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Xq28 Duplication Syndrome, Int22h1/Int22h2 Mediated

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Summary

Clinical characteristics

The int22h1/int22h2-mediated Xq28 duplication syndrome is an X-linked intellectual disability syndrome characterized by variable degrees of cognitive impairment (typically more severe in males), a wide spectrum of neurobehavioral abnormalities, and variable facial dysmorphic features. Affected males also exhibit a peculiar combination of recurrent sinopulmonary infections and atopy, findings that have not been observed in affected females. All males reported to date with the syndrome have moderate-to-severe intellectual disability; in contrast, a minority of heterozygous females have been reported to have mild intellectual disability, while the majority have no discernible health or learning issues and are considered clinically unaffected.

Diagnosis/testing

The diagnosis of int22h1/int22h2-mediated Xq28 duplication in a hemizygous male or a heterozygous female is established by detection of a 0.5-Mb duplication within the q28 region of the X chromosome extending between 154.1 Mb and 154.6 Mb in the reference genome (NCBI Build GRCh37/hg19).

Management

Treatment of manifestations: Early intervention with speech and physical therapy for children with neurodevelopmental delays; enrollment in special education programs of school-aged children with intellectual disability; cognitive behavioral therapy and standard treatment with antidepressants and/or antipsychotics for individuals with mood and psychotic disorders; standard treatment per orthopedist for those with kyphoscoliosis; bacterial culture-driven antibiotic treatment of affected individuals who have recurrent

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infections; vaccinations against *Strep pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* and annual influenza A vaccine; standard medical treatment of sleep issues, asthma, allergic rhinitis, eczema, hearing loss, and refractive error; standard surgical correction of congenital malformations (e.g., strabismus, hypospadias, cryptorchidism, heart defects, limb anomalies).

Surveillance: Measurement of growth parameters and assessment of neurodevelopmental progress, cognitive abilities, behavioral/psychiatric symptoms, and motor functioning at each visit; reassessment of special education needs annually in childhood and adolescence; routine follow up with orthopedist for those with contractures and/or kyphoscoliosis; pulmonary function testing as clinically indicated for those with severe asthma; at least annual audiologic and ophthalmologic evaluations.

Evaluation of relatives at risk: Clinically asymptomatic sibs of affected individuals who also have the duplication should be regularly assessed and carefully monitored for achievement of neurodevelopmental milestones with the goal of instituting early intervention if or when neurodevelopmental delays are noted.

Genetic counseling

The int22h1/int22h2-mediated Xq28 duplication syndrome is inherited in an X-linked manner. Most affected individuals inherited the duplication from their heterozygous and often asymptomatic mother. However, individuals with *de novo* duplications have also been identified. Because offspring inherit one X chromosome from the mother, each child of a mother with an int22h1/int22h2-mediated Xq28 duplication has a 50% chance of inheriting the duplication. In other words, a female with an int22h1/int22h2-mediated Xq28 duplication has a 50% chance of passing the duplication to her offspring at each conception. Being hemizygous for X-linked genes, males who inherit the duplication are affected. In contrast, females who inherit the duplication will be heterozygous and thus, will either exhibit a milder phenotype or be clinically unaffected. Females in whom the X-inactivation pattern is skewed toward inactivation of the X chromosome bearing the duplication are more likely to be clinically unaffected. Once an int22h1/int22h2-mediated Xq28 duplication has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

The int22h1/int22h2-mediated Xq28 duplication syndrome **should be considered in males** with the following clinical findings:

- Mild-to-moderate intellectual disability, with or without mild-to-moderate neurodevelopmental delays
- Any of the following features presenting in infancy or childhood:
  - Characteristic neurobehavioral profile consisting of aggression and irritability, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, anxiety, socialization deficits, and sleep disturbances – typically insomnia
  - Recurrent sinopulmonary infections (including otitis media) with existent atopic conditions (e.g., asthma, allergic rhinitis, eczema)
  - Obesity with or without tall stature
  - Nonspecific but consistent facial features (See Clinical Characteristics and Figure 1A-E.)

The int22h1/int22h2-mediated Xq28 duplication syndrome **should be considered in females** with the following clinical findings:

- Mild learning disabilities

- Neurobehavioral manifestations resembling those of the inattentive-type childhood ADHD (impulsivity, inattention, and emotional lability)
- Mild-to-moderate socialization deficits
- Nonspecific but consistent facial features (See Clinical Characteristics and Figure 1F-K.)

Establishing the Diagnosis

The diagnosis of int22h1/int22h2-mediated Xq28 duplication syndrome **is established** in hemizygous males and heterozygous females by detection of a 0.5-Mb duplication of the subregion extending from 154.1 Mb to 154.6 Mb within the q28 region of the X chromosome in the reference genome (NCBI Build GRCh37/hg19).

More specifically, the duplicated segment extends from a low copy repeat (LCR) region within intron 22 of *F8*, also known as intron 22 homologous region 1 (int22h1), to another LCR region located about 0.5 Mb telomeric to the former region and known as intron 22 homologous region 2 (int22h2). This duplication is likely mediated by a nonallelic homologous recombination event between the int22h1 and int22h2 LCR regions.

However, it is worth noting that several reported individuals have duplications nested within or partially overlapping with the typical int22h1/int22h2-mediated 0.5-Mb Xq28 duplication (see Genotype-Phenotype Correlations and Genetically Related Disorders).

Molecular genetic testing for an individual with neurodevelopmental delays and/or intellectual disability typically begins with a chromosomal microarray analysis.

Chromosomal microarray (CMA) performed either with oligonucleotide arrays or SNP (single-nucleotide polymorphism) genotyping arrays is capable of detecting the presence of an int22h1/int22h2-mediated Xq28 duplication. However, the ability of the specific array used to size the detected duplication depends largely on the type and probe density of the array itself. The int22h1/int22h2-mediated Xq28 duplication cannot be identified through routine analysis of G-banded chromosomes or other conventional cytogenetic banding techniques.

Note: (1) Most individuals with an int22h1/int22h2-mediated Xq28 duplication can be identified with the current CMA performed routinely for a clinical indication of neurodevelopmental delay and/or intellectual disability. (2) Routine CMA platforms before 2011 did not include coverage for this region and thus, could not detect this duplication. Likewise, the earlier BAC (bacterial artificial chromosome)-based arrays were also incapable of detecting this duplication. (3) Metaphase FISH is not reliable for detecting a duplication of this size (i.e., ~0.5 Mb). However, interphase FISH (iFISH) may be used if appropriate control studies are performed. (4) FISH analysis can also be sought to determine whether the duplicated segment may have been inserted elsewhere in the genome (i.e., insertion translocation).

Targeted duplication analysis is not typically performed as a first-line test in the absence of a known family history of the condition (see Evaluation of Relatives at Risk). Targeted duplication analysis should not be sought for an individual in whom an int22h1/int22h2-mediated Xq28 duplication could not be detected by a CMA platform designed to cover this region. Moreover, targeted duplication analyses cannot be routinely used to size the detected duplication – unlike CMA, which may allow for size determination.

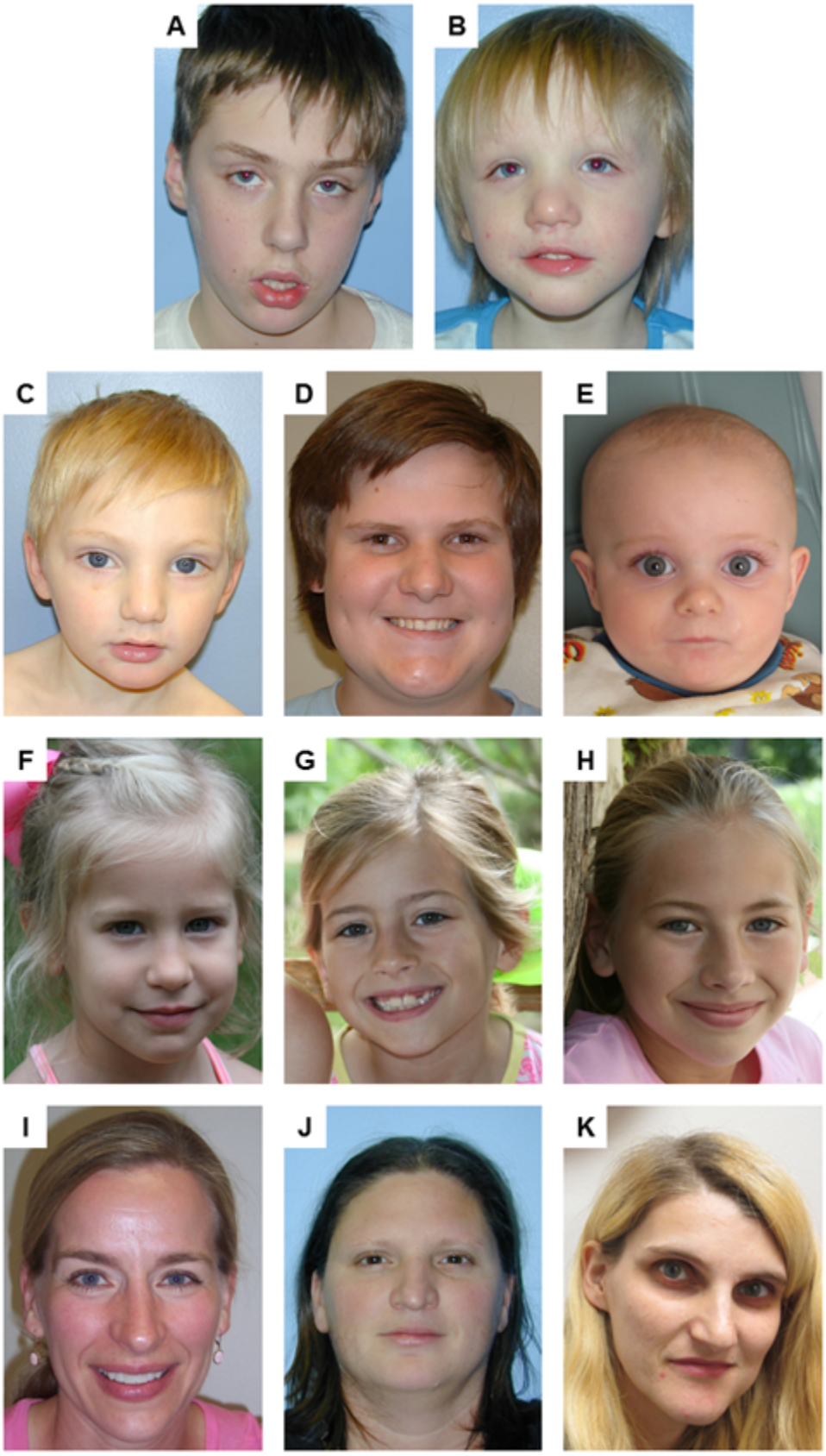

Figure 1. Facial features of affected males (A-E) and heterozygous females (F-K) with int22h1/int22h2-mediated Xq28 duplication syndrome

A and B are brothers, ages 11 and 3 years, respectively.

C, D, and E are ages 3 years, 15 years, and 9 months, respectively.

F, G, and H are sisters, ages 4, 6, and 8 years, respectively.

I, J, and K are ages 32, 25, and 47 years, respectively.

Note the tall forehead, large ears, wide and depressed nasal bridge, high nasal root, and thick vermilion of the lower lip in most of these individuals [El-Hattab et al 2011, El-Hattab et al 2015, Ballout et al 2020].

Table 1. Genomic Testing Used in Xq28 Duplication Syndrome, Int22h1/Int22h2 Mediated

Duplication [1]	ISCA ID [2]	Region Location [3, 4]	Method	Sensitivity	
				Proband	At-risk family members
0.5-Mb duplication at Xq28 (hemizygous in males; heterozygous in females)	Pending	GRCh37/hg19 chrX:154124111-154564398	CMA [5]	100% [6]	100% [6]
			Targeted duplication analysis [7]	NA [7]	100% [6]

1. See Molecular Genetics for details of the duplication.
2. Standardized clinical annotation and interpretation for genomic variants from the Clinical Genome Resource (ClinGen) project (formerly the International Standards for Cytogenomic Arrays [ISCA] Consortium)
3. Genomic coordinates represent the minimum duplication size associated with the int22h1/int22h2-mediated Xq28 duplication as designated by ClinGen. Duplication coordinates may vary slightly based on array design used by the testing laboratory. Note that the size of the duplication as calculated from these genomic positions may differ from the expected duplication size due to the presence of segmental duplications near breakpoints.
4. See Molecular Genetics for genes of interest included in this region.
5. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including int22h1/int22h2). CMA designs in current clinical use target the Xq28 region. The ability to determine the size of the duplication depends on the type of microarray used and the density of probes in the Xq28 region. Note: The int22h1/int22h2-mediated Xq28 duplication may not have been detectable by older oligonucleotide or BAC platforms.
6. El-Hattab et al [2011], Lannoy et al [2013], Vanmarsenille et al [2014], El-Hattab et al [2015], Ballout et al [2020]
7. Not applicable. Targeted duplication analysis methods can include quantitative PCR (qPCR), multiplex ligation-dependent probe amplification (MLPA), and iFISH as well as other targeted quantitative methods. Targeted duplication analysis is not appropriate for an individual in whom the int22h1/int22h2-mediated Xq28 duplication was not detected by CMA designed to target this region.

Clinical Characteristics

Clinical Description

The int22h1/int22h2-mediated Xq28 duplication syndrome is a relatively newly identified X-linked intellectual disability syndrome characterized by cognitive impairment, neurobehavioral abnormalities, and a peculiar combination of recurrent sinopulmonary infections (e.g., otitis media, sinusitis, recurrent upper respiratory tract infections) and atopic conditions (i.e., asthma, allergic rhinitis, and eczema) in affected males, who also often have obesity and exhibit nonspecific facial dysmorphic features (Table 2). Because affected males are hemizygous, they exhibit more severe manifestations than heterozygous females, who display a milder phenotype that predominantly consists of mild learning disabilities, inattentive-type childhood attention-deficit/hyperactivity disorder (ADHD)-like manifestations, and nonspecific facial dysmorphic features similar to those seen in affected males (Table 2). However, the majority of heterozygous females are clinically unaffected or have inconspicuous abnormalities.

To date, approximately 35 individuals (19 males and 16 females) with int22h1/int22h2-mediated Xq28 duplication syndrome have been identified and reported within the literature. The clinical features discussed

below are based on the phenotypic manifestations of all 35 affected individuals identified to date (see Table 2) [El-Hattab et al 2011, Lannoy et al 2013, Vanmarsenille et al 2014, El-Hattab et al 2015, Ballout et al 2020].

Table 2. Clinical Manifestations in Individuals with Int22h1/Int22h2-Mediated Xq28 Duplication Syndrome

Manifestation		Males (n=19) [1]	Females (n=16)
Neurobehavioral abnormalities	ID or cognitive impairment	16 [2] (~85%)	8 (50%)
	Aggression & irritability	6 (32%)	1 (6%)
	ADHD	6 (32%)	3 (19%)
	ASD	2 (11%)	1 (6%)
	Anxiety	2 (11%)	2 (13%)
	Socialization deficits	2 (11%)	2 (13%)
	Motor tics	1 (5%)	–
	Self-mutilation	1 (5%)	–
Psychiatric disorders	Mood disorders (mainly depression or bipolar disorder)	2 (11%)	1 (6%)
	Psychotic disorders (e.g., schizophrenia)	1 (5%)	–
Sleep disturbance(s)		3 (16%)	2 (13%)
Recurrent sinopulmonary infections	Otitis media	8 (42%)	–
	Pneumonia	4 (21%)	–
	Upper respiratory tract infections	2 (11%)	–
Atopic conditions	Asthma	6 (32%)	–
	Allergic rhinitis	5 (26%)	–
	Eczema	2 (11%)	–
Anthropometric abnormalities	Obesity	5 (26%)	1 (6%)
	Tall stature	3 (16%)	–
	Microcephaly	1 (5%)	1 (6%)
Facial dysmorphic (nonspecific) features	Tall forehead	11 (58%)	9 (56%)
	Sparse scalp hair	3 (16%)	3 (19%)
	Sparse eyebrows	3 (16%)	2 (13%)
	Highly rooted nasal bridge	2 (11%)	3 (19%)
	Depressed nasal bridge	2 (11%)	3 (19%)
	Thin vermilion of upper lip	3 (16%)	2 (13%)
	Thick vermilion of lower lip	5 (26%)	7 (44%)
	Large ears	4 (21%)	3 (19%)
	Bulbous nose	3 (16%)	–
	Long eyelashes	2 (11%)	2 (13%)

Table 2. continued from previous page.

Manifestation		Males (n=19) [1]	Females (n=16)
Limb &/or digital abnormalities	Clinodactyly	2 (11%)	1 (6%)
	Preaxial polydactyly	1 (5%)	–

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; ID = intellectual disability
1. Two males were diagnosed while fetuses (i.e., in utero), one of which was terminated, while the other was born with multiple malformations and subsequently lost to follow up. Therefore, several of the features listed in Table 2 for int22h1/int22h2-mediated Xq28 duplication syndrome could not be assessed in these two individuals, which warrants reader caution when assessing the "frequency" of a specific feature in affected males. It is likely that the provided percentage estimates for each feature under-predict the true prevalence of those features in affected males.
2. Intellectual disability could not be assessed in three affected males because one of them was still an infant (age <1 year) at the time of writing this report, another was an aborted fetus, and the third was never formally evaluated for cognitive impairment because he was lost to follow up.

Intellectual disability. All affected males who could be formally evaluated (i.e., excluding the two prenatally diagnosed cases and the newborn affected male) have been found to have intellectual disability. In contrast, only half of the heterozygous females identified to date with int22h1/int22h2-mediated Xq28 duplication syndrome have been found to have intellectual disability, which is consistent with the milder phenotype seen for the duplication in heterozygous females, compared with affected males, who are hemizygous. Moreover, while neurodevelopmental delays are typically noted early in childhood in affected males, they are often inconspicuous or identified later in heterozygous females. Additionally, the severity of intellectual disability (ID) associated with the syndrome differs between the sexes: while typically in the mild-to-moderate range in affected males, ID is occasionally mild in heterozygous females, or (more commonly) not apparent.

Neurobehavioral abnormalities. The neurobehavioral manifestations are more common and pervasive in affected males than in heterozygous females. The most common findings:

- ADHD, the predominant associated neurobehavioral manifestation in either sex
- Aggression and irritability, seen in nearly one third of males but only one female
- Autism spectrum disorder
- Anxiety, which affects both sexes equally
- Various socialization deficits

Psychiatric pathology also appears to be more prevalent in affected males than in females; two males and one female were reported to have a mood disorder, while another male has been reported to have schizophrenia, a psychotic disorder. No heterozygous females have been reported to date to have a psychotic disorder (see Table 2).

Sleep disturbances. While sleep disturbances appear to be equally prevalent in affected males and heterozygous affected females (16% and 13%, respectively), it has been recently noted that the "type" of insomnia experienced is different between the sexes. Both heterozygous females with sleep disturbances had difficulty falling asleep (i.e., sleep initiation), while all three affected males had difficulty remaining asleep (i.e., sleep maintenance) [Ballout et al 2020].

Recurrent sinopulmonary infections and atopic diseases. Almost 75% of males have experienced recurrent sinopulmonary infections such as otitis media, pneumonia, and/or upper respiratory tract infections. Likewise, around 70% of affected males have a history of atopic diseases, namely, asthma, eczema, and allergic rhinitis. It is worth noting that almost all the males with recurrent sinopulmonary infections were also the ones who had atopic diseases, making this peculiar combination somewhat a "signature" feature of the syndrome in affected males.

In contrast, none of the heterozygous affected females have been reported to have either recurrent sinopulmonary infections or atopic diseases (see Table 2).

Anthropometric abnormalities. Obesity is seen in nearly one quarter of affected males (i.e., 5/19), but in only one of 16 heterozygous females.

Tall stature was identified in three affected males and no heterozygous females. However, males and females showed similar prevalence of acquired microcephaly (~5%).

Nonspecific facial dysmorphic features. The most common facial feature associated with the syndrome in both sexes was a tall forehead, with more than half of affected males (58%) and heterozygous females (56%) having this feature. Tall forehead is followed in prevalence by thick and broad vermilion of the lower lip, reported in one quarter of affected males (26%) and fewer than half of heterozygous females (44%). The third most common discernible feature in both sexes is large ears, seen in 21% of affected males and 19% of heterozygous females (see Table 2 and Figure 1). Other less common facial features include sparse scalp hair and sparse eyebrows, a thin vermilion of the lower lip, an elongated and smooth philtrum, and long eyelashes.

Two additional features involving the morphology of the nose appear to discriminate by sex among affected individuals. While three reported males have a bulbous nose, no heterozygous female has been reported with this feature. In contrast, heterozygous females appeared to be nearly twice as likely as affected males (19% vs 11%, respectively) to have a high nasal root and depressed nasal bridge, long eyelashes, large ears, and depressed nasal bridge.

The following additional findings (either rare manifestations of the condition or rare, unrelated co-occurrences) have each been reported in a single male unless otherwise specified:

- Limb and digital anomalies
  - A single palmar crease
  - Fetal finger pads
  - Rocker bottom feet
  - Pes valgus
  - Pes planus
  - Metatarsus adductus
  - Sandal gap
  - 2-3 toe syndactyly
  - Short second toe
  - Short heel cords
  - Arthrogryposis of the lower limbs with bilateral clubfoot [Ballout et al 2020]
- Skeletal anomalies
  - Kyphoscoliosis (1 male / 2 male fetuses and 1 heterozygous female. In 1 male fetus, kyphoscoliosis was associated with thoracic vertebral malformations and unilateral missing ribs.)
  - Sacral agenesis
  - Hip dysplasia
- Sensorineural hearing loss
- Genitourinary malformations [Ballout et al 2020]
  - Micropenis with hypospadias
  - Bilateral grade I hydronephrosis
  - Cryptorchisim with phimosis
- Imperforate anus [Ballout et al 2020]
- Motor mannerisms and stereotypy (1 male, 1 heterozygous female) [Ballout et al 2020]
- Recurrent seizures (1 heterozygous female) [Ballout et al 2020]

- Eye anomalies/refractive error
  - Strabismus (2 males)
  - Myopia
  - Astigmatism
- Micrognathia (3 males and 1 heterozygous female)
- A café au lait macule with multiple facial freckles (1 heterozygous female) [Ballout et al 2020]
- Esophageal atresia with tracheoesophageal fistula, associated with cleft lip and cleft palate (2 males)
- Atrial septal defects (2 males, 1 of whom had a concomitant patent ductus arteriosus, while the other had a ventricular septal defect)
- Hemihyperplasia (1 heterozygous female)
- Hypothyroidism (1 heterozygous female)
- Generalized hypotonia that is worse on one side of the body [Ballout et al 2020]
- Multiple malignancies with no underlying hereditary cancer syndromes identified on genetic testing [Ballout et al 2020]

X-chromosome inactivation in heterozygous females. X-chromosome inactivation analyses are reported to be skewed in ten of 13 heterozygous females with int22h1/int22h2-mediated Xq28 duplication who have been studied. However, the skewed inactivation of an X chromosome has been found to be inconsistent and somewhat nonspecific; that is, X-chromosome inactivation has been shown to occur at nearly equal frequencies in the normal X chromosome and the X chromosome containing the duplication. Moreover, no association could be appreciated between the X-chromosome inactivation pattern and the corresponding cognitive phenotype in the studied females, with random and skewed inactivation patterns being seen at nearly equal rates in heterozygous females with or without intellectual disability [El-Hattab et al 2015]. However, it is also worth noting that X-chromosome inactivation analyses have not been performed for all heterozygous females with the duplication.

Genotype-Phenotype Correlations

The region located between int22h1 and int22h2 on Xq28, which is the segment typically duplicated in int22h1/int22h2-mediated Xq28 duplication syndrome, includes several genes: *FUNDC2*, *MTCP1*, *BRCC3*, *VBP1*, *RAB39B*, *CLIC2*, and part of *F8*. However, the cognitive and neurobehavioral manifestations seen in individuals with the syndrome has been speculated to be the result of increased dosages of *CLIC2* and *RAB39B* (see Molecular Genetics), based on the consistent detection of both loci within the smallest region of overlap between the duplicated segments of all affected individuals identified to date.

An atypical shortened version (~0.26 Mb) of the classic 0.5-Mb duplication reported in int22h1/int22h2-mediated Xq28 duplication syndrome has been reported in a newborn male, with his duplicated segment spanning only the centromeric half of the classically involved segment; that is, his duplication extended from 154.1 Mb to ~154.3 Mb of the q28 region of the X chromosome in the reference genome (NCBI Build GRCh37/hg19) [Ballout et al 2020]. This proband was a recently identified nine-week-old infant at the time of reporting. As such, it is currently unclear how much of the typical phenotype of the syndrome he may develop.

For information about other Xq28 duplications with partially overlapping breakpoints compared to the int22h1/int22h2-mediated Xq28 duplication syndrome, see Genetically Related Disorders.

Prevalence

Int22h1/int22h2-mediated Xq28 duplication has been reported in only 35 individuals (19 males and 16 females) to date [El-Hattab et al 2011, Lannoy et al 2013, Vanmarsenille et al 2014, El-Hattab et al 2015, Ballout et al 2020]. As a result, exact estimates on the prevalence of this duplication remain unknown.

Vanmarsenille et al [2014] estimated its prevalence at 1:1,000 among males with X-linked intellectual disability syndromes. In the absence of population-based studies, however, and due to the rarity of the syndrome, this may be an overestimate.

Genetically Related (Allelic) Disorders

Other Xq28 duplications with overlapping breakpoints

- Three sibs were reported to have a 0.8-Mb Xq28 duplication that extends from 154.4 to 155.2 Mb, overlapping the duplicated segment of int22h1/int22h2-mediated Xq28 duplication syndrome, and including the genes *RAB39B* and *CLIC2*. These sibs showed some overlapping features with individuals having the int22h1/int22h2-mediated Xq28 duplication syndrome, including intellectual disability, nonspecific facial dysmorphic features (tall forehead, wide and highly rooted nasal bridge, and thick vermilion of the lower lip), and neurobehavioral abnormalities (autism spectrum disorder, aggression and irritability, and attention-deficit/hyperactivity disorder) [Andersen et al 2014].
- A 0.8-Mb Xq28 duplication overlapping with the 0.5-Mb duplicated region in int22h1/int22h2-mediated Xq28 duplication syndrome has also been reported in individuals sharing some of the clinical features of int22h1/int22h2-mediated Xq28 duplication syndrome.
- A 0.2-Mb telomerically shifted and slightly shortened version (~0.4 Mb) of the classic 0.5-Mb duplication reported in int22h1/int22h2-mediated Xq28 duplication syndrome has been reported in two sibs with typical manifestations of the syndrome. Their duplications were identical and extended between 154.3 Mb and 154.7 Mb of the q28 region of the X chromosome, according to the reference genome (NCBI Build GRCh37/hg19) [Ballout et al 2020].

The reciprocal int22h1/int22h2-mediated Xq28 deletion has been reported in five heterozygous females with normal cognition, who were found to have skewed X-chromosome inactivation, with the selective inactivation of the X chromosome containing the deletion. As such, this reciprocal deletion has been suggested to have no phenotypic effects on carrier females, due to the apparently selective inactivation of the X chromosome containing the deletion. However, it remains unknown whether this deletion exists in a male, or is simply embryonic lethal in males, which would result in higher miscarriage rates in heterozygous females for this deletion who conceive a male fetus [El-Hattab et al 2011, El-Hattab et al 2015].

Differential Diagnosis

Because the phenotypic features associated with int22h1/int22h2-mediated Xq28 duplication syndrome are not sufficient on their own to make a diagnosis of the condition, all other X-linked intellectual disability syndromes (XLIDS) without specific distinctive features should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

***MECP2* duplication syndrome.** Several other duplications involving the Xq28 region also result in distinct XLIDS. One notable example is the *MECP2* duplication syndrome, a severe neurodevelopmental disorder characterized by early-onset hypotonia, feeding difficulty, gastrointestinal abnormalities such as gastroesophageal reflux and constipation, neurodevelopmental delays, severe intellectual disability, progressive spasticity, recurrent respiratory infections, and seizures. *MECP2* duplication syndrome is 100% penetrant in affected males. In contrast, heterozygous females with a *MECP2* duplication have been reported to have a wide range of possible findings, ranging from mild intellectual disability to a set of manifestations that phenocopy those of affected males. In addition to the aforementioned core features of the syndrome, autism spectrum disorders, nonspecific neuroradiologic findings on brain MRI, mottled skin, and urogenital anomalies have also been reported in affected males.

The syndrome is caused by duplications in the q28 region of the X chromosome spanning the *MECP2* locus (153.3 Mb), ranging from 0.3 to 4 Mb. In contrast, the int22h1/int22h2-mediated Xq28 duplication syndrome is caused by 0.5-Mb duplication in Xq28, in the int22h1/int22h2 region that is located telomeric to the *MECP2* locus and extending from 154.1 to 154.6 Mb.

Intellectual disability and recurrent infections are common findings in both syndromes, with males being more severely affected than females. However, spasticity has not been reported to date in int22h1/int22h2-mediated Xq28 duplication syndrome, and seizures and hypotonia have only recently been reported – each in a single affected individual [Ballout et al 2020].

Management

No evidence-based or consensus guidelines have been established to date for the management of individuals with int22h1/int22h2-mediated Xq28 duplication syndrome. Thus, the clinical management of affected individuals remains primarily supportive at this time.

Although the features of int22h1/int22h2-mediated Xq28 duplication syndrome are typically more pronounced in affected males compared with heterozygous females, affected males and heterozygous females are managed with a similar clinical approach.

Evaluations Following Initial Diagnosis

In order to establish the extent and severity of manifestations in individuals with the int22h1/int22h2-mediated Xq28 duplication syndrome, Table 3 summarizes the different evaluations recommended to be performed (if not already performed as part of the evaluation that led to the diagnosis):

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with the Int22h1/Int22h2-Mediated Xq28 Duplication Syndrome

System/Concern	Evaluation	Comment
Growth/ Anthropometrics	Measurement of weight, length/height, & head circumference	For those w/obesity, consider referral to nutritionist & dietician.
Neurodevelopmental milestones & cognition	Age-appropriate neurodevelopmental & cognitive assessments	• Neurodevelopmental milestone assessment should incl motor, cognitive, & speech-language eval. • Early identification of neurodevelopmental delays would allow for early intervention.
Neurobehavioral & psychiatric abnormalities	Neuropsychiatric evals [1]	For persons age ≥12 mos, screen for neurobehaviorial concerns such as aggression & irritability, emotional lability, self-mutilation, motor tics &/or findings suggestive of ASD, based on individual presentation.
Sleep	Consider consulting a sleep specialist for a possible sleep study.	
Neurologic	Assessment of muscle tone & strength on both sides of body, & proximally & distally [2]	If motor skills are noted to be abnormal, refer to PT (to improve gross motor skills) or OT (to improve fine motor skills).

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	Physical exam for hand & foot (i.e., limb) anomalies incl pes planus, polydactyly, syndactyly	Orthopedic eval w/adjunct rehab medicine / PT & OT eval, if & when needed
	Assessment of spine & vertebrae via spinal radiographs to detect features incl abnormal spinal curvature (e.g., kyphoscoliosis), vertebral malformations, missing ribs	If kyphoscoliosis is identified, consider referral to orthopedist & PT for mgmt.
Allergy/ Immunology	Screen for recurrent infections & atopy, [3] esp in affected males.	Incl history of recurrent & severe or protracted sinopulmonary infections & comorbid atopic conditions (asthma, allergic rhinitis, or eczema)
Hearing	Audiologic eval	Assess for hearing loss.
Vision	Ophthalmologic eval	Assess for strabismus, myopia, & astigmatism.
Genitourinary	Eval for cryptorchidism, hypospadias, or micropenis in males	If present, consider referral to pediatric urologist &/or pediatric endocrinologist.
Cardiovascular	Consider echocardiography.	To assess for congenital heart defects
Genetic counseling	By genetics professionals [4]	To inform affected persons & their families or caregivers re nature, MOI, & implications of int22h1/int22h2-mediated Xq28 duplication syndrome to allow for informed decision making in medical care, as well as future family planning
Family support/ resources	Help connect affected person &/or their families w/other affected persons & families.	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental/caregiver support; • Home nursing referral.

ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. For psychiatric conditions (e.g., attention-deficit/hyperactivity disorder, anxiety, mood or psychotic disorders), follow the DSM-V criteria for screening and diagnosing the respective condition(s) based on age group.
2. Evaluations for (e.g.,) hypotonia, spasticity, atrophy, and hemihypertrophy are suggested.
3. Through obtaining a thorough history of prior infections and vaccinations, any reactions to the latter, and history of allergic reactions (e.g., seasonal allergies)
4. Medical geneticist, certified genetic counselor, and/or certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with the Int22h1/Int22h2-Mediated Xq28 Duplication Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Obesity	Refer for nutritional counseling & recommend regular exercise.	
Neurodevelopmental delays/ID	See Neurodevelopmental Delay / Intellectual Disability Management Issues.	
Neurobehavioral & psychiatric abnormalities	Standard treatment (e.g., SSRIs for anxiety or depression, antipsychotics for psychotic disorders, stimulants for ADHD)	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Sleep disturbance	For those w/insomnia, consider conservative treatment w/proper sleep hygiene practices.	In more severe cases, consider melatonin supplementation after consultation w/caring physician or sleep specialist.
Kyphoscoliosis	Refer to orthopedist for standard treatment, w/or w/o requesting add-on help from PT/OT.	
Recurrent sinopulmonary infections	Standard antibiotic treatment for active bacterial infections & vaccination against *S pneumoniae*, *H influenzae*, & *N meningitidis*	Consider: • Referral to pulmonologist, immunologist, &/or infectious disease specialist in those w/recurrent infections; • Chest PT & mucolytics for those w/ recurrent pneumonia; • Referral to otolaryngologist for consideration of PE tube placement in those w/recurrent otitis media.
	Annual vaccination against influenza virus to ↓ risk of contracting or experiencing severe infection	
Asthma	Standard treatment (e.g., bronchodilators, allergen exposure prevention)	Consider referral to pulmonologist & pulmonary function testing for those w/severe asthma.
Allergic rhinitis	Standard treatment (e.g., decongestants, antihistamines, nasal steroids, allergen exposure prevention)	
Eczema	Standard treatment	Consider referral to dermatologist for those w/ severe eczema.
Hearing loss	Hearing aids may be helpful; to be decided by otolaryngologist.	Consider community hearing services through early intervention or school district.
Refractive errors &/or strabismus	Standard treatment(s) per ophthalmologist	
Undervirilization in males	Standard treatment per urologist	Consider referral to pediatric endocrinologist also for possible hormonal therapy as appropriate.
Congenital heart defects	Standard treatment per cardiologist	
Family/ Community	• Ensure appropriate involvement of social workers to connect affected persons &/or their families w/local resources, respite, or support. • Help coordinate care to manage multiple subspecialty appointments, mobility assistance or other needed medical equipment, & medications & supplies.	• Ongoing assessment for need for palliative care involvement &/or home nursing for cases w/severe congenital malformations & severe ID • Consider involvement in adaptive sports or Special Olympics.

ADHD = attention-deficit/hyperactivity disorder; ID = intellectual disability; OT = occupational therapy; PE = pressure equalizing; PT = physical therapy; SSRI = selective serotonin reuptake inhibitor

Neurodevelopmental Delay / Intellectual Disability Management Issues

The following information summarizes the typical management recommendations for individuals with developmental delay or intellectual disability in the United States.

It is worth noting that standard recommendations may vary from country to country for the management of individuals with developmental delay and/or intellectual disability.

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 tailored to meet individual therapy needs.

Ages 3-5 years. In the US, referral to a developmental preschool available 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 evaluated motor, language, social, or cognitive skills. The early intervention program typically assists with this transition. Developmental preschool is often center based. For children too medically unstable to attend, home-based services can be arranged.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) that can support parents in maximizing the quality of life of their affected child. Services to consider include the following:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually and amended or updated as needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school, with inclusion in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be part of the child's IEP team to help support access to appropriate academic material.
  - PT, OT, and speech therapy services will be provided within the IEP to the extent needed to support 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 the developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated into the existing IEP. For those receiving IEP services, the public school district is required to provide services up until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for individuals requiring special accommodations or educational modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Enrollment at the Developmental Disabilities Administration (DDA) is also recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is generally determined by diagnosis and/or associated intellectual and 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 reduce the risk for later-onset orthopedic complications (e.g., scoliosis, hip dislocation).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skill deficits or abnormalities that affect adaptive functions such as feeding, grooming, dressing, and writing.

Communication issues. For individuals with deficits in expressive language, consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]). An AAC evaluation can be completed by a speech therapist with expertise in the area. The evaluation will consider cognitive abilities and

sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech (such as picture exchange communication) to high-tech (such as voice-generating devices). Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social and Behavioral Concerns

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

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

Concerns about serious aggressive, destructive, or self-mutilating behaviors can be discussed with and addressed by a child and adolescent psychiatrist.

Surveillance

Table 5. Recommended Surveillance and Follow Up for Individuals with Int22h1/Int22h2-Mediated Xq28 Duplication Syndrome

System/Concern	Evaluation	Frequency
Growth	Measurement of growth/anthropometric parameters	At each visit
Neurodevelopmental milestones & cognitive abilities	Monitor progress along age-expected neurodevelopmental milestones.	
	Reassess special educational needs.	Annually in childhood & adolescence
Neurobehavioral & psychiatric evaluations	Conduct thorough assessment & screening for anxiety, irritability & aggression, self-injurious behaviors, attention deficits, hyperactivity, impulsivity, & sleep disturbances.	At each visit
Musculoskeletal	PT/OT assessment of gross & fine motor skills, mobility, & self-care skills	
	Orthopedics follow up	As needed for those w/contractures &/or kyphoscoliosis
Allergy/ Immunology	Repeat pulmonary function testing as needed in those w/moderate-to-severe asthma, & assess response to prescribed medications.	As clinically indicated or per pulmonologist
Hearing	Audiology eval	At least annually in infancy & childhood, or more frequently if otherwise clinically indicated
Vision	Ophthalmology eval	At least annually
Family & community support/resources	Assess family or caregiver need for social work support (e.g., palliative/respite care, home nursing, other local resources), equipment & assistive medical devices, &/or any other special disability benefits.	At each visit

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

It is relevant from clinical and family planning standpoints to evaluate the genetic status of asymptomatic relatives of an affected individual in order to identify as early as possible those who would benefit from early intervention services.

Targeted duplication analysis can be performed by quantitative PCR (qPCR), multiplex ligation-dependent probe amplification (MLPA), or interphase FISH (iFISH) to test the relatives of a proband who is known to have the int22h1/int22h2-mediated Xq28 duplication.

Note: Clinically asymptomatic children identified as having the familial duplication should be assessed and monitored regularly for neurodevelopmental delays and neurobehavioral abnormalities.

See Genetic Counseling for issues related to the testing of at-risk relatives, from a genetic counseling perspective.

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 are no registered, recruiting, or ongoing clinical trials for int22h1/int22h2-mediated Xq28 duplication syndrome as of the chapter posting date.

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 int22h1/int22h2-mediated Xq28 duplication syndrome is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the int22h1/int22h2-mediated Xq28 duplication; therefore, he does not require further testing.
- In contrast, in a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (i.e., a carrier). Note: If a woman has more than one affected child and no other affected relatives and if the duplication cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If the proband is the only affected family member (i.e., a simplex case), the mother may be heterozygous for the duplication; or the duplication may have occurred *de novo* in the proband, in which case the mother is not heterozygous. Alternatively, the mother of the proband may have germline mosaicism.
- Most of the mothers of the individuals reported to date with the int22h1/int22h2-mediated Xq28 duplication syndrome have been found to be heterozygous (i.e., carriers) for the duplication.
- Genomic testing capable of detecting the int22h1/int22h2-mediated Xq28 duplication is recommended for the mother of a proband. Note: Testing of maternal leukocyte DNA may not always detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Parents of a female proband

- A female proband may have inherited an int22h1/int22h2-mediated Xq28 duplication from her mother or, theoretically, her father if he has germline mosaicism. Alternatively, the duplication may have occurred *de*

novo in the proband. *De novo* int22h1/int22h2-mediated Xq28 duplications were recently reported in two heterozygous females [Ballout et al 2020].
- Genomic testing capable of detecting the int22h1/int22h2-mediated Xq28 duplication is recommended for the mother of a proband.

Sibs of a proband

- The risk to sibs of a male proband of inheriting the duplication depends on the genetic status of the mother. (However, if the proband is female, the risk to sibs of inheriting the duplication depends on the genetic status of the mother and, theoretically, the father because of the possibility of paternal germline mosaicism.)
- If the mother is heterozygous for the int22h1/int22h2-mediated Xq28 duplication, the chance of transmission of the duplication is 50% in each pregnancy.
  - Males who inherit the maternal X chromosome containing the int22h1/int22h2-mediated Xq28 duplication will be affected.
  - Females who inherit the maternal X chromosome containing the int22h1/int22h2-mediated Xq28 duplication will be heterozygous and will therefore be likely have a milder phenotype than affected males or be clinically unaffected (see Clinical Description).
- If the proband represents a simplex case (i.e., a single occurrence within the family), and the int22h1/int22h2-mediated Xq28 duplication cannot be detected in the leukocyte DNA of the mother, the risk to sibs of inheriting the duplication is low, albeit greater than that of the general population due to the possibility of maternal germline mosaicism. (Note: Testing of maternal leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.)

Offspring of a male proband. Only one affected male, recently reported, has been known to reproduce, having a healthy 16-year-old son [Ballout et al 2020].

Offspring of a female proband. Females heterozygous for the int22h1/int22h2-mediated Xq28 duplication have a 50% chance of transmitting the duplication to offspring in each pregnancy:

- Males who inherit the int22h1/int22h2-mediated Xq28 duplication will be affected.
- Females who inherit the int22h1/int22h2-mediated Xq28 duplication will be heterozygous, often exhibiting a milder phenotype than affected males or, alternatively, being clinically unaffected (see Clinical Description).

Other family members. The genetic risk of other family members depends on the genetic status of the proband's mother. If the mother is heterozygous for the int22h1/int22h2-mediated Xq28 duplication, her family members (e.g., her biological mother and sibs) may also have the duplication.

Note: Genomic testing capable of detecting the int22h1/int22h2-mediated Xq28 duplication in the proband can help identify the family member in whom a *de novo* duplication occurred. Such information can help to determine the genetic risk of extended family members.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are at risk of having a child with the int22h1/int22h2-mediated Xq28 duplication syndrome.

Prenatal Testing and Preimplantation Genetic Testing

Pregnancies known to be at increased risk for an int22h1/int22h2-mediated Xq28 duplication. Once the int22h1/int22h2-mediated Xq28 duplication has been identified in an affected family member, prenatal and preimplantation genetic testing for a pregnancy at increased risk are possible.

Pregnancies not known to be at increased risk for an int22h1/int22h2-mediated Xq28 duplication. Chromosomal microarray (CMA) performed in a pregnancy not known to be at increased risk may detect this duplication.

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

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. Xq28 Duplication Syndrome, Int22h1/Int22h2 Mediated: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CLIC2	Xq28	Chloride intracellular channel protein 2	CLIC2 @ LOVD	CLIC2	CLIC2
RAB39B	Xq28	Ras-related protein Rab-39B	RAB39B @ LOVD	RAB39B	RAB39B

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 Xq28 Duplication Syndrome, Int22h1/Int22h2 Mediated (View All in OMIM)

300138	CHLORIDE INTRACELLULAR CHANNEL 2; CLIC2
300774	RAB39B, MEMBER RAS ONCOGENE FAMILY; RAB39B
300815	CHROMOSOME Xq28 DUPLICATION SYNDROME

Molecular Pathogenesis

The int22h1/int22h2-mediated Xq28 duplication breakpoints are located at the directly oriented LCRs: int22h1 (located within intron 22 of *F8*) and int22h2 (situated ~0.5 Mb telomerically to int22h1). The duplication is mediated by nonallelic homologous recombination between the int22h1 and int22h2 loci [El-Hattab et al 2011].

It is worth noting that a third homologous region, int22h3, is located 0.6 Mb telomeric to int22h1, or about 0.1 Mb telomeric to int22h2. Until recently, no duplications involving the int22h3 locus (which is in opposite orientation to int22h1) had been identified. However, in the recent case series by Ballout et al [2020], a heterozygous female and her affected brother were both reported to have an atypical and telomerically shifted version of the int22h1/int22h2-mediated Xq28 duplication (cases 4 and 5), in which the distal breakpoint falls within the int22h3 region, rather than int22h2 (see Genetically Related Disorders). Interestingly, both reported individuals exhibited features consistent with and resembling those seen in individuals with int22h1/int22h2-mediated Xq28 duplication syndrome [Ballout et al 2020].

Genomic inversions between int22h1 and either int22h2 or int22h3 are known to disrupt *F8* in nearly half of individuals with severe hemophilia A [Bagnall et al 2005]. However, the int22h1/int22h2-mediated Xq28 duplication does not result in hemophilia A because the complete copy of *F8* is preserved after formation of this duplication [El-Hattab et al 2011].

Genes of interest in this region. The 0.5-Mb duplicated region between int22h1 and int22h2 includes several genes. However, the intellectual disability of individuals with the int22h1/int22h2-mediated Xq28 duplication syndrome has been speculated to be likely due to increased dosages of two of those genes in particular: *RAB39B* and *CLIC2* [Andersen et al 2014, El-Hattab et al 2015].

- ***CLIC2*** encodes the unique intracellular transmembrane chloride channel 2 (CLIC2) protein, present in cardiac and skeletal muscle cells where it functions as a regulator of calcium release via the ryanodine receptor 2 (RyR2) [Board et al 2004, Meng et al 2009]. A missense pathogenic variant in *CLIC2* has been reported to be associated with a distinct form of X-linked intellectual disability syndrome in two brothers having intellectual disability, cardiomegaly, atrial fibrillation, heart failure, and seizures [Takano et al 2012].
- ***RAB39B*** encodes a specific member of the Rab family of GTPases that is highly expressed in central nervous system neurons, particularly in the hippocampus, where it has been shown to play a key role in the trafficking of an AMPA glutamate receptor (GluA2) and facilitate synaptogenesis and neuronal branching [Ng & Tang 2008, Mignogna et al 2015].
  - Loss-of-function pathogenic variants in *RAB39B* reported in two families have been associated with intellectual disability, autism spectrum disorders, epilepsy, and microcephaly [Giannandrea et al 2010]. Loss-of-function pathogenic variants in *RAB39B* have also been associated with early-onset Parkinson disease [Wilson et al 2014, Lesage et al 2015].
  - In contrast, increased dosages of *RAB39B* have been reported in four males to be associated with intellectual disability and neurobehavioral abnormalities [Vanmarsenille et al 2014]. Overexpression of Rab39b in mouse primary hippocampal neurons was then shown to result in decreased neuronal branching and total number of synapses, suggesting that increased dosages of *RAB39B* disrupt neuronal branching [Vanmarsenille et al 2014].

Chapter Notes

Author Notes

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