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Autism or Atypical Autism in Maternally but Not Paternally Derived Proximal 15q Duplication

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Summary

Duplications of proximal 15q have been found in individuals with autistic disorder (AD) and varying degrees of mental retardation. Often these abnormalities take the form of a supernumerary inverted duplicated chromosome 15, more properly described as an isodicentric chromosome 15, or idic(15). However, intrachromosomal duplications also have been reported. In a few cases, unaffected mothers, as well as their affected children, carry the same duplications. During the course of the genotyping of trios of affected probands with AD and their parents, at the positional candidate locus D15S122, an intrachromosomal duplication of proximal 15q was detected by microsatellite analysis in a phenotypically normal mother. Microsatellite and methylation analyses of the pedigree in the following report show that, among three children, the two with autism or atypical autism have maternal inheritance of a 15q11-q13 duplication whereas the third child, who is unaffected, did not inherit this duplication. Their mother's 15q11-q13 duplication arose de novo from her father's chromosomes 15. This finding documents, for the first time, the significance of parental origin for duplications of 15q11-q13. In this family, paternal inheritance leads to a normal phenotype, and maternal inheritance leads to autism or atypical autism.

Introduction

Autism is a complex genetic disorder involving abnormal social, language, and cognitive development (American Psychiatric Association 1994). It occurs in 5–10/10,000 live births and predominantly affects males (male:female ratio 4:1) (Bryson et al. 1988). Twin studies strongly implicate genetic factors in the etiology of autism (Folstein and Rutter 1977; Bailey et al. 1995). Estimates of recurrence risk to siblings have ranged from 4.5% (Jorde et al. 1991) to 8.9% (Ritvo et al. 1989). However, the specific genetic basis and mode of transmission remain largely unknown.

Proximal 15q duplications that include the critical region for Prader-Willi syndrome (PWS) and Angelman syndrome (AS) have been reported in several patients with autism (Gillberg et al. 1991; Baker et al. 1994; Bundey et al. 1994; Hotof and Bolton 1995; Flejter et al. 1996). However, in a few such cases, a parent who was not autistic was found to have the same duplication (Callen et al. 1992; Hirsch et al. 1995).

Of the cases of autism reported to have duplications of the PWS/AS critical region, all have been maternal in origin (Robinson et al. 1993; Leana-Cox et al. 1994; Schinzel et al. 1994; Flejter et al. 1996). Paternally derived duplications documented to include the PWS/AS region have not been reported previously, leading to discussion, in two recent reports, of the possibility that paternally derived duplications may not be viable (Flejter et al. 1996; Mignon et al. 1996). In addition, in the absence of evidence regarding paternal duplications, the role of parent-of-origin effects in proximal 15q duplication remains uncertain (Robinson et al. 1993).

We describe here a family in which autism segregates with maternal inheritance of a proximal 15q duplication. This pedigree provides the first evidence that paternal inheritance results in a normal phenotype, and it confirms a parent-of-origin effect for these duplications.

Subjects and Methods

Subjects

Family W was seen as part of a collaborative project examining linkage disequilibrium for candidate genes in autism. Subjects participated after written informed consent, including parental consent, when appropriate, was obtained.

Autism Diagnostic Interview—Revised (ADI-R), a parent interview that yields scores, on the basis of history, at ages 4–5 years [Lord et al. 1994]), and Autism

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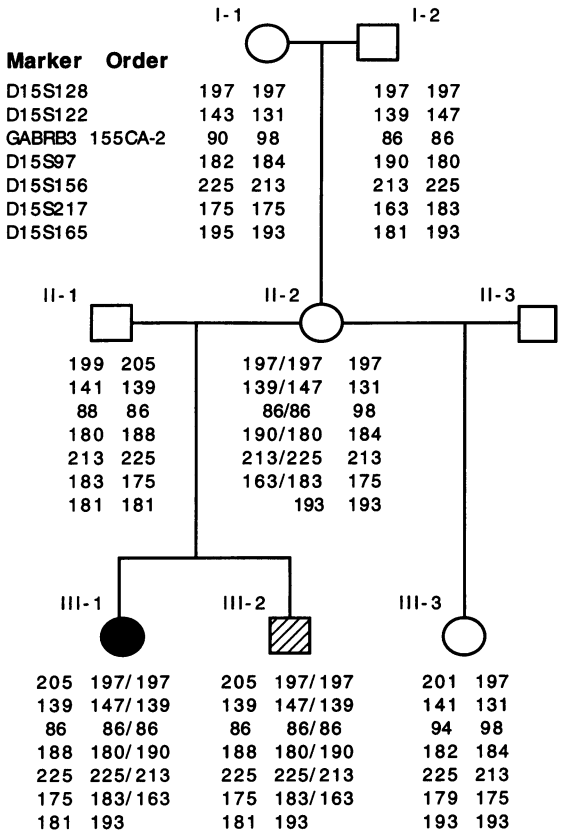

Figure 1 Pedigree of family W, summarizing microsatellite data. Both paternal origin of a de novo duplication in the proband's mother (II-2) and transmission of the duplication to the proband (III-1) and her affected brother (III-2) are shown. The blackened symbol represents autism, and the striped symbol represents atypical autism.

Diagnostic Observation Schedule—Generic (ADOS-G; a revised version of the ADOS, submitted by C. Lord, M. Rutter, and P. DiLavore), a standard observation scale that yields scores on the basis of current behavior [Lord et al. 1989]), were administered, by trained research interviewers, who were blind to the proximal 15q duplication, to children in the family suspected of having autistic disorder, to confirm clinical diagnosis of a pervasive developmental disorder by use of DSM-IV criteria (American Psychiatric Association 1994). Nonverbal intelligence was measured by the Raven's Coloured Progressive Matrices (RCPM) (Raven 1993). Receptive language was assessed by the Peabody Picture Vocabulary Test—Revised (PPVT-R) (Dunn and Dunn 1981). Adaptive skills were evaluated by the Vineland Adaptive Behavior Scales (VABS) (Sparrow et al. 1984).

BW (III-1; fig. 1) began to speak at age 12–14 mo but shortly thereafter lost her single-word speech and became more withdrawn. She walked at age 15 mo. The initial clinical diagnosis of autistic disorder was made at age 30 mo. BW also had poor joint attention, poor sustained attention, and hyperactivity. She had sleep problems, mild hypotonia, joint hyperextensibility, clumsiness, a left epicanthal fold, and a high-arched palate with lateral palatine ridges. Head circumference at age 6 years 9 mo was 52 cm (77%-ile). She has a history of hand flapping, self-biting, and hair pulling. An electroencephalogram revealed occasional temporal spikes during sleep, at age 6 years 10 mo. Results of a magnetic-resonance imaging (MRI) study were within normal limits, and quantitative measurement revealed normal average brain and intracranial volumes. Quantitative urinary amino acids and organic acids were within normal limits. A fragile X (FRAXA) DNA study was negative.

BW was found to have autistic disorder, by at least four separate clinicians and by the ADI-R standard criteria and ADOS-G overall judgment for diagnosis of autistic disorder (see table 1). Her RCPM nonverbal intelligence quotient was 81 (low average). She had severe delays in receptive language (PPVT-R age equivalent 3 years 1 mo at chronological age 9 years 4 mo). At age 9 years 4 mo, she also had severe deficits in adaptive skills as measured by the VABS, with age equivalents of 3 years 1 mo in Communication (standard score = 42); 2 years 7 mo in Daily Living Skills (standard score 20); and 1 year 10 mo in Socialization (standard score = 48).

BW's brother, NW (III-2), was examined when he was 8 years old. Methylphenidate (10 mg/d) was being administered for impulsivity, inattention, and hyperactivity, and desmopressin acetate was being administered intranasally for treatment of nightly nocturnal enuresis. He did not have dysmorphic features and, specifically, did not have an epicanthal fold. His nonverbal intelligence quotient was 98 (average), and his receptive-language functioning was 81 (low average). On the VABS, NW received age equivalents of 6 years 8 mo in Communication (standard score = 80); 3 years 5 mo in Daily Living Skills (standard score = 40); and 2 years 11 mo in Socialization (standard score = 56). He met the ADI-R standard criteria for autistic disorder, on the basis of history, and received an overall clinical judgment of pervasive developmental disorder—not otherwise specified (atypical autism) on the ADOS-G (see table 1). NW showed limited social reciprocity, inflexible communication, and repetitive behaviors but had better eye contact and better coordinated use of gesture than most children with autism. A diagnosis of a pervasive developmental disorder, atypical autism, was made.

BW's half-sister (III-3) is an above-average student who is taking regular and accelerated classes. Her social and emotional development has been normal, without evidence of either communicative impairment or routines, rituals, obsessions, or compulsions. BW's mother (II-2) was a low-average student who did not receive special education services. After her daughter was diag-

Table 1

Autism Diagnostic Data

Diagnostic Data	Rating in[a]			
	BW (III-1)		NW (III-2)	
	ADI-R	ADOS-G	ADI-R	ADOS-G
Social deficits:				
Nonverbal social behavior	2	2	2	0
Peer interaction	2	NT	2	NT
Shared affect	2	1	2	0
Reciprocal interactions	2	2	2	1
Communication deficits:				
Delayed language and failure to compensate	2	0	2	0
Stereotyped phases	2	2	2	1
Conversation	2	2	2	1
Spontaneous play and imitation	2	2	2	2
Restricted, repetitive behaviors and interests:				
Unusual preoccupations or circumscribed interests	2	0	1	1
Compulsive behaviors or rituals	1	1	0	0
Unusual hand or body movements	2	1	1	0
Interests in parts of objects	0	2	1	0

[a] 0 = No abnormality associated with autism; 1 = present but less frequent or severe than 2; 2 = definite with severe impairment; and NT = not tested by the ADOS-G.

nosed with autism, she developed a generalized anxiety disorder, which was treated with paroxetine. She did not have any communication or social impairment and communicated fluently. Specifically, there was no clinical evidence of a social/pragmatic language deficit, since she maintained topics well, did not include excessive detail in conversation, showed appropriate turn taking, and told engaging stories. She did not have dysmorphic features, was thin, and had normal muscle tone.

DNA Studies

DNA was extracted from lymphocytes (for all subjects, for microsatellites and methylation blots) and from saliva (for II-2 only) by use of the Pure Gene (Gentra) kit. Microsatellite analysis was conducted with CA-repeat markers for D15S97 (Hudson et al. 1992), GABRB3 155 CA-2 (Glatt et al. 1994), D15S122, D15S128, D15S156, and D15S165 (Gyapay et al. 1994) and for a tetranucleotide marker for D15S217 (Sheffield et al. 1995). DNA was amplified by standard PCR methods using fluorescent end-labeled primers (Research Genetics and Applied Biosystems) and were sized by capillary electrophoresis on an ABI Prism™ 310 Genetic Analyzer using POP4 polymer (Applied Biosystems). Although definitive evidence of triplication was provided by three differently sized alleles, peak heights were used to determine probable triplication for loci that were not fully informative by length. If the peak height of an allele was more than twice that of another allele, it was considered to be present in two copies.

For methylation blots, DNA was digested with *Hin*dIII and *Cfo*I and was hybridized with PW71b (D15S63) (a kind gift from B. Horsthemke). Maternal and paternal bands were quantified by Image Quant software (Molecular Dynamics). The ratio of the area under the curve of the maternal band relative to that under the paternal band was determined for two subjects (II-2 and III-4) with a normal karyotype and was averaged. The ratios for BW, SW, and NW were normalized by dividing by this factor (maternal:paternal density for normal karyotype = 1.06).

Cytogenetic Studies

Cytogenetic analyses were performed by standard techniques. FISH studies employed the Oncor probe for D15S10 and the Vysis probe for SNRPN with PML and classical satellite sequences (D15Z1) according to the manufacturer's specifications. Imaging was done on a Vysis Smart Capture system.

Results

Because duplication in the PWS/AS region of maternal origin had been found in several cases of autistic disorder, we added D15S122 as a positional candidate locus for our transmission-disequilibrium-test studies of autism. Because of its location within the AS critical region, and because the behavioral phenotype of autistic disorder has been found in several patients with AS (Steffenburg et al. 1996), D15S122 was chosen as a candidate

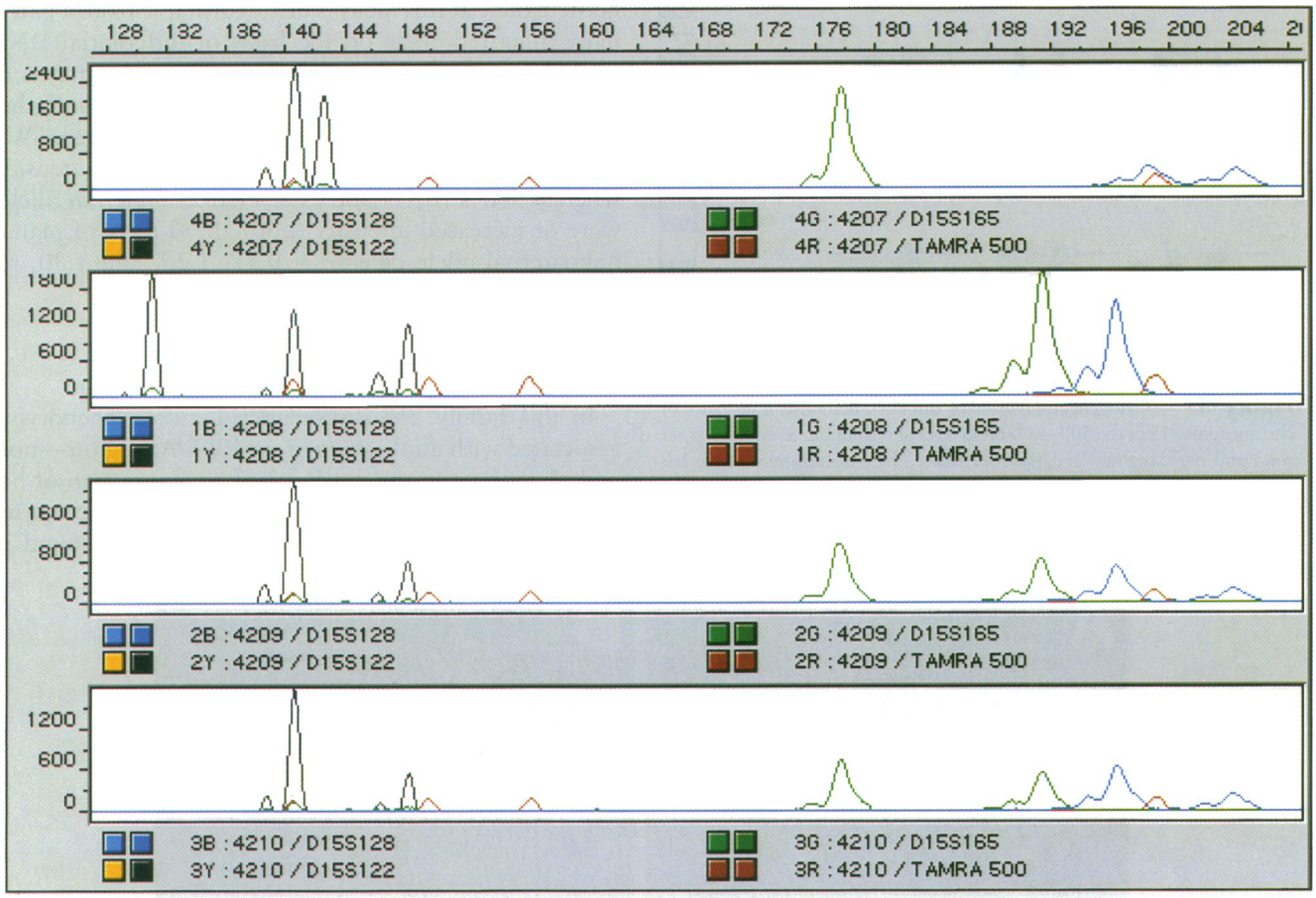

Figure 2 Electropherograms for markers D15S122 (*black*), D15S128 (*blue*), and D15S165 (*green*) and the size standard (*red*), for the father (II-1), mother (II-2), and two children (III-1 and III-2) (top to bottom). The mother has three different alleles at D15S122. The children have an increased amplitude of the 139-mobility-unit (mu) peak at D15S122 and the 197-mu peak at D15S128, consistent with inheritance of two alleles from the mother but not from the father. D15S165 does not appear to have a different peak height for maternal or paternal alleles in the affected children.

locus. In the process of genotyping trios consisting of probands with autism and their parents, we found that BW's mother (SW [II-2]) had three different alleles at D15S122 in lymphocytes (fig. 2). Analysis of D15S122 in DNA from SW's saliva also detected three differently sized alleles, of equal peak height. Microsatellite analysis of additional proximal chromosome 15 markers of SW's parents demonstrated that the duplication extended at least from D15S128 to D15S217 and arose de novo from her father's chromosomes 15. Analysis of her husband's and children's markers showed that BW (III-1) and NW (III-2) inherited their mother's proximal 15q duplication. The unaffected daughter (III-3) inherited her mother's normal chromosome 15 (fig. 1). The mother (SW) had four live siblings, none of whom had the proximal 15 q duplication, and the maternal grandmother (I-1) had had one known miscarriage.

Cytogenetic studies tended to confirm these findings. The maternal grandfather (I-2) had an apparently unrelated balanced translocation, t(7;22)(p13;q13.31), first detected in BW's maternal uncle and in his son. However, this translocation was not inherited by SW. High-resolution chromosome analysis of SW and BW, performed with knowledge of the microsatellite findings, revealed a subtle duplication of 15q11.2-q12 (fig. 3); NW was not karyotyped. The abnormal chromosome 15 was usually identifiable in a given cell on the basis of a q11.2-q13 region slightly longer than normal. However, in some cells the homologues were difficult to distinguish. FISH analysis similarly revealed a probable duplication of the SNRPN gene in the proband, her brother, and her mother. Figure 4 illustrates the range of observations, from two distinct signals in prometaphase chromosomes to the more typical merging of double signals or to a large single signal in metaphase chromosomes. Analysis with a probe for D15S10 yielded similar results (data not shown).

Methylation analysis at D15S63 (fig. 5) also tended to confirm the microsatellite findings. A maternally in-

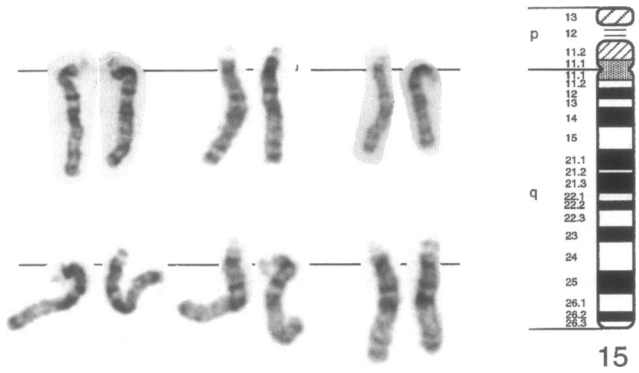

Figure 3 Cytogenetic analysis of dup(15), demonstrating pairs of chromosomes 15 at the 500–800-band level of resolution, from II-2 (*upper row*) and her daughter III-1 (*bottom row*). The chromosome on the left of each pair is the one with the duplication in the region q11.2-q13. An ideogram of chromosome 15 at the 550-band level is shown on the right, for reference.

herited allele at this locus is distinguishable from a paternally inherited allele on the basis of differential DNA methylation of the maternal allele. Normal patterns of roughly equal allele intensity were found in the father (II-1) and unaffected half-sister (III-3). However, SW's (II-2) *paternal* allele showed an increased intensity, whereas BW's (III-1) and NW's (III-2) *maternal* alleles were of increased intensity (normalized ratio of maternal:paternal allele density = 0.77, 1.25, and 1.30, respectively).

Discussion

In this family, the discrepancy between phenotypes associated with duplication of the PWS/AS region—normal phenotype in the mother and autism in two of her children—can be explained by inheritance patterns. Maternal inheritance of the duplication was found in

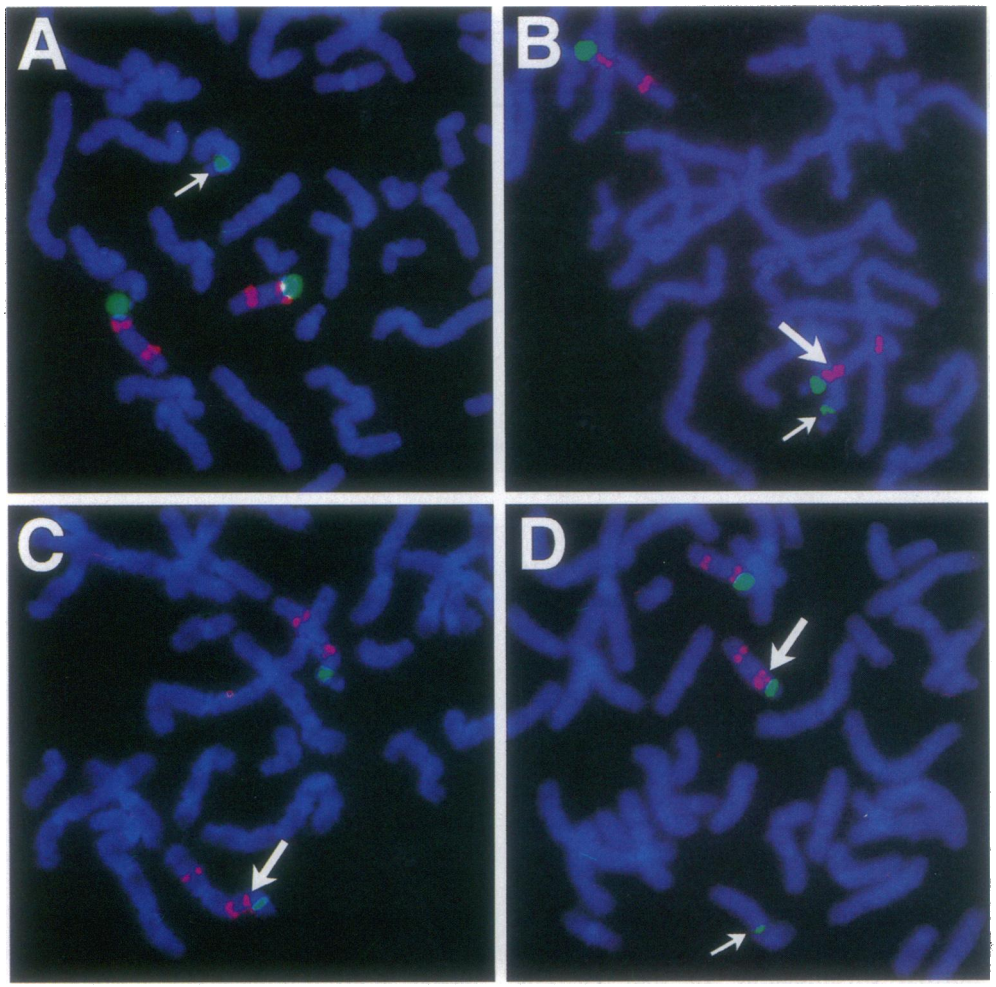

Figure 4 FISH analysis with the Vysis SNRPN probe (*proximal red signal*) of individuals I-1 (*A*), II-2 (*B*), III-1 (*C*), and III-2 (*D*). This probe also contains control probe PML (*distal red signal* [at 15q22]) and classical satellite III (D15Z1) probe (*green signal* [near the centromere]). The larger arrows indicate the abnormal chromosome 15 with two distinctly separate sites of hybridization at the SNRPN locus in panel *C* and with less clearly separated sites in panels *B* and *D*, as was more typically observed. The smaller arrows indicate D15Z1 hybridization with chromosome 14, a known polymorphism (Stergianon et al. 1992), which is segregating independently of the duplicated 15 in this family.

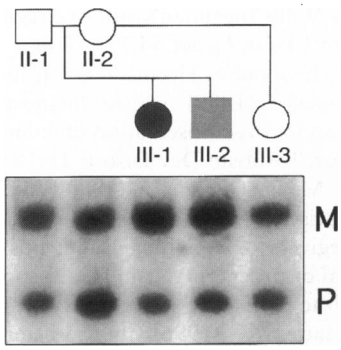

Figure 5 Methylation status at D15S63. Lymphocytic DNA was digested with *Hin*dIII and the methylation-sensitive enzyme *Cfo*I and then was hybridized with probe PW71b. The upper band (6.6 kb) in each lane is from the maternally derived chromosome, and the lower band (3.4 kb) is from the paternally derived chromosome. Individuals II-1 and III-3 have normal patterns, with relatively equal intensity of the two bands. Individual II-2 has a more intense paternal band, and individuals III-1 and III-2 have more intense maternal bands, indicating paternal and maternal inheritance, respectively, of the duplication.

the children in the family with pervasive developmental disorders—either autism or atypical autism—in agreement with previous data and conclusions (Gillberg et al. 1991; Baker et al. 1994; Bundey et al. 1994; Hotof and Bolton 1995; Flejter et al. 1996). Paternal inheritance of the duplication did not lead to symptoms typical of either autism or another pervasive developmental disorder.

It is likely that the subtle chromosome abnormality present in this family would have been missed in routine chromosome or FISH analysis, without prior knowledge of the microsatellite data. Careful examination of proximal 15q is now indicated for cytogenetic studies of patients with autism or atypical autism. Interphase FISH with PWS/AS-region probes might be useful in screening for small proximal 15q duplications, such as that seen in this case.

It is possible that the duplication arose postzygotically in the mother and that mosaicism accounts for her unaffected phenotype. Although mosaicism was not detected in cytogenetic studies or in microsatellite analysis of both lymphocytes and buccal epithelial cells, these methods cannot completely exclude the possibility of mosaicism. The more severe phenotype of the affected sister, compared with that of the brother, may be explained by intersibling differences at other loci contributing to the autism phenotype (Pickles et al. 1995). Concordance for autism (60%) in MZ twins is significantly less than concordance for a broader spectrum of related cognitive or social dysfunction (92%) (Bailey et al. 1995). Therefore, it is likely that environmental, stochastic, or non-Mendelian genetic factors (e.g., mitochondrial factors) contribute to the severity of autism and related disorders.

There are unavoidable limitations to how much may be understood about parent-of-origin effects of proximal 15q duplications from a single family. For example, although our subject with a paternally derived duplication dates the onset of clinical symptoms of an anxiety disorder to the diagnosis of her daughter's autistic disorder, she had subthreshold separation anxiety, probably related to her father's alcoholism as a child. Since social phobia and other anxiety disorders have been found at increased frequency in parents of children with autism (Piven et al. 1991; Smalley et al. 1995), it is possible that paternal duplications lead to an increased susceptibility to anxiety but not to autism or atypical autism. When more individuals with paternally derived duplications are identified, group studies of the prevalence of features seen in the broader autism phenotype may be assessed.

The percentage of autistic patients who have large, cytologically detectable abnormalities in the critical PWS/AS 15q11-q13 region is likely to be small (<3% of cases in our clinic). Nonetheless, among those remaining autistic cases, it is possible that a larger percentage have mutations of an autism-susceptibility gene(s) within this region. Studies investigating this possibility will be feasible once maternally expressed gene(s) within this region are identified. In addition to this particular genetic basis and mode of transmission of an autistic phenotype, it is likely that other genetic and nongenetic pathways contribute to the phenotype of individuals with autism and other pervasive developmental disorders (Bailey et al. 1995; Pickles et al. 1995).

Although our information comes from a single family, it appears that paternally inherited duplications of 15q11-q13 lead to a normal phenotype, whereas maternally inherited duplications usually lead to autism or atypical autism. This suggests that an imprinted gene may contribute to susceptibility to autism in some cases.

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