

Phelan-McDermid Syndrome

****IMPORTANT****

It is possible that the main title of the report (Phelan-McDermid Syndrome) is not the name you expected. Please check the SYNONYMS listing to find the alternate name(s) and disorder subdivision(s) covered by this report.

SYNONYMS
22q13 Deletion Syndrome, Deletion 22q13 syndrome, Distal 22q deletion, Distal 22q monosomy, Partial Monosomy 22q13

Information on the following diseases can be found in the Related Disorders section of this report:

Chromosome 22 Ring
Chromosomal Disorders (General)

GENERAL DISCUSSION

****REMINDER****

The information contained in the Rare Disease Database is provided for educational purposes only. It should not be used for diagnostic or treatment purposes. If you wish to obtain more detailed information about this disorder, please contact your personal physician and/or the agencies listed in the "Resources" section this report.

Phelan-McDermid Syndrome is a rare chromosomal disorder in which a portion of the distal long arm (q) of chromosome 22 is missing (deleted or monosomic). Although the range and severity of symptoms may vary, Phelan-McDermid syndrome is generally characterized by low muscle tone, normal to accelerated growth, absent to severely delayed speech, moderate to profound mental retardation, and minor dysmorphic features. A rare number of cases with submicroscopic deletions of 22q13 are reported to have mild developmental delay. Current research indicates that haploinsufficiency of the SHANK3 (PROSAP2) gene in the 22q13 region may be responsible for most of the neurologic symptoms (developmental delay and absent speech) associated with this disorder.

SYMPTOMS

Phelan-McDermid Syndrome is characterized by moderate to profound mental retardation. Speech is typically absent or severely delayed. Receptive communication tends to be more advanced than expressive language. Individuals are delayed in the acquisition of skills requiring the coordination of mental and muscular activity (psychomotor retardation).

Most infants with Phelan-McDermid Syndrome exhibit normal intrauterine growth with normal to above average growth postnatally. The first physical sign associated with Phelan-McDermid Syndrome is neonatal hypotonia (low muscle tone) which may be accompanied by feeding difficulties, weak cry, and poor head control. Children also experience significant delay in reaching early

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developmental milestones, such as rolling over, crawling and walking, associated with low muscle tone.

The facial features of Phelan-McDermid syndrome include dolicocephaly (long head shape), large/prominent ears, full brow, deepset eyes, long eyelashes, full or puffy eyelids, ptosis (droopy eyelids), flat midface, full or puffy cheeks, wide nasal bridge, bulbous nose, and pointed chin. Other features include relatively large hands and dysplastic (underdeveloped) toenails. Behavior is described as “autistic-like” with tactile defensiveness, anxiety in social situations, avoidance of eye contact, and self-stimulatory behavior. Other behavioral traits include increased tolerance to pain and obsessive chewing of non-food items.

About 25% of individuals with Phelan-McDermid Syndrome have kidney abnormalities, including multi-cystic kidneys, one non-functioning (under-developed or dysplastic) kidney, kidney stones, and ureteral reflux.. All children diagnosed with Phelan-McDermid Syndrome should have a renal ultrasound performed to check for kidney defects.

Over 15% of individuals with Phelan-McDermid syndrome have arachnoid cysts (fluid filled sacs on the surface of the brain) compared to about 1% of the general population. While small arachnoid cysts may remain asymptomatic, larger cysts may cause increased intracranial pressure resulting in irritability, incessant crying bouts, severe headaches, cyclic vomiting, and seizures. Brain imaging with magnetic resonance imaging and computed tomography are indicated if an arachnoid cyst is suspected based on symptoms of increased intracranial pressure.

Although significant information is not available on older individuals with Phelan-McDermid syndrome, current data suggests that lymphedema (accumulation of fluid in the arms and legs) and cellulitis (inflammation of subcutaneous tissue due to infection) may develop during the teenage and early adult years.

CAUSES

Phelan-McDermid Syndrome is caused by the deletion or disruption of the segment of the long arm (q) of chromosome 22 that is identified as 22q13. Chromosomes are found in the nucleus of all body cells. They carry the genetic characteristics of each individual. Pairs of human chromosomes include the autosomes – numbered from 1 to 22- and the sex chromosomes - X and Y.. Females have two X chromosomes while males have one X and one Y chromosome. Each chromosome has a short arm designated as "p" and a long arm identified by the letter "q." The short arm is the region of the chromosome above the centromere (primary constriction) and the long arm is the region below the centromere. Chromosomes are further subdivided into bands that are numbered consecutively outward from the centromere to the end of the chromosome arm. Therefore, "chromosome 22q13" refers to band 13 on the long arm (q) of chromosome 22.

Most cases of Phelan-McDermid syndrome are due to a spontaneous (de novo) break in the long arm of chromosome 22 that occurs for unknown reasons (sporadic). The segment of chromosome 22 distal to the break is lost (deleted). In such cases, called simple deletions, the disorder is not inherited from the parents. That is, the parents have normal chromosomes but the break in chromosome 22 has occurred as a “new mutation” in the egg or in the sperm that contributes to the formation of the embryo. As in many other distal deletion syndromes, the deletion of 22q13 is more likely to occur on the chromosome 22 that is inherited from the father (in the sperm) than the chromosome 22 inherited from the mother (in the egg).

Because the deletion of chromosome 22 typically occurs on the distal portion of the long arm of the chromosome, it is often referred to as a “terminal” deletion. In this sense, “terminal” refers to the end of the chromosome. It is important that families and health care providers understand that in this

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context “terminal” refers to the distal portion of the chromosome and does not imply that the Phelan-McDermid syndrome is a “terminal” or lethal (life-threatening) condition.

About 20% of deletions of 22q13 are due to unbalanced translocations. Translocations may be balanced or unbalanced, and may be inherited or may occur de novo (new mutation). Translocations typically occur when breaks occur on two different chromosomes and the segments distal to the breakpoints trade places. For example, consider a translocation between the short arm (p) of chromosome 2 and the long arm (q) of chromosome 22. One break occurs in 2p and a second break occurs in 22q. The segment distal to the breakpoint on 2p trades places with the segment distal to the breakpoint on 22q. Such a translocation is called “balanced” because the correct amount of genetic material is present although its position has been altered. Balanced translocations are usually harmless to the carrier. However, a parent with a balanced rearrangement is at risk of transmitting an unbalanced translocation to a child. Chromosomal testing can determine whether or not a parent has a balanced translocation and is at risk of passing an unbalanced translocation to his or her offspring.

Unbalanced translocations may also occur de novo, or as a new mutation, when both parents have normal chromosomes. Even though neither parent carries a balanced translocation, a segment of chromosome 22 may switch places with a segment from another chromosome (example: chromosome 2) during the formation of the germ cell (egg or sperm). If the mature egg or sperm carries the translocated chromosome 22 but a normal copy of chromosome 2, an unbalanced translocation results. The embryo will be missing a piece of chromosome 22 but will have an extra copy of a segment of chromosome 2. The loss of 22q13 leads to Phelan-McDermid syndrome. The extra piece of chromosome 2 may also be associated with unusual features. Although chromosome 2 was used in this example, a translocation can occur between chromosome 22 and any of the other autosomes (chromosomes 1 to 22), or the sex chromosomes (X and Y). About half of the unbalanced translocations in Phelan-McDermid syndrome are inherited while the other half occur de novo.

AFFECTED POPULATION

Phelan-McDermid syndrome was initially described in the medical literature in 1985. Since that time, over 70 cases have been reported in the literature, with over 200 diagnoses known to the 22q13 Deletion Support Group (www.22q13.com). Males and females are equally likely to be affected. Based on limited statistical analysis the occurrence rate has been estimated to fall in the range 2.5-10 per million births, although this is likely to be a gross underestimate. Due to the subtle appearance of the deletion of chromosome 22 and the relatively mild physical features of affected individuals, diagnosis of Phelan-McDermid syndrome is often difficult. Over 30% of individuals with this deletion have required two or more chromosome studies before the deletion is detected. It is likely that there are many individuals who had “normal” chromosome studies at an earlier age but who actually carry this subtle chromosome abnormality.

DIAGNOSIS

The diagnosis of Phelan-McDermid syndrome is based on the demonstration of a deletion or disruption of the chromosome region 22q13. A simple deletion of 22q13 is often difficult to detect by high resolution chromosome studies. The deletion may be “submicroscopic” or beyond the level of resolution at the microscope. Likewise, unbalanced translocations may be “cryptic” or hidden because 22q13 has been replaced by a chromosomal segment that is similar in size and staining pattern. In these cases, fluorescence in situ hybridization (FISH) is required to detect the deletion. FISH is a “molecular cytogenetic” technique because it uses methods common to cytogenetic (chromosome) studies as well as methods common to molecular (DNA) studies. In FISH, a DNA segment (probe) that matches the genetic sequence at 22q13 is used to indicate whether this region of chromosome 22 is present or absent. FISH is recommended in addition to chromosome studies to diagnosis Phelan-McDermid syndrome. In particular, if the chromosome studies appear normal but the diagnosis of Phelan-McDermid syndrome is suspected based on clinical evaluation, FISH should be performed to

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confirm the diagnosis. FISH studies for deletion 22q13 are indicated in any infant with hypotonia (floppy muscle tone) of unknown cause and in older individuals with a history of hypotonia and absent speech

There are no characteristic structural abnormalities that would lead to the diagnosis of deletion 22q13 by prenatal ultrasound. Nonetheless, some renal abnormalities have been detected in fetuses that were found postnatally to have Phelan-McDermid syndrome. In some cases, the diagnosis of Phelan-McDermid Syndrome can be determined before birth (prenatally) by specialized tests such as amniocentesis, and/or chorionic villus sampling (CVS). During amniocentesis, a sample of fluid that surrounds the developing fetus is removed and studied. During chorionic villus sampling, a tissue sample is removed from a portion of the placenta. Chromosome and FISH studies performed on this fluid or tissue sample may indicate a partial monosomy, or deletion, of chromosome 22q.

Phelan-McDermid Syndrome can also be diagnosed and/or confirmed after birth (postnatally) by a thorough clinical evaluation, characteristic physical findings, and laboratory studies including chromosome analysis, FISH and/or molecular analysis.

RELATED DISORDERS

Symptoms of the following disorders can be similar to those of Phelan-McDermid Syndrome.

Chromosome 22 Ring is a rare chromosomal disorder in which chromosome 22 breaks at both ends (i.e., the ends of the long arm [22q] and the short arm [22p]). The chromosomal ends then join together, forming a ring. The formation of the ring is usually accompanied by a similar loss of genetic material as seen in most cases of 22q13 Deletion, and the symptoms observed to date appear to be consistent between the two conditions.

Phelan-McDermid syndrome should also be considered in individuals suspected of having Angelman syndrome but without the characteristic chromosomal or molecular defects associated with Angelman syndrome. Several individuals previously classified as “atypical Angelman syndrome” have been subsequently shown to have deletion 22q13. Features that these conditions have in common include moderate to profound developmental delay, absent speech, wide-based or ataxic gait, and autistic-like behavior.

Other chromosomal and non-chromosomal diagnoses that have been carried by individuals ultimately found to have Phelan-McDermid syndrome include autism, deletion 22q11.2 (Velocardiofacial/DiGeorge syndrome), Williams syndrome, trichorhinophalangeal syndrome, and spastic paraplegia

TREATMENT

The treatment for Phelan-McDermid syndrome addresses the individual symptoms of each patient and typically requires the coordinated efforts of a team of specialists: pediatricians, neurologists, nephrologists, gastroenterologists, immunologists, orthopedists, and others. Cardiac abnormalities are not typical of Phelan-McDermid syndrome, but if present will require assessment and appropriate management. In some cases, treatment may include surgical repair of certain malformations. The surgical procedures will depend on the severity of the anatomical abnormalities and their associated symptoms. Other treatment is symptomatic and supportive.

STANDARD THERAPIES

Therapies for Phelan-McDermid Syndrome are directed toward the specific developmental delays that are apparent in each individual and require the coordinated efforts of a team of specialists. Physical therapists, occupational therapists, speech and language pathologists, and others who specialize in

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social or vocational services should systematically and comprehensively plan therapy to ensure that the child with Phelan-McDermid syndrome reaches his or her full potential.

RESEARCH

Research that is currently conducted through the Deletion 22q13 Foundation and Support Group is focused on examining the longitudinal development of individuals with Phelan-McDermid syndrome. Physical features, developmental characteristics, and behavioral traits are being evaluated to help parents and health care professionals meet some of the challenges resulting from the physical, cognitive, and language deficits in children with Phelan-McDermid syndrome. The goal of current research is to provide families and health care professionals with a better understanding of the natural development of this disorder. The information obtained through various research projects is shared with the parents through quarterly newsletter, personal communications, and through scientific presentations at biennial meetings of the Deletion 22q13/Phelan-McDermid Syndrome Support Group. Information for professionals is published in scientific journals and shared through personal communications.

For information on potential participation in these studies or for more general information concerning this research, physicians and parents may contact:

Katy Phelan, Ph.D., FACMG
Director, Cytogenetics
Molecular Pathology Laboratory Network
250 East Broadway
Maryville, TN 37804
865-380-9746
kphelan@mplnet.com

Gail Stapleton, MS, C.G.C
Genetic Counselor
Greenwood Genetic Center – Greenville
2 Doctors Drive
Greenville, SC 29605
864-250-7944
gail@ggc.org

Randy Riddle
Chair, New Members Committee
22q13 Deletion Support Group
the5riddles@earthlink.net

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RESOURCES

For more information on Phelan-McDermid Syndrome, please contact:

National Organization for Rare Disorders, Inc.
(NORD)
P.O. Box 8923
New Fairfield, CT 06812-8923
Telephone: (203) 746-6518
Fax: (203) 746-6481
Toll free: (800) 999-6673
TDD: (203) 746-6927
e-mail: orphan@rarediseases.org
Home Page: <http://www.rarediseases.org>

UNIQUE - Rare Chromosome Disorder Support
Group
P.O. Box 2189
Caterham
Surrey, CR3 5GN
United Kingdom
4401(883) 33-0766
e-mail: info@rarechromo.org
Home Page: <http://www.rarechromo.org>

The Deletion 22q13 Foundation
www.22q13.com

Alliance-22-FR
2 Rue des Airelles
25560 Frasné, France
03 81 49 84 51

The 22q13 Support Group – UK
Del22q13@hotmail.com

<http://www.c22c.org>
Chromosome 22 Central
Website for individuals with abnormalities of
chromosome 22 including simple deletions,
translocations, and rings.

Chromosome Deletion Outreach (CDO)
<http://www.chromodisorder.org/>
Provides information and support for
families and professionals affected by
chromosome abnormalities

ONLINE DISCUSSION GROUPS:

General: <http://health.groups.yahoo.com/group/22q13>
Teachers, Doctors, Therapists: <http://health.groups.yahoo.com/group/22q13Professionals>
French Language: <http://health.groups.yahoo.com/group/22q13Francais>
German Language: <http://health.groups.yahoo.com/group/22q13Deutsche>
Spanish Language: <http://health.groups.yahoo.com/group/22q13Espanol>
Italian Language: <http://health.groups.yahoo.com/group/22q13Italiano>

REFERENCES

TEXTBOOKS

Phelan MC, GA Stapleton, RC Rogers: Deletion 22q13 Syndrome (Phelan-McDermid Syndrome), in The Management of Genetic Syndromes, in press, 2005.

JOURNAL ARTICLES

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 Mas P, N Chassaing, Y Chaix, MC-Vincent, S Julia, G Bourrouillou, P Calvas, E Beith: Molecular characterization of a ring chromosome 22 in a patient with severe language delay: a contribution to the refinement of the subtelomeric 22q deletion syndrome. *Journal of Medical Genetics* 39.e17, 2002.

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.

Havens JM, J Visootsak J, MC Phelan, JG Graham: 22q13 deletion syndrome: an update and review for the primary pediatrician. *Clinical Pediatrics* 43:43-53, 2004.

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, D Cataldi, ML Begleiter, LM Pasztor, MJ Dasouki, MG Butler: Five new subjects with ring chromosome 22. *Clinical Genetics* 63:410-414, 2003.

Luciani JJ, P de Mas, D Depris, C Mignon-Ravix, A Bottani, M Prieur, P Jonveaux, A Phillippe, G Bourrouillou, B de Martinville, B Delobel, L Vallee, M-F Croquette, M-G Mattei: Telomeric 22q13 deletions resulting from rings, simple deletions, and translocations: cytogenetic, molecular, and clinical analyses of 32 new observations. *Journal of Medical Genetics* 40:690-696, 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

Manning MA, Cassidy SB, Clericuzio C, Cherry AM, Schwartz S, Hudgins L, Enns GM, Hoyme HE: Terminal 22q deletion syndrome: a newly recognized cause of speech and language disability in the autism spectrum. *Pediatrics* 114:451-457, 2004.

Narahara K, Takahashi Y, Murakami M, Tsuji K, Yokoyama Y, Murakami R, Ninomiya S et al: 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, 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: Research Review: 22q13 Deletion Syndrome, *Am J Med Genet* 101:91-99, 2001.

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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.

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.

Wilson HL, ACC Wong, SR. Shaw, W-Y Tse, GA Stapleton, MC Phelan, S Hu, Marshall J, HE McDermid: Molecular characterization of the 22q13 deletion syndrome supports the role of haploinsufficiency of *SHANK3/PROSAP2* in the major neurological symptoms. *Journal of Medical Genetics* 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.

INTERNET

www.orphanet.net

Select "Rare Diseases" and Search for "22q13 deletion"

www.genetests.org

GeneReviews: 22q13.3 Deletion Syndrome

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