ARTICLE

22q13.3 Deletion Syndrome: A Recognizable Malformation Syndrome Associated With Marked Speech and Language Delay

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The 22q13.3 deletion syndrome is a recognizable malformation syndrome associated with developmental delay, hypotonia, delayed or absent speech, autistic-like behavior, normal to accelerated growth and dysmorphic facies. The prevalence of this disorder is unknown, but it is likely under-diagnosed. Age at diagnosis has varied widely, from cases diagnosed prenatally to 46 years. Males and females are equally affected. The distal 22q deletion can be detected occasionally by routine or high resolution chromosome analysis; however, the majority of cases are detected by FISH analysis, associated with deletion of the ARSA (control) probe when performing a FISH analysis for the velocardiofacial syndrome (del 22q11.2). The 22q13.3 deletion syndrome can accompany a simple chromosome deletion, an unbalanced translocation, or a ring chromosome. Primary care physicians, in addition to numerous specialists, play an important role in caring for patients with this disorder. Although the dysmorphic features observed in this condition are nonspecific, it is an important consideration in the differential diagnosis of children with developmental delay, hypotonia, marked speech and language disability, autistic-like features, multiple minor anomalies, and normal growth and head circumference.

KEY WORDS: deletion 22q13.3; terminal 22q deletion syndrome; chromosome anomaly; dysmorphology; autism; speech and language delay; developmental disabilities

How to cite this article: Cusmano-Ozog K, Manning MA, Hoyme HE. 2007. 22q13.3 deletion syndrome: A recognizable malformation syndrome associated with marked speech and language delay. Am J Med Genet Part C Semin Med Genet 145C:393–398.

INTRODUCTION

Cryptic subtelomeric chromosome rearrangements account for 6–10% of cases of idiopathic of mental retardation. In 1995, Flint et al. [1995] evaluated 99 patients with idiopathic mental retardation for subtelomeric chromosomal rearrangements and identified three individuals with monosomy. Two of these patients were noted to have a terminal deletion of 22q. No such deletion was identified in a study of a control population of normal individuals. Since that time, a number of reports of this disorder have been published, and the pattern of malformation associated with this finding has been delineated.

Patients with terminal deletions of 22q share a common phenotype, including developmental delay, hypotonia, delayed or absent speech, autistic-like behavior, normal to accelerated growth and head circumference, and dysmorphic facial features. The prevalence of this condition is unknown, but it is likely under-diagnosed. Age at diagnosis has

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DOI 10.1002/ajmg.c.30155

varied widely, from cases diagnosed prenatally to 46 years. Males and females are equally affected [Manning et al., 2004].

The purpose of this report is to review the existing literature regarding deletion 22q13.3 syndrome and to suggest clinical management and genetic counseling guidelines for affected individuals and their families.

CYTOGENETIC DESCRIPTION

22q13.3 deletions result from the loss of genetic material from the terminus of the long arm of one copy of chromosome 22. Monosomy 22q13.3 can accompany a simple deletion, an unbalanced translocation, or a ring chromosome. About 75% of all cases are simple deletions, with the remaining 25% of cases resulting from structural rearrangements of the affected segment. Deletion 22q13.3 is usually a de novo finding; however, approximately 20% of cases are familial, in which a child receives an unbalanced chromosome complement from a parent who carries a balanced reciprocal translocation. Mosaic cases have also been described. The deletion is usually terminal and includes the telomere; however, interstitial deletions have been demonstrated in which the telomere is spared. The deletion occasionally can be detected by high resolution chromosome analysis, but the majority of cases are detected by fluorescence in situ hybridization (FISH) analysis using either the arylsulfatase A (ARSA) or D22S1726 (subtelomeric) probe. Use of both probes is recommended, since distal deletions may be missed with the ARSA probe alone, and interstitial deletions may be missed with the D22S1726 probe alone. Using both probes detects 100% of cases. Comparative genomic hybridization (CGH) can be used to not only identify the deletion in suspected cases, but also to further characterize the size of the deletion. Although the deletion may be intentionally identified, it is frequently discovered serendipitously when the velocardiofacial syndrome (del 22q11.2) is suspected. On several occasions an affected individual with deletion 22q13.3 has been identified because he or she was used as a control for VCF FISH analysis or was being evaluated for VCF by FISH analysis. [Phelan et al., 2001; Havens et al., 2004; Manning et al., 2004; Phelan, 2005].

MOLECULAR CHARACTERIZATION

Nesslinger et al. [1994] characterized the critical area for the del 22q13.3 syndrome in seven patients with deletions ranging in size from 5 to 8 Mb, demonstrating that the critical area for the deletion breakpoint occurred between D22S92 and D22S94. Wong et al. [1997] subsequently reduced the critical area to an area of 130 kb. Anderlid et al. [2002] further refined the area to 100 kb, which contains three genes, *ProSAP2* (*SHANK3*), *ACR* and *RABL2B*.

Schroder et al. [1998] compared cytogenetic findings with molecular data obtained by FISH and an array of bacterial artificial chromosome (BAC) recombinants. Clinical features shared by these three individuals included normal to accelerated growth, hypotonia, and delayed psychomotor and speech development. Hearing loss was detected in three patients and kidney abnormalities were noted in two. One had a deletion with the breakpoint between D22S40 and D22S97. Another had a 38 cM deletion with the breakpoint between D22S92 and D22S95. The last had a 26 cM deletion with the breakpoint between D22S97 and D22S94. These breakpoints occurred within the critical area reported by Nesslinger.

Bonaglia et al. [2001] suggested that proline rich synapse associated protein 2, *ProSAP2* (*SHANK3*), was a good candidate gene for the 22q13.3 deletion syndrome, as it is preferentially expressed in the cerebral cortex and cerebellum and it encodes a scaffolding protein involved in the postsynaptic density of excitatory synapses. They identified a boy with developmental delay, severe speech delay, hypotonia and dysmorphic features. Chromosome analysis showed a translocation; 46,XY,t(12;22)(q24.1;q13.3). Sequence analysis identified the breakpoint on 22 at position 296489/296494, within exon 21 of the human homologue of the rat ProSAP2 (Shank-3 and SPANK-2). The ProSAP2 gene spans a 60-kb region on chromosome 22. It has 22 exons and lies between ARSA and acrosin. Northern blot analysis of human tissues showed a 3-kb band expressed in heart, kidney, liver and placenta and two transcripts (7- and 8-kb) seen in brain.

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Wilson et al. [2003] further characterized the role of *SHANK3* in 22q13.3 deletion syndrome by evaluating 56 patients. The size of the deletion varied from 130 kb to over 9 Mb, and all cases that could be analyzed (45/56) demonstrated a deletion of an area containing *SHANK3*. Nine of these patients previously had been reported [Zwaigenbaum et al., 1990; Phelan et al., 1992; Powell et al., 1993; Nesslinger et al., 1994; Feldman et al., 1995; Flint et al., 1995; Eydoux et al., 1996; Wong et al., 1997]. Eleven patients exhibited unbalanced translocations, three of which were inherited. One was mosaic and one had a complex chromosome rearrangement involving chromosomes 21 and 22. Parental origin of the deletion was determined in 39 cases; 27 were paternal and 12 maternal. There was a statistically significant correlation between the size of the deletion and the degree of developmental delay.

Clinical features such as hypotonia showed increased severity or higher incidence with larger deletions. Characterization of the *SHANK3* gene by cDNA analysis and RT-PCR products demonstrated two exons (22 and 23) not previously described. Exon 24 presumably corresponds to exon 22 in the above paper. There are a number of alternative products with an alternative splice site between exons 10 and 13 and three alternative 3′ ends identified. Northern blot analysis revealed that the 8 kb transcript, initially only seen in brain, is also expressed in the heart. A 2 kb transcript was observed strongly in heart and weakly in liver and kidney. A 10 kb transcript was strongly expressed in cerebellum and present at low levels in most tissue. The 7.5 and 8 kb transcripts showed moderate expression in all brain tissue with lower expression in medulla spinal cord. Genotype–phenotype correlations were noted in these individuals.

Bonaglia et al. [2006] presented an additional two cases, one previously reported by Anderlid et al. [2002], that share the same breakpoint as the individual described by Wong et al. [1997]. FISH analysis with the n85a3 probe confirmed the deletion. The breakpoint was localized to the proximal part of n85a3, which contains the *SHANK3* gene. The size of the deletion was estimated to be 100 kb. The breakpoints occurred within 15 bp of each other, inside a short simple repeat located between exons 8 and 9 of *SHANK3*.

REVIEW OF CASES FROM THE LITERATURE

In 1994, Nesslinger et al. [1994] reported on seven cases of deletion 22q13.3 detected by chromosome analysis. Although the deletion had been reported previously [Watt et al., 1985; Herman et al., 1988; Kirshenbaum et al., 1988; Romain et al., 1990; Narahara et al., 1992; Phelan et al., 1992], these authors were the first to suggest that individuals with this microdeletion share a common phenotype. In their study, which included the patient of Phelan et al. [1992], there were four males and three females, ages 2–5 years. They all shared a common phenotype of developmental delay, hypotonia, normal to accelerated growth, severe expressive speech delay and minor facial dysmorphic features. The authors noted that the individuals previously reported also shared some of the characteristics.

Flint et al. [1995] discovered two cases of 22q13.3 deletion by screening the subtelomeric regions of chromosomes in individuals with mental retardation. One case was a 22-year-old female with facial dysmorphism and absent language. The other was a non-dysmorphic 12-year-old male with speech impairment who did not begin speaking until age 4. Wong et al. [1997] further characterized the deletion discovered in the male patient first reported by Flint. The deletion was found to span the terminal 130 kb of chromosome 22.

Subsequently, a number of case reports and small series of affected patients further delineated a recognizable del 22q13.3 syndrome [Doheny et al., 1997; Slavotinek et al., 1997; Fujita et al., 2000; Praphanphoj et al., 2000; Prasad et al., 2000; Anderlid et al., 2002; Barakat et al., 2004; Lindquist et al., 2005; Tabolacci et al., 2005; Babineau et al., 2006]. In addition, several larger series of affected individuals have delineated a widely variable disorder in which normal to accelerated growth, hypotonia and marked speech and language impairment are the most reproducible features. Phelan et al. [2001] reported on 37 individuals, 17 males and 20 females aged 12 months to 26 years. Five of these had been previously described [Nesslinger et al., 1994; Doheny et al., 1997]. Twenty-nine individuals were noted to have terminal deletions and 8 had unbalanced translocations. Of these eight, four were de novo and four were inherited, three maternal and one paternal. Age at the time of diagnosis varied from prenatal to 20 years. Common features included developmental delay, marked speech and language delay, hypotonia and normal to accelerated growth. Dysmorphic features included dolichocephaly, epicanthal folds, ptosis, prominent or dysplastic ears, pointed chin, large and fleshy or broad hands, and 2–3 toe syndactyly. Luciani et al. [2003] documented 33 affected patients ranging from 1 to 34 years of age, including one previously reported in the literature [De Mas et al., 2002]. Seventeen were females and 16 were males. Seventeen exhibited a ring 22 chromosome, 12 had a simple terminal deletion and 4 had an unbalanced translocation, 1 of which was inherited. The size of the deletion was variable, ranging from 160 kb to 9 Mb. Parental studies revealed that the deletion was inherited from the father 74% of the time and from the mother 26% of the time. Developmental delay, severe expressive speech delay and behavior disorders were observed in all patients. Hypotonia and large or dysplastic ears were the next most common findings. Seizures were noted in a few individuals. Although not a universal finding, accelerated growth was seen in those with deletions or translocations, and growth restriction was seen in those with a ring chromosome. There was a positive correlation between the severity of features and the size of deletion. Manning et al. [2004] reported on 11 cases, 10 female and 1 male, ranging in age from 5 months to 46 years. All patients exhibited delayed development with severe expressive speech and language delay and varying degrees of hypotonia. Six individuals had autistic-like behavior. Dysmorphic features included epicanthal folds, full supraorbital ridges, large cupped ears, underdeveloped philtrum and loss of cupid's bow. The deletion was microscopically visible in six patients, five of whom had inherited an unbalanced translocation. The deletion was detected by FISH analysis in five patients; four of these were detected serendipitously during a FISH study to evaluate for del 22q11.2.

Several authors have documented prenatal diagnosis of the 22q13.3 syndrome by genetic amniocentesis and fetal karyotype and FISH studies [Phelan et al., 2001; Chen et al., 2003].

A similar phenotype has been documented in a large number of patients with ring chromosome 22. Battini et al. [2004] presented a patient with a ring 22 chromosome who

demonstrated hypotonia, speech impairment, mental retardation, unusual behavior and dysmorphic features. FISH analysis confirmed a distal deletion approximately 2.5 Mb in size.

Delcan et al. [2004] reported on a case of ring chromosome 22 with a deletion of 22q13.3 identified by amniocentesis in a 16-week gestation fetus. Chromosome analysis revealed the ring 22 chromosome, and FISH analysis demonstrated the deletion of 22q13.3. The pregnancy was terminated and autopsy revealed agenesis of the corpus callosum, septum pellucidum, and fornix as well as absence of the optic chiasm. Jeffries et al. [2005] collected data on 35 individuals with a ring 22 chromosome. Thirty-one families participated (13 from the UK, 10 USA, 3 Australia, 2 France, 1 Belgium, 1 Italy, 1 South Africa). The mean age was 10 years. The majority demonstrated weight and height appropriate for their age. Two had growth failure and two had accelerated growth. Impairment was noted in all areas of development. Evaluation for autistic traits by the SCQ revealed that two-thirds scored above the cut-off, and evaluation for ADHD by the SDQ revealed one-third scored above the cut-off. Dysmorphic features were noted, but were not consistent. The origin of the ring was determined in 28 individuals; 16 were paternal and 12 maternal.

Although the majority of patients with del 22q13.3 have been detected by FISH analysis, Koolen et al. [2005] characterized nine patients using chromosome specific array-based CGH. Three cases had been previously published. The deletions were initially identified by chromosome analysis in two and FISH analysis in seven. The two identified by chromosome analysis were confirmed by FISH analysis. One individual had a de novo translocation. The deletions ranged in size from 8.4 to 3.3 Mb. One individual with a 3.9 Mb deletion also had a 2.0 Mb duplication. There were five females and four males. Developmental delay and severe speech delay to absent speech were noted in all individuals. Hypotonia was noted in most of them. There was no correlation between the size of the deletion and the severity of symptoms and signs.

SUMMARY OF CLINICAL FINDINGS

Patients with terminal deletions of 22q share a common phenotype, including developmental delay, hypotonia, delayed or absent speech, autistic-like behavior, normal to accelerated growth and dysmorphic facial features. As above, several authors have described the phenotype in detail [Phelan et al., 2001; Luciani et al., 2003; Manning et al., 2004; Lindquist et al., 2005]. Clinical features are summarized in Table I, and Figures 1 and 2 depict affected children with deletion 22q13.3.

TABLE I. Clinical Features of Terminal 22q Deletion Syndrome

Feature	Number reported
Total cases reviewed	107
Perinatal	
Term	18
AGA	26
Growth	
Normal/accelerated	95
Neurodevelopment	
Developmental delay	105
Delayed/absent speech	103
Hypotonia	92
Autistic behaviors/ chewing	47
Regression	5
Seizures	25
High pain threshold	33
Lack of perspiration	19
Craniofacial	
Epicanthal folds	32
Large/dysplastic ears	58
Pointed chin	29
Dolichocephaly	32
Ptosis	25
Extremities	
2–3 toe syndactyly	25
Abnormal nails	39
Large hands	35

Hypotonia can be identified in the neonatal period, associated with poor head control, weak cry and poor suck. Developmental delay is usually in the moderate to severe range, and primarily affects the major milestones. For example, the average age for rolling over is 8 months (compared to 4–5 months), the average age for crawling is 16 months and the average age for walking is three years (compared to 12 months). Hypotonia contributes to the delay in obtaining these milestones.

Speech delay or severe language impairment with little to no speech is common. Some individuals may begin to babble and develop limited vocabulary before there is loss of speech. Most patients eventually are able to communicate by other means, such as a communication board. Receptive language skills exceed expressive language in this condition, and individuals are often able to follow one-step commands.

Mental retardation is frequently observed, with the majority of individuals in the moderate to severe range. In addition to mental retardation, most patients meet diagnostic criteria for autism and demonstrate behavioral issues including: poor eye contact, stereotypical behaviors, self-stimulation, repetitive chewing behaviors, bruxism, biting, hitting and abnormal sleep patterns. Increased tolerance to pain and other behavioral abnormalities, such as inappropriate chewing of clothes or toys, has also been described.

Dysmorphic features commonly exhibited by affected individuals include dolichocephaly, abnormal ears, pointed chin, ptosis, epicanthal folds, 2/3 toe syndactyly, dysplastic/hypoplastic toenails, large hands, clinodactyly and a tendency to become overheated with decreased perspiration. Abnormalities in growth have been observed. At birth, patients are appropriate for gestational age; however, as they continue to grow, they are often described as being tall and thin and some may have large head size. There have been a few reports of intrauterine growth restriction and failure to thrive.

Symptoms and signs in essentially every organ system have been reported.

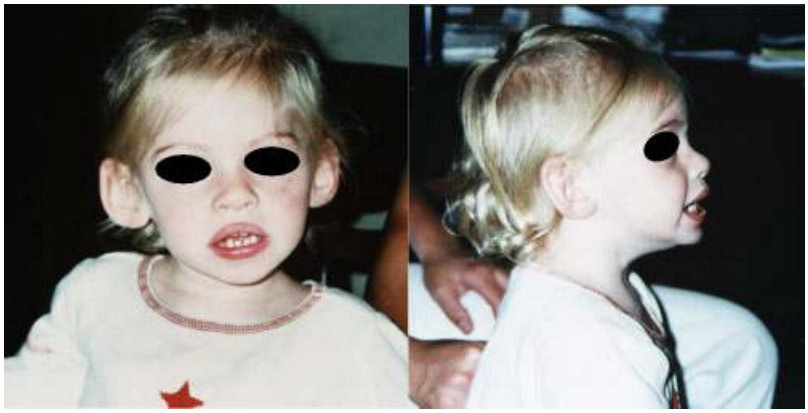

Figure 1. This girl demonstrates periorbital fullness, anteverted nares, smooth philtrum with absence of cupid's bow, downturned mouth and prominent cupped ears (reprinted with permission from: Manning et al. [2004], Pediatrics 114:451–457). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Some individuals have been noted to have hearing loss and/or visual impairment. Dental problems, such as malocclusion, are common. A few individuals have demonstrated neurological findings, including seizures and abnormal deep tendon reflexes or abnormal findings on magnetic resonance imaging of the brain. Congenital heart defects, such as patent ductus arteriosus and ventricular septal defect, have been reported on occasion. Gastroesophageal reflux and cyclic vomiting have been documented in a few patients, and vesicoureteral reflux has also been described.

MANAGEMENT

Primary care physicians play an important role in caring for patients with the del 22q13.3 syndrome. Neurologists and physical therapists can assist with treating hypotonia and neurologists can manage associated seizure disorders. Infant development specialists and child psychiatrists can evaluate for developmental delay and autistic-features and provide medications as needed to treat specific behavior problems. Routine ophthalmologic and audiologic evaluations are needed to assess for and treat confounding vision or hearing issues that may affect development. Speech and language evaluations and speech therapy are needed to ensure maximum communication potential. Dental evaluation is needed on a regular basis, especially if there are problems such as malocclusion. Finally, evaluation for malformations of other organ systems, including the cardiac, gastrointestinal, and genitourinary systems is necessary, and appropriate follow-up for specific abnormalities identified is essential.

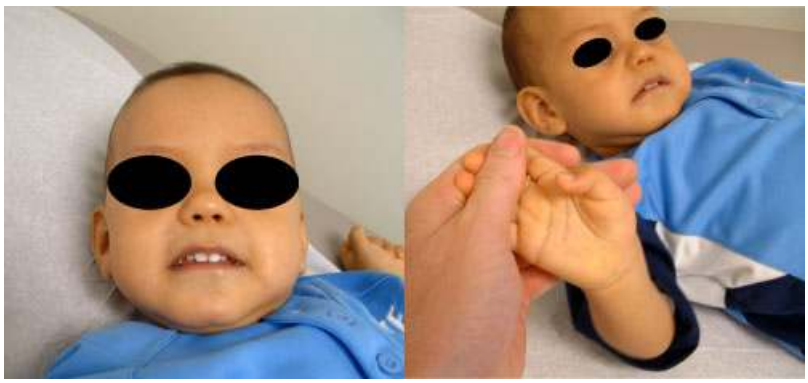

Figure 2. Affected boy with periorbital fullness, ptosis, large ears, anteverted nares, downturned mouth, and an altered "hockey stick" upper palmar crease. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Routine ophthalmologic and audiologic evaluations are needed to assess for and treat confounding vision or hearing issues that may affect development. Speech and language evaluations and speech therapy are needed to ensure maximum communication potential.

SUMMARY

Cryptic subtelomeric chromosome rearrangements account for 6–10% of idiopathic cases of mental retardation, of which deletions of 22q13.3 represent a significant proportion. The deletion can be detected occasionally by chromosome analysis; however, the majority of cases are detected by FISH analysis (either targeted or by screening subtelomeres) or by array CGH. The 22q13.3 deletion can accompany a simple deletion, unbalanced translocation, or ring chromosome. Patients with terminal deletions of 22q share a common phenotype, including developmental delay, hypotonia, markedly delayed or absent speech, autistic-like behavior, normal to accelerated growth and nonspecific dysmorphic facial features. A careful review of the literature indicates that all patients with hypotonia, marked

expressive speech and language delay, nonspecific dysmorphic features and normal karyotypes should be screened for this common disorder.

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