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15q Duplication Syndrome and Related Disorders

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Summary

Clinical characteristics

15q duplication syndrome and related disorders (dup15q) are caused by presence of at least one extra maternally derived copy of the Prader-Willi/Angelman critical region (PWACR) within chromosome 15q11.2-q13.1. The extra copy or copies most commonly arise by one of two mechanisms:

- A maternal isodicentric 15q11.2-q13.1 supernumerary chromosome – idic(15) – typically comprising two extra copies of 15q11.2-q13.1 and resulting in tetrasomy for 15q11.2-q13.1 (~80% of cases);
- A maternal interstitial 15q11.2-q13.1 duplication that typically includes one extra copy of 15q11.2-q13.1 within chromosome 15, resulting in trisomy for 15q11.2-q13.1 (~20% of cases).

Dup15q is characterized by hypotonia and motor delays, intellectual disability, autism spectrum disorder (ASD), and epilepsy including infantile spasms. Rarely, dup15q may also be associated with psychosis or sudden unexplained death. Those with maternal idic(15) are typically more severely affected than those with an interstitial duplication.

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Diagnosis/testing

The diagnosis of dup15q is established by detection of at least one extra maternally derived copy of the PWACR, a region approximately 5 Mb long within chromosome 15q11.2-q13.1.

Management

Treatment of manifestations: It is suggested that a multidisciplinary team evaluate infants for motor and speech development and later assist in referrals for appropriate educational programs. Supportive care may include: occupational and physical therapy, alternative and augmentative communication, behavioral therapy (e.g., applied behavioral analysis therapy), psychotropic medications for behavioral manifestations, and standard management for seizures.

Surveillance: Periodic: neurodevelopmental and/or developmental/behavioral assessments, and monitoring for evidence of seizures and/or change in seizure type.

Agents/circumstances to avoid: Seizure triggers (e.g., sleep deprivation, stress) and failure to follow medication regimen.

Evaluation of relatives at risk: Consider genetic testing of sibs of a proband (known to be at increased risk for an inherited maternal interstitial 15q11.2-q13.1 duplication) in order to refer those with the interstitial duplication promptly for multidisciplinary team evaluation.

Genetic counseling

Dup15q caused by:

- Maternal idic(15) has been *de novo* in all affected individuals reported to date; thus, risk to sibs is low, but presumed to be marginally greater than in the general population because of the possibility of maternal germline mosaicism;
- Maternal interstitial 15q11.2-q13.1 duplication has been *de novo* in 85% of probands and inherited from the mother in 15%. If the mother has the 15q interstitial duplication, the risk to each child of inheriting the duplication is 50%.

Prenatal testing or preimplantation genetic diagnosis using chromosomal microarray (CMA) will detect the 15q interstitial duplication; however, prenatal test results cannot reliably predict the severity of the phenotype even in a pregnancy known to be at increased risk for dup15q.

GeneReview Scope

15q Duplication Syndrome and Related Disorders: Included Genetic Mechanisms
• Maternal isodicentric 15q11.2-q13.1 supernumerary chromosome [idic(15)] resulting in tetrasomy or hexasomy for 15q11.2-q13.1 • Maternal interstitial 15q11.2-q13.1 duplication or triplication

For synonyms and outdated terms see Nomenclature.

Diagnosis

No formal diagnostic criteria have been published for 15q duplication syndrome and related disorders (referred to in this *GeneReview* as dup15q).

Suggestive Findings

15q duplication syndrome and related disorders (dup15q) **should be suspected** in individuals with the following:

- Moderate to severe hypotonia in infancy and motor delays
- Developmental delay, which can manifest as intellectual disability (ID) and/or speech and language delays
- Autism spectrum disorder (ASD)
- Seizures, particularly infantile spasms

Also seen frequently in individuals with dup15q:

- Mild-to-moderate dysmorphic features including upturned nose, epicanthal folds, and downslanting palpebral fissures [Battaglia et al 1997, Wolpert et al 2000, Orrico et al 2009, Hogart et al 2010, Urraca et al 2013]
- Behavioral difficulties including hyperactivity, anxiety, or emotional lability [Battaglia et al 1997, Wolpert et al 2000, Piard et al 2010, Al Ageeli et al 2014]

Establishing the Diagnosis

The diagnosis of 15q duplication syndrome and related disorders (dup15q) **is established** by detection of at least one extra maternally derived copy of the Prader-Willi/Angelman critical region (PWACR), a region approximately 5 Mb long within chromosome 15q11.2-q13.1.

The proximal 15q region includes five regions of segmental duplications or low copy repeats (designated by breakpoints [BPs]), which result in increased susceptibility to genomic rearrangements [Hogart et al 2010]. These five regions are termed BP1 through BP5. The PWACR lies between BP2 and BP3 (Figure 1) and is always included in the interstitial duplications or the idic(15) that cause dup15q. The PWACR is imprinted: maternally derived increases in copy number cause dup15q (the topic of this *GeneReview*) while paternally derived increases are typically associated with more variable and sometimes different neurodevelopmental phenotypes (see Genetically Related Disorders) [Cook et al 1997, Urraca et al 2013].

The extra copy or copies of the PWACR most commonly arise by one of two mechanisms (Figure 1):

- A maternal isodicentric 15q11.2-q13.1 supernumerary chromosome – idic(15) – that typically comprises two extra copies of 15q11.2-q13.1, resulting in tetrasomy for 15q11.2-q13.1 (~80% of cases [Dup15q Alliance International Registry; 3-14-14])

  OR

- A maternal interstitial 15q11.2-q13.1 duplication that typically includes one extra copy of 15q11.2-q13.1 within chromosome 15, resulting in trisomy for 15q11.2-q13.1 (~20% of cases [Dup15q Alliance International Registry; 3-14-14])

For this *GeneReview*, the disorder commonly known as dup15q is defined as the presence of one or more extra copies of 15q11.2-q13.1 that include the PWACR at the approximate position of 23651570-28664979 in the reference genome (NCBI Build GRCh37/hg19, seen here). Duplications may vary in size and have been seen up to 12 Mb long (as seen here) but must contain the PWACR to be causative of dup15q.

Although several genes of interest (e.g., *ATP10A*, *CYFIP1*, *MAGEL2*, *NECDIN*, *SNRPN*, *UBE3A*, *snoRNAs*, and a cluster of genes encoding $GABA_A$ receptor subunits) are within the 4.5- to 12-Mb recurrent duplication, no single gene that – when duplicated – causes dup15q has been identified (see Molecular Genetics for genes of interest in the duplicated region).

Genomic testing methods that determine the copy number of sequences can include **chromosomal microarray analysis** (CMA) or **targeted duplication analysis.** Note: (1) Interstitial 15q11.2-q13.1 duplications cannot typically be identified by routine analysis of G-banded chromosomes or other conventional cytogenetic banding techniques; however, idic(15) and large interstitial duplications (>5 Mb) that extend beyond the PWACR can be identified through cytogenetic analysis. (2) Mosaicism has been reported for idic(15) suggesting some degree of mitotic instability [Wang et al 2008], which may affect the phenotype and the sensitivity of genomic testing strategies used for diagnosis.

- **CMA** using oligonucleotide arrays or SNP arrays can detect increases in copy number of the 15q11.2-q13.1 region in a proband. The ability to size the region involved depends on the type of microarray used and the density of probes in the 15q11.2-q13.1 region. CMA cannot reliably differentiate between idic(15) and interstitial triplication of 15q11.2-q13.1.

  Note: (1) Most individuals with dup15q are identified by CMA performed for the purpose of determining the cause of developmental delay, intellectual disability, or autism spectrum disorder. (2) FISH or a cytogenetic study is required to determine whether the duplication is supernumerary or interstitial and to determine whether there is evidence for mosaicism.

- **Targeted duplication 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 the 15q11.2-q13.1 recurrent duplication.

  Note: (1) Targeted duplication testing is not appropriate for an individual in whom the 15q11.2-q13.1 recurrent duplication was not detected by CMA designed to target this region. (2) It is not possible to size the duplication routinely by use of targeted methods.

Parent of origin of the 15q11.2-q13.1 duplication is identified by either of the following:

- Genotyping or methylation analysis, including PCR-based methylation analysis [Zielinski et al 1988, Urraca et al 2010]
- Identification of a 15q11.2-q13.1 interstitial duplication in a parental sample

Table 1. Genomic Testing used in 15q Duplication and Related Disorders (dup15q)

Duplication [1]	ISCA ID [2]	Region Location [3]	Method	Test Sensitivity	
				Proband	At-risk family members
4.5- to 12-Mb duplication at 15q11.2-q13.1 (includes PWACR)	ISCA-37404 [4] or ISCA-37478 [5]	GRCh37/hg19 chr15: 21483759-32644465	CMA [6, 7]	100%	100%
			Targeted duplication analysis [8]	Not applicable [9]	100%

1. See Molecular Genetics for details of the duplication and genes of interest in this region.
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 15q11.2-q13.1 recurrent 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. The phenotype of significantly larger or smaller duplications within this region may be clinically distinct from the 15q11.2-q13.1 recurrent duplication (see Genetically Related Disorders).
4. Class 1 duplication, approximately 6 Mb, extending from BP1 to BP3
5. Class 2 duplication, approximately 5 Mb, extending from BP2 to BP3
6. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 15q11.2-q13.1 region. Note: 15q duplication and related disorders may not have been detectable by older oligonucleotide or BAC platforms.
7. FISH or cytogenetic analysis (e.g., G-banded chromosome study) should be completed as a follow up to CMA in most cases in order to determine whether the duplication is interstitial or contained within a supernumerary chromosome. Although CMA results may indicate whether the duplication is interstitial, this is not common.
8. Targeted duplication analysis methods can include FISH, quantitative PCR (qPCR), and multiplex ligation-dependent probe amplification (MLPA) as well as other targeted quantitative methods.
9. Targeted duplication analysis is not appropriate for diagnosis of an individual in whom the 15q11.2-q13.1 duplication was not detected by CMA designed to target this region.

Evaluating at-risk relatives. FISH, qPCR, or other quantitative methods of targeted duplication analysis can be used to identify the 15q11.2-q13.1 recurrent duplication in at-risk relatives of the proband.

- **Maternal isodicentric 15q11.2-q13.1 supernumerary chromosome – idic(15).** Familial occurrence has not been reported. Parental testing is not routinely indicated but can be considered on a case-by-case basis (see Genetic Counseling).
- **Maternal interstitial 15q11.2-q13.1 duplication.** Parental testing is indicated as these duplications may be inherited from a mother with a paternally derived *de novo* or inherited duplication (see Genetic Counseling).

Clinical Characteristics

Clinical Description

15q duplication syndrome and related disorders (dup15q) are characterized by hypotonia and motor delays, intellectual disability, autism spectrum disorder (ASD), and epilepsy including infantile spasms. These clinical findings differ significantly between people with a maternal interstitial duplication and those with a maternal isodicentric supernumerary chromosome, or idic(15) (Table 2). Those with a maternal idic(15) are typically more severely affected than those with an interstitial duplication. However, severity varies even among individuals who have increased dosage by the same genetic mechanism. Some phenotypic features, such as ASD, are more consistently observed in individuals with a maternal idic(15) or large (>5-Mb) interstitial duplications that extend beyond the PWACR [Hogart et al 2010].

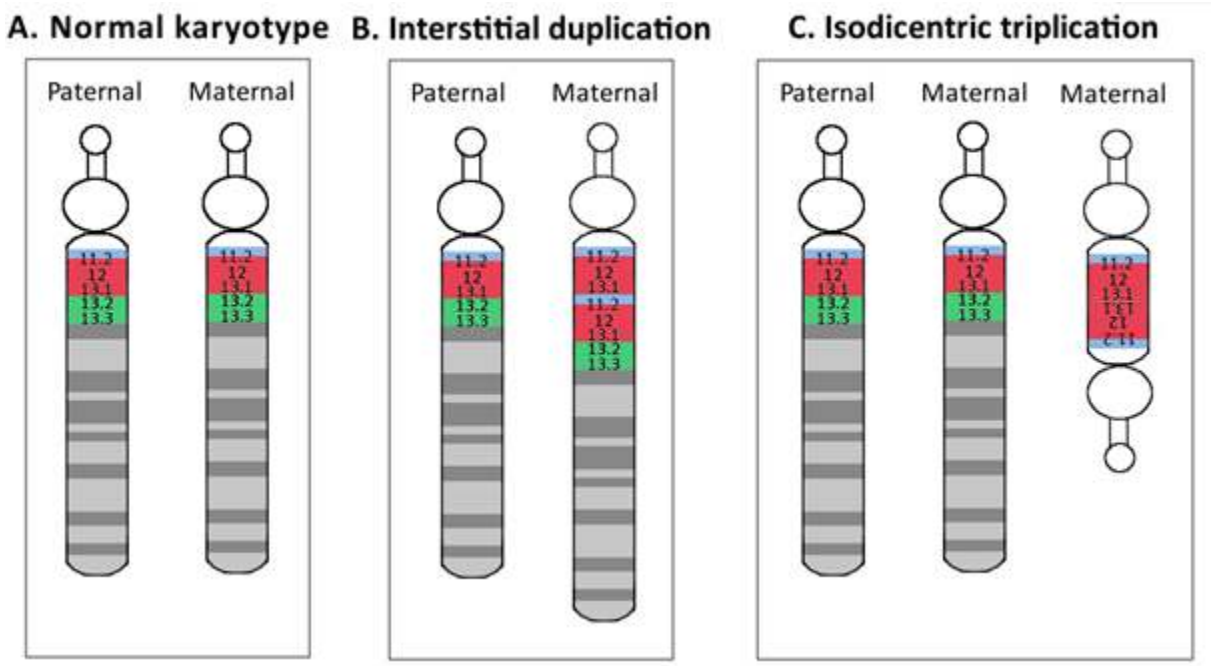

Figure 1. A. Schematic of the normal paternal and maternal chromosome 15

B. & C. The most common causes of dup15q:

— B. Interstitial duplication of 15q11.2-13.1

— C. Isodicentric triplication of 15q11.2-13.1

Note: Light blue denotes breakpoint 1(BP1) to breakpoint 2 (BP2), red denotes BP2 to BP3 (PWACR), and green denotes BP3 to BP5.

Table 2. 15q Interstitial Duplication and Idic(15): Comparison of Clinical Features

Feature	Maternal Interstitial Duplication	Maternal Isodicentric Supernumerary Chromosome
Hypotonia	Mild to moderate	Severe
Developmental delay / intellectual disability	Moderate	Severe
Autism spectrum disorder (ASD)	≥50% [1, 2]	≥80% [1, 3, 4]
Epilepsy	~25% [5]	~65% [5]

1. Al Ageeli et al [2014]
2. Urraca et al [2013]
3. Hogart et al [2010]
4. Battaglia et al [2010]
5. Conant et al [2014]

Hypotonia and motor skills. Hypotonia in newborns and infants with dup15q is associated with feeding difficulties and gross motor delays [Depienne et al 2009, Hogart et al 2010, Urraca et al 2013].

Although childhood hypotonia impairs motor development, most children achieve independent walking after age two to three years (younger in children with an interstitial duplication) [Dennis et al 2006, Depienne et al 2009, Orrico et al 2009, Hogart et al 2010, Piard et al 2010, Al Ageeli et al 2014].

A wide-based or ataxic gait is common [Bundey et al 1994]. Delays and persistent impairment in both fine and gross motor skills affect adaptive living skills and distinguish children with dup15q syndrome from children with nonsyndromic ASD [DiStefano et al 2016].

Developmental delay and intellectual disability. Developmental delay in early childhood is nearly universal. This can be more specifically diagnosed as intellectual disability after age five years.

Most children and adults with dup15q function in the moderate to severe range of intellectual disability; however, there is some variability, with a higher range of cognitive abilities seen in those with an interstitial duplication.

Speech and language development is particularly affected, with universal delays ranging from moderate to severe [Grammatico et al 1994, Borgatti et al 2001, Hogart et al 2010]. Some individuals exhibit echolalia, pronoun reversal, and stereotyped utterances, while others may lack functional speech [Battaglia et al 1997, Battaglia 2008].

Autism spectrum disorder (ASD). Most children and adults with dup15q meet criteria for ASD. Compared to other CNVs known to cause ASD, dup15q confers the greatest risk, with an odds ratio of 42.6 or higher [Malhotra & Sebat 2012, Moreno-De-Luca et al 2013]. Manifestations of ASD, particularly difficulties with social interaction, may increase from early to late childhood [Simon et al 2010].

Compared to children with nonsyndromic ASD, children with dup15q/ASD demonstrate a distinctive behavioral profile, including preserved responsive social smile and directed facial expressions towards others – features that may inform behavioral interventions [DiStefano et al 2016].

Epilepsy. More than half of individuals with dup15q have epilepsy, usually involving multiple seizure types including infantile spasms and myoclonic, tonic-clonic, absence, and focal seizures [Conant et al 2014]. Seizures most often begin between ages six months and nine years [Battaglia 2008].

Dup15q is one of the most common known causes of infantile spasms [Conant et al 2014]. Infantile spasms in dup15q often progress to Lennox Gastaut syndrome and other complex seizure patterns that may be difficult to control. As many as 40% of individuals with seizures present initially with infantile spasms; of this group, approximately 90% subsequently develop other seizure types. Alternatively, individuals with dup15q may present with focal seizures only.

Intractable epilepsy in dup15q may result in disabling secondary effects, including falls or developmental regression. This occurs in more than half of individuals with frequent, uncontrolled seizures or nonconvulsive status epilepticus [Battaglia et al 1997].

In a small study, children with epilepsy were found to have lower cognitive and adaptive function than those without epilepsy [DiStefano et al 2016].

Dysmorphic features. Minor dysmorphic features often reported in dup15q include flattened nasal bridge with a short upturned nose, long philtrum, anteverted nostrils, downslanting palpebral fissures, micrognathia, low-set ears, flat occiput, low forehead, high-arched palate, and full lips [Battaglia et al 1997, Borgatti et al 2001, Hogart et al 2010, Urraca et al 2013]. These features are typically subtle and may be missed in infancy.

Psychosis. Although maternal idic(15) has been reported in schizophrenia cohorts [Bassett 2011, Ingason et al 2011, Costain et al 2013, Rees et al 2014], psychosis is not a commonly ascertained comorbidity in dup15q – a finding that may reflect the difficulty of recognizing and diagnosing psychosis in individuals with low cognitive functioning and limited verbal skills. For instance, psychosis is a common comorbidity in Prader-Willi syndrome caused by uniparental disomy, which similarly involves a duplication of the maternally contributed 15q11.2-13.1 [Boer et al 2002, Vogels et al 2003, Bassett 2011]. These individuals tend to have higher cognitive and verbal abilities than individuals with dup15q. Conversely, with a high rate of ASD in dup15q, psychosis related to mood disorder may be misdiagnosed as schizophrenia.

Sudden unexpected death in epilepsy (SUDEP) occurs in a small but significant minority of individuals with dup15q [Devinsky 2011, Wegiel et al 2012]. In dup15q, these deaths almost always occur during sleep and most (though not all) have occurred in teenagers and young adults with epilepsy.

SUDEP also occurs in other neurodevelopmental disorders involving severe cognitive impairments and treatment-resistant epilepsy. The mechanism underlying SUDEP is not well understood; however, available evidence suggests that in most cases a tonic-clonic seizure is followed by a shutdown of brain function and cardio-respiratory arrest. SUDEP occurs in 9% of individuals with epilepsy; the rate of SUDEP in dup15q is unknown.

Penetrance

In maternal idic(15) penetrance is 100%; expressivity is variable.

In maternal interstitial 15q11.2-q13.1 duplication, although penetrance appears to be complete, some individuals may have such mild features as to appear unaffected, reflecting variable expressivity rather than true non-penetrance.

Penetrance is the same for males and females.

Nomenclature

Terms used to refer to15q duplication syndrome and related disorders:

- 15q11.2-q13.1 duplication syndrome
- Dup15q syndrome
- Inverted duplication 15 (inv dup15)
- Partial trisomy 15
- Isodicentric chromosome 15 syndrome [Idic(15)]
- Supernumerary marker chromosome 15 (SMC15)
- Partial tetrasomy 15q

Prevalence

Dup15q is one of the most common cytogenetic anomalies in persons with ASD.

- The prevalence of dup15q in the general population is unknown but may be as high as 1:5,000 [Kirov et al 2014].
- In patients referred for clinical CMA testing due to developmental concerns (developmental delay, intellectual disability, or ASD) or multiple congenital anomalies, the prevalence of dup15q is approximately 1:508 [Moreno-De-Luca et al 2013].
- In ASD cohorts, the prevalence of dup15q is 1:253-1:522 [Depienne et al 2009, Malhotra & Sebat 2012, Moreno-De-Luca et al 2013].
- In intellectual disability cohorts, the prevalence of dup15q is 1:584 [Malhotra & Sebat 2012].

Genetically Related Disorders

Paternal interstitial duplications of 15q11.2-q13.1. Because this duplicated region is imprinted, the phenotypes resulting from paternal and maternal duplications differ: paternal interstitial duplications are associated with a more variable phenotype that includes sleep concerns such as parasomnia (abnormal or unusual behavior during sleep). Clinical findings, particularly autistic features, may be present in up to 50% of affected individuals [Urraca et al 2013]. Because there is some overlap in the phenotypic features of maternal and

paternal duplications, parent of origin testing should be performed to determine whether a proband has dup15q syndrome or a paternal interstitial duplication.

Prader-Willi syndrome (PWS) is caused by a deletion, uniparental disomy, or an imprinting defect that results in the loss of the paternally contributed 15q11.2-q13.1 region. Despite some phenotypic similarities, PWS is distinct from dup15q: individuals with PWS typically have characteristic facial features, infantile hypotonia, hypogonadism, mild intellectual disability, hyperphagia, and obsessive-compulsive behaviors [Cassidy & Driscoll 2009]. Individuals with PWS are also verbal and typically have milder cognitive impairment (average IQ: 60-70s) than individuals with dup15q [Cassidy & Driscoll 2009].

Angelman syndrome (AS) is caused by a deletion, uniparental disomy, imprinting defect, or mutation of *UBE3A* that results in a loss of function of the maternally contributed *UBE3A* allele. AS is distinct from both PWS and dup15q and is characterized by distinctive facial features, severe intellectual disability, profound expressive language impairment, seizures, ataxia, and an unusually happy or excitable disposition [Dagli et al 2012].

Deletions involving 15q11.2 or 15q13.3 – both of which flank but do not include the PWACR – can be pathogenic with distinct neurobehavioral phenotypes.

- Deletions of 15q13.3 (typically BP4 through BP5) are associated with cognitive deficits, ASD, epilepsy, speech problems, and behavioral/psychiatric conditions including schizophrenia, attention problems, poor adaptive skills, and mood disorders [Lowther et al 2015, Zhou et al 2016, Ziats et al 2016]. No consistent patterns of dysmorphic features have been reported [Lowther et al 2015].
- Deletions of 15q11.2 (BP1 through BP2) are associated with speech delay and cognitive deficits, and less commonly epilepsy, congenital heart disease, and behavioral issues including attention problems, hyperactivity, and ASD [Cox & Butler 2015, Vanlerberghe et al 2015]. No consistent patterns of dysmorphic features have been reported [Cox & Butler 2015, Vanlerberghe et al 2015].

Duplications involving 15q11.2 or 15q13.3 but not the PWACR have been implicated in developmental delay and autism [Miller et al 2009, van Bon et al 2009, Burnside et al 2011], but are considered variants of uncertain significance [Kaminsky et al 2011, Chaste et al 2014].

Differential Diagnosis

Classic Rett syndrome is a neurodevelopmental disorder caused by mutation of the X-linked gene *MECP2* [Chahrour & Zoghbi 2007]. Rett syndrome is primarily seen in females and assumed to be fatal in most males. Features of classic Rett syndrome include normal development in the first six to 18 months of life followed by developmental stagnation, rapid regression of skills across developmental domains, and stabilization. A hallmark feature of Rett syndrome is the replacement of purposeful hand use with repetitive, stereotypic hand movements. Additional features include bruxism (teeth grinding), disordered breathing, sleep disturbances, autistic features, seizures, and unprovoked crying or screaming.

Findings similar to those of 15q duplication syndrome and related disorders (dup15q) include motor and language impairments, autistic features, and seizures. However, individuals with dup15q:

- Tend to show delays from early infancy and rarely have psychomotor regression in the absence of intractable epilepsy;
- Do not have loss of purposeful hand movements or the behavioral phenotypes of Rett syndrome.

See *MECP2* Disorders.

Pathogenic variants in *CDKL5* (OMIM 300203), an X-linked gene, have been identified in (1) females with early-onset severe seizures who have poor cognitive development but little in the way of Rett syndrome-like

features [Archer et al 2006, Bahi-Buisson et al 2008] and (2) males with severe-to-profound intellectual disability and early-onset intractable seizures [Elia et al 2008].

Individuals with dup15q and those with pathogenic *CDKL5* variants can both present with severe cognitive delays, intellectual disability, and early-onset seizures; however, moderate-to-severe infantile hypotonia is more characteristic of dup15q.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with 15q duplication syndrome or related disorders (dup15q), the following evaluations are recommended:

- Complete review of systems
- Physical examination
- Assessment of possible feeding difficulties associated with hypotonia
- Neurologic examination including assessment for seizure activity and baseline EEG
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

A multidisciplinary team evaluation is recommended beginning in early infancy to evaluate motor and speech development and later to assist in referrals for appropriate educational programs.

Supportive care may include the following:

- Occupational and physical therapy
- Alternative and augmentative communication
- Behavioral therapy (e.g., applied behavioral analysis therapy)
- Psychotropic medications for behavioral manifestations
- Standard management for seizures including medications, vagus nerve stimulators, and/or ketogenic diets [Conant et al 2014]. Effectiveness of antiepileptic drug (AED) treatment varies by seizure type and severity. No prospective or randomized-controlled data on AED therapy in dup15q have been published. See Conant et al [2014] for parent-reported effectiveness of various medications and treatments.

Seizure management is important in preventing secondary complications, including (in the most severe cases) brain damage, developmental regression, and sudden unexpected death in epilepsy (SUDEP) [Devinsky 2011].

Approximately half of seizure-related deaths are not due to SUDEP, but to other causes including status epilepticus, drowning, falls, and accidents. Many of these are preventable. For example, status epilepticus may be prevented with the use of rescue medications such as rectal diazepam or nasal midazolam. Some evidence suggests that prompt identification of a seizure and basic care (e.g., repositioning a person on the side instead of face down) after a seizure may help prevent SUDEP [Ryvlin et al 2013]. However, the only known preventive therapy is the best possible seizure control [Ryvlin et al 2011]. Although a variety of monitors can help detect SUDEP (e.g., wrist and mattress accelerometers), none can prevent it [Devinsky 2011].

Caregivers. For information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy & My Child Toolkit (pdf).

Prevention of Secondary Complications

Ongoing pediatric care with regular immunizations is indicated.

Surveillance

The following are appropriate:

- Periodic neurodevelopmental and/or developmental/behavioral assessments
- Periodic monitoring for evidence of seizures and/or change in seizure type

Agents/Circumstances to Avoid

Seizure triggers (e.g., sleep deprivation, stress, and failure to follow medication regimen) should be avoided.

Evaluation of Relatives at Risk

Consider genetic testing of sibs of a proband who is known to have an inherited maternal interstitial 15q11.2-q13.1 duplication in order to refer sibs with an interstitial duplication promptly for developmental evaluation and early intervention services

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

Therapies Under Investigation

Currently, no clinical trials for dup15q exist. However, ongoing work regarding treatment in Angelman syndrome and autism spectrum disorder (ASD) may inform future treatments in dup15q.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Dup15q caused by a maternal isodicentric 15q11.2-q13.1 supernumerary chromosome – idic(15) – has been *de novo* in all probands reported to date.

Dup15q caused by maternal interstitial 15q11.2-q13.1 duplication has been *de novo* in 85% and inherited from the mother in 15%.

Risk to Family Members

Maternal Isodicentric 15q11.2-q13.1 Supernumerary Chromosome – Idic(15)

Parents of a proband

- Idic(15) has been *de novo* in all probands reported to date.
- Parental testing is not routinely indicated. However, based on one report of maternal transmission of supernumerary partial trisomy of the region [Michelson et al 2011], suggestive clinical manifestations in a mother (epilepsy, ASD, schizophrenia, or other reported findings) should prompt consideration of parental testing.

Sibs of a proband. The risk to sibs appears to be low as the idic(15) is *de novo* in all affected individuals reported to date. However, because of the possibility of maternal germline mosaicism, the risk is presumed to be marginally greater than in the general population.

Offspring of a proband. Individuals with idic(15) are not known to reproduce.

Other family members. Given that all instances of idic(15) reported to date have been *de novo*, the risk to other family members is presumed to be low.

Maternal 15q Interstitial Duplication

Parents of a proband

- To date, maternally derived 15q interstitial duplications have been *de novo* in approximately 85% of reported individuals and inherited in approximately 15%.
- If the maternal 15q interstitial duplication found in the proband cannot be detected in maternal leukocyte DNA, the most likely explanation is a *de novo* 15q interstitial duplication in the proband.
- Evaluation of the mother by genomic testing that will detect the 15q interstitial duplication present in the proband is recommended.

  Note: If the mother of a proband inherited a 15q interstitial duplication from her father (i.e., the maternal grandfather of the proband), the mother will not have dup15q syndrome. Instead, she may appear to be unaffected or have features associated with paternal duplications, which – although distinct from those of the proband – may share some similarities (see Genetically Related Disorders).

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the mother: if the mother of the proband has the 15q interstitial duplication, the risk to each sib of inheriting the duplication is 50%. However, it is not possible to reliably predict the severity of the phenotype of the individual.
- If the maternal 15q interstitial duplication identified in the proband cannot be detected in maternal leukocyte DNA, the risk to sibs is presumed to be low as the 15q interstitial duplication is most likely *de novo* in the proband.

Offspring of a proband. Each child of an individual with a 15q interstitial duplication has a 50% chance of inheriting the duplication.

- If the proband is female, offspring who inherit a 15q interstitial duplication are at risk for dup15q.
- If the proband is male, offspring who inherit a 15q interstitial duplication are at risk for features associated with paternal interstitial duplications of 15q11.2-q13.1 (see Genetically Related Disorders).

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the 15q interstitial duplication, his or her family members may also have the duplication.

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 testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk family members are best made before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are at risk of having a child with dup15q.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

Maternal idic(15). Risk to future pregnancies is presumed to be low, as to date all reported instances of idic(15) have been *de novo*. However, couples may wish to consider prenatal testing or preimplantation genetic diagnosis as risk may be slightly greater than in the general population due to the possibility of parental germline mosaicism.

Maternal 15q interstitial duplication

- **Pregnancies known to be at increased risk for the 15q interstitial duplication**. Prenatal testing or preimplantation genetic diagnosis using CMA that will detect the 15q interstitial duplication found in the proband may be offered when:
  - The mother has a paternally derived or inherited 15q interstitial duplication;
  - The parents do not have the duplication but have had a child with a 15q interstitial duplication. In this instance, the recurrence risk associated with the possibility of parental germline mosaicism or other predisposing genetic mechanisms is probably <1%.
- **Pregnancies not known to be at increased risk for idic(15) or a 15q interstitial duplication.** CMA performed in a pregnancy not known to be at increased risk for dup15q may detect increased copy numbers of 15q11.2-q13.1 due to an interstitial duplication or idic(15).

Note: Prenatal test results cannot reliably predict the severity of the phenotype (see Clinical Description) whether the pregnancy is known or not known to be at increased risk for dup15q.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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.

- **Dup15q Alliance**
  PO Box 674
  Fayetteville NY 13066
  Phone: 855-DUP-15QA
  Email: info@dup15q.org
  www.dup15q.org
- **Unique: The Rare Chromosome Disorder Support Group**
  G1 The Stables
  Station Road West
  Oxted Surrey RH8 9EE

United Kingdom
Phone: +44 (0) 1883 723356
Email: info@rarechromo.org; rarechromo@aol.com
www.rarechromo.org

- **Dup15q Alliance International Registry**
  PO Box 674
  Fayetteville NY 13066
  Email: coordinator@dup15qregistry.org
  www.dup15qregistry.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. 15q Duplication Syndrome and Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	ClinVar
Not applicable	15q11.2-q13.1	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 15q Duplication Syndrome and Related Disorders (View All in OMIM)

608636	CHROMOSOME 15q11-q13 DUPLICATION SYNDROME

Molecular Pathogenesis

The extra copy or copies of the PWACR most commonly arise by one of two mechanisms (Figure 1):

- A maternal isodicentric 15q11.2-q13.1 supernumerary chromosome – idic(15) – that typically comprises two extra copies of 15q11.2-q13.1, resulting in tetrasomy for 15q11.2-q13.1 (~80% of cases [Dup15q Alliance International Registry, 3-14-14])

  OR

- A maternal interstitial 15q11.2-q13.1 duplication that typically includes one extra copy of 15q11.2-q13.1 within chromosome 15, resulting in trisomy for 15q11.2-q13.1 (~20% of cases [Dup15q Alliance International Registry, 3-14-14])

The proximal 15q region includes five regions of segmental duplications or low copy repeats (designated by breakpoints [BPs]), which result in increased susceptibility to genomic rearrangements [Robinson et al 1993, Robinson et al 1998, Christian et al 1999]. These five regions are termed BP1 through BP5. The Prader-Willi/Angelman critical region (PWACR) lies between BP2 and BP3 (Figure 1) and is always included in the interstitial duplications or the idic(15) that cause dup15q. Duplications that extend from BP1 to BP3 are referred to as Class I duplications; those that span BP2 and BP3 only are Class II duplications. The PWACR is imprinted: maternally derived increases in copy number cause dup15q while paternally derived increases are typically associated with more variable and sometimes different neurodevelopmental phenotypes [Cook et al 1997, Urraca et al 2013].

The maternal isodicentric 15q11.2-q13.1 – or idic(15) – is typically a bisatellited chromosome thought to arise from U-type exchange during meiosis. Idic(15), which typically includes two mirrored copies of 15pter-q13.1 (p arm of chromosome 15, centromere, and 15q11.2-q13.1) [Roberts et al 2003], is sometimes referred to as inv dup

(15). The distal breakpoint is typically BP3 (approximate position [hg19] 28800000) on both sides of truly isodicentric chromosomes and BP4 and BP5 (approximate positions [hg19] 30700000 and [hg19] 32500000) for asymmetric supernumerary chromosomes (Figure 2) [Hogart et al 2010]. Idic(15) usually results in tetrasomy for 15q11.2-q13.1.

Interstitial duplications leading to dup15q arise by nonallelic homologous recombination (NAHR) between two different breakpoint regions (e.g., BP1 and BP3). The distal breakpoint for maternal interstitial duplications is typically BP3 (approximate position [hg19] 28812406), and the proximal breakpoint is typically either BP1 or BP2 (approximate positions [hg19] 22964304 or [hg19] 23966600, respectively). Interstitial duplications usually result in trisomy for 15q11.2-q13.1.

Variations of these primary mechanisms include the following:

- Interstitial 15q11.2-q13.1 triplication, which results in tetrasomy of 15q11.2-q13.1. This phenotype tends to be more severe than that of maternal interstitial 15q11.2-q13.1 duplication and more like that of maternal isodicentric 15q11.2-q13.1 supernumerary chromosome [Ungaro et al 2001, Hogart et al 2010] (Figure 3).
- Isodicentric 15q hexasomy. The phenotype is severe, including profound intellectual disability, intractable epilepsy, and more prominent dysmorphic features (myopathic facies and low-set ears) [Mann et al 2004] (Figure 3).
- Asymmetric isodicentric or interstitial maternal triplications, which typically result in tetrasomy for 15q11.2-q13.2 and trisomy for 15q13.2-13.3. These asymmetric copy number variations are observed in approximately 10%-15% of isodicentric and interstitial chromosomes [Dup15q Alliance International Registry, 3-14-14] (Figure 2).
- Ring chromosome 15. Rarely, supernumerary ring chromosomes that include the PWACR have been seen. These are typically mosaic, indicating the unstable nature of ring chromosomes [Wang et al 2008].

Genes of interest in this region

- ***UBE3A*,** the gene implicated in Angelman syndrome, is thought to contribute specifically to the intellectual impairment and autism features of dup15q [Glessner et al 2009, Greer et al 2010]. *UBE3A* is imprinted with maternal-specific expression in postnatal neurons, and thus expressed at a higher dosage in brain from individuals with a maternally derived duplication. Paternally inherited 15q11.2-q13.1 duplications do not consistently have a clear autism phenotype [Cook et al 1997, Hogart et al 2010, Urraca et al 2013].

- ***GABRB3*, *GABRA5*, and *GABRG3*,** genes that encode $GABA_A$ receptor subunits, are implicated in the seizures observed in dup15q [Menold et al 2001, Samaco et al 2005, Hogart et al 2007]. Knockout mouse models of these genes develop neurologic problems including seizures [DeLorey et al 1998, DeLorey et al 2008]. Seizures in transgenic mouse models overexpressing $GABA_A$ receptors have not been characterized to date [Nakatani et al 2009].

  GABRB3 may also contribute to the autism phenotype in dup15q [Conant et al 2014], as single-nucleotide polymorphisms in this gene are associated with autism [Menold et al 2001] and expression is reduced in brain tissue samples of individuals with ASD [Samaco et al 2005, Hogart et al 2007]. *GABRB3* is the only gene in 15q11.2-q13.1 that has been implicated in ASD by genome-wide *de novo* single-nucleotide variant studies [Sanders et al 2015].

- ***HERC2*** is an E3 ubiquitin ligase. Individuals with biallelic *HERC2* pathogenic variants can have intellectual disability [Puffenberger et al 2012] or a severe Angelman syndrome-like neurodevelopmental disorder [Harlalka et al 2013].

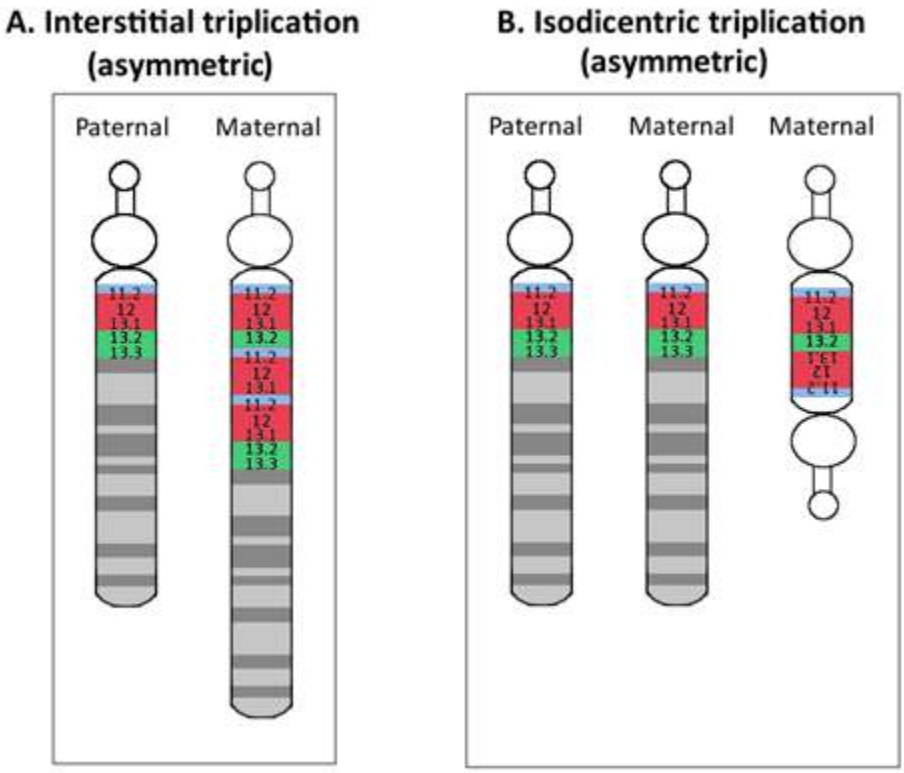

Figure 2. Asymmetry in dup15q, as seen in:

A. Interstitial triplication of 15q11.2-13.1; and

B. Isodicentric triplication of 15q11.2-13.1.

Note: Light blue denotes BP1 to BP2, red denotes BP2 to BP3 (PWACR), and green denotes BP3 to BP5.

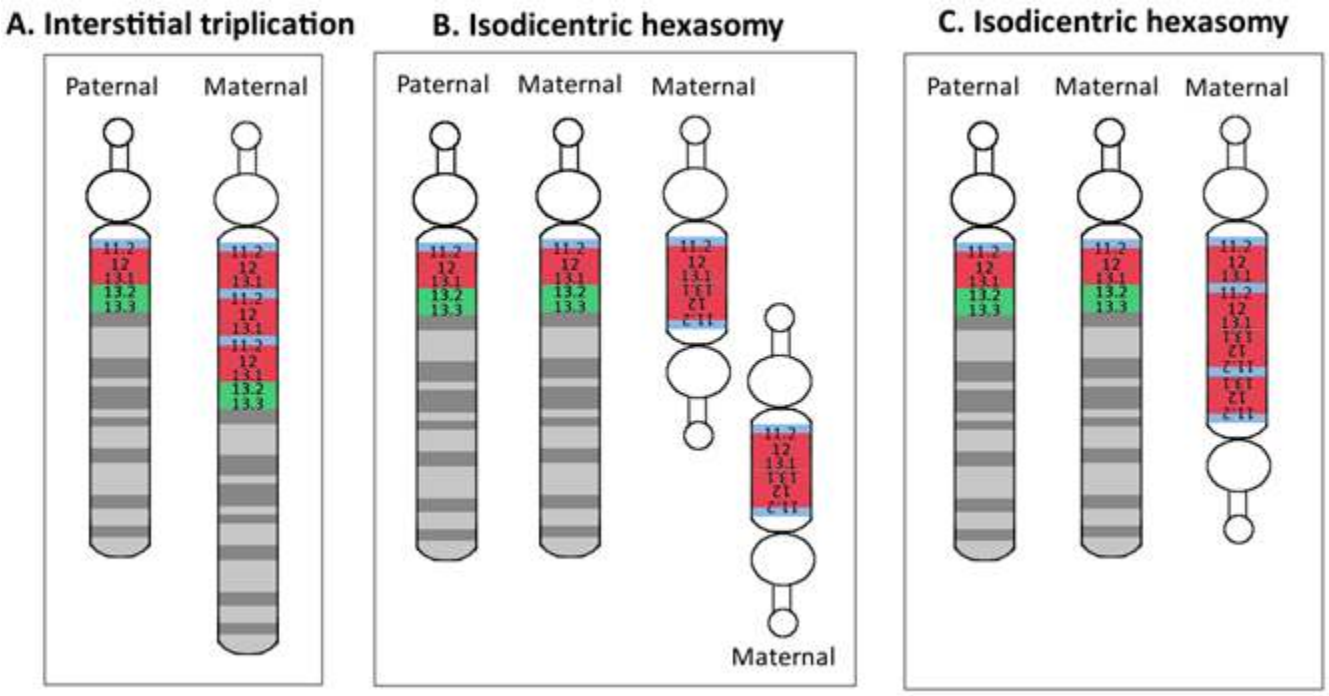

Figure 3. Uncommon variations in copy number seen in dup15q

A. Interstitial triplication of 15q11.2-13.1

B. Supernumerary hexasomy of 15q11.2-13.1, manifest as two isodicentric chromosomes

C. A larger isodicentric chromosome

Note: Light blue denotes BP1 to BP2, red denotes BP2 to BP3 (PWACR), and green denotes BP3 to BP5.

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Chapter Notes

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