chad R Haldeman-Englert, MD (2011-present)
Tamison Jewett, MD; Wake Forest University School of Medicine (2011-2024)

Revision History

- 1 February 2024 (ma) Comprehensive update posted live
- 12 November 2015 (me) Comprehensive update posted live
- 24 February 2011 (me) Review posted live
- 30 November 2010 (che) Original submission

References

Literature Cited

Bernier R, Steinman KJ, Reilly B, Wallace AS, Sherr EH, Pojman N, Mefford HC, Gerdts J, Earl R, Hanson E, Goin-Kochel RP, Berry L, Kanne S, Snyder LG, Spence S, Ramocki MB, Evans DW, Spiro JE, Martin CL, Ledbetter DH, Chung WK; Simons VIP Consortium. Clinical phenotype of the recurrent 1q21.1 copy-number variant. Genet Med. 2016;18:341-9. PubMed PMID: 26066539.

Bourgois A, Bizaoui V, Colson C, Vincent-Devulder A, Molin A, Gérard M, Gruchy N. Phenotypic and genotypic characterization of 1q21.1 copy number variants: a report of 34 new individuals and literature review. Am J Med Genet A. 2023. Epub ahead of print. PubMed PMID: 37881147.

Brunetti-Pierri N, Berg JS, Scaglia F, Belmont J, Bacino CA, Sahoo T, Lalani SR, Graham B, Lee B, Shinawi M, Shen J, Kang SH, Pursley A, Lotze T, Kennedy G, Lansky-Shafer S, Weaver C, Roeder ER, Grebe TA, Arnold GL, Hutchison T, Reimschisel T, Amato S, Geragthy MT, Innis JW, Obersztyn E, Nowakowska B, Rosengren SS, Bader PI, Grange DK, Naqvi S, Garnica AD, Bernes SM, Fong CT, Summers A, Walters WD, Lupski JR, Stankiewicz P, Cheung SW, Patel A. Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. Nat Genet. 2008;40:1466–71. PubMed PMID: 19029900.

Ceroni F, Aguilera-Garcia D, Chassaing N, Bax DA, Blanco-Kelly F, Ramos P, Tarilonte M, Villaverde C, da Silva LRJ, Ballesta-Martínez MJ, Sanchez-Soler MJ, Holt RJ, Cooper-Charles L, Bruty J, Wallis Y, McMullan D, Hoffman J, Bunyan D, Stewart A, Stewart H, Lachlan K; DDD Study; Fryer A, McKay V, Roume J, Dureau P, Saggar A, Griffiths M, Calvas P, Ayuso C, Corton M, Ragge NK. New GJA8 variants and phenotypes highlight its critical role in a broad spectrum of eye anomalies. Hum Genet. 2019;138:1027-42. PubMed PMID: 29464339.

Chapman G, Alsaqati M, Lunn S, Singh T, Linden SC, Linden DEJ, van den Bree MBM, Ziller M, Owen MJ, Hall J, Harwood AJ, Syed YA. Using induced pluripotent stem cells to investigate human neuronal phenotypes in 1q21.1 deletion and duplication syndrome. Mol Psychiatry. 2022;27:819-30. PubMed PMID: 34112971.

Chen CP, Huang JP, Chen YY, Chern SR, Wu PS, Chen SW, Wang W, Lee CC. Detection of a familial 1q21.1 microdeletion and concomitant CHD1L mutation in a fetus with oligohydramnios and bilateral renal dysplasia on prenatal ultrasound. Taiwan J Obstet Gynecol. 2019;58:859-63. PubMed PMID: 31759543.

Chen MJ, Wei SY, Yang WS, Wu TT, Li HY, Ho HN, Yang YS, Chen PL. Concurrent exome-targeted next-generation sequencing and single nucleotide polymorphism array to identify the causative genetic aberrations of isolated Mayer-Rokitansky-Küster-Hauser syndrome. Hum Reprod. 2015;30:1732–42. PubMed PMID: 25924657.

Christiansen J, Dyck JD, Elyas BG, Lilley M, Bamforth JS, Hicks M, Sprysak KA, Tomaszewski R, Haase SM, Vicen-Wyhony LM, Somerville MJ. Chromosome 1q21.1 contiguous gene deletion is associated with congenital heart disease. Circ Res. 2004;94:1429–35. PubMed PMID: 15117819.

Digilio MC, Bernardini L, Consoli F, Lepri FR, Giuffrida MG, Baban A, Surace C, Ferese R, Angioni A, Novelli A, Marino B, De Luca A, Dallapiccola B. Congenital heart defects in recurrent reciprocal 1q21.1 deletion and duplication syndromes: rare association with pulmonary valve stenosis. Eur J Med Genet. 2013;56:144–9. PubMed PMID: 23270675.

Edwards SD, Schulze KV, Rosenfeld JA, Westerfield LE, Gerard A, Yuan B, Grigorenko EL, Posey JE, Bi W, Liu P. Clinical characterization of individuals with the distal 1q21.1 microdeletion. Am J Med Genet A. 2021;185:1388-98. PubMed PMID: 33576134.

Emanuel BS, Shaikh TH. Segmental duplications: an "expanding" role in genomic instability and disease. Nat Rev Genet. 2001;2:791–800. PubMed PMID: 11584295.

Gillentine MA, Lupo PJ, Stankiewicz P, Schaaf, CP. An estimation of the prevalence of genomic disorders using chromosomal microarray data. J Hum Genet. 2018;63:795-801. PubMed PMID: 29691480.

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

Gollob MH, Jones DL, Krahn AD, Danis L, Gong X-Q, Shao Q, Liu X, Veinot JP, Tang ASL, Stewart AFR, Tesson F, Klein GJ, Yee R, Skanes AC, Guiraudon GM, Ebihara L, Bai D. Somatic mutations in the connexin 40 gene (GJA5) in atrial fibrillation. New Eng J Med. 2006;354:2677–88. PubMed PMID: 16790700.

Guida V, Ferese R, Rocchetti M, Bonetti M, Sarkozy A, Cecchetti S, Gelmetti V, Lepri F, Copetti M, Lamorte G, Cristina Digilio M, Marino B, Zaza A, den Hertog J, Dallapiccola B, De Luca A. A variant in the carboxyl-

terminus of connexin 40 alters GAP junctions and increases risk for tetralogy of Fallot. Eur J Hum Genet. 2013;21:69–75. PubMed PMID: 22713807.

Harvard C, Strong E, Mercier E, Colnaghi R, Alcantara D, Chow E, Martell S, Tyson C, Hrynchak M, McGillivray B, Hamilton S, Marles S, Mhanni A, Dawson AJ, Pavlidis P, Qiao Y, Holden JJ, Lewis SM, O'Driscoll M, Rajcan-Separovic E. Understanding the impact of 1q21.1 copy number variant. Orphanet J Rare Dis. 2011;6:54. PubMed PMID: 21824431.

Huang X, Xiao X, Jia X, Li S, Li M, Guo X, Liu X. Zhang Q1. Mutation analysis of the genes associated with anterior segment dysgenesis, microcornea and microphthalmia in 257 patients with glaucoma. Int J Mol Med. 2015;36:1111–7. PubMed PMID: 26310487.

Hwang DY, Dworschak GC, Kohl S, Saisawat P, Vivante A, Hilger AC, Reutter HM, Soliman NA, Bogdanovic R, Kehinde EO, Tasic V, Hildebrandt F. Mutations in 12 known dominant disease-causing genes clarify many congenital anomalies of the kidney and urinary tract. Kidney Int. 2014;85:1429–33. PubMed PMID: 24429398.

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

Li J, Zhou G, Ji W, Feng G, Zhao Q, Liu J, Li T, Li Y, Chen P, Zeng Z, Wang T, Hu Z, Zheng L, Wang Y, Shen Y, He L, Shi Y. Common variants in the BCL9 gene conferring risk of schizophrenia. Arch Gen Psychiatry. 2011;68:232-40. PubMed PMID: 21383261.

Lupski JR, Stankiewicz P. Genomic disorders: molecular mechanisms for rearrangements and conveyed phenotypes. PLoS Genet. 2005;1:e49. PubMed PMID: 16444292.

Mackay DS, Bennett TM, Culican SM, Shiels A. Exome sequencing identifies novel and recurrent mutations in GJA8 and CRYGD associated with inherited cataract. Hum Genomics. 2014;8:19. PubMed PMID: 25403472.

Mefford HC, Sharp AJ, Baker C, Itsara A, Jiang Z, Buysse K, Huang S, Maloney VK, Crolla JA, Baralle D, Collins A, Mercer C, Norga K, de Ravel T, Devriendt K, Bongers EM, de Leeuw N, Reardon W, Gimelli S, Bena F, Hennekam RC, Male A, Gaunt L, Clayton-Smith J, Simonic I, Park SM, Mehta SG, Nik-Zainal S, Woods CG, Firth HV, Parkin G, Fichera M, Reitano S, Lo Giudice M, Li KE, Casuga I, Broomer A, Conrad B, Schwerzmann M, Raber L, Gallati S, Striano P, Coppola A, Tolmie JL, Tobias ES, Lilley C, Armengol L, Spysschaert Y, Verloo P, De Coene A, Goossens L, Mortier G, Speleman F, van Binsbergen E, Nelen MR, Hochstenbach R, Poot M, Gallagher L, Gill M, McClellan J, King MC, Regan R, Skinner C, Stevenson RE, Antonarakis SE, Chen C, Estivill X, Menten B, Gimelli G, Gribble S, Schwartz S, Sutcliffe JS, Walsh T, Knight SJ, Sebat J, Romano C, Schwartz CE, Veltman JA, de Vries BB, Vermeesch JR, Barber JC, Willatt L, Tassabehji M, Eichler EE. Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. N Engl J Med. 2008;359:1685–99. PubMed PMID: 18784092.

Nagy S, Maurer GW, Hentze JL, Rose M, Werge TM, Rewitz K. AMPK signaling linked to the schizophrenia-associated 1q21.1 deletion is required for neuronal and sleep maintenance. PLoS Genet. 2018;14:e1007623. PubMed PMID: 30566533.

Nielsen J, Fejgin K, Sotty F, Nielsen V, Mørk A, Christoffersen CT, Yavich L, Lauridsen JB, Clausen D, Larsen PH, Egebjerg J, Werge TM, Kallunki P, Christensen KV, Didriksen M. A mouse model of the schizophrenia-associated 1q21.1 microdeletion syndrome exhibits altered mesolimbic dopamine transmission. Transl Psychiatry. 2017;7:1261. PubMed PMID: 29187755.

Prokudin I, Simons C, Grigg JR, Storen R, Kumar V, Phua ZY, Smith J, Flaherty M, Davila S, Jamieson RV. Exome sequencing in developmental eye disease leads to identification of causal variants in GJA8, CRYGC, PAX6 and CYP1B1. Eur J Hum Genet. 2014;22:907–15. PubMed PMID: 24281366.

Qiao Y, Badduke C, Tang F, Cowieson D, Martell S, Lewis SME, Peñaherrera MS, Robinson WP, Volchuk A, Rajcan-Separovic E. Whole exome sequencing of families with 1q21.1 microdeletion or microduplication. Am J Med Genet A. 2017;173:1782-91. PubMed PMID: 28475290.

Rabinowitz SS, Ahuja N, Gottfried J. Aripiprazole reversed gastroparesis in a child with 1q21.1-q21.2 microdeletion. BMJ Case Rep. 2018;2018:bcr2017223231. PubMed PMID: 29545430.

Rees E, Walters JT, Georgieva L, Isles AR, Chambert KD, Richards AL, Mahoney-Davies G, Legge SE, Moran JL, McCarroll SA, O'Donovan MC, Owen MJ, Kirov G. Analysis of copy number variations at 15 schizophrenia-associated loci. Br J Psychiatry. 2014;204:108-14. PubMed PMID: 24311552.

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

Shaffer LG, Kashork CD, Saleki R, Rorem E, Sundin K, Ballif BC, Bejjani BA. Targeted genomic microarray analysis for identification of chromosome abnormalities in 1500 consecutive clinical cases. J Pediatr. 2006;149:98-102. PubMed PMID: 16860135.

Soemedi R, Topf A, Wilson IJ, Darlay R, Rahman T, Glen E, Hall D, Huang N, Bentham J, Bhattacharya S, Cosgrove C, Brook JD, Granados-Riveron J, Setchfield K, Bu'lock F, Thornborough C, Devriendt K, Breckpot J, Hofbeck M, Lathrop M, Rauch A, Blue GM, Winlaw DS, Hurles M, Santibanez-Koref M, Cordell HJ, Goodship JA, Keavney BD. Phenotype-specific effect of chromosome 1q21.1 rearrangements and GJA5 duplications in 2436 congenital heart disease patients and 6760 controls. Hum Mol Genet. 2012;21:1513–20. PubMed PMID: 22199024.

Stefansson H, Rujescu D, Cichon S, Pietiläinen OP, Ingason A, Steinberg S, Fossdal R, Sigurdsson E, Sigmundsson T, Buizer-Voskamp JE, Hansen T, Jakobsen KD, Muglia P, Francks C, Matthews PM, Gylfason A, Halldorsson BV, Gudbjartsson D, Thorgeirsson TE, Sigurdsson A, Jonasdottir A, Jonasdottir A, Bjornsson A, Mattiasdottir S, Blondal T, Haraldsson M, Magnusdottir BB, Giegling I, Möller HJ, Hartmann A, Shianna KV, Ge D, Need AC, Crombie C, Fraser G, Walker N, Lonnqvist J, Suvisaari J, Tuulio-Henriksson A, Paunio T, Toulopoulou T, Bramon E, Di Forti M, Murray R, Ruggeri M, Vassos E, Tosato S, Walshe M, Li T, Vasilescu C, Mühleisen TW, Wang AG, Ullum H, Djurovic S, Melle I, Olesen J, Kiemeney LA, Franke B. GROUP, Sabatti C, Freimer NB, Gulcher JR, Thorsteinsdottir U, Kong A, Andreassen OA, Ophoff RA, Georgi A, Rietschel M, Werge T, Petursson H, Goldstein DB, Nöthen MM, Peltonen L, Collier DA, St Clair D, Stefansson K. Large recurrent microdeletions associated with schizophrenia. Nature. 2008;455:232–6. PubMed PMID: 18668039.

Velinov M, Dolzhanskaya N. Clavicular pseudoarthrosis, anomalous coronary artery and extra crease of the fifth finger-previously unreported features in individuals with class II 1q21.1 microdeletions. Eur J Med Genet. 2010;53:213–6. PubMed PMID: 20573555.

Wagh VV, Vyas P, Agrawal S, Pachpor TA, Paralikar V, Khare SP. Peripheral blood-based gene expression studies in schizophrenia: a systematic review. Front Genet. 2021;12:736483. PubMed PMID: 34721526.

Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, Nord AS, Kusenda M, Malhotra D, Bhandari A, Stray SM, Rippey CF, Roccanova P, Makarov V, Lakshmi B, Findling RL, Sikich L, Stromberg T, Merriman B, Gogtay N, Butler P, Eckstrand K, Noory L, Gochman P, Long R, Chen Z, Davis S, Baker C, Eichler EE, Meltzer PS, Nelson SF, Singleton AB, Lee MK, Rapoport JL, King MC, Sebat J. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science. 2008;320:539–43. PubMed PMID: 18369103.

Wang J, Wang XC, Gu ZH, Ren GW, Zhao XH, Qu XK, Xu YJ, Yang YQ. A novel GJA5 variant associated with increased risk of essential hypertension. Am J Transl Res. 2023;15:1259-70. PubMed PMID: 36915790.

Yoon J, Mao Y. Dissecting molecular genetic mechanisms of 1q21.1 CNV in neuropsychiatric disorders. Int J Mol Sci. 2021;22:5811. PubMed PMID: 34071723.

Zaidi S, Choi M, Wakimoto H, Ma L, Jiang J, Overton JD, Romano-Adesman A, Bjornson RD, Breitbart RE, Brown KK, Carriero NJ, Cheung YH, Deanfield J, DePalma S, Fakhro KA, Glessner J, Hakonarson H, Italia MJ, Kaltman JR, Kaski J, Kim R, Kline JK, Lee T, Leipzig J, Lopez A, Mane SM, Mitchell LE, Newburger JW, Parfenov M, Pe'er I, Porter G, Roberts AE, Sachidanandam R, Sanders SJ, Seiden HS, State MW,

Subramanian S, Tikhonova IR, Wang W, Warburton D, White PS, Williams IA, Zhao H, Seidman JG, Brueckner M, Chung WK, Gelb BD, Goldmuntz E, Seidman CE, Lifton RP. De novo mutations in histone-modifying genes in congenital heart disease. Nature. 2013;498:220–3. PubMed PMID: 23665959.

License