Increased Prevalence of ADHD in Turner Syndrome with No Evidence of Imprinting Effects

Heather F. Russell,1,2,3 PhD, Deean Wallis,1,3 PhD, Michèle M. M. Mazzocco,4 PhD, Thomas Moshang,5 MD, Elaine Zackai,1 MD, Andrew R. Zinn,6 MD, PhD, Judith L. Ross,7 MD, and Maximilian Muenke,1,3 MD

1Division of Human and Molecular Genetics, Department of Pediatrics, The Children’s Hospital of Philadelphia, 2Shriners Hospitals for Children-Philadelphia, 3Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, 4Kennedy Krieger Institute, Johns Hopkins University, School of Medicine, 5Division of Endocrinology, Department of Pediatrics, The Children’s Hospital of Philadelphia, 6McDermott Center for Human Growth and Development and Department of Internal Medicine, University of Texas Southwestern Medical School, and 7Department of Pediatrics, Thomas Jefferson University and duPont Hospital for Children

Background Turner syndrome (TS) results from the loss of part or all of one X chromosome in females. It can result in short stature, various dysmorphic findings, and difficulties with psychosocial adjustment. Girls with TS have previously been found to exhibit increased levels of hyperactivity and inattention. However, no studies have assessed whether individuals with TS meet strict (DSM-IV) criteria for attention-deficit/hyperactivity disorder (ADHD).

Objective We looked at the prevalence of ADHD in girls with TS and evaluated the contribution of imprinting on cognitive performance (IQ) and ADHD.

Methods We tested 50 girls with TS for ADHD, IQ, academic performance, and parental origin of the X chromosome.

Results We report an 18-fold increase in the prevalence of ADHD in girls with TS (24%) compared with girls in the general population (1.3%) (p < .01) and a 4.8 fold increase when compared with boys and girls in the general population (5%) (p < .05). In contrast to previous reports, our molecular studies in females with 45,X also showed no association between IQ scores and the parental origin of the intact X chromosome.

Conclusions We find an increased prevalence of ADHD in girls with TS but no evidence for imprinting effects for cognitive performance.

Key words ADHD; imprinting; social cognition; Turner syndrome; X-inactivation.
have been shown to demonstrate verbal abilities within the average range and specific deficits in visual–spatial and mathematics abilities (Buckley, 1971; Downey et al., 1991; Garron, 1977; Mazzocco, 2001; Money, 1963, 1964; Pennington et al., 1985; Rovet & Netley, 1982; Schucard, Schucard, Clopper, & Schachter, 1992; Shaffer, 1962). Although the degree of discrepancy between average verbal cognitive performance (VIQ) and performance cognitive performance (PIQ) varies between studies, girls with TS consistently demonstrate better verbal skills and higher VIQ than nonverbal skills and PIQ. TS is also associated with deficits in memory with decreases in both short- and long-term visual memory skills (Romans et al., 1998).

The Turner Syndrome Phenotype

With respect to executive functioning, girls with TS have been shown to have weak ability to plan, organize, monitor, and execute multiple-step problem solving (Romans, Roeltgen, Kushner, & Ross, 1997). More specifically, and from another group of researchers, it has been hypothesized that girls with TS have the ability to plan and organize steps toward a goal; however, their poor search strategies and speed of responding during verbal fluency tasks interfere with reaching the goal (Kirk, Mazzocco, & Kover, 2005; Temple et al., 1996).

In addition, girls with TS have been consistently shown to demonstrate weaknesses in spatial and perceptual skills, visual–motor integration, word fluency, left/right orientation, rapid automatized naming, cognitive flexibility, and working memory when compared with females in a VIQ-matched comparison group (Mazzocco, 2001; Romans et al., 1997).

The underlying etiology of the behavioral deficits associated with TS is unknown. However, some studies suggest that genomic imprinting may contribute to behavioral differences. Genomic imprinting involves the phenomenon of parent of origin gene expression, where the expression of a gene depends upon the parent who passed on the gene. Genomic imprinting plays a critical role in fetal growth and development.

In one study, females with a paternally derived X chromosome (45,Xp) were significantly better adjusted than females with a maternally derived X chromosome (45,Xm), showing superior verbal and higher-order executive function skills, alleged to be involved in mediating social interactions (Skuse et al., 1997). According to Skuse, Elgar, & Morris (1999), girls with 45,Xp also had higher VIQ scores and superior inhibitory abilities relative to girls with 45,Xm. These data implicate that a paternally expressed imprinted X locus is involved in what these authors describe as social cognition. In contrast, additional studies show that girls with 45,Xm have more accurate visual–spatial functioning than females with 45,Xp, as measured by both the copy and recall subtests of the Rey complex figure drawing task (Bishop et al., 2000). Together, these studies suggest that one or more imprinted genes on the X chromosome affect brain development.

Researchers have compared children with TS to children who have a diagnosis of a nonverbal learning disability (NLD) (Rovet, 1995; Williams, Richman, & Yarbrough, 1992). NLDs are characterized by specific weaknesses in visual perceptual skills, which in turn result in weaknesses in mathematics, nonverbal reasoning, and socialization. A hallmark feature of NLD is a significantly higher verbal than PIQ score. NLDs are most frequent in children who have disorders such as neurofibromatosis, head injuries, absence of brain tissue, and who have undergone radiation treatment for cancer (Rourke, 1985). The cognitive and behavioral characteristics of the TS population are largely consistent with Rourke’s description of NLD, as are a number of other genetic disorders including Williams syndrome and velocardiofacial syndrome.

Attention-Deficit/Hyperactivity Disorder

In addition to conforming with the NLD cognitive profile, the behavioral characteristics of girls with TS are similar to those of children with attention-deficit/hyperactivity disorder (ADHD). According to the DSM-IV (American Psychiatric Association, 1994), the main characteristic of ADHD is a “persistent pattern of inattention, hyperactivity, and/or impulsivity at levels more frequent and severe than observed in individuals at a comparable level of development.” Individuals with ADHD tend to have high rates of comorbidity with other psychiatric disorders such as oppositional defiant disorder, conduct disorder, mood disorders, and tic disorders (Palacio et al., 2004).

The causes of ADHD are unknown, but there is strong evidence for a genetic component. This evidence comes from various genetic studies including adoption, twin, and family studies, all of which have been conducted over the past 30 years. From these studies, we have learned that ADHD shows familiality (i.e., it runs in families) and heritability (i.e., it has a genetic component). In addition, this genetic contribution is seen regardless of whether ADHD is treated as a diagnostic category or a continuum of symptoms, or when using latent class analysis to define the phenotype.

ADHD has typically been described as a complex genetic trait with multiple genes playing a role in its
Increased Prevalence of ADHD in Turner Syndrome

Method

Participants

This study was approved by the Institutional Review Board of the Children’s Hospital of Philadelphia and the other participating institutions. Informed consent or assent was obtained, as appropriate, from all participants and their parents. Recruitment was conducted through the Endocrinology Departments at the Children’s Hospital of Philadelphia and duPont Hospital for Children in Wilmington, DE, with assistance from attending physicians and other departmental staff members. All children had been referred for long-term medical follow-up secondary to a diagnosis with TS as a result of chromosomal analysis. We enrolled 50 females, ages 7–16 years, with TS, and their parent(s). A total of 27 participants had a monosomic karyotype, and 23 had a mosaic or other karyotype. Mosaic and other karyotypes included partial deletions, ring chromosomes, 45,X; 46,XX, and 45,X; 46,XY. Cognitive and behavioral test results are presented for girls with a VIQ ≥ 70. Demographic characteristics are summarized in Table I.

Measures

Cognitive and Academic Measures

Overall cognitive functioning was assessed with either the Wechsler Intelligence Scale for Children, Revised (WISC-R) (Wechsler, 1974) or the Wechsler Intelligence Scale for Children, Third Edition (WISC-III) (Wechsler, 1991). For the purposes of comparison, all WISC-R values were adjusted to corresponding WISC-III values (Wechsler, 1991), in accordance with published guidelines. To adjust the WISC-R full-scale cognitive

| Table I. Frequencies of Nominally Characterized Variables in the Sample of Girls with Turner Syndrome |
|-----------------|-----------------|-----------------|
| Demographic variables | Frequency (n = 50) | Percent |
| Ethnicity         |                 |       |
| Caucasian         | 43              | 86 |
| African–American  | 3               | 6   |
| Asian–American    | 2               | 4   |
| Other             | 2               | 4   |
| Socioeconomic status |           |       |
| Lower class       | 0               | 0   |
| Lower middle class| 2               | 4   |
| Middle class      | 7               | 14  |
| Upper middle class| 22              | 44  |
| Upper class       | 19              | 38  |
| Currently receiving special education | 19 | 38 |
| History of grade retention | 10 | 20 |
| Current use of stimulant medication | 6 | 12 |
| Special education and medication | 4 | 8 |
performance (FSIQ) scores to be equivalent to the corresponding WISC-III FSIQ score, 5 points were subtracted. Furthermore, the WISC-R VIQ and PIQ scores were decreased by 2 and 7 points, respectively, to correspond with the appropriate WISC-III values. These differences in scores are expected and on par with those found with previous revisions of the Wechsler scales (Wechsler, 1991). Twenty-three subjects completed the WISC-R and 25 subjects completed the WISC-III. The measures were administered between 1998 and 2000. Academic scores were assessed with the Wechsler Individual Achievement Test (Wechsler, 1992).

Assessment of ADHD
Symptomatology of ADHD was assessed via telephone conversation using the diagnostic interview for children and adolescents (DICA) (Reich, 2000). The DICA is a semi-structured interview administered to the child’s parents by a trained clinician. Additional information regarding ADHD status was obtained from the Conners’ parent rating scales—revised (CPRS-R): long version and the Conners’ teacher rating scale—revised (CTRS-R): long version (Conners, 1997), which are well-established, standardized informant reports used to screen specifically for ADHD-related behaviors. Ratings from the two Conners’ forms are compared with age- and gender-specific normative data, whereas all remaining variables are age-referenced but not specific to girls.

The following criteria were used to diagnose children from the ages of 7–16 years as having ADHD:

1. A percentile of >90 on the DSM-IV: Inattentive subscale and/or a percentile >90 on the DSM-IV hyperactive/impulsive subscale from the Conners’ ratings scales—revised, parent version.
2. A percentile of >90 on the DSM-IV: Inattentive subscale and/or a percentile >90 on the hyperactive/impulsive subscale from the Conners’ ratings scales—revised, teacher version.
3. A positive endorsement of at least 6 of 9 of the inattentive and/or the hyperactive/impulsive symptoms on the DICA.
4. The behavioral symptoms must have been present before the age of 7 years on the DICA.
5. The behavioral symptoms must have been present across settings on the DICA.
6. The behavioral symptoms must interfere with the ability to function at a developmentally appropriate level on the DICA.
7. A VIQ score must be higher than 70 on the WISC-III.

All seven criteria must have been met to make a diagnosis of ADHD.

Socioeconomic Status
Socioeconomic status (SES) was assessed using the Socio-economic Status Questionnaire (Hollingshead, 1975), which is completed by the parent and which has been used in numerous studies.

Statistical Analysis
Chi-square analysis was used to determine whether there were differences in rates of ADHD in girls with TS vs. girls in the general population. We used a Fisher’s exact test to look at possible parent of origin effects on ADHD status, special education needs, stimulant drug usage, and grade retention. Finally, because of our small sample size (n = 50), we utilized the Kruskal–Wallis U test, run by Statistica software to compare the cognitive performances between groups with paternal vs. maternal parent of origin. A paired t-test was utilized to demonstrate that VIQ was statistically higher than PIQ in girls with TS.

Determination of Parent of Origin
The parent of origin of the intact X chromosome was determined for each participant by comparing the alleles in the children with those of their parents for many highly heterogeneous markers along the entire length of the X chromosome. These markers include: DXS1060, DXS8051, DXS987, DXS1226, DXS991, DXS1217, DXS1001, DXS1047, DXS8043, and DXS1073.

Results
Demographic Characteristics
Specific demographic data for all girls with TS (n = 50) were collected to provide a description of the average respondent, which we compared with data reported for girls in the general population with respect to these variables (Table I). The average age of our participants with TS was 12 years [standard deviation (SD) = 2.7 years]. The SES of the participants’ families was shifted toward the high end of the scale as the “upper-middle class” and “upper class” are overrepresented in this sample.

Table II is a summary of the means and SDs of scores obtained by girls with TS on the WISC-III and Wechsler Individual Achievement Test (WIAT). These data show that girls with TS have average FSIQ and VIQ scores, and low average PIQ scores, on the WISC-III. Analysis of these data yields a significantly higher VIQ than PIQ in girls with TS (p < .000001 based on a paired t-test), consistent with the literature on TS. These data were also compared as a function of parent of origin. Girls
Increased Prevalence of ADHD in Turner Syndrome

With a maternally derived X chromosome (X_M, n = 20) had comparable scores to girls with a paternally derived X chromosome (X_P, n = 7).

The same pattern was observed for WIAT scores: girls with either a maternally or paternally derived X chromosome had somewhat higher scores in “reading” than in “math,” consistent with the notion that math-learning disability occurs more frequently in girls with TS than in the general population (Mazzocco, 2001). Moreover, although group means for “reading” and “math” scores were within the average range for both groups of participants, the within-group difference between these scores was comparable (about 8 points) for girls with maternally or paternally derived X chromosomes. Of the girls who received a score of less than 80 on either the reading task or the math task, only 2 of 11 (18%) were diagnosed with ADHD.

Table III is a summary of the frequency of clinically significant behavioral ratings for girls with TS from the CPRS-R and CTRS-R. (Clinically significant scores are those at the 90th percentile or higher.) Two CTRS-R ratings, specifically the hyperactivity/impulsivity and inattention scales, fell within the average range, based on age-referenced data for girls in the general population. The hyperactivity/impulsivity and inattention scales from the CPRS-R, and the social problems subscale from both the CTRS-R and the CPRS-R, fell within the high-average range, indicating an increased level of problem behaviors in girls with TS, although this increase did not reach levels of clinical significance. Of the girls who earned scores above the 90% on the parent social problems scale of the Conners’ rating scale, 6 of 12 (50%) were diagnosed with ADHD and 11 of 38 (29%) were not diagnosed with ADHD. Of the girls who earned scores above the 90% on the teacher social problems scale of the Conners’ rating scale, 5 of 12 (42%) were diagnosed with ADHD and 10 of 38 (26%) were not diagnosed with ADHD.

We found a 24% prevalence of ADHD in this sample of girls with TS (Table IV), which is high compared to either the 1.3% prevalence rate in girls in the general population (Biederman et al., 1999) and the 5% prevalence rate of ADHD reported for all school-age children (American Psychiatric Association, 1994). Among the girls with TS who participated in this study, the frequency of each subtype of ADHD is as follows: (a) 25% combined type, (b) 33.3% predominantly inattentive

Table II. Group Means and Standard Deviations (SDs) from Cognitive Testing of the Girls with Turner Syndrome

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Overall [Mean (SD)] (n = 50)</th>
<th>X_P [Mean (SD)] (n = 7)</th>
<th>X_M [Mean (SD)] (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WISC-III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSIQ</td>
<td>92.74 (13.46)</td>
<td>90.29 (15.43)</td>
<td>92.9 (13.37)</td>
</tr>
<tr>
<td>VIQ</td>
<td>101.08 (11.87)</td>
<td>97.0 (13.25)</td>
<td>102.2 (11.24)</td>
</tr>
<tr>
<td>PIQ</td>
<td>84.9 (14.63)</td>
<td>84.71 (15.76)</td>
<td>84.5 (15.05)</td>
</tr>
<tr>
<td>VIQ–PIQ</td>
<td>15.98 (10.09)</td>
<td>12.29 (7.70)</td>
<td>17.7 (10.48)</td>
</tr>
<tr>
<td>WIAT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic reading</td>
<td>101.58 (13.48)</td>
<td>96.43 (13.81)</td>
<td>103.55 (15.41)</td>
</tr>
<tr>
<td>Numerical operations</td>
<td>92.22 (14.43)</td>
<td>88.43 (17.16)</td>
<td>95.65 (13.55)</td>
</tr>
</tbody>
</table>

FSIQ, full-scale cognitive function; PIQ, performance cognitive function; VIQ, verbal cognitive function; WISC-III, Wechsler Intelligence Scale for Children, Revised; X_M, maternally derived X chromosome; X_P, paternally derived X chromosome.

Table III. The Frequency of Girls with Turner Syndrome for Select Scores* from the Conners’ Parent and Teacher Behavioral Ratings

<table>
<thead>
<tr>
<th>Instrument</th>
<th>X_P (n = 7)</th>
<th>X_M (n = 20)</th>
<th>Mosaic (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPRS-R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity/impulsivity</td>
<td>2</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Inattention</td>
<td>1</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Social problems</td>
<td>2</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>CTRS-R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity/impulsivity</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Inattention</td>
<td>2</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Social problems</td>
<td>1</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

CPRS-R. Conners’ parent rating scales—revised; CTRS-R. Conners’ parent rating scales—revised; X_M, maternally derived X chromosome; X_P, paternally derived X chromosome.

*Reported only scores for which significant effects emerged.

Table IV. The Frequencies of ADHD Subtypes According to Ratings obtained on the Parent and Teacher Versions of the Conners’ Rating Scales.

<table>
<thead>
<tr>
<th>ADHD status</th>
<th>Frequency (n = 50)</th>
<th>% of total sample</th>
<th>% of ADHD sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>No diagnosis</td>
<td>38</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>ADHD-total</td>
<td>12</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Combined type</td>
<td>3</td>
<td>6</td>
<td>25.0</td>
</tr>
<tr>
<td>Inattentive type</td>
<td>4</td>
<td>8</td>
<td>33.3</td>
</tr>
<tr>
<td>Hyperactive/impulsive type</td>
<td>5</td>
<td>10</td>
<td>41.7</td>
</tr>
</tbody>
</table>

ADHD, attention-deficit/hyperactivity disorder.
Discussion

Turner Syndrome and Attention-Deficit/Hyperactivity Disorder

The findings from the present study are a replication and expansion of earlier research on the TS behavioral phenotype. Our findings are a replication of earlier reports that behavioral questionnaires reflect a heightened level of hyperactivity and inattention in girls with TS (McCauley, Feuillan, Kushner, & Ross, 2001). In addition, we documented a high incidence of ADHD in girls with TS (24%), based on both parent and teacher reports. This is in contrast to the results from epidemiological studies of ADHD, from which prevalence rates for girls with ADHD range from 0.3 to 3.5% (Cohen et al., 1993; Lewinsohn, Hops, Robers, Seeley, & Andrews, 1993; McGee, Williams, & Freehan, 1992; Offord et al., 1987; Robinson, Sclar, Skaer, & Galin, 1999; Shen, Wang, & Yan, 1985; Woolraich, Hanna, Pinnoch, Baumgaertel, & Brown, 1996). Moreover, the results from our study indicate that girls with TS are more likely to have the Predominantly hyperactive/impulsive subtype of ADHD, relative to girls from the general population, who are in turn more likely to have the combined subtype. This finding is especially interesting as the prevalence of the predominately hyperactive/impulsive subtype is extremely low and some researchers even doubt its existence.

There are several possible explanations for the higher rate of this relatively rare subtype of ADHD, but these possibilities must be considered in the context that only 10% of the study participants with TS met the criteria for the hyperactivity/impulsive ADHD subtype. Possible explanations range from the haploinsufficiency of X chromosome genes that result TS to the frequently occurring learning and cognitive deficits associated with TS, such as executive dysfunction and processing speed difficulties (Kirk et al., 2005), that may predispose a child to this subtype of ADHD. Future studies of TS could shed light on this association, which may inform the broader question concerning influences on the manifestation of ADHD in general.

Turner Syndrome and Academic Performance

In addition to replicating findings concerning ADHD, in the present study, we replicated the finding that girls with TS demonstrate dysfunction in school-related behaviors. In our study, 38% of girls with TS were receiving special education services, in contrast to 2% in the general U.S. population (Biederman et al., 1999). This is relatively comparable with the frequency found by Skuse, who reported that 33% of girls with TS.
were in special education classes in the United Kingdom, despite the fact that the United States and United Kingdom have different criteria for inclusion in special education. Skuse reported that girls with X<sup>M</sup> needed extra help at school, whereas girls with X<sup>F</sup> functioned relatively well in school (Skuse et al., 1999). However, our findings did not show this disparity; we found that, of the 20 participants with X<sup>M</sup>, 8 (40%) were receiving special education, and 3 of the 7 participants with X<sup>F</sup> (43%) also received special education. The rate of grade retention in the girls with TS was reported to be 16% in our study vs. 2% in the general U.S. population (Biederman et al., 1999). In a large sample of girls with ADHD, the rates of students receiving special education services and those who had repeated a grade were 18 and 19%, respectively (Biederman et al., 1999). In comparison with girls with ADHD from the Biederman study, the girls with TS who participated in the present study had a similar level of grade retention and an increased need for special education services. This could be interpreted to mean that the girls with TS had more learning difficulties than the girls with only ADHD, perhaps associated with the executive function and visual–spatial difficulties reflected in the significantly lower PIQ and lower mathematics scores often reported for this population (Kirk et al., 2005; Mazzocco, 2001; Rovet & Ireland, 1994). However, these learning difficulties are not severe enough to require a greater amount of grade retention than other girls with ADHD alone, particularly in view of the intact reading and verbal skills observed in girls with TS.

**Turner Syndrome and Medication Use**

In view of the higher incidence of ADHD, it is important to consider psychopharmacological intervention that girls with TS may be receiving. Among the participants in the present study, who had both TS and ADHD, 42% were reported as “currently using stimulant medication.” The same statistic in a school-based sample of girls diagnosed with ADHD was 72%, whereas in a control group (i.e., girls without ADHD) in this same study, the rate was 1% (Biederman et al., 1999). The relatively lower rate of stimulant medication use in girls with TS and ADHD may be because of a lack of awareness of the secondary diagnosis of ADHD in this special population. It is possible that, if parents and physicians were made more aware of the significant increase in ADHD in girls with TS, stimulant medication in combination with behavioral modification therapy could be prescribed for those who meet the strict criteria for ADHD, if warranted. Physicians, teachers, and parents may be attributing the academic and social problems present to the TS without considering possible comorbidity of ADHD, which could respond to therapeutic intervention. Therefore, the quality of life for these previously undiagnosed girls and their families could be improved. However, it is also important to note that past stimulant use was not measured in the present study, and that therefore it is possible that more than 42% of the sample had been on stimulant medication at some time.

**No Evidence of Parent of Origin Effects**

In contrast to previously published studies, our findings indicate that there is no difference in cognitive performance in girls with TS as a function of whether the single or intact X chromosome present in the girl’s karyotype is inherited from her mother or father. Because our IQ data is not in agreement with results showing an imprinting effect on IQ (Skuse et al., 1997), we assessed an additional 39 females with 45,X for cognitive performance and parental origin of the X chromosome (Mazzocco, M. M., unpublished data). When this second cohort of 39 was combined with the original cohort of 50 (n = 89), the results persisted. That is, females with TS had significantly higher VIQ than PIQ scores (p = .000001 based on a paired t-test). These data did not differ across females with a maternally derived X chromosome vs. females with a paternally derived X chromosome. Therefore, the cognitive profile in these girls could be a result of factors other than imprinting such as haploinsufficiency (Skuse et al., 1997). The haploinsufficiency model explains the abnormal TS phenotype as the result of insufficient dosage of gene product from the X chromosome. Although not statistically significant because of such a small number of participants, our studies also indicate a trend for the 12 girls with TS and ADHD to be more likely to have a 45,X karyotype (n = 8, 67%) than to have a mosaic karyotype (n = 4, 33%). In addition, of those 8 girls with 45,X and ADHD, many had an X chromosome that was maternally derived (n = 7), and only one had a paternally derived X chromosome. This difference was not statistically significant relative to the general 69% prevalence of X<sup>M</sup> in girls with TS overall. A larger sample size may indicate otherwise.

How can we account for the previous findings that imprinting is involved in cognitive performance, when we see no such effect? Some of the effects reported by others were small in magnitude; a larger sample size in all studies could result in greater power. Familial covariance may also explain the differences seen by Skuse et al. (Haverkamp et al., 2000). The measures of social cognition used by Skuse and colleagues included a nonstandardized parent report instrument that has not been
validated. Moreover, the same instrument was administered for individuals of a wide age range of 6–16 years. Although the Conners’, an instrument used in the present study, is also used with children from a wide age range, the resulting scores are standardized and age-referenced.

**X Chromosome Genes and the TS Behavioral Phenotype**

Although the increased incidence of ADHD in girls with TS may suggest an ADHD locus on the X chromosome, we believe that it is more likely that the deletion of all or part of the X chromosome results in a subtle, undetectable alteration in brain development, structure, or function that eventually may manifest itself as ADHD, even if the underlying causes differ from the causes of ADHD in the general population. Although some researchers may argue that it is the haploinsufficiency of an ADHD locus in girls with TS that results in their susceptibility to ADHD, this argument is weakened by the fact that boys and men with Klinefelter’s syndrome (who have a 47,XXY karyotype) also have an increase in attentional difficulties and executive dysfunction (Boone et al., 2001; Samango-Sprouse & Law, 2001). Interestingly, ADHD is a feature in many genetic disorders (for review, see Acosta et al., 2004). For example, in poorly treated phenylketonuria, ketone levels have been associated with brain dysfunction and ADHD. In addition, mutations in the sonic hedgehog gene (SHH) frequently result in holoprosencephaly (HPE), a common developmental defect of the forebrain and face. However, a given mutation has been associated with both severe HPE in some individuals and ADHD with normal IQ and brain phenotype in different members of the same family (Heussler, Suri, Young, & Muenke, 2002). Furthermore, specific anatomic brain abnormalities and/or volumetric differences of specific brain regions have been linked to ADHD (Castellanos et al., 2002, 2003). These examples support the idea that slight alterations in brain development, structure, or function due to a variety of different causes may lead to ADHD.

**Limitations and Clinical Implications**

There are a number of limitations to this study. First, the sample was small, predominantly Caucasian, skewed toward higher SES, and almost exclusively recruited through endocrinology outpatient clinics at large medical centers. Therefore, we cannot generalize the findings of this study to all girls with TS. Second, there was no control group included in this study, although our data were compared with values found in the published literature that are based on widely used and well-validated instruments. Third, we based the diagnosis of ADHD largely on behavioral rating scales completed by the child’s parent(s) and teacher. These measures are susceptible to bias on the part of the respondent, although they are the best diagnostic criteria available, and are commonly used to assess ADHD status in children. Fourth, for the girls who were administered the WISC-R, scores had to be adjusted to be compatible with the scores from the WISC-III. Lastly, the SD for the difference between the VIQ and PIQ scores of the girls was large (average = 15.2, SD = 10.6). However, large variability within the TS phenotype has been reported by others (Pennington et al., 1985), and thus, our sample appears representative of girls from the TS population.

Despite these limitations, our study makes important contributions to the field. First, we replicated earlier findings, suggesting that the levels of attention difficulties and hyperactivity behaviors are elevated in girls with TS, relative to girls in the general population. Moreover, we specifically established the increased prevalence of ADHD in girls with TS, indicating the rate of comorbid TS and ADHD that occurs in roughly one quarter of females with TS. This prevalence figure was comparable among younger and older females with TS, suggesting that ADHD is not only more frequent in girls with TS but also a stable, persistent condition.

We were not able to replicate findings indicating “parent of origin” effects. Earlier work citing such effects was based on nonstandardized behavior surveys for participants from a wide age range. Such findings need to be replicated, and specified, if parent of origin effects are to be accepted. Our failure to replicate these earlier reports sheds doubt on the extent to which parent of origin effects in TS can be generalized or applied to the TS phenotype.

In addition, clinical geneticists will be better able to address the possible future characteristics of an infant with TS, although based on our study there is presently no prognostic value to determining the parental origin of the single X chromosome in 45,X girls. Parents and healthcare providers may want to carefully monitor girls with TS for increased amounts of inattention and hyperactivity/impulsivity. If these symptoms lead to significant impairment, treatment (medically and/or behaviorally) may be considered. Teachers will be better able to address the needs of their students with TS both educationally and behaviorally. Finally, parents will be better able to address the needs of their daughters with TS.
Acknowledgments

We thank the participants in the study and their families. We thank Mauricio Arcos-Burgos for statistical advice. This work was supported in part by the Division of Intramural Research, National Human Genome Research Institute, National Institutes of Health, Department of Health and Human Services, and the following NIH grants NS32531, NS32532, and NS42777 to J.L.R.; NS35554 to A.R.Z.; and NICHD 34061 to M.M.M. M.M.M. received additional support from NS35554.

Received July 15, 2005; revision revised October 31, 2005, February 1, 2006; accepted February 9, 2006

References


increased prevalence of ADHD in Turner Syndrome

955


