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Deletion of Chromosome 2 q37 and Autism: A Distinct Subtype?

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Several reports have described the occurrence of chromosome abnormalities in autism, a neurodevelopmental disorder characterized by social deficits, communication impairment, and a restricted range of interests. These include the fragile X abnormality and 15q duplications. In this report, we describe two cases of chromosome 2q37 and review the literature on this topic. We propose that deletion of the distal portion of the long arm of chromosome 2 (2q37) may be associated with some cases of autism and with a distinct phenotype. Increased awareness of the dysmorphic features associated with 2q37 deletions may aid in the molecular genetic analysis of this chromosome anomaly and clarify its relationship with autism.

KEY WORDS: Autism; chromosome 2; genetics.

INTRODUCTION

Autism is a neurodevelopmental disorder characterized by a distinct pattern of social deficits, communication impairment, and rigid ritualistic interests. Although most cases of autism do not have an identifiable cause, several disorders have been implicated in its etiology. These include infectious agents, metabolic disorders, and a variety of chromosome abnormalities. Among the latter, both sex chromosome and autosomal aberrations have been described. The list of chromosomes associated with autism is long; however, the extent to which any of the reported abnormalities bear a specific relationship with autism is unclear. Most cases with autism and related pervasive developmental disorders do not show chromosome abnormalities on cytogenetic examination (Weidmer-Mikhail, Sheldon, & Ghaziuddin, 1998). While several chromosome defects have been identified with autism, the association is perhaps the strongest with fragile X syndrome. Prevalence rates of the fragile X anomaly in autism samples have ranged between 2 and 16%, depending on the sample studied (Bailey *et al.*, 1993; Gillberg & Wahlstrom, 1985). Another chromosome abnormality that may have more than a chance association with autism is tetrasomy 15. Gillberg *et al.* (1991) described six boys with tetrasomy 15 and autism all of whom had certain common physical abnormalities such as kyphosis, epicanthic folds, seizure disorder, and hypotonus. Similar findings were noted in a girl with tetrasomy 15 (Ghaziuddin, Sheldon, Venkataramann, Tsai, & Ghaziuddin, 1993) and in a further case (Hotopf & Bolton, 1995). Recently, Cook *et al.*(1997), described a proximal duplication in the Angelman syndrome region of chromosome 15 in autistic children.

In the following report, we describe the occurrence of autism in two children with deletion of the terminal band of chromosome 2 (q37). The cytogenetic and physical characteristics of the first patient, Patient J, have been described in an earlier report (Gorski, Cox, Kyine, Uhlmann, & Glover, 1989).

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Patient 1

J is a 12-year-old Caucasian boy with severe mental retardation (Fig. 1). According to his parents, J's main symptoms are his difficulty in relating to others and his tendency to indulge in self-stimulatory movements. He shows several stereotypic behaviors such as repeatedly tapping his fingers on the floor, feeling the texture of objects, turning the pages of magazines, and so forth. When interrupted, he tends to bite himself on his hands. His expressive language is limited to occasional words.

J's family history is positive for depression on his mother's side. Family history on father's side is unremarkable. There is no family history of autism, mental retardation, or any chromosome abnormalities. J was born 2 weeks premature. There were no complications during the pregnancy. During the first 6 months, he was noted to be very sensitive to touch and would not look at his mother. His milestones were delayed. At the age of 1 year, he was placed in a special program for developmentally delayed children. At 28 months, he weighed 30 pounds (50th percentile), his height was 35 inches (25th percentile), and his head circumference was 49 cm (25th percentile). At the age of 2 years 8 months, he was assessed and found to pass items at the 7-month level on the Cattel Infant Intelligence Scale. Between 3 and 3 years 6 months of age, he seemed to have lost the use of some words. In the classroom, he was aloof and passive, seldom interacting with his peers. He had several investigations done, including chromosome analysis, which revealed a small deletion of the terminal region of chromosome 2.

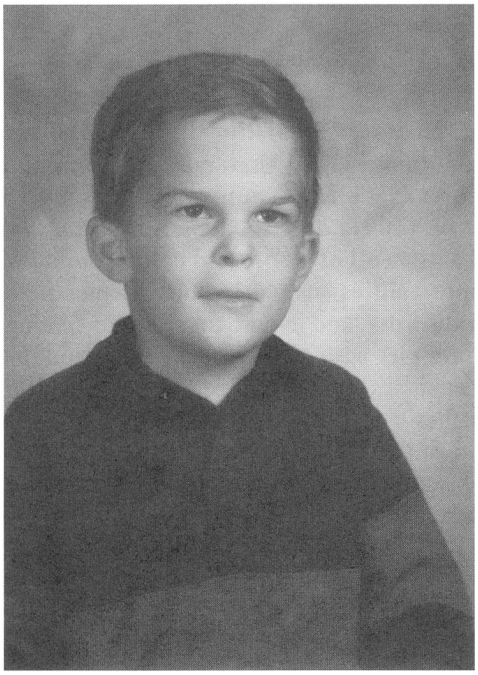

Fig. 1. Patient J. Age 12 years.

On examination, J came across as a tall youngster of average height. His eyes were sunken, almost sad-looking, with dark circles under them. He had a bulging forehead and a slightly depressed nasal bridge with long eyelashes. His eye contact was fleeting and unfocused, and his facial expression was usually flat. He preferred to sit at the same spot during the interviews. As soon as he settled down, he started manipulating the window drapes repeatedly. At times, he would sit on the floor, bending his head at a certain angle, looking persistently at the furniture. There was occasional rocking. His left hand showed callosities due to repeated self-biting. He had no functional speech. He would inconsistently utter words such as "no" out of context. He usually indicated his desire to terminate the interview by suddenly getting up and walking toward the door.

On the Autism Behavior Checklist (ABC; Krug, Arick, & Almond, 1980) his scores were as follows: 118 (mother); 77 (father); usual range for autism is over 77. In addition, on the Autism Diagnostic Interview (ADI; Le Couteur *et al.*, 1989), modified by omitting items relating to family and school history without altering the algorithm, he met the cutoff for autistic disorder. His scores on the three domains of social interaction, communication, and repetitive behaviors were 27, 14, and 8, respectively.

Based on the history and the above examination, J met the criteria for autistic disorder, as defined in the DSM-IV (American Psychiatric Association [APA], 1994). This is because of his combination of reciprocal social deficits and communication deficits with rigid ritualistic interests. Cytogenetic studies revealed a terminal deletion of band q37 of chromosome 2; 46, XY, del(2)(pter—q37::). Parental chromosomes were normal (see Gorski *et al.*, 1989).

Patient 2

A is a 6-year-old boy with a diagnosis of severe mental retardation (Fig. 2). He is placed in a program for children with severe mental retardation. He lives with his parents and two male siblings.

His family history was negative for psychiatric illness. His father, age 36 years, worked as an agronomist. His mother, age 31 years, worked as a part-time accountant. His siblings, ages 7 and 2 years, were said to be in good health. His parents' karyotype was normal. His siblings had not been tested for any chromosome abnormalities.

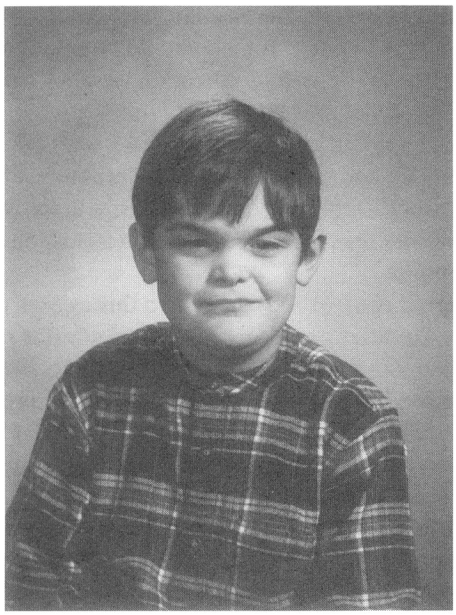

Fig. 2. Patient A. Age 5 years.

A was the product of a planned pregnancy. His mother was 26 years at the time of his birth. He was born after a full-term normal delivery. In the first 6 months of life, he was noted to be somewhat underactive. His motor milestones were delayed. At the age of 30 months, he had a height of 89 cm (25th percentile), weight of 26 pounds (25th percentile), and a head circumference of 52 cm (95th percentile). He started walking without support at the age of 17 months, and speaking single words by 2 years of age. He appeared to suddenly lose most of his words around the age of 3 years. His phrase speech never developed. At the time of evaluation, he was reported to have a vocabulary of about 25 words. At about 9 months of age, he was diagnosed as suffering from developmental delay by a neurologist. At about 1 year of age, he was noted to be excessively fixated on diapers; he would hold a diaper and repeatedly manipulate it. At age 2, a variety of repetitive movements were noted such as repeatedly flicking his fingers across his eyes, flapping of hands, and so forth. Around this time, he was also assessed for problems with his coordination. Between 2 and 4 years of age, he received speech, language, and occupational therapy. At about age 4, he was found to have occasional head-banging movements and frequent temper tantrums for which he was assessed by a psychiatrist. A detailed medical examination was performed and chromosome analysis revealed a deletion of the distal portion of chromosome 2; 46,XY,del(2)(q37.2).

At the time of evaluation, age 5 years, A had little social gaze or smiling. He did not offer to share or show things that he liked. His range of facial expression was limited. At times, he would smile for no apparent reason. He had no imaginative play and, when placed with other children his age, he seemed to withdraw from them. He regularly used his parents' hands to demonstrate for him. His occasional single words were uttered in a gruff monotone; at times he repeated words out of context. He was not able to point to objects appropriately or use such common gestures as nodding and shaking head. He was fixated on strings; he would manipulate them, arrange them according to their color, and insist on carrying them with him. At other times, he indulged in an elaborate ritual when he would stuff the strings between crevices in the house and then go through a process of removing them systematically. He showed marked distress when any of these rituals and patterns of behaviors were interrupted. Also, he showed some unusual sensory interests such as sniffing of food and of objects. Occasionally, he flapped his hands and fingers. In addition, he liked to spin, especially when excited. His medical and surgical history was unremarkable except for the detection of the chromosome abnormality. There was no history of seizure disorder.

At interview, A appeared his stated age. He paid no attention to the examiner and his eye contact was minimal. He walked with a somewhat awkward gait, as if he was bearing his weight on the inner sides of his feet. He sat in a stooping posture, his expression usually flat. Like the patient J, he too had a bulging forehead, a depressed nasal bridge, and long eyelashes. Occasionally he flapped his hands and flicked his fingers across his eyes, especially when anxious.

Based on the history and the examination, he met the criteria for autistic disorder based on the DSM-IV symptom checklist (APA, 1994). He showed deficits in all the three areas of functioning: social interaction, communication and play, and imagination. On the ABC (Krug *et al.*, 1980), his score was 96. On the ADI (Le Couteur *et al.*, 1989), which was modified to omit fam-

Table I. Autistic Symptoms in Other Reported Cases with 2q37 Deletion

Study	Symptom
Stein *et al.* (1992)	Mental retardation, hypotonia, autism
Conrad *et al.* (1995)	Repetitive behaviors; no formal diagnosis of autism
Burd *et al.* (1988)	Diagnosis of autism; however, trisomy 6p also present

ily and introductory questions without altering the algorithm, he met the cutoff for autistic disorder. His scores were 25, 14, and 9 on the social, communication, and repetitive behavior domains, respectively.

DISCUSSION

Deletions of chromosome 2 are said to be rare. Most cases are associated with complex duplication-deletion syndromes among progeny of balanced reciprocal translocation carriers (Schinzel, 1984). Clinical manifestations depend on the site of the 2q deletion and its type. In general, the larger the deletion, the more severe the phenotype. Deletions covering the same segment may vary in size but produce very similar phenotypes as some of the genes in the deleted region may be crucial for embryonic development. Monosomy for that region could produce clinical abnormalities involving the central nervous system and physical abnormalities usually reflect the size of the deleted segment (Lin *et al.,* 1992).

To our knowledge, detailed reports about the occurrence of autistic symptoms in chromosome 2q37 have not been published. In a brief abstract, Stein, Del Signore, Bellinger, and Bryke (1992) stated that their patient, age 21 months, with 2q37 deletion, presented with mental retardation, hypotonia, autism, and abnormal facies. The patient's physical features were similar to those described in earlier reports. Parental chromosomes were normal. The authors said that at 21 months, "clinical findings led to a diagnosis of infantile autism," but provided no further details.

When patient J was first assessed at the age of 30 months (see Gorski *et al.,* 1989), he showed "self-stimulatory teeth grinding and ritualistic hand waving behavior." Prior to this report, two other reports had described the occurrence of uncomplicated deletions involving 2q37 (Sanchez & Pantano, 1984; Young *et al.,* 1983). The patient of Sanchez and Pantano, monosomic for 2q35 to 2q terminus, showed mental retardation, downward slanting palpebral fissures, hypotonia, and so forth. However, the patient was 9 months old at the time of evaluation and details of her behavior were not described. The report by Young *et al.* (1983) described two cases with isolated deletions of the long arm of chromosome 2, one an interstitial deletion (46, XY, del(2)(q31q33)) and the other a terminal deletion (46, XX, del(2)(q36)). Both patients were in their infancy at the time of evaluation; therefore, details of their behavior that would have raised the possibility of autism were not given.

Burd, Martsolf, Kerbeshian, and Jalal (1988) described a child with chromosome 2q37 deletion with a partial trisomy (6p with duplication ranging from 6p21 to 6p25) who met the DSM-III-R criteria for autistic disorder. The authors compared this case with other cases of trisomy 6p and suggested that the presence of autism and seizures differentiated it from others thereby raising the possibility that the 2q37 deletion was responsible for the symptoms.

Conrad *et al.* (1995) described three cases of chromosome 2q deletion all of whom had similar physical and behavioral abnormalities. Patient 1, a 16-month-old male, showed rocking movements and repetitive behaviors. Patient 2, a 5-year-old male, also showed "repetitive behaviors," "hyperactivity," and "delayed social skills." Patient 3, at age 5 years, also showed "repetitive behaviors," "head banging," and "psychomotor retardation." All the patients showed frontal bossing, macrocephaly, hypotonia, and depressed nasal bridge. Thus, although none of the patients had been evaluated for autistic disorder, all showed features strongly suggestive of that disorder.

Lin *et al.* (1992) described "the smallest terminal deletion of the long arm of chromosome 2." This 4-year-old male twin also showed the same clinical features of frontal bossing, mental retardation, depressed nasal bridge, and hypotonia. His language was delayed and so were his motor skills. Also, there was a history of febrile seizures. Details about the behavior focusing on the diagnosis of autism were not described.

Both patients described in this report, J and A, had similar physical characteristics. Both had frontal bossing, deep set eyes with dark circles underneath, depressed nasal bridge, and long eyelashes. Their facial appearance was remarkably similar to each other and to other 2q37 deletion cases described in the literature. So far as their behavioral symptoms were concerned, both showed social deficits of the autistic kind, nonverbal communication impairment, and rigid restricted range of interests consistent with a diagnosis of autistic disorder. Since several cases described with this chromosome abnormality appear to have repetitive behaviors, communication, and social deficits with mental retardation, this raises the possibility that autistic symptoms are common in patients with deletion 2q37 and that this abnormality may form a distinct subgroup within the spectrum of autistic disorders. The authors are aware of two other children with chromosome 2q37 abnormality both of whom have social and communication abnormalities with repetitive behaviors suggestive of autism who could not be interviewed for this report. From a clinical point of view, this suggests that autistic persons

with dysmorphic features such as bulging forehead, should be carefully screened for chromosome deletions. From a research point of view, this raises the possibility that this association may index a distinct though a rare subtype of autism. Although the chromosome deletions were visible cytogenetically, it is important to note that minute deletions may require more sophisticated techniques for identification. A parallel can be seen between another cytogenetic abnormality, 22q11 deletions, and association with schizophrenia. Chromosome 22q deletions are associated with the velocardiofacial syndrome (VCFS), a disorder characterized by cardiac abnormalities, cleft palate, and dysmorphic features. It is now known that some patients with schizophrenia may show deletions of 22q11 with dysmorphic features and/or heart defects without the full diagnosis of VCFS (Gothelf *et al.*, 1997; Karayiorgou *et al.*, 1995). Similarly, it is possible that a subgroup of autistic patients may show small 2q37 deletions with the specific dysmorphic features described in this report. Thus, taken together, the findings of these two cases suggest that a gene in the 2q37 region, when deleted, may contribute to the etiology of autism, and that mutatations confined to that gene may lead to susceptibility to autism. Genes currently known to map to 2q37 region that might be considered candidate genes include the serotonin 2B receptor (Le Coniat, Choi, Maroteaux, Launay, & Berger, 1996); a homeobox gene expressed in brain, GBX2 (Lin *et al.*, 1996); and a G-protein coupled receptor gene (Libert *et al.*, 1991). However, it is equally possible that the gene in 2q37 ultimately found to be involved in autism may be an unexpected or a novel gene.

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