Of the chronic mental disabilities of childhood, autism is causally least well understood. The former view that autism was rooted in exposure to humorless and perfectionistic parenting has given way to the notion that genetic influences are dominant underlying factors. Still, identification of specific heritable factors has been slow with causes identified in only a few cases in unselected series. A broad search for genetic and environmental influences that cause or predispose to autism is the major thrust of the South Carolina Autism Project. Among the first 100 cases enrolled in the project, abnormalities of chromosome 15 have emerged as the single most common cause. The four abnormalities identified include deletions and duplications of proximal 15q. Other chromosome aberrations seen in single cases include a balanced 13;16 translocation, a pericentric inversion 12, a deletion of 20p, and a ring 7. Candidate genes involved in the 15q region affected by duplication and deletion include the ubiquitin-protein ligase (UBE3A) gene responsible for Angelman syndrome and genes for three GABA<sub>A</sub> receptor subunits. In all cases, the deletions or duplications occurred on the chromosome inherited from the mother.

INTRODUCTION

Autism, a most severe and enigmatic disturbance of brain function, manifests in early childhood and usually persists throughout life. Impairments in three categories of behavior (reciprocal social interactions, verbal and nonverbal communications, and age appropriate activities and interests) become evident prior to school age (3–5 years). Standardized tests for autism (DSM IV, ADI-R) are based on parental or caregiver observation of these behaviors. A 4–6:1 male-to-female ratio exists and over 70% of individuals with autism have coexisting cognitive impairments [Minshew and Payton, 1988; Mauk, 1993].

Systematic studies involving unselected series of patients with autism have documented a specific cause in only a minority, generally less than 20%, of cases [Ritvo et al., 1990; Folstein and Piven, 1991; Rutter et al., 1994]. The causes are heterogeneous, including genetic defects and environmental insults. In addition to the association of autism with specific heritable disorders (e.g., phenylketonuria and tuberous sclerosis), evidence for a genetic contribution includes increased recurrence risk in sibs, increased concordance in monozygotic twins, and occurrence of cognitive, language, and behavioral disturbances in close relatives [Gillberg and Colemen, 1996; Bailey et al., 1995; Rutter et al., 1994; Folstein and Piven, 1991; Smalley, 1991].

Preliminary results from the South Carolina Autism Project and reports from the literature indicate that aberrations of chromosome 15 may be the single most common identifiable cause of autism. These aberrations include duplications and deletions involving the proximal long arm of chromosome 15.

The Department of Disabilities and Special Needs (DDSN) is the public agency responsible for services for autism in South Carolina; 921 patients with autism are included among the 19,246 individuals served by the agency. The South Carolina Autism Project (SCAP) is a
research study to determine causes. The study seeks to enroll 200 individuals with autism, age 5–21 years, from among the 604 individuals in that age group. No selection is made by the study team; however, the time commitment, transportation, and other factors have influenced enrollment of some families.

The study is multifaceted. A three-generation pedigree is prepared, and pregnancy, birth, development, medical, and educational records are abstracted. All families are interviewed using the Autism Diagnostic Interview-Revised, and cognitive and adaptive functions are tested. A complete medical examination is performed with attention to somatic measurements and to the presence of minor facial anomalies. Laboratory testing includes plasma amino acids, urine organic acids, plasma serotonin, and urine metabolic screen. High-resolution chromosome preparations are examined for structural abnormalities, microdeletions or duplications, fragile sites, and, in a small subset, sister chromatid exchanges. DNA samples are used for FRAXA (FMR1) and FRAXE (FMR2) analysis, and to test for evidence of uniparental disomy for chromosomes 15, 17, 18, 20, and 22.

An advisory group composed of members of the study team, parents, autism workers, and DDSN monitors progress of the study. The study has been approved by our institutional review board and all families gave written consent to participate. This report is based on findings in the first 100 cases enrolled in the SCAP. Several characteristics of this study group are given in Table I.

### MATERIALS AND METHODS

#### Chromosome Analysis

Lymphocyte cultures were established from peripheral blood samples and chromosome preparations made using standard methods for chromosome elongation, cell synchronization, fragile site induction, and BrdU induction of sister chromatid exchange [Lawce and Brown, 1991; Spurbeck, 1991]. Fluorescence in situ hybridization (FISH) was performed according to manufacturer's recommendations using one or more of the following probes: D15S510 (Oncor P5153), SNRPN (Oncor P5152), D15S11 (Oncor P5150), and GABRB3 (Oncor P5151).

#### Molecular Analysis

Quantitative Southern blot analysis was performed using the 28s3-H3 probe from the GABRB3 gene [Wagstaff et al., 1991] and a control probe from the D4S12 locus (probe A1) [Gilliam et al., 1984]. Densitometry was performed using a Molecular Dynamics 300A computing densitometer. Control samples known to have the GABRB3 region present in one, two, three, or four copies were used to establish the relationship between gene copy number and band density ratio. Microsatellite markers were amplified using standard protocols for incorporating P32-labelled dCTP into the PCR product. Samples were electrophoresed through a 6% polyacrylamide/7 M urea gel and visualized by autoradiography.

#### Cognitive and Adaptive Function

Two tests of cognitive function were used. Those with exceedingly limited language were administered the Bayley Scales of Infant Development [Bayley, 1993]. Higher functioning patients were administered the Stanford-Binet Intelligence Scale: Fourth Edition [Thorndike et al., 1986]. Adaptive function was evaluated using the Vineland Adaptive Behavior Scale [Sparrow et al., 1984].

#### Autism Confirmation

The Autism Diagnostic Interview-Revised (ADI-R) is a standardized semistructured, investigator-based interview for caregivers of autistic individuals [Lord et al., 1994], which emphasizes autism-specific disturbances in reciprocal social interaction; language, communication, and play; and restricted repetitive and stereotyped behaviors and interests. The ADI-R is rapidly becoming a standard research and clinical instrument for identifying individuals with autism. It was administered by a clinical psychologist (M.C.) and two trained interviewers.

### CASE REPORTS AND RESULTS

#### Case 1

T.A.B. (GGC-71120) is the second of three children born to healthy parents. The pregnancy was uncomplicated except for a second trimester respiratory illness treated with penicillin. Delivery at term was vaginal with forceps assistance; birth weight was 3.9 kg, length was 53.3 cm, and head circumference was 35.5 cm. As an infant, T.A.B. had a poor suck reflex, poor head control, hypotonia, and decreased alertness. He walked at 3 years and began saying words at 5 years. His gait was clumsy and words were parroted and inappropriate. Generalized seizures began at 4 years. A Stanford-Binet IQ at 6 years was 46. Behavior problems began in childhood and now consist of aggressiveness toward...
others, biting of self, and scratching when his routine is changed or he is upset. At 17 3/12 years, his height was 184 cm (90th centile), weight was 93 kg (95th centile), and head circumference (OFC) was 58 cm (90th centile). ADI-R, cognitive, and adaptive function results are given in Tables II and III.

Chromosome analysis showed a supernumerary bi-satellited marker chromosome (Fig. 1a). FISH demonstrated two copies of D15S10 and SNRPN on the dicentric chromosome. Based on FISH and G-banding results, the marker was identified as a dicentric chromosome 15, commonly referred to as an inverted duplicated 15. T.A.B.’s karyotype was designated 47,XY,+ dic(15)(q13). Parental karyotypes were normal.

The quantitative Southern blot assay confirmed the cytogenetic findings (Table IV). The density of the band seen after hybridization with probe 28β3-H3 from the GABRB3 gene was consistent with this genomic segment being present in four copies. Microsatellite analysis indicated the inv dup(15) in T.A.B. contained the D15S165 microsatellite marker but not the D15S144 marker located approximately 6 cM distal to D15S165. The results from the D15S165 marker demonstrated that the extra chromosome 15 material was maternal in origin (Table IV).

**Case 2**

T.W. (GGC-58645) was the first of two sons. The mother had uterine fibroids which were treated with Lupron(R) followed by surgery 4–5 months prior to conception. The pregnancy was complicated by a urinary tract infection treated with Macrodantin(R) and by hypertension in the last month. The mother felt that in utero movement was decreased. Cesarean delivery was elected at 37 weeks because of the prior uterine surgery. Apgar scores were 8 and 9. Birth weight was 2.9 kg, length was 50.2 cm, and head circumference was 33.7 cm. T.W. had a soft cry and was a slow feeder. He was hypotonic. Gross motor development was delayed with sitting at 1 year, crawling at 2 years, and walking at 3.5 years. Brief episodes of unresponsiveness with head nodding were first noted at about 2 9/12 years. A sleep deprived EEG at 3 6/12 years showed frequent bursts of generalized spike activity. Cranial MRI was normal. At 4 1/12 years of age his height was 103.5 cm (55th centile), weight was 16.8 kg (55th centile), and OFC was 51 cm (50th centile). He had vocalizations but no speech or language. He had an awkward gait, leaning somewhat forward with flexed knees, everted feet, and some flailing or flapping of the arms. Craniofacial structure was normal. He had fifth finger clinodactyly. ADI-R results are in Table III.

Chromosome analysis showed a small supernumerary satellited marker chromosome (Fig. 1b). FISH detected single signals on the marker for D15S10 and SNRPN. A signal for the PML chromosome 15 control probe at 15q22 was not present on the marker. The marker was identified as a supernumerary chromosome 15 with a terminal deletion at q14. The karyotype was designated 47,XY,+ del(15)(q14). Parental karyotypes were normal.

The quantitative Southern blot assay confirmed the cytogenetic findings (Table IV). The density of the band seen after hybridization with probe 28β3-H3 from the GABRB3 gene was consistent with this genomic segment being present in three copies. Microsatellite analysis indicated the del(15) was large enough to include the GABRB3 marker from 15q12-q13 but did not extend far enough to include the ACTC marker from 15q12-q13. Parental microsatellite was consistent with this genomic segment being present in four copies. Microsatellite analysis indicated the del(15) was large enough to include the GABRB3 marker from 15q12-q13 but did not extend far enough to include the ACTC marker from 15q12-q13. The GABRB3 data also demonstrated that the extra chromosome 15 material was maternal in origin (Table IV).

**Case 3**

G.A. (GGC-56377) is the only child of healthy parents. A maternal half sister is normal. The 37–39 week pregnancy was complicated by depression and a fall during the third trimester that triggered premature contractions. Complications of labor and delivery included decelerations of the heartbeat during contractions, fetal distress, meconium staining of the amniotic fluid, and a nuchal cord. Birth weight was 2.8 kg. G.A. had a poor suck reflex and feeding problems initially. He used a few single words but stopped when he began walking at 17 months. Hyperactivity, poor attention, twirling, waving of his hands, and poor social interaction were noted by 3 years. At 7 11/12 years, his physical findings were normal except for a pit in the right

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**TABLE II. Results of Cognitive and Adaptive Function***

<table>
<thead>
<tr>
<th>Patient</th>
<th>IQ</th>
<th>CA</th>
<th>Comm</th>
<th>Daily Living</th>
<th>Soc</th>
<th>Comp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>54</td>
<td>79</td>
<td>53</td>
<td>26</td>
<td>53</td>
<td>43</td>
</tr>
<tr>
<td>Case 2</td>
<td>12</td>
<td>61</td>
<td>50</td>
<td>47</td>
<td>55</td>
<td>47</td>
</tr>
<tr>
<td>Case 3</td>
<td>36</td>
<td>91</td>
<td>39</td>
<td>47</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>Case 4</td>
<td>37</td>
<td>63</td>
<td>62</td>
<td>62</td>
<td>69</td>
<td>59</td>
</tr>
</tbody>
</table>

---

**TABLE III. Scores on the Four Domains of the Autism Diagnostic Interview—Revised**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reciprocal social interaction</td>
<td>20</td>
<td>25</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Communication</td>
<td>22</td>
<td>14</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Repetitive behavior/</td>
<td>8</td>
<td>4</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>stereotypical patterns</td>
<td>&lt;36 months</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

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*IQ, Intelligence quotient; Stanford-Binet Intelligence Scale: Fourth Edition (partial); Bayley Scales of Infant Development—Ratio score level/chronological age.

CA, Chronological age in months.

preauricular area and several small café-au-lait spots scattered on trunk. His height was 127 cm (70th centile), weight was 24 kg (50th centile), and head circumference was 53.5 cm (75th centile). At 7 8/12 years of age his Stanford-Binet IQ was 36 and at 10 years his CARS score was 40.3. His ADI-R results are given in Table III.

G.A. had an interstitial duplication of the proximal long arm of chromosome 15 confirmed by FISH (Figure 1c). The karyotype was designated 46,XY,dup(15) (q11q13)mat. Using probes D15S10, SNRPN, D15S11, and GABRB3, two signals were detected on the duplicated chromosome at 15q11.2. His normal mother carried the same duplicated chromosome 15; paternal chromosomes were normal. The maternal grandmother had normal chromosomes. The grandfather was deceased.

The quantitative Southern blot assay was consistent with the presence of three copies of the GABRB3 gene in G.A. and his mother (Table IV). Microsatellite analysis indicated that the duplicated alleles in G.A. were derived from his mother (C.A.). The mother’s duplicated alleles were derived from her father (Fig. 2).

### Table IV. Molecular Analysis of Chromosome 15 Abnormalities

<table>
<thead>
<tr>
<th>Quantitative Southern blot</th>
<th>Microsatellite analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Band density ratio $^a$</td>
<td>Mother’s alleles</td>
</tr>
<tr>
<td>1 copy (n = 4)</td>
<td>0.48</td>
</tr>
<tr>
<td>2 copies (n = 4)</td>
<td>0.82</td>
</tr>
<tr>
<td>3 copies (n = 4)</td>
<td>1.42</td>
</tr>
<tr>
<td>4 copies (n = 4)</td>
<td>2.03</td>
</tr>
</tbody>
</table>

$^a$Ratio of the densities of the bands representing hybridization by the probes from the GABRB3 gene (28q3-h3)/D4S12CA1.

**Case 4**

D.E. (GGC-82611) is the first of two sons born to healthy parents. His mother had nausea treated with Phenergan(R) during the pregnancy. Delivery was assisted by midforceps at 38 weeks of gestation. Apgar scores were 9 and 9. Birth weight was 3.5 kg and length was 52 cm. He had feeding and sucking difficulties for the first 9 months. He sat at 15 months, crawled at 2 years, and walked at 35 months. He began babbling at 11 months. He has a ten-word vocabulary which he seldom uses. Mixed generalized seizures began at about 2 years. On EEG there were almost continuous spike-waves with relative suppression of the background. On cranial MRI, there was a small lacunar infarct in the right parietal region. At 8 10/12 years, his head circumference was 52 cm (40th centile). He tended to keep his mouth open, had an everted lower lip, laughed when anxious, had arm flapping, and walked with an awkward broad-based and stiff-legged gait, all manifestations of Angelman syndrome. His ADI-R results are in Table III.

D.E. had an interstitial deletion of chromosome 15 confirmed by FISH (Fig. 1d). Using probe D15S10, no...
signal was detected at 15q11.2 on the abnormal chromosome. Karyotype designation was 46,XY,del(15) (q11q12). Parental karyotypes were normal. Based on microsatellite markers the deleted chromosome was derived from the mother (Table IV).

**DISCUSSION**

Aberrations of several types affecting proximal 15q are represented in the cases reported here. Case 1 has four copies of proximal 15q; 47,XY,+dic(15)(q13), case 2 has three copies: 47,XY,+del(15)(q14), case 3 has three copies: 46,XY,dup(15)(q11q13)mat, and case 4 has one copy: 46,XY,del(15)(q11q12). The aberrations occurred on chromosomes derived from the mother in all cases.

**Supernumerary Dicentric 15**

Small supernumerary chromosomes occur in less than 1:1,000 newborns and 0.65 to 1:5:1,000 prenatal diagnoses [Friedrich and Nielsen, 1974; Buckton et al., 1985; Sachs et al., 1987]. Of these small supernumerary chromosomes, derivatives of chromosome 15, particularly dicentric 15, are the most frequent [Buckton et al., 1985]. The small dicentrics are commonly referred to as inverted duplications (inv dup) of chromosome 15. In a review of 50 structurally abnormal supernumerary chromosomes studied with fluorescence in situ hybridization, 27 were derived from chromosome 15 and of these 27, 23 were inv dup 15s [Blennow et al., 1995].

There are two general cytogenetic types of inv dup 15 [Maraschio et al., 1988]. One is a metacentric or submetacentric and mostly or entirely heterochromatic chromosome smaller or similar in size to a G group chromosome. The cytogenetic description is dic(15)(q11). Most individuals with this heterochromatic inverted duplication 15 have normal phenotypes. Molecular studies in the few cases of Prader-Willi syndrome and Angelman syndrome associated with small inverted duplicated 15 have shown concurrent uniparental disomy or 15q deletion to be the cause of the phenotype [Robinson et al., 1993a; Cheng et al., 1994; Spinner et al., 1995].

**The second type of inverted duplicated 15 is as large as, or larger than, a G group chromosome and has 15q euchromatin. Molecular studies indicate that the critical regions for Prader-Willi/Angelman syndromes are included [Blennow et al., 1995; Robinson et al., 1993b]. The cytogenetic description is dic (15)(q12 or q13). Dicentric 15s of this type are usually derived from the two homologous maternal chromosomes at meiosis, are associated with increased maternal age, and are associated with an abnormal phenotype [Maraschio et al., 1988].**

The predominant phenotype of the larger inverted duplication 15 includes developmental delay, mental retardation, neurologic signs, and behavior disturbances [Schinzel, 1984]. The findings and the natural course in these patients are variable (Table V). As infants, they may be hypotonic and the mother may recall decreased fetal movements. Development, including motor and speech, is delayed. The gait is abnormal, variously described as awkward, unsteady, clumsy, and ataxic. Speech is often absent and, when present, is described as parroted, echolalic, or otherwise abnormal. Seizures are common and have an onset from infancy through adolescence. Growth may be slow but is normal in most. Microcephaly is more common than macrocephaly, but both are reported. Other findings are variable and inconsistent but include minor facial

**TABLE V. Characteristics in Literature Cases of Supernumerary Inv Dup 15 (n = 107)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>65</td>
</tr>
<tr>
<td>Female</td>
<td>42</td>
</tr>
<tr>
<td>Delayed development and/or MR</td>
<td>105c</td>
</tr>
<tr>
<td>Behavior (mutually exclusive)</td>
<td></td>
</tr>
<tr>
<td>Autisma</td>
<td>7</td>
</tr>
<tr>
<td>Autistic behavior</td>
<td>21</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>21</td>
</tr>
<tr>
<td>Aggressive/Violent</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>18</td>
</tr>
<tr>
<td>Macrocephaly</td>
<td>3</td>
</tr>
<tr>
<td>Short stature</td>
<td>21</td>
</tr>
<tr>
<td>Aphasia</td>
<td>15</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>40</td>
</tr>
<tr>
<td>Non-ambulatory</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal gait</td>
<td>16</td>
</tr>
<tr>
<td>Seizures</td>
<td>46</td>
</tr>
<tr>
<td>Strabismus</td>
<td>29</td>
</tr>
<tr>
<td>Downslanted palpebral fissures</td>
<td>26</td>
</tr>
<tr>
<td>Epicanthal folds</td>
<td>31</td>
</tr>
</tbody>
</table>

*aCriteria for autism given.
*bDescribed as autistic.

cNumbers are considered minimum since incomplete information is given in some articles. Information tabulated from reports by Cook et al., 1997; Battaglia et al., 1997; Feletjer et al., 1996; Abuelo et al., 1995; Crolla et al., 1995; Blennow et al., 1995; Hotopf et al., 1995; Baker et al., 1994; Cheng et al., 1994; Leena-Cox et al., 1994; Townier et al., 1993; Plattner et al., 1993; Ghazuddin et al., 1993; Robinson et al., 1992; De Lorey et al., 1992; Callen et al., 1992; Gillberg et al., 1991; Plattner et al., 1991; Shibuya et al., 1991; Lazarus et al., 1991; Nicholls et al., 1989; Maraschio et al., 1988; Wisniewski et al., 1985; Gilmore et al., 1984; Yip et al., 1982; Voss et al., 1982; Schinzel et al., 1981; Maraschio et al., 1981; Zanotti et al., 1980; Matti et al., 1980; Wisniewski et al., 1979; DeAlco et al., 1978; Hongel et al., 1978; Van Dyke et al., 1977; Schreck et al., 1977; Power et al., 1977; Watson et al., 1977; Rasmussen et al., 1976; Pfeiffer et al., 1976; Centerwall et al., 1975; Crandall et al., 1973; and Magenis et al., 1972.*
feature anomalies, downslanting palpebral fissures, epicanthal folds, and strabismus [Schinzel et al., 1994]. Inverted duplicated 15s are frequently associated with abnormal behavior including hyperactivity, aggressiveness, short attention span, agitation, low frustration tolerance, ritualistic behavior, stereotypic movements, self mutilation, and autistic behavior [Schinzel, 1981; Wisniewski et al., 1979].

Interpretation of the association between autism/autistic behaviors and inverted duplicated 15 is complicated by lack of detailed behavioral descriptions and standardized testing for autism in reported cases (Table V). Schinzel's review [1981] of behavior symptoms in autosomal chromosome aberrations noted that manifestations of autism were "repeatedly reported" in patients with inverted duplication 15. In the 1977 study by Schreck et al. of eight supernumerary G-like chromosomes, six were derived from chromosome 15. Of these six cases with mild to profound mental retardation, four had behavior disorders (one infantile autism, one a personality disorder, and two hyperactivity). In 1977, Hansen et al. described a single case with childhood autism. The description of one of five cases with inv dup 15 by Wisniewski et al. [1979] suggested autistic behavior. All five cases had mental retardation, hyperactivity, and aggressiveness and four of five had parroted speech. In reviewing the 19 cases of inv dup 15 in the literature, Wisniewski et al. [1979] noted that five, including the one reported by Schreck et al. [1977], had autism.

One of two cases reported by Nicholls in 1989 had autism. The other had autistic-like behavior. Autism in five of six males with inv dup 15s reported by Gillberg et al. was confirmed by DSM-III and DSM-III Revised [Gillberg et al., 1991; Wahlström et al., 1989]. Ghazi et al. was confirmed by DSM-III and DSM-III Revised five of six males with inv dup 15s reported by Gillberg et al. was confirmed by DSM-III and DSM-III Revised five of six males with inv dup 15s reported by Gillberg et al. had autism. The other had autistic-like behavior. Autism in 1977, had autism.

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apparent doubling of the signal for GABRB3. The long arm breakpoint on chromosome 15 was not designated, but the abnormal cell line was reportedly trisomic for the long arm of 15 into band q12 and, based on the FISH results, possibly tetrasomic for the GABRB3 region.

**Interstitial 15q Duplication**

Ludowese et al. [1991] noted an absence of a consistent phenotype among 10 cases of cytogenetic dup(15)(15q12.2-15q13.1). However, it is of note that two of the five propositi, both males, had autistic-like behaviors. In 1994, Baker et al. reported a mosaic FISH-confirmed interstitial dup(15)(q11.2-1q31) in a patient with DSM-III-R criteria for autism. Bundey et al. [1994] reported a male with Medical Research Council Handicaps Skills and Behavior Schedule criteria for autism and a maternally derived dup(15)(q11-q13). Schinzel et al. [1994] reported autistic behavior in a patient with triplication 15q11-q13 containing both maternal alleles confirmed by fluorescent in-situ hybridization and molecular polymorphism analyses. There is considerable variation in the cytogenetic appearance of proximal 15q and deletions and duplications in this area require molecular confirmation. In the present study, case 3 with an interstitial duplication is known to have inherited the duplication from the mother. The mother’s duplication occurred on the chromosome 15 inherited from her father. Cook et al. [1997] reported a similar family.

**15q Deletion**

Autism has been reported with deletions of proximal chromosome 15, but in many cases interpretation is complicated by lack of confirmation of the autism by standardized testing and lack of confirmation of the cytogenetic findings by fluorescence in situ hybridization and molecular studies. Kerbeshian et al. [1990] reported the first case of autism associated with 15q12 deletion in a 33-year-old woman with autism, profound mental retardation, and atypical bipolar disorder. They thought the patient had some indications of Angelman syndrome. Angelman syndrome comprises profound mental retardation, severe speech abnormality (usually absent), seizures, easily excitable personality, tongue thrusting, chewing/mouthing behaviors, stiff, uncoordinated gait, and stereotypic mannerisms such as unprovoked laughter and hand flapping. Angelman syndrome is caused by a deletion in the maternally derived chromosome 15s, paternal uniparental disomy for 15q, a deletion or mutation in the imprinting center of proximal 15q, or mutation in the ubiquitin-protein ligase gene (UBE3A) [Matsuura et al., 1997; Kishino et al., 1997].

Steffenberg et al. [1996] concluded that autism was frequent in Angelman syndrome. Among 98 6–13-year-olds with mental retardation and active epilepsy, four had clinical criteria for Angelman syndrome. Two had cytogenetic deletions confirmed by molecular studies and the other two had apparently normal chromosomes. All four had autistic disorder/childhood autism. In a similar population study of Prader-Willi syndrome, none of the 11 cases (5 deleted) had autism [Akefeldt et al., 1991].

Mosaic deletions of 15q11 or q13 deletion and mosaic unbalanced translocation 7;15 with 15q11q13 loss have been reported in hypomelanosis of Ito [Turleau et al., 1990; Pellegrino et al., 1995]. Hypomelanosis of Ito is characterized by streaks, swirls, and whorls of hypopigmentation in association with various neurologic and physical abnormalities. Akefeldt and Gillberg [1991] reported on three cases of hypomelanosis of Ito with autism and autistic-like conditions and calculated a prevalence of 0.5% for hypomelanosis of Ito in autism/atypical autism or Asperger syndrome. In 25 children with hypomelanosis of Ito reported by Zapella [1992], 10 had autism, 3 autistic-like manifestations, 1 with prior autistic behaviors, and 2 with “disintegrative psychosis.” In the same study, 6 of 32 children with autism/autistic behaviors attending a neuropsychiatric clinic had dermatologic findings of hypomelanosis of Ito. Two of sixty-eight mentally retarded children attending the same clinic during the same time period had hypomelanosis of Ito. An estimated 70% of cases of hypomelanosis of Ito have chromosome mosaicism but not of any consistent type, and it has been proposed that the condition is a nonspecific marker for mosaicism [Flannery, 1990; Donnai et al., 1988]. Pellegrino et al. [1995] proposed that mosaic deletion of genes involved in pigmentation, such as the p gene on proximal 15q, may be the cause of hypopigmentation in hypomelanosis of Ito.

It is the putative imprinting of genes in proximal 15q that provides a plausible biological basis for variability in clinical phenotype resulting from duplication or deletion of genes in this region. For genes expressed only if paternally derived, the duplication or deletion of genes from the mother is phenotypically neutral. The converse should be expected as well, i.e., for genes expressed only if derived from the mother, duplication or deletion of genes from the father is phenotypically neutral. However, maternal duplication or deletion of regions in which only maternally derived genes are expressed may consistently produce abnormal phenotype(s) on the basis of gene dosage. Maternally derived supernumerary large dicentric 15q, supernumerary 15q-, interstitial duplicated 15q, and deletion 15q would be functionally trisomic, disomic, disomic, and nullisomic, respectively, for genes in the region of duplication or deletion. Hence, none of these chromosome aberrations would lead to functional monosomy, the normal state. Paternally derived duplications and deletions in these regions would be phenotypically neutral. This interpretation is consistent with the association of autism with a maternally derived interstitial duplication of 15q found in our case 3. The phenotypically normal mother had the same duplication but it occurred on the chromosome 15 derived from her father. This same circumstance was shown in the family reported by Cook et al. [1997].

The leading candidates for genes from proximal 15q that may be linked to autism are the GABA_A receptors subunit genes and the ubiquitin-protein ligase gene UBE3A. Three GABA_A receptor subunit genes (GABRB3, GABRA5, and GABRG3) are located in...
proximal 15q in the region of duplication or deletion in the patients presented [Wagstaff et al. 1991; Phillips et al., 1993; Sinnett et al., 1993]. An imbalance in the availability of GABA receptor subunits may alter receptor activity and hence alter the activity of the brain's major inhibitory neurotransmitter [Olsen and Tobin, 1990]. Protein-truncating mutations of UBE3A have recently been shown to cause Angelman syndrome [Matsuura et al., 1997; Kishino et al., 1997]. Mutations in this gene may interfere with normal brain development or function by disrupting ubiquitin mediated proteolysis or by other as yet undefined mechanism(s).

In the first 100 patients enrolled in the S.C. Autism Project, 4 have duplication or deletion of the maternally derived chromosome 15. This constitutes the single most common causative factor thus far described in an unscreened series of patients with autism. A prevalence for autism among persons inheriting maternally derived duplications or deletions of chromosome 15q cannot yet be given; however, since formal testing for autism and parent of origin studies are not available in most of the literature cases.

In summary, duplications and deletions of the maternally derived chromosome 15 should be considered in all cases of autism, and particularly in those associated with mental retardation and seizures. Fluorescence in situ hybridization and molecular studies may be necessary to identify and delineate chromosome 15 abnormalities. Mosaicism for chromosome 15 abnormalities or uniparental disomy for chromosome 15 or regions of chromosome 15 may be considerations in the etiology of autism in some cases. While linkage between autism and genes on proximal 15q should be pursued, the causal heterogeneity found among individuals with autism currently frustrates this approach.

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