

Deletion 22q13 Syndrome

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Abstract

The deletion 22q13 syndrome is a microdeletion syndrome characterized by neonatal hypotonia, global developmental delay, normal to accelerated growth, absent to severely delayed speech, and minor dysmorphic features. Facial features include dolicocephaly, full brow, ptosis, long eye lashes, wide nasal bridge, flat midface, puffy eyelids, full cheeks, bulbous nose, large or unusual ears, and pointed chin. Other features are large hands, dysplastic toenails, lack of perspiration, and sacral dimple. Behavior is described as "autistic-like" and includes high tolerance to pain and habitual chewing or mouthing.

The loss of sub-band 22q13.3 on the long arm of chromosome 22 can be very subtle and is often undetected by routine chromosome analysis. Fluorescence in situ hybridization (FISH) is typically required to confirm the presence of this deletion. Over 30% of affected individuals have required two or more chromosome studies before the abnormality was detected. Due to difficulties in detection, this chromosome deletion syndrome is under-diagnosed and its true incidence remains unknown.

No apparent life-threatening organic abnormalities accompany the diagnosis of deletion 22q13. Affected individuals benefit from early intervention programs, intense occupational and communication therapies, adaptive exercise and sports programs, and other therapies to strengthen their muscles and increase their communication skills.

Key words

hypotonia, absent speech, global developmental delay, normal/accelerated growth, *SHANK3*

Name of the disease and synonyms

Deletion 22q13 syndrome

Phelan-McDermid syndrome

chromosome 22. Other causes of neonatal hypotonia are excluded as well.

Excluded diseases

The deletion 22q13 syndrome excludes the diagnoses of other chromosomal disorders unrelated to deletion of the distal long arm of

Diagnostic criteria

The diagnosis of Phelan-McDermid syndrome is based on the cytogenetic, molecular cytogenetic, and/or molecular demonstration of loss of the

distal segment of the long arm of chromosome 22.

The characteristic features of this syndrome are the following:

- neonatal hypotonia (>97%);
- severe global developmental delay (>98%);
- absent or severe language delay (>98%);
- normal to accelerated growth (95%);
- minor dysmorphic features.

Differential diagnosis

At birth the features of Phelan-McDermid syndrome are quite mild. Birth weight is appropriate for gestational age and physical features are often unremarkable. The presence of neonatal hypotonia may be the only indicator that genetic studies are warranted. As in the Prader-Willi syndrome, hypotonia, feeding problems, and developmental delay are often the early presenting symptoms of deletion 22q13 syndrome. The Phelan-McDermid syndrome should be considered in all cases of neonatal hypotonia of unknown etiology.

[Angelman syndrome](#) has been initially suspected in a number of individuals with Phelan-McDermid syndrome. Features common to Angelman syndrome and deletion 22q13 include global developmental delay, absent speech, ataxic gait, and minor dysmorphic features. Absence of the laboratory confirmation of Angelman syndrome has led to the diagnosis of "atypical Angelman syndrome". Patients later shown to have deletion of 22q13 have also carried initial diagnoses of velocardiofacial syndrome, Williams syndrome, trichorhinophalangeal syndrome, Smith-Magenis syndrome, fragile X syndrome, FG syndrome, cerebral palsy, spastic paraplegia, and autism.

Frequency

The incidence of deletion 22q13 syndrome has not been determined. This syndrome is clearly under-diagnosed at both the laboratory and the clinical levels. Over 30% of individuals with Phelan-McDermid syndrome have required two or more chromosome studies, typically with confirmation by FISH, before the deletion was successfully diagnosed. Until improved clinical and laboratory recognition of the Phelan-McDermid syndrome, the true frequency will be underestimated.

Clinical description

The characteristic features of deletion 22q13 are neonatal hypotonia, normal to accelerated growth, absent to severely delayed speech, and severe global developmental delay. The newborn may experience feeding problems secondary to hypotonia. The physical features are variable but include dolicocephaly, wide brow, full eyelids, ptosis, long eye lashes, flat

midface, full cheeks, prominent or dysplastic ears, large hands, and dysplastic toenails. Individuals with Phelan-McDermid syndrome often have an increased tolerance to pain, decreased perspiration with increased risk of overheating, and mouthing or chewing behaviors. In older children, lymphedema and cellulitis may become a problem.

Few children with submicroscopic telomere deletion of 22q13 have been described to have mild developmental delay. The majority of individuals with deletion 22q13 have moderate to profound delay with cognitive ability less than an age equivalent of 23 months, regardless of chronological age. Motor milestones are typically delayed: the average age for rolling over is 8.2 months (range 3 months to 24 months), for crawling is 16 months (range 7 months to 36 months), and for walking is 32 months (range 13 months to 8 years).

Individual with deletion 22q13 may exhibit "autistic-like" behaviors such as poor eye contact and stereotypic movements. The diagnosis of autism has been made in at least two children with this chromosome deletion. However, because the clinical features of autism overlap with the features of profound mental retardation, it is difficult to establish a diagnosis of autism in a child with severe or profound mental retardation as in deletion 22q13. For a diagnosis of autism, a child must exhibit qualitative differences in language and socialization when compared to non-autistic children with the same degree of impairment. In children with deletion 22q13, the deficits in language and socialization are consistent with their decreased cognitive abilities.

Management

A neurologist should be consulted regarding neonatal hypotonia. Brain imaging studies, such as MRI, may be indicated. An occupational therapist, physical therapist and nutrition specialist should evaluate feeding problems and early motor delays related to hypotonia. A child development specialist should assess children for autism or autistic-like features. Medication to reduce hyperactivity and self-stimulatory behavior is helpful in certain children.

Recurrent ear infections, along with the lack of expressive language, may lead to concerns about hearing deficits. Tympanostomy tubes may be required to treat recurrent ear infections. A specialist experienced in testing children with severe developmental delay and communication deficits should evaluate hearing in children with deletion 22q13 syndrome.

Children with Phelan-McDermid syndrome often have more advanced perceptive language than expressive language. Therapies should be

directed at improving verbal and nonverbal communication. Sign language, computer touch screens, voice based systems, and picture exchange systems have been used to increase communication skills. Adaptive sports, music therapy, and sensory integration increase the child's awareness and often improve their desire to communicate. Children with deletion 22q13 greatly benefit from aggressive infant stimulant programs and individual education plans to improve their motor skills and communication skills.

Gastroesophageal reflux is generally controlled by medication. In persistent cases, surgery may be required. Recurrent vomiting may require intravenous fluids to prevent dehydration. For cyclic vomiting, a neurosurgical consult is appropriate to address issues related to increased intra-cranial pressure. Arachnoid cysts occur more frequently in children with deletion 22q13 than in the general population. Other neurological problems include ventriculomegaly and reduced myelination. Cardiac, renal, respiratory, immunologic, and other medical issues should be treated in the same manner as they would be handled in any other child.

Etiology

The Phelan-McDermid syndrome is a microdeletion syndrome resulting from loss of 22q13, either by simple deletion, unbalanced translocation, ring chromosome formation, or other unbalanced structural change. The chromosome abnormality may be inherited or may occur *de novo*. The deletion occurs with equal frequency in males and females and has been reported in mosaic and non-mosaic forms. Haploinsufficiency of the *SHANK3/PROSAP2* gene is the cause of the major neurologic features associated with deletion 22q13. The *SHANK3* gene maps to 22q13.3 and codes for a structural protein found in the post-synaptic density. *SHANK3* functions to connect ion channels and receptors in the post-synaptic membrane to the cytoskeleton and to signal transduction pathways.

Diagnostic methods

Chromosome analysis at or above the 550-band level will detect most deletions of 22q13. FISH using a probe specific for 22q13 is indicated to confirm the presence of the deletion and rule out the presence of a cryptic translocation. The probe for arylsulfatase A (ARSA) successfully detects the vast majority of 22q13.3 deletions. Rare cases of microdeletions distal to ARSA may require FISH analysis of the sub-telomeric region of chromosome 22. Alternatively,

microsatellite studies can be performed to demonstrate the presence of this deletion.

Genetic counseling

Targeted chromosome analysis is warranted in parents of individuals with deletion 22q13. Although the majority of individuals with Phelan-McDermid syndrome have simple deletions of 22q13, cryptic and half-cryptic rearrangements have also been identified. As with other *de novo* chromosome rearrangements, the recurrence risk for future pregnancies is negligible when parental karyotypes are normal.

Structural abnormalities most commonly associated with deletion 22q13 syndrome are unbalanced translocations and ring chromosomes. At least 20% of cases of deletion 22q13 result from unbalanced translocations. The identification of a balanced translocation involving chromosome 22 in one parent significantly increases the risk of recurrence in future pregnancies. At least two families have experienced multiple cases of deletion 22q13 secondary to familial chromosome translocations. Mother to son transmission of an insertional translocation resulting has resulted in deletion 22q13 in the son. Recombination of a maternal pericentric inversion has also led to deletion 22q in a child.

Transmission of ring chromosome 22 from parent to offspring has been described. In familial cases of ring 22, the ring chromosome results from an end-to-end fusion of the long and short arms of chromosome 22, with no apparent loss of genetic material. No cases of deletion 22q13 are known to result from the inheritance of a parental ring chromosome.

Antenatal diagnosis

Deletion of 22q13 can be detected by prenatal chromosome analysis. As in postnatal studies, the deletion is subtle and is often difficult to detect. If deletion of 22q13 is suspected by banded chromosome analysis, FISH using a probe specific for 22q13 should be performed to confirm this finding.

Antenatal diagnosis should be offered to parents who carry structural rearrangements that predispose to deletion of 22q13. Simple deletion of 22q13 has not recurred in offspring of parents with normal karyotypes.

Unresolved questions

Although a plausible role for *SHANK3* has been determined, no additional genetic and/or environmental factors important in the pathogenesis of this syndrome have been identified.

References

- Anderlid BM**, Schoumans J, Anneren G, Tapia-Paez I, Dumanski J, Blennow E, Nordenskjold M: FISH-mapping of a 100 kb terminal 22q13 deletion. *Hum Genet* 110:439-443, 2002.
- Bonaglia MC**, Giorda R, Borgatti R, Felisari G, Gagliardi C, Selicorni A, Zuffardi O: Disruption of the ProSAP2 gene in a t(12;22)(q24.1;q13.3) is associated with the 22q13.3 deletion syndrome. *Am J Hum Genet* 69:261-268, 2001.
- de Vries BB**, Tyson J, Winter RM, Malcolm S: No evidence for submicroscopic 22qter deletions in patients with features suggestive for Angelman syndrome. *Am J Med Genet* 109:117-120, 2002.
- de Vries BB**, White SM, Knight SH, Regan R, Homfray T, Young ID, Super M, McKeown C, Splitt M, Quarrell OW, Trainer AH, Niermeijer MF, Malcolm S, Flint J, Hurst JA, Winter R: Clinical studies on submicroscopic subtelomeric rearrangements: a checklist. *J Med Genet* 38:145-150, 2001.
- de Vries BB**, Bitner-Glindzicz M, Knight SJ, Tyson J, MacDermont KD, Flint J, Malcolm S, Winter RM: A boy with submicroscopic 22qter deletion, general overgrowth and features suggestive of FG syndrome. *Clin Genet* 58:483-487, 2000.
- Doheny KF**, McDermid HE, Harum K, Thomas GH, Raymond GV: Cryptic terminal rearrangement of chromosome 22q13.32 detected by FISH in two unrelated patients. *J Med Genet* 34:640-644, 1997.
- Flint J**, Wilkie AOM, Buckle VJ, Winter RM, Holland AJ, McDermid HE. 1995. The detection of subtelomeric chromosomal rearrangements in idiopathic mental retardation. *Nature Genet* 9:132-140.
- Fujita Y**, Mochizuki D, Mori Y, Nakamoto N, Kobayashi M, Omi K, Kodama H, Yanagawa Y, Abe T, Tsuzuku T, Yamanouchi Y, Takano T: Girl with accelerated growth, hearing loss, inner ear anomalies, delayed myelination of the brain, and del(22)(q13.1q13.2). *Am J Med Genet* 92:195-199, 2000.
- Goizet C**, Excoffier E, Taine L, Taupiac E, El Moneim AA, Arveiler B, Bouvard M, Lacombe D: Case with autistic syndrome and chromosome 22q13 deletion detected by FISH. *Am J Med Genet* 96:839-844, 2000.
- Herman GE**, Greenberg F, Ledbetter DH: Multiple congenital anomaly/mental retardation (MCA/MR) Syndrome with Goldenhar complex due to a terminal del(22q). *Am J Med Genet* 29:909-915, 1988.
- Ishmael HA**, Cataldi C, Begleiter ML, Pasztor LM, Dasouki MJ, Butler MG: Five new subjects with ring chromosome 22. *Clin Genet* 63: 410-414. 2003.
- MacLean JE**, Teshima IE, Szatmari P, Nowaczyk MJ: Ring chromosome 22 and autism: report and review. *Am J Med Genet* 90:382-385, 2000
- Narahara K**, Takahashi Y, Murakami M, Tsuji K, Yokoyama Y, Murakami R, Ninomiya S, Seino Y: Terminal 22q deletion associated with a partial deficiency of arylsulfatase A. *J Med Genet* 29:432-433, 1992.
- Nesslinger NJ**, Gorski JL, Kurczynski TW, Shapira SK, Siegel-Bartelt J, Dumanski JP, Cullen RF, French BN, McDermid HE: Clinical, cytogenetic, and molecular characterization of seven patients with deletions of chromosome 22q13.3. *Am J Hum Genet* 54:464-472, 1994.
- Ning Y**, Rosenberg M, Biesecker LG, Ledbetter DH: Isolation of the human chromosome 22 telomere and its application to detection of cryptic chromosomal abnormalities. *Hum Genet* 97:765-769, 1996.
- Phelan MC**, Rogers RC, Stevenson RE. 1988. A de novo terminal deletion of 22q. *Am J Hum Genet*, 43:A118.
- Phelan MC**, Thomas GR, Saul RA, Rogers RC, Taylor HA, Wenger DA, McDermid HE: Cytogenetic, biochemical, and molecular analyses of a 22q13 deletion. *Am J Med Genet* 43:872-876, 1992.
- Phelan MC**, Rogers RC, Saul RA, Stapleton GA, Sweet K, McDermid H, Shaw SR, Claytor J, Willis J, Kelly DP: 22q13 Deletion Syndrome. *Am J Med Genet* 101:91-99, 2001.
- Phelan MC**: Prenatal diagnosis of mosaicism for deletion 22q13.3. *Prenat Diagn* 21:1100, 2001.
- Praphanphoj V**, Goodman BK, Thomas GH, Raymond GV: Cryptic subtelomeric translocations in the 22q13 deletion syndrome. *J Med Genet* 37:58-61, 2000
- Prasad C**, Chodirker BN, Lee C, Dawson AK, Jocelyn LJ, Chudley AE: 22q13 deletion syndrome: a genetic basis for neurobehavioral disorders? *Genet Med* 1:60, 1999.
- Prasad C**, Prasad AN, Chodirker BN, Lee C, Dawson AK, Jocelyn LJ, Chudley AE: Genetic evaluation of pervasive developmental disorders: the terminal 22q13 deletion syndrome may represent a recognizable phenotype. *Clin Genet* 57:103-109, 2000.
- Precht KS**, Lese CM, Spiro RP, Huttenlocher PR, Johnston KM, Baker JC, Christian SL, Kittikamron K, Ledbetter DH: Two 22q telomere deletions serendipitously detected by FISH. *J Med Genet* 35:939-942, 1998.
- Riegel M**, Baumer A, Wisser J, Acherman J, Schinzel A: Prenatal diagnosis of mosaicism for a deletion (22)(q13). *Prenat Diagn* 20:76-79, 2000.
- Romain DR**, Goldsmith J, Cairney H, Columbano-Green LM, Smythe RH, Parfitt RG.

1990. Partial monosomy for chromosome 22 in a patient with del(22)(pter->q13.1::q13.33->qter). *J Med Genet* 27:588-589.

Slavotinek A, Maher E, Gregory P, Rowlandson P, Huson SM: The phenotypic effects of chromosome rearrangement involving bands 7q21.3 and 22q13.3, *J Med Genet* 34(10):857-861, 1997.

Watt JL, Olson IA, Johnston AW, Ross HS, Couzin DA, Stephen GS. 1985. A familial pericentric inversion of chromosome 22 with a recombinant subject illustrating a 'pure' partial monosomy syndrome. *J Med Genet* 22:283-287.

Wilson HL, Wong AAC, Shaw SR, Tse W-Y, Stapleton GA, Phelan MC, Hu S, Marshall H, McDermid HE: Molecular characterisation of the

22q13 deletion syndrome supports the role of haploinsufficiency of SHANK3/PROSAP2 in the major neurological symptoms, *J Med Genet* 40:575-584, 2003.

Wong AC, Bell CJ, Dumanski JP, Budarf ML, McDermid, HE: Molecular characterization of a microdeletion at 22q13.3, *Am J Hum Genet* 57:A130, 1995.

Wong D, Ning Y, Fint J et al: Molecular characterization of a 130 kb terminal microdeletion at 22q in a child with mild mental retardation, *Am J Hum Genet* 60:113-120, 1997.

Zwaigenbaum L, Siegel-Bartelt J, Teshima I, Ho C: Two patients with 22q13.3 deletions have similar facies and developmental patterns, *Am J Hum Genet* 47:A45, 1990