Terminal 22q Deletion Syndrome: A Newly Recognized Cause of Speech and Language Disability in the Autism Spectrum

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ABSTRACT. *Objective.* **Cryptic subtelomeric chromosome rearrangements account for 6% to 10% of idiopathic mental retardation. As cytogenetic and molecular techniques have become more sophisticated, the number of genetic syndromes attributed to these microdeletions has increased. To date, 64 patients have been described in the literature with a more recently recognized microdeletion syndrome, del 22q13.3. The purpose of this study is to present 11 new cases of this recently described syndrome to delineate further the phenotype and to alert the clinician to another genetic condition that should be considered in the differential diagnosis of early hypotonia, delayed speech acquisition, and autistic behavior.**

Methods. **Eleven patients were evaluated in 3 academic institutions. Clinical features and results of cytogenetic testing were recorded and tabulated. Reasons for referral for genetic evaluation included developmental delay, severe expressive speech and language delay, and dysmorphic features.**

Results. **Age of presentation ranged from 5 months to 46 years. There were 10 female patients and 1 male patient. All of the patients exhibited delayed motor development, some degree of hypotonia, and severe expressive speech and language delay. Dysmorphic facial features included epicanthal folds, large cupped ears, underdeveloped philtrum, loss of cupid's bow, and full supraorbital ridges. Six patients exhibited autistic-like behaviors. Microscopically visible chromosome deletions were observed in 6 patients. In the remainder, the deletion was detected with the use of fluorescence in situ hybridization.**

Conclusions. **Hypotonia and developmental delay are nonspecific findings observed in many malformation and genetic syndromes. However, in association with severe speech and language delay and autistic-like behavior, this phenotype may be a significant indication to consider the 22q13 deletion syndrome as a potential cause.** *Pediatrics* **2004;114:451–457;** ***22q deletion syndrome, autism, speech and language disability, fluorescence in situ hybridization.***

ABBREVIATIONS. MR, mental retardation; FISH, fluorescence in situ hybridization; VCF, velocardiofacial; ARSA, arylsulfatase A; DGS, DiGeorge sequence; ProSAP2, proline-rich synapse associated protein 2.

Cryptic subtelomeric chromosome rearrangements are estimated to account for 6% to 10% of idiopathic mental retardation (MR).[1] The number of malformation syndromes attributed to these microdeletions is increasing as more are identified through improved molecular diagnostic techniques. To date, 64 patients have been reported in the peer-reviewed literature with a microdeletion of the terminus of the long arm of chromosome 22 at band q13.3. Some of these cases were diagnosed unexpectedly after the telomeric control probe at 22q13 was discovered to be deleted in fluorescence in situ hybridization (FISH) studies assessing the possibility of the DiGeorge/velocardiofacial syndrome (del 22q11). We present 11 new cases of del 22q13.3 to characterize further the clinical phenotype of this unique, recently described syndrome. These data suggest that pediatricians should consider this syndrome in the differential diagnosis of patients with severe speech delay and autistic-like behavior.

METHODS

Eleven patients were referred for genetics evaluation because of developmental delay, severe expressive speech and language delay, and/or dysmorphic features to 3 academic centers throughout the United States. Physical examination, review of medical and family histories, and standard or high-resolution chromosome analyses were performed on each patient. In addition, FISH analyses were performed on 7 individuals. In all cases, the diagnosis of the terminal 22q deletion was not suspected before its identification by cytogenetic or molecular diagnostic studies.

Cytogenetic Analyses

Peripheral blood was cultured in RPMI 1640 with 10% fetal calf serum and stimulated with phytohemagglutinin. Cultures were synchronized with amethopterin, released with excess thymidine, and harvested using a Colcemid arrest, a hypotonic treatment using potassium chloride and fixed with 3:1 methanol:acetic acid. Slides were made using standard techniques and G-banded using trypsin and Wright's stain. Twenty metaphases were analyzed.[2]

FISH

Metaphase FISH was performed using combinations of the following probes: TUPLE1 located at 22q11.2 and arylsulfatase A

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(ARSA) located at 22q13.3 (Vysis, Downers Grove, IL), D22S75 located at 22q11.2 and D22S39 located at 22q13.3 (Oncor, Gaithersburg, MD), and D17S379 located at 17p13.3 and RARA located at 17q21.1 (Oncor). Slide preparation, treatment, and hybridizations all were done according to the manufacturers' recommended protocols (Vysis and Oncor). The TUPLE1 and D22S75 probes both are specific for the deletion of chromosome 22 that is commonly observed in velocardiofacial (VCF) syndrome and DiGeorge sequence (DGS). FISH using the Multiprobe T system (Cytocell), to detect cryptic rearrangements, was done in 1 case (case 4).

RESULTS

Cytogenetic Analyses

Each of the 11 patients underwent standard or high-resolution chromosome analysis with GTG banding. In 6 patients, a microscopically visible de novo deletion of band q13.3 was observed. Five of these patients had deletions of band q13.3 from inheritance of the unbalanced meiotic disjunction products of a parental translocation.

One patient had a bisatellited 22 with an additional ring 22. All of the cases had in common the deletion of the 22q13.3 band. FISH studies were performed in 8 cases. In 4 of those cases, the 22q13.3 deletion was detected serendipitously when the telomeric marker probe (D22S39 or ARSA) was deleted in studies assessing for the VCF syndrome. One case was detected using the Multiprobe T system (Cytocell). Table 1 summarizes the karyotypic and FISH findings for each case.

Clinical Features

The 11 patients described in this study included 10 female patients and 1 male patient. Five patients were of white ancestry; 1 was Chinese; 1 was black; 2 were Latina; and 1 was of mixed race ancestry, which included black, French Creole, and Cherokee Indian. Race was not recorded for 1 individual. The patients presented for initial evaluation between the ages of 5 months and 46 years.

Birth and perinatal history included 3 preterm deliveries. There were 8 vaginal deliveries and 1 cesarean section, performed because of failure of labor to progress. One child exhibited intrauterine growth retardation. The majority of patients had normal growth parameters; however, 2 individuals demonstrated height and weight deficits postnatally. Three patients were microcephalic, and 1 was macrocephalic.

All 11 patients were described as having global developmental delay with severely delayed or absent speech. Five exhibited autistic-like behaviors, which included decreased socialization; self-injurious behaviors; and repetitive, self-stimulatory actions. Four patients demonstrated developmental regression, with loss of previously attained motor milestones in 2 and loss of acquired language in 2. Nine patients were hypotonic, and 1 was hypertonic. This last individual was the woman who presented at 46 years of age; limited early history suggested generalized infantile hypotonia, however. She also demonstrated hyperreflexia and clonus on presentation. Additional neurologic findings included focal and petit mal seizures, ataxia, and decreased ambulation. Four patients had magnetic resonance imaging evaluations: 1 study demonstrated decreased white matter, hypoplastic corpus callosum, increased ventricular size, and periventricular leukomalacia; the second patient's study showed generalized white matter atrophy. Two patients had normal magnetic resonance imaging studies. One patient had a computed tomography that demonstrated patchy ethmoid opacification but otherwise normal brain structure.

The physical features noted in the 11 patients are set forth in Table 2. A variety of ocular features were observed. Epicanthal folds were the most common finding, noted in 8 of the 11 patients. Six individuals displayed supraorbital fullness, and 5 others had long lashes and hypertelorism. Additional features included iris heterochromia, bushy eyebrows, and downslanting palpebral fissures. Other craniofacial anomalies were large and cupped ears, short blunted nasal tip, palatal anomalies, and smooth philtrum with loss of the cupid's bow. (Figs 1–3).

Skeletal and connective tissue anomalies were also described. The most common finding was partial 2,3 toe syndactyly, found in 5 patients. Other findings included hyperextensibility, pectus excavatum, prominent or "spatulate" fingertips, and nail abnormalities. Miscellaneous anomalies were recorded, including deep sacral dimples, genital anomalies (hypoplastic labia minora and large penis and testes), inverted nipples, velvety skin, and natal teeth.

DISCUSSION

Subtelomeric regions are gene rich and have been shown to be involved in chromosomal rearrangements.[3,4] Submicroscopic subtelomeric chromosome rearrangements have been identified as a major cause of MR.[1] In fact, chromosomal telomeric abnormalities may be the most common cause of MR in children with moderate to severe idiopathic MR.[5] A

TABLE 1. Cytogenetic Results

Case 1: 46,XX, der(22)t(17;22)(q25.3;q13.3) pat.ish der(22)t(17;22)(q25.3;q13.3) (D22S39-, ARSA-)
Case 2: 46,XX.ish 15q11.2(D15S10x2), 22q11.2(TUPLE1x2), del(22)(q13)(ARSA-)
Case 3: 46,XX.ish 22q11.2(TUPLE1X2), del(22)(q13.3q13.3)(ARSA-)
Case 4: 46,XX.ish del (22)(q13.3q13.3)(ARSA-, D22S1726-, MS607-)
Case 5: 46,XX, der(22)t(10;22)(q26.1;q13.3)mat.ish der(22)t(10;22)(ARSA-)
Case 6: 46,XX.ish del(22)(q13.3q13.3)(ARSA-)
Case 7: 46,XX, del(22)(q13.3).ish del(22)(q13.3)(ARSA-)
Case 8: 46,XX, del(22)(q13.3q13.33).ish 15q11.2(D15S10x2, SNRPNx2), del(22)(q13.31q13.33)(D22S39-)
Case 9: 47,XY, der(22)t(22;14/22)(q13.31;p11),+r(14/22)(p11q11)
Case 10: 46,XX, der(22)t(12;22)(p13.31;q13.2)
Case 11: 46,XX, der(22)t(14;22)(q32.31;q13.33)

TABLE 2. Clinical Characteristics: Current Cases and Literature Review

	Current Cases ($N = 11$; n [%])	Literature Cases ($N = 64$; n [%])
Perinatal		
Term	7 (64)	28 (44)
Preterm	3 (27)	1 (1.5)
AGA	10 (91)	28 (44)
SGA	1 (9)	-
LGA	-	1 (1.5)
Growth		
Normal growth	9 (82)	57 (89)
Neurodevelopment		
Developmental delay	11 (100)	61 (95)
Delayed/absent speech	11 (100)	60 (94)
Hypotonia	9 (82)	52 (81)
Autistic behavior	6 (54)	3 (4.8)
Developmental regression	4 (36)	1 (1.5)
Seizures	3 (27)	14 (22)
High pain threshold	-	34 (53)
Craniofacial		
Epicanthal folds	8 (73)	22 (34)
Large/dysplastic ears	3 (27)	33 (54)
Long lashes	5 (45)	*
Hypertelorism	4 (36)	*
Supraorbital fullness	5 (45)	23 (36)†
Upturned/blunt nasal tip	5 (45)	*
Extremities		
2–3 toe syndactyly	5 (45)	19 (31)
Joint hyperextensibility	3 (27)	*
Bulbous/squared fingertips	3 (27)	*
Abnormal nails	3 (27)	31 (49)

* Fewer than 5 descriptions in the literature.
† Described as ptosis in literature review.

pilot screening study for submicroscopic chromosome anomalies by Slavotinek et al[6] determined an aberration frequency of 7.5%; Knight et al[5] demonstrated a similar frequency in a screening of 284 patients with moderate to severe MR. It was suggested that a submicroscopic chromosome analysis is appropriate for children with learning disabilities and dysmorphic features in which physical characteristics are similar to known segmental aneusomy syndromes. To improve the diagnostic detection rate of subtelomeric defects, deVries et al[7] suggested a checklist of clinical criteria that includes family history of MR, postnatal growth retardation, 2 or more dysmorphic facial features, and/or nonfacial dysmorphism and congenital anomalies. To delineate better MR syndromes and identify genes involved with neurodevelopment, cognitive function, and development, Anderlid et al[8] recommended screening with FISH for subtelomeric rearrangements in all children who have idiopathic MR and also display pre- or postnatal growth retardation, dysmorphic features, or a family history of MR.

One of the more recently characterized microdeletion syndromes is that of the terminal region of the long arm of chromosome 22. Watt et al[9] described the first nonring deletion of the distal portion of 22q in 1985. They reported on a 14-year-old boy with absent speech, profound MR, minor dysmorphic features, and normal tone. His karyotype showed a del 22q12 → qter. The deletion was found to be the result of meiotic recombination of a maternal pericentric inversion. Subsequent to that report, several groups described additional patients with terminal deletion 22q. Herman et al[10] reported on a male infant with de novo del 22q13.3 with Goldenhar complex. Also in 1988, Kirshenbaum et al[11] published a brief case report of a 13-year-old boy with a seizure disorder and developmental delay, who was found to have a distal 22 long arm deletion with a breakpoint (22q12) similar to the case described by Watt et al.[9] Phelan et al[12] were the first to report hypotonia in association with a 22q13 deletion. Their patient, a newborn boy, had minor anomalies as well as hypotonia. A follow-up report[13] further defined the cytogenetic breakpoint to 22q13.31. At 3 years of age, this patient now demonstrated global developmental delay along with hypotonia and anomalous features (dolichocephaly, epicanthal folds, abnormal ears).

In 1990, Zwaigenbaum et al[14] described 2 children with de novo del (22)(q13.3). They concluded that monosomy of the distal portion of 22q results in a recognizable syndrome of mildly dysmorphic facial features (long, narrow face; prominent ears and chin; flattened midface; deep nasal labial grooves) and developmental delay, with expressive language delay the most prominent characteristic. Also in 1990, Romain et al[15] described an 18-month-old girl with global developmental delay, hypotonia, and dysmorphic features. Chromosome analysis revealed an interstitial deletion involving band 22q13. Narahara et al[16] described a terminal 22q deletion in a 7-month-old girl with psychomotor retardation, hypotonia, and minor malformations. Because of a partial deficiency of ARSA and a normal level of NADH diaphorase 1, they theorized that the ARSA locus could be assigned to the 22q13.31 → qter region, whereas the diaphorase 1 locus could be excluded (Fig 4). Nesslinger et al[17] documented 7 cases (2 of which were previously reported by Zwaigenbaum et al[14] and Phelan et al[12,13]) with 22q13.3 deletions and noted a common phenotype of generalized developmental delay, hypotonia, severe delays in expressive speech, normal or accelerated growth, and mildly dysmorphic facial features.

Additional cytogenetic characterization of the terminal 22q deletion came in 1995, when Flint et al[1] demonstrated deletions in 2 patients in a focused study in which chromosomal telomeres were examined in 99 patients with idiopathic MR. A combination of techniques (hypervariable DNA polymorphisms, FISH, pulsed-field gel electrophoresis, and reverse chromosome painting) were used to characterize cryptic chromosomal rearrangements. One patient, a 22-year-old woman, had a deleted 22q as a result of an unbalanced translocation between the long arms of chromosomes 9 and 22. In addition to the monosomy 22, she had partial trisomy for 9q. The phenotype in this patient was severe with MR, absent speech, and congenital anomalies, including micrognathia, prominent nose, simple ears, gap between the 2 upper incisors, 2–3 toe syndactyly, right talipes equinovarus with pes cavus, and left calcaneovalgus deformity. Molecular characterization showed that the proximal breakpoint in this patient was between loci D22S97 and D22S94 and included the subtelomeric locus D22S163 (Fig 4). The second

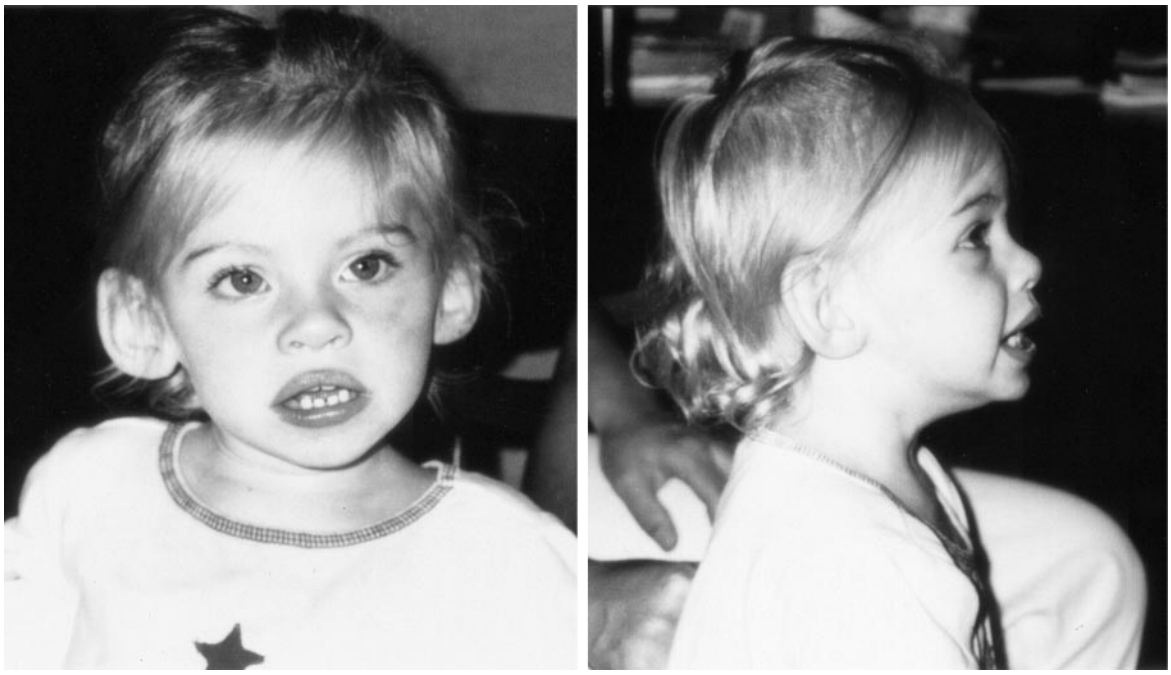

Fig 1. Case 2 demonstrating periorbital fullness, upturned nasal tip, smooth philtrum with absence of cupid's bow, and prominent cupped ears.

Fig 2. Case 7 also demonstrates periorbital fullness, epicanthal folds, blunted nasal tip, smooth philtrum with loss of cupid's bow, dysplastic ears, and high forehead.

of Flint's patients demonstrating a 22q deletion was a 12-year-old boy, less severely affected with only mild MR, normal physical features, and expressive speech delay. It is interesting that his deletion involved only the most distal locus on 22q (D22S163).

Another case of terminal 22q deletion as a result of a cryptic translocation was reported by Smith et al,[18] an infant boy with multiple congenital anomalies (micrognathia, prominent nose, midface hypoplasia, lowset ears, high arched palate, wide alveolar ridges, hypoplastic toenails, laterally displaced nipples, rocker bottom feet, tricuspid insufficiency with unusual aortic arch, agenesis of the corpus callosum, probable microgyria), hypotonia, and anemia. A

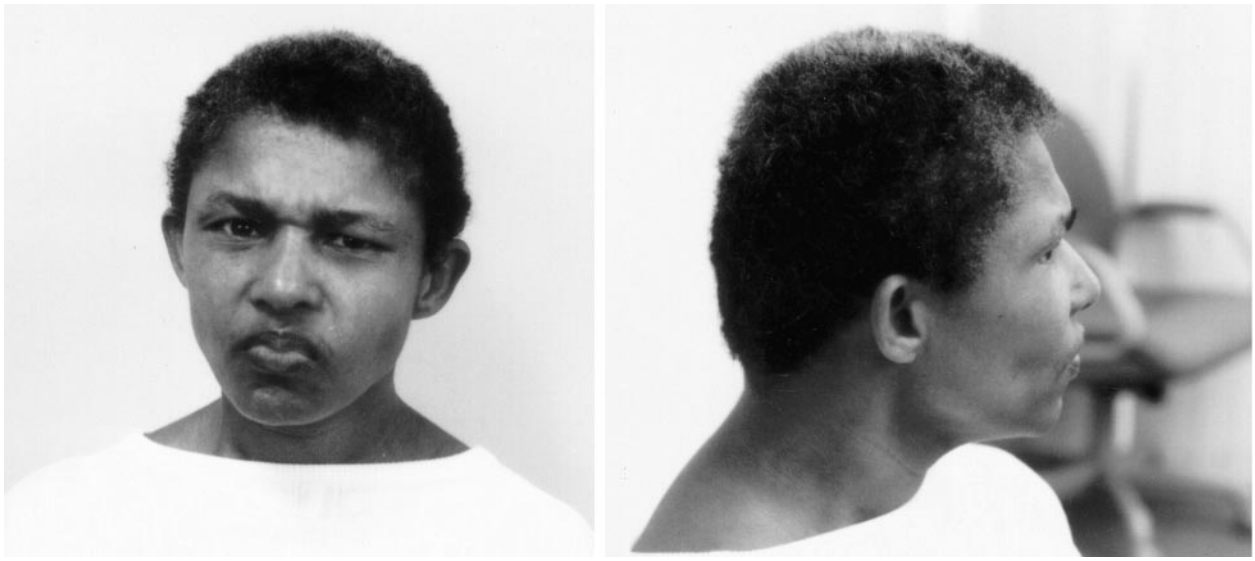

Fig 3. Case 8, a 46-year-old woman, displays a narrowed bitemporal diameter, epicanthal folds, periorbital fullness, and flattened midface.

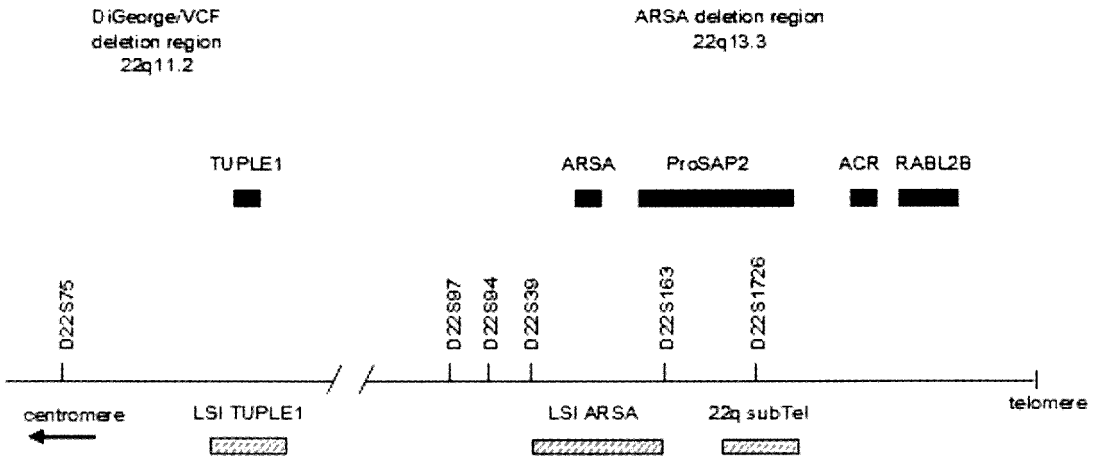

Fig 4. Schematic representation of 22q map with genes and cytogenetic probes. Genes are designated with solid dark bars. Deleted clones are depicted as gray striped bars.

cryptic t(17;22) was discovered with a deletion of locus D22S39 on 22q. He died at 6 months of age with persistent anemia and pneumonia.

In 1997, Doheny et al[19] reported on 2 additional cases of terminal 22q deletion determined by the use of FISH. The technique was used to define further the abnormal terminal regions of 22q seen on routine chromosome analysis.[19] They discovered that the D22S39 control probe used in conjunction with the D22S75 probe for DiGeorge syndrome was absent in 2 children who had been referred for evaluation because of developmental delay (Fig 4). The patients shared features of developmental delay, hypotonia, and expressive language delay. Since that report, additional cases have been described[20–24] that further delineate the phenotype and lend credence to a clinically recognizable terminal 22q deletion syndrome.[23] The 2 cases described by Precht et al[20] were fortuitously discovered when FISH was used to rule out other microdeletion syndromes. The first patient was referred to rule out Angelman syndrome secondary to her developmental delay, unsteady gait, and expressive speech delay. When used as a control for DGS/VCF in another patient, it was noticed that her sample was deleted for the distal D22S39 control probe. A second patient was referred to rule out VCF as a result of characteristic physical features (epicanthal folds, narrow palpebral fissures, broad nasal root), hypotonia, and developmental delay including no speech at age 5. He also had a deletion of the D22S39 distal 22q probe.

Goizet et al[25] reported on a 14-year-old girl with an autism spectrum disorder and a de novo 22q13.3 deletion that was detected by FISH. This case emphasized that although autism had not been previously reported in association with del 22q13, it should be considered part of the syndrome.

In the most comprehensive review to date, Phelan et al[26] reviewed the 24 previously reported cases with a terminal 22q deletion. In addition, they compiled a series of 37 unreported patients. They found the features most frequently associated with the deletion of q13.3 to be global developmental delay, generalized hypotonia, severely delayed speech, and

normal to advanced growth. Minor anomalies included abnormal ears, ptosis, dolichocephaly, and relatively large hands. Two features, hypoplastic toenails (78%) and hyperthermia accompanying hypohidrosis (51%), were noted in their patients, not having been documented in previous literature reports. Although an increased tolerance to pain had been previously reported in only 1 patient, it was observed in 86% of the patients reported on by Phelan et al.[26]

In addition to simple deletions or translocations, more complex mechanisms of chromosomal rearrangements resulting in deletion of 22q13 have been reported. Slavotinek et al[27]presented a family in which the mother had a submicroscopic deletion of band 22q13.3 as the result of a direct insertion of band 7q21.3 into chromosome 22 at 22q13.3. She had a history of delayed speech, special education requirement in school, and dysmorphic features (bulbous nose, micrognathia, high arched palate). Her son inherited an unbalanced chromosome complement, which resulted in trisomy for 7q21.3 and monosomy for 22q13.3. He also was affected with global developmental delay, hypotonia, and dysmorphic features (micrognathia, prominent long forehead, wide nasal bridge, short philtrum, prominent cupid's bow, lowset ears). Yong et al[28] reported on a patient who was mosaic for deletion of 22q13.2 and demonstrated seizures, failure to thrive, long philtrum, prominent ears, abnormal skin pigmentation, and developmental delay. Another case of mosaic 22q13 deletion was described in a prenatally detected case by Riegel et al.[29] A cystic tumor of the neck and upper thoracic aperture was noted on a 21-week ultrasound, and subsequent chorionic villus sampling showed a chromosome 22 long arm deletion. FISH analysis revealed mosaicism for deletion of 22q13. At autopsy, the fetus demonstrated minor dysmorphic features in addition to the neck mass.

Current research is focusing on determining genes in the region that may be responsible for the clinical presentation of the distal 22q deletion syndrome. The microdeletion in the patient first presented by Flint et al[1] and Wong et al[30] has been characterized further from a molecular standpoint.[31,32] The distal end of the 22q was cloned by constructing a cosmid/P1 contig that covered the terminal 150-kb and encompassed the 130-kb microdeletion identified in the patient.[31] With this region cloned, it was possible to isolate genes involved in the 22q13 deletion syndrome. At least 2 genes have been identified in this region. ACR (acrosin), a gene that codes for a serine protease in the acrosome of sperm heads, is located distally to the ARSA and D22S163 genes (Fig 4). It likely does not contribute to the del 22q13 phenotype but may affect fertility.[31]

Another gene, RABL2B, has been mapped directly adjacent to the subtelomeric (TTAGGG)n boundary element and is thought to be the proximal domain of the subtelomeric region of 22q[32] (Fig 4). RABL2B shares similarities with the RAB family of GTPases, which are involved in the control of vesicular trafficking cells. Because the function of RABL2B is currently unknown, it is also hard to predict whether this gene contributes to the del 22q13 phenotype. However, no other RAB family mutations have previously been described in association with MR.[32]

Bonaglia et al[33] identified another gene in the distal 22q region that has a greater potential of contributing to the del 22q13 phenotype than other previously identified genes. Proline-rich synapse associated protein 2 (ProSAP2) spans a 60-kb region on the distal 22q between ARSA and ACR (Fig 4). It is coded by 22 exons. Bonaglia et al[33] described a patient with severe expressive language delay, mild MR, minor facial dysmorphisms, hypotonia, joint laxity, and dolichocephaly in which the breakpoints of a de novo balanced translocation (46,XY,t[12,22][q24.1;q13.3]) interrupted the ProSAP2 gene within exon 21. As ProSAP2 is known to encode a scaffold protein involved in the postsynaptic density of excitatory synapses[3] and is preferentially expressed in the cerebral cortex and cerebellum, they suggested that ProSAP2 was a good candidate gene for the del 22q13 syndrome. Additional evidence to support this hypothesis came from Anderlid et al[3] in their report of a 33-year-old woman who demonstrated a submicroscopic 22q13 deletion. The patient displayed mildly dysmorphic facial features, mild MR, speech delay, and autistic features. The deletion was estimated to be ~100 kb and was mapped using FISH with cosmid probes from the 22q13 terminus. Three genes were affected: ACR and RABL2B were deleted, and ProSAP2 was disrupted. With the known expression pattern and protein function of ProSAP2, the authors proposed ProSAP2 to be a strong candidate gene for the developmental delay and autistic features observed in their patient.

CONCLUSIONS

Data from the patients described herein enlarge the phenotype of the distal 22q deletion syndrome. It is clear that patients with terminal 22q deletions share a common neurologic phenotype, which includes developmental delay, hypotonia, severely delayed or absent speech,[20] and behavior within the autistic spectrum.[3] The craniofacial phenotype encompasses ear anomalies, short nose, supraorbital fullness, smooth philtrum, and full lips with obliteration of the cupid's bow. It has been suggested[20,21,26] that variable additional features and severity of the phenotype likely result from variable sizes and/or mechanisms of deletions in affected patients. Our cases support this theory, because a variety of minor anomalies were observed in our patients in addition to a spectrum of developmental delay, including the 5 patients with loss of 22q13.3 as a result of an unbalanced chromosomal rearrangement. However, the phenotype of the patients with a simple 22q13.3 deletion did not differ significantly from those with a more complex karyotype. The paucity of significant dysmorphic features and the clinical variability observed may lead to underrecognition of this syndrome in the newborn period (because in the absence of multiple major and/or minor anomalies, a chromosomal abnormality would not usually be suspected[26]). As more cases are reported and the phenotype is better delineated, associated structural anomalies

that will aid in improved recognition of the syndrome may become apparent.

Hypotonia and developmental delay are nonspecific findings observed in many genetic and malformation syndromes, including the del 22q13 syndrome. Data from our patients suggest that neonatal hypotonia without identifiable cause should prompt the clinician to consider del 22q13 syndrome as well as Prader-Willi syndrome as possible genetic causes.[26] In older infants and children, hypotonia and developmental delay, associated with absent or severely delayed speech and language, autistic-like behavior, and minor craniofacial anomalies, should suggest del 22q13 as a possible diagnosis.[25,26] Specialty referral for genetics evaluation of infants or children with these findings is recommended to formulate the most appropriate testing algorithm for accurate genetic diagnosis.

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