10-2007

Autistic Spectrum Disorders in Velo-cardio Facial Syndrome (22q11.2 Deletion)

Kevin M. Antshel
SUNY Upstate Medical University

Alka Aneja
SUNY Upstate Medical University

Leslie A. Strunge

Jena Peebles
SUNY Upstate Medical University

Wanda Fremont
SUNY Upstate Medical University

See next page for additional authors

Recommended Citation

Antshel, K. M., Aneja, A., Strunge L. A., Peebles, J., Fremont, W., Stallone, K., AbdulSabur, N. ... Kates, W. R. (2007). Autistic spectrum disorders in velo-cardio facial syndrome (22q11.2 deletion). *Journal of Autism and Developmental Disorders, 37*(9), 1776–1786.

Autistic Spectrum Disorders in Velo-cardio Facial Syndrome (22q11.2 Deletion)

Article *in* Journal of Autism and Developmental Disorders · November 2007

DOI: 10.1007/s10803-006-0308-6 · Source: PubMed

10 authors, including:

Kevin M. Antshel
Syracuse University
161 PUBLICATIONS **4,523** CITATIONS
SEE PROFILE

Wanda Fremont
State University of New York Upstate Medical University
70 PUBLICATIONS **2,147** CITATIONS
SEE PROFILE

Robert Shprintzen
The Virtual Center for Velo-Cardio-Facial Syndrome
206 PUBLICATIONS **11,906** CITATIONS
SEE PROFILE

Wendy Kates
State University of New York Upstate Medical University
150 PUBLICATIONS **4,671** CITATIONS
SEE PROFILE

J Autism Dev Disord (2007) 37:1776–1786
DOI 10.1007/s10803-006-0308-6

ORIGINAL PAPER

Autistic Spectrum Disorders in Velo-cardio Facial Syndrome (22q11.2 Deletion)

Kevin M. Antshel · Alka Aneja · Leslie Strunge · Jena Peebles · Wanda P. Fremont · Kimberly Stallone · Nuria AbdulSabur · Anne Marie Higgins · Robert J. Shprintzen · Wendy R. Kates

Published online: 19 December 2006

Abstract The extent to which the phenotype of children comorbid for velocardiofacial syndrome (VCFS) and autism spectrum disorders (ASD) differs from that of VCFS-only has not been studied. The sample consisted of 41 children (20 females) with VCFS, ranging in age from 6.5 years to 15.8 years. Eight children with VCFS met formal DSM-IV diagnostic criteria for autism based upon the ADI-R. These eight plus an additional nine participants met diagnostic criteria for an autistic spectrum disorder (VCFS + ASD). Ninety-four percent of the children with VCFS + ASD had a co-occurring psychiatric disorder while 60% of children with VCFS had a psychiatric disorder. Children with VCFS + ASD had larger right amygdala volumes. All other neuroanatomic regions of interest were statistically similar between the two groups.

Keywords Velocardiofacial syndrome · 22q11.2 deletion · Autism spectrum disorder · Amygdala

K. M. Antshel (✉) · A. Aneja · J. Peebles · W. P. Fremont · K. Stallone · N. AbdulSabur · A. M. Higgins · R. J. Shprintzen · W. R. Kates
State University of New York - Upstate Medical University, Syracuse, NY, USA
e-mail: AntshelK@upstate.edu

L. Strunge
Kennedy Krieger Institute, Baltimore, MD, USA

W. R. Kates
Johns Hopkins University School of Medicine, Baltimore, MD, USA

Introduction

Velocardiofacial syndrome (VCFS) is a microdeletion disorder of chromosome 22q11.2 that is associated with well-characterized congenital heart malformations, palatal abnormalities and a characteristic facial appearance (Shprintzen, 2000). Learning disorders, intellectual delay, and speech delay are ubiquitous (Gerdes et al., 1999; Glaser et al., 2002; Shprintzen, 2000; Swillen, Devriendt et al., 1999; Swillen, Vandeputte et al., 1999). The mean IQ of these children is in the Borderline range of mental retardation (Swillen, Vandeputte et al., 1999). Their psychiatric phenotype during childhood can include ADHD, anxiety disorders and depression (Antshel et al., 2006; Feinstein, Eliez, Blasey, & Reiss, 2002). As youth with VCFS approach adulthood, they are at high risk for developing schizophrenia (Chow, Bassett, & Weksberg, 1994; Murphy, Jones, & Owen, 1999) or bipolar disorder (Papolos et al., 1996).

VCFS and Autistic Spectrum Disorders

In addition to these psychiatric vulnerabilities, others have reported a relatively high incidence of autism spectrum disorders (ASD) in VCFS (Chudley, Gutierrez, Jocelyn, & Chodirker, 1998; Fine et al., 2005; Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2001; Roubertie et al., 2001; Vorstman, Morcus et al., 2006). This is probably not surprising, since it is estimated that 10% of autism cases are part of genetic neuropathology syndromes (Polleux & Lauder, 2004). Due to the complex genetic etiology of ASD (for review, see (Polleux & Lauder, 2004), there is a growing interest in the association between the neurobehavioral phenotype of autism and co-existent medical conditions

(Gillberg, 1992), such as Fragile X Syndrome (Goodlin-Jones, Tassone, Gane, & Hagerman, 2004; Kau et al., 2004), Down Syndrome (Capone, Grados, Kaufmann, Bernad-Ripoll, & Jewell, 2005), and tuberous sclerosis (Curatolo, Porfirio, Manzi, & Seri, 2004). However, the extent to which the neuroanatomic, cognitive and behavioral phenotype of children comorbid for VCFS and ASD differs from that of VCFS-only has not been investigated. Accordingly, this study aims to extend our current understanding of a sizeable subset of VCFS-affected children by specifying the neuroanatomic, cognitive and psychiatric correlates of ASD in children with VCFS.

ASD and VCFS Neuroanatomy

Neuroanatomical deficits in children with idiopathic autism include the cortex, limbic structures, cerebellum and brainstem (for review, see (Brambilla et al., 2003). Key anatomical substrates identified by functional magnetic resonance imaging (fMRI) in idiopathic autism are the amygdala (Critchley et al., 2000; Howard et al., 2000; Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004), superior temporal sulcus (Boddaert et al., 2004), and fusiform gyrus (Critchley et al., 2000; Hadjikhani et al., 2004; Schultz et al., 2000). Structural MRI studies are discordant in regard to the specific amygdalar abnormality, however most studies demonstrate enlarged amygdalar (Howard et al., 2000; Sparks et al., 2002) and hippocampal volumes (Sparks et al., 2002). Other volumetric studies show smaller volumes of the frontal lobe (Kates et al., 2004, 1998) and cerebellum (Courchesne et al., 2001; Kates et al., 1998). Total brain volumes are enlarged in children with ASD, however there is some evidence that brain growth slows throughout childhood, eventually resulting in relatively smaller volumes in adolescence (Courchesne et al., 2001).

Similar to children with autism, children with VCFS have smaller cerebellar volumes (Eliez et al., 2001; van Amelsvoort et al., 2004) and larger amygdala volumes (Kates et al., 2006). Although several studies report that the total frontal lobe is relatively preserved in VCFS (Eliez et al., 2000; Kates et al., 2001), a recent preliminary report has suggested that prefrontal subregions may be reduced (Kates et al., 2005). The overlapping neuroanatomic phenotypes in VCFS and autism raise the question of whether neuroanatomic variations in VCFS predict autism comorbidity. For example, we would expect that relative to children with VCFS-only, children with comorbid VCFS and ASD (VCFS + ASD) would exhibit larger volumes of the amygdala yet a smaller prefrontal cortex and cerebellum.

Cognition and Behavior in ASD and VCFS

Individuals with VCFS exhibit deficits in executive function (Bearden et al., 2004), which many investigators consider a core deficit in autism (Hill, 2004; Ozonoff, Pennington, & Rogers, 1991; Pennington & Ozonoff, 1996). Executive functions are necessary for control and execution of complex behaviors, such as planning, working memory, set maintenance and shifting, and inhibition of prepotent processes. These specific executive functions have been investigated in autism. Children with autism show impairments in planning (Joseph, McGrath, & Tager-Flusberg, 2005; Ozonoff & Jensen, 1999), mental flexibility (Ozonoff & Jensen, 1999), and working memory (Joseph et al., 2005), yet normal response inhibition (Ozonoff & Jensen, 1999). On the other hand, classic working memory deficits in children with autism has been an area of controversy. Although some studies have failed to demonstrate working memory impairments (Ozonoff & Strayer, 2001), others have reported deficits (Bennetto, Pennington, & Rogers, 1996; Joseph et al., 2005).

Children with autism display impaired communication, language, and reciprocal social skills along with stereotypic, repetitive behaviors (American Psychiatric Association, 1994). Atypical behaviors emerge within the first year of life, characterized by marked passivity, decreased activity, extreme distress reactions, tendency to fixate on objects in the environment, and decreased social interest and affect and imitation (Zwaigenbaum et al., 2005). Even high-functioning children with autism show social impairments, such as an inability to recognize emotions and socially inappropriate behavior (Walker et al., 2004). In addition, children with autism are likely to develop comorbid anxiety and mood disorders (Bradley, Summers, Wood, & Bryson, 2004).

Children with VCFS have a similarly heightened predisposition to psychopathology and have difficult temperaments (Antshel et al., in press; Gerdes et al., 1999; Swillen et al., 1997). Other shared features between ASD and VCFS include language delays, although the nature of language deficit associated with VCFS is generally less profound (Glaser et al., 2002) than language deficits observed in ASD.

Importance of Current Project

Within the last ten years, there has been an increasing recognition of the prevalence of autism in genetic syndromes, especially single gene disorders and chromosomal abnormalities such as Fragile X and tuberous

sclerosis complex (Cohen et al., 2005). It is hoped that by studying a well-defined medical condition, like VCFS, that is associated with autism, in which we have identified the pathogenesis (e.g., 22q11.2 deletion), we may be able to gain more knowledge about autism in the general population. Akin to the use of animal models, which provide simple systems to study complex disorders, VCFS and other genetic syndromes may provide us with a human model of autism. The goal would not be to explain all autism, but rather to further the research of autism in the general population if these genetic disorders are a suitable model for aspects of autism's heterogeneous etiology and pathophysiology (Wing, 1997).

The aim of this study is to characterize the cognitive, behavioral and neuroanatomical phenotype of a cohort of children with VCFS and autism in order to improve diagnostic accuracy and possibly lead to increased recognition of ASD in VCFS. In this report, children with VCFS + ASD are compared to children with VCFS—only. Our hypotheses are as follows:

1. Children with VCFS + ASD will have significantly more communication and social difficulties as well as stereotyped/repetitive behaviors than children with VCFS without ASD.
2. Relative to children with VCFS-only, children with VCFS + ASD will exhibit lower scores on executive function tests of working memory and cognitive flexibility, yet not response inhibition.
3. Children with VCFS + ASD will exhibit larger volumes of the amygdala and smaller volumes of the prefrontal cortex and the cerebellum.

Methods

Participants

The sample consisted of 41 children (20 females) with VCFS, ranging in age from 6.5 years to 15.8 years (Mean = 10.6; *SD* = 2.4). Children with VCFS were recruited from the Center for the Diagnosis, Treatment, and Study of VCFS at SUNY-Upstate Medical University. The children described in this report were recruited for a larger study of risk factors for psychosis in VCFS. All children had a fluorescence in situ hybridization (FISH)-confirmed deletion in the q11.2 region of chromosome 22. We excluded any child with an identifiable neurological condition in addition to VCFS (e.g., traumatic brain injury, seizure disorder, birth weight below 2,500 gm as reported by parent) that is known to affect cognitive or neuropsychiatric function. Seizures, especially hypocalcaemic seizures, are quite common in VCFS (Shprintzen et al., 2005); seizure disorders, however, are less common (< 7%) in VCFS (Kao et al., 2004). Therefore, children with a history of seizures, yet not prescribed anti-epileptic medications, were included in our sample. However, four children with VCFS who were medicated for a seizure disorder were excluded from participating in the larger study.

ASD Diagnosis

Autism Diagnostic Inventory-Revised (ADI-R)

Lord, Rutter, & Le Couteur, (1994). Autism spectrum disorder was assessed by the ADI-R, a standardized semi-structured interview conducted with the child's caregiver (usually the mother). The ADI-R provides scores for the three domains in which children with ASD exhibit deficits: Reciprocal Social Interaction, Communication Impairment, and Repetitive Behaviors and Stereotyped Patterns. In order to obtain a diagnosis of autism, the child must meet threshold criteria in all three domains, and developmental problems must have occurred prior to the age of three years.

We utilized criteria that have been specified for children who exhibit significant ASD behaviors yet who do not necessarily meet the full criteria for autism. Following the criteria outlined by Kaufmann (Kaufmann et al., 2004), our ASD group included children who met the criteria for Reciprocal Social Interaction and either Communication Impairment or Repetitive Behaviors and Stereotyped Patterns.

The ADI-R was telephone administered by a clinician (L.S.) who was trained in the reliable administration of the instrument. At the time of the research assessment, all families were told that a staff member would contact them to administer the ADI-R. However, due to scheduling difficulties, only 45% of the families participated in the ADI-R interview. Participants whose parents completed the ADI-R data were younger, F (1, 91) = 12.70, P < .001, η^2 = 0.12, had higher IQ scores, F (1, 91) = 12.12, P < .001, η^2 = 0.12, and were from a higher socioeconomic status, F (1, 91) = 4.43, P = .039, η^2 = 0.06 than those who did not complete the ADI-R. Despite differing on these background and intellectual variables, those participants who completed an ADI-R and those who did not do not differ on any cognitive, behavioral or neuroanatomical variables. Only those participants whose parents completed the ADI-R interview were included in the analyses.

Psychiatric, Cognitive and Behavioral Measures

All of our measures were chosen based upon our a priori hypotheses. Participants in the study received:

Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)

The K-SADS-PL (Kaufman et al., 1997) is a semi-structured diagnostic interview schedule that provides DSM-IV (APA, 1994) psychiatric diagnoses, based on interviews with the child's primary caregiver (almost always his/her mother) and the child. A child psychiatrist or clinical child psychologist administered the KSADS. Interrater reliability, based on 12 interviews and was calculated with the kappa coefficient, was .91.

Young Mania Rating Scale-Parent Version, (Gracious, Youngstrom, Findling, & Calabrese, 2002)

This is 11-item, parent-rated scale consisting of items that describe symptoms associated with mania. Comparisons between parent ratings on this scale and clinical ratings based on standard psychiatric interviews indicate that the scale has adequate discriminative validity (Youngstrom, Danielson, Findling, Gracious, & Calabrese, 2002).

Child Behavior Checklist (CBCL)

Parents were asked to complete the CBCL (Achenbach, 1991), a widely used and highly reliable scale consisting of 113 items. Only *T*-scores for the Social Problems Scale were analyzed for this report.

Vineland Adaptive Behavior Scales (Sparrow, Balla, & Cichetti, 1983)

This inventory, which was administered by a clinician to the child's parent, assesses functioning within the domains of communication, daily living skills and socialization. Standard scores (Mean = 100; *SD* = 15) for the socialization scale were analyzed for this report.

Behavior Assessment Scale for Children-Parent Rating Scale (BASC)

The BASC (Reynolds & Kamphaus, 1992) is a parent rating scale that assesses a wide range of distinctive dimensions, including internalizing and externalizing behaviors, inattention, hyperactivity, social behavior and adaptive behavior skills. We used the *T*-score for Atypicality for this report.

Wechsler Intelligence Scale for Children— 3rd edition (WISC-III)

The WISC-III (Wechsler, 1991) is comprised of 13 subtests. The current analyses only utilized the general measure of intellectual functioning, the Full Scale IQ (FSIQ).

Complete WISC-III (Antshel, AbdulSabur, Roizen, Fremont, & Kates, 2005) and K-SADS-PL (Antshel et al., 2006) data for the entire sample of children in this study have been previously reported.

Visual Span Test

This test (Davis, 1998) assesses working memory and is conceptually similar to the Corsi Block Design (Milner, 1971). It consists of an irregular array of squares displayed on the screen; a sequence of squares is illuminated briefly and the child must reproduce these sequences of increasing length. Scores for forward and backward memory span were obtained.

Wisconsin Card Sorting Test (WCST)

The WCST (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) is a classic test of cognitive flexibility. We used the standard scores for perseverative and nonperseverative errors for the current set of analyses.

Gordon Diagnostic System

This continuous performance task (Gordon, McClure, & Aylward, 1989) assesses sustained attention, requires the child to respond (press a button) each time a "9" follows a "1" on a computer screen. Our primary outcome variables from the continuous performance task were errors of omission (the child failed to respond when he/she needed to respond) and errors of commission (the child responded when he/she should not have responded).

MRI Imaging Acquisition and Measurement

Magnetic resonance imaging scans were acquired in the axial plane on a 1.5 T Philips Gyroscan scanner (Philips Medical Systems, Best, The Netherlands), utilizing the following T-1 weighted inversion recovery 3-D pulse sequence: TE = 4.6; TR = 20; 2 repetitions;

matrix size 256 × 154; FOV 24; multishot = 32; TFE pre IR shortest (394 ms), 1.5 mm slice thickness.

Raw, formatted image data were transferred from the MRI scanner to Apple Macintosh Power PC workstations via existing network connections. The image data were imported into the program BrainImage (Reiss, 2002) for removal of non-brain tissue and measurement of whole brain volume. The isolated brain tissue was then transferred to the software program Measure for regional volumetric measurement. After aligning the 3D images along the anterior–posterior commissures and interhemispheric fissure, the amygdala and the prefrontal cortex were isolated.

The protocol for measuring the prefrontal cortex, which consisted of its dorsal and orbital subregions, was adapted from Gur and coworkers (Gur et al., 2000) and has been described previously (Kates et al., 2005, 2006). The protocols for measuring the amygdala and the cerebellum have also been described previously (Kaplan et al., 1997; Kates, Abrams, Kaufmann, Breiter, & Reiss, 1997). Interrater reliability, assessed with the intraclass correlation coefficient, exceeded .85 for all regions of interest.

Statistical Analyses

Chi-square analyses were used to compare children with VCFS ± ASD on categorical variables (gender, psychiatric diagnosis). Multivariate and univariate analyses of variance (ANOVA) were conducted to compare the groups on continuous behavioral, cognitive and neuroanatomic variables. Pairwise comparisons of our two groups were based on least-squares means adjusted by the Bonferroni method. Eta squared (η^2) is also reported for all analyses.

Results

ASD Prevalence Data

Seventeen of the 41 participants (42%) met diagnostic criteria for ASD. (Included in these seventeen children are eight children with VCFS who met strictly defined autism.) As shown in Table 1, children with VCFS + ASD did not differ from those with VCFS on demographic data. Full Scale IQ differences between the two groups approached significance, F (1, 39) = 3.14, P = .08, η^2 = 0.07. Although IQ differences between the two groups were not statistically significant, given the medium effect size between our two groups, we sought to control for the effects of IQ on our dependent variables. Thus, IQ was entered as a covariate in MANOVA models assessing hypotheses one and two.

Table 1 Background, behavioral & cognitive mean (*SD*) data

Variable	VCFS (n = 24)	VCFS + ASD (n = 17)
Age (years)	10.8 (2.7)	10.4 (1.9)
Sex (% male)	46	59
Socioeconomic status	53.2 (11.5)	48.6 (10.0)
WISC-III Full Scale IQ	78.3 (10.9)	71.5 (13.4)
BASC Atypicality *T*-score	52.3 (10.3)	67.6 (16.1) **
CBCL Social Problems *T*-score	61.8 (6.8)	70.3 (7.4) **
VABS Socialization Standard Score	80.6 (16.7)	66.2 (14.5) *
CPT Errors of Omission *z*-score	–1.2 (4.0)	–3.5 (3.6)
CPT Errors of Commission *z*-score	–1.6 (2.9)	–2.3 (3.1)
WCST Perseverative Error Standard Score	77.3 (20.7)	64.6 (9.7)
WCST Nonperseverative Error Standard Score	94.6 (13.9)	81.7 (11.6) *
Visual Span Forward *z*-score	–0.5 (0.9)	–1.0 (0.5)
Visual Span Backward *z*-score	–0.9 (0.8)	–1.3 (1.0)

Note. WISC-III = Wechsler Intelligence Scale for Children - 3rd edition Wechsler (1991); BASC = Behavior Assessment Scale for Children, Reynolds & Kamphaus (1992). CBCL = Child Behavior Checklist, Achenbach (1991). VABS = Vineland Adaptive Behavior Scales, Sparrow et al. (1983). CPT = Continuous Performance Test—Gordon Diagnostic System; Gordon et al. (1989). WCST = Wisconsin Card Sorting Test, Heaton et al. (1993). * P < .05. ** P < .01

Hypothesis 1—Behavioral Differences

The omnibus MANCOVA on communication, social deficits and stereotyped behaviors was significant, Wilk's λ = 0.24, F (3, 34) = 5.15, P = .005, η^2 = .33. Univariate analyses revealed that children with VCFS + ASD were rated by parents as having more odd/repetitive behaviors on the BASC Atypicality scale, F (1, 39) = 9.57, P = .004, η^2 = 0.22, engaged in less socialization as indexed on the Vineland Socialization scale F (1, 39) = 6.15, P = .018, η^2 = 0.15, and had more social difficulties with their peers as indexed on the CBCL Social Problems F (1, 39) = 11.59, P = .002, η^2 = 0.25. Group means are reported in Table 1.

Children with VCFS + ASD also had more psychiatric diagnoses than children with VCFS, $\chi^2 = 4.99$, P = .026. Ninety-four percent of the children with VCFS + ASD had a co-occurring psychiatric disorder while 60% of children with VCFS had a psychiatric disorder. ADHD was the most frequently occurring disorder in both groups, yet occurred twice as often in the VCFS + ASD group (80%) compared to the VCFS group $\chi^2 = 5.60$, P = .020. Similarly, specific phobias were prevalent twice as often in the VCFS + ASD group (60%) compared to the VCFS group, $\chi^2 = 3.15$, P = .08. Finally, children with VCFS + ASD were rated by parents as having more mania symptoms on the YMRS, F (1, 39) = 8.23, P = .007, $\eta^2 = 0.20$.

Hypothesis 2—Executive Functioning Profile

The omnibus MANCOVA on executive functioning measures failed to reach significance, Wilk's $\lambda = 0.74$, F (6, 31) = 1.72, P = .150, $\eta^2 = .26$. As shown in Table 1, univariate analyses suggested differences between VCFS + ASD and VCFS groups on only one executive functioning measure. Children with VCFS + ASD made more nonperseverative errors on the WCST, F (1, 39) = 7.85, P = .008, $\eta^2 = .18$. Although working memory and cognitive flexibility differences did not emerge between the two groups as robustly as hypothesized, performance on one of the executive functioning measures was consistent with predictions. The two groups did not differ on CPT Errors of Commission, F (1, 39) = 0.58, P = .454, $\eta^2 = .02$.

Hypothesis 3—Neuroanatomical Differences

Whole brain volume differences between children with VCFS + ASD and VCFS failed to reach significance, F (1, 39) = 1.79, P = .192, $\eta^2 = .06$. Thus, whole brain volume was not entered as a covariate in the model. As shown in Table 2, and partially consistent with hypotheses, the only neurological region to differ significantly between our two groups was the right amygdala. Children with VCFS + ASD had larger right amygdala volumes than children with VCFS, F (1, 39) = 9.21, P = .005, $\eta^2 = .24$. All other neuroanatomic regions of interest were statistically similar between the two groups. See Table 2 for group volumetric mean data.

Table 2 Neuroanatomic regions of interest volumetric data

Variable	VCFS (n = 24)	VCFS + ASD (n = 17)
Whole Brain Volume	1303.00 (142.77)	1363.44 (132.21)
Prefrontal Cortex	164.45 (26.25)	167.38 (22.12)
Left Amygdala	2.29 (0.45)	2.22 (0.50)
Right Amygdala	1.98 (0.32)	2.34 (0.34) **
Left Cerebellum	52.51 (6.64)	54.70 (8.51)
Right Cerebellum	53.05 (6.61)	54.24 (7.44)

Note. Measurement unit is square centimeters (cm^2). ** P < .01

Discussion

Prevalence of ASD in VCFS

Children with VCFS are at increased risk for ASD. Twenty percent of our sample met strictly defined criteria for autism while over 40% of our sample of children with VCFS met criteria for ASD. These prevalence rates of autism and ASD are higher than a previous group reported using a similar research design (Fine et al., 2005). Our relatively higher rate may be due to ascertainment biases, our relatively low rate of ADI-R completion, the criteria used to define ASD cases, or other methodological factors. Although we found no behavioral differences between the subset of children in our sample who received the ADI-R and those who did not, children whose parents participated in the ADI-R interview were, on the whole, younger and had higher IQ scores. Moreover, parents who participated tended to have higher SES levels. Accordingly, it is possible that non-participants faced parenting and work demands that reduced available time to participate in a telephone interview. This may limit the generalizabiity of our following findings. However, our relatively high rates of autism and ASD in VCFS are consistent with previous groups (Niklasson et al., 2001; Vorstman, Morcus et al., 2006) who reported that 33–50% of their samples of children with VCFS met diagnostic criteria for ASD. Others (Chudley et al., 1998; Ogilvie, Moore, Daker, Palferman, & Docherty, 2000) have reported that the inverse (e.g., high rates of VCFS in samples ascertained for autism) is not true.

At this point, multiple groups have reported that ASD is quite prevalent in children with a 22q11.2 deletion. Molecular genetic research has identified diverse risk regions such as 2q37, 3p24-26, 5p15, 11q25, 16q22.3, 17p11.2, 18q21.1, 18q23, 22q11.2, 22q13.3 and Xp22.2-p22.3 as harboring possible candidate genes (Muhle, Trentacoste, & Rapin, 2004; Veenstra-VanderWeele & Cook, 2004; Vorstman, Staal et al., 2006; Ylisaukko-oja et al., 2006). Thus far, the strongest implicated chromosomal regions with susceptibility

genes for autism are 2q, 7q and 15q (IMGSAC, 2001; Philippe et al., 1999). Nonetheless, given the impressive prevalence of ASD in this population, future molecular genetic work should continue to investigate 22q11.2 genes as etiologically relevant to ASD.

Behavioral & Cognitive Findings

ASD is a behaviorally defined disorder and thus it is not surprising that parents of children with ASD would report higher levels of atypical behaviors and lower levels of socialization and communication. We view these findings as further supporting the validity of our ADI-R diagnoses. It has been reported in literature that children with VCFS have problems in social functioning (Swillen et al., 1997; Swillen, Devriendt et al., 1999). Our findings raise the question of whether the presence of ASD in a sizeable subset of children with VCFS may substantially account for the high incidence of deficits in social interaction that has been reported in previous studies of children with this disorder.

More novel behavioral findings from our data include the between group comparisons between VCFS + ASD and VCFS. Relative to children with VCFS, children with VCFS + ASD have more psychiatric comorbidity including ADHD and specific phobias and more symptoms of mania. Our finding that the presence of ASD in VCFS is associated with higher scores on mania is consistent with several that documented co-occurrence of mania among children with ASD (Komoto, Usui, & Hirata, 1984; Sovner, 1989; Wozniak et al., 1997). Moreover, our finding that children with VCFS + ASD had an increased incidence of DSM-IV diagnoses, particularly ADHD and specific phobias, is similar to findings reported in literature suggesting that children with ASD are at an increased risk for wide variety of psychiatric disorders, especially anxiety disorders (Bradley et al., 2004; Sverd, 2003; Weisbrot, Gadow, DeVincent, & Pomeroy, 2005). For example, using a modified version of the structured psychiatric interview employed in the current study, others (Leyfer et al., 2006) have reported that 44% of children with autism have comorbid specific phobias, 37% have comorbid obsessive compulsive disorder and 30% have ADHD, most commonly the Inattentive subtype. In all, 72% of children with autism had a comorbid psychiatric disorder (Leyfer et al., 2006). Thus, ASD appears to be accompanied by coexisting psychopathology in both ''pure'', non-syndromal ASD populations as well as syndromal ASD populations.

Children with VCFS made more nonperseverative errors on a measure of cognitive flexibility. In addition, as predicted, the two groups did not differ on a measure of executive inhibition. However, the lack of working memory and more robust cognitive flexibility differences between the groups was more surprising. Children with VCFS have been previously demonstrated to have executive dysfunction (Bearden et al., 2004). Thus, the fact that we did not find significant between group executive function differences suggests that ASD in children with VCFS may not contribute to executive dysfunction over and above what is already incurred by VCFS.

Neuroanatomic Findings

Children with VCFS + ASD have larger right amygdala. This is consistent with extant research in the general autism population documenting amygdala alterations (Howard et al., 2000; Munson et al., 2006; Pelphrey, Adolphs, & Morris, 2004; Sparks et al., 2002). An amygdala theory of autism has been forwarded (Baron-Cohen et al., 2000) positing that amygdala alterations are etiologically relevant to autism symptoms. The amygdala is thought to play a role in very quickly evaluating the emotional valence of incoming information (LeDoux, 1992). Being very early in the emotional processing circuit, the amygdala is thus, well positioned to evaluate information ''downstream'' at the cortical route (Amaral, Bauman, & Schumann, 2003; LeDoux, 1992).

The Munson et al. (2006) research also cited enlarged right amygdala as being positively associated with a variety of ASD variables including socialization and communication deficits. Our group has previously reported that the amygdala is enlarged in VCFS, and that increased volume is associated with increases in anxiety (Kates et al., 2006). All of the above suggests that the amygdala, possibly the right more than the left, is worthy of further consideration as etiologically associated with ASD.

Limitations and Clinical Implications

Our data need to be considered in light of our methodological limitations. First and foremost, over half of our sample did not complete the ADI-R. Although those who did and did not complete the ADI-R do not differ on behavioral or most cognitive domains, there were several sociodemographic differences between ADI-R participants and non-participants. Second, we relied solely on parent report of child behavior. By not including others (e.g., teachers) who have regular contact with the child we may have increased our potential for response biases. For

example, it is possible that the high rate of psychiatric comorbidity in our VCFS + ASD sample is a reflection of parental reporter bias.

Third, autism and ASD diagnoses were made exclusively on parent report on the ADI-R. Since both the ADI-R and Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 1999) make independent contributions to the diagnosis of autism(-Risi et al., 2006), we recommend that future studies investigating the incidence of ASD in VCFS samples include the ADOS in the research protocol. Finally, although we operationalized ASD in a manner that has precedence in the literature, other research groups may operationalize ASD differently. All of the above suggest that these data need to be considered preliminary until other groups can replicate our findings.

The high rate of ASD in VCFS that we report here is consistent with several previous reports. Nonetheless, the question of whether ASD in VCFS should be considered a distinct and separable diagnosis remains debatable (Eliez, in press). Diagnostic overshadowing (Jopp & Keys, 2001) (i.e., the attribution of behaviors to one disorder without considering additional diagnoses and treatment of comorbid conditions) may account for the possibility that ASD has been attributed to the VCFS phenotype without being considered a distinct diagnosis. Whereas autism is a lifetime diagnosis, however, we do not know if the features of the VCFS phenotype that are consistent with autism change over time. Our sample is currently being reevaluated as part of a longitudinal study of risk factors for psychosis; accordingly, we will soon be in a position to address the issue of stability in the VCFS behavioral phenotype.

To the extent that ASD can be considered a separate diagnosis, we recommend that children with VCFS be screened for ASD at a young age. The use of screening instruments such as the Childhood Autism Rating Scale (CARS) (Schopler, Reichler, & Ro, 1998) or the Modified Checklist for Autism in Toddlers (M-CHAT) (Robins, Fein, Barton, & Green, 2001) may prove fruitful in identifying children with VCFS+ASD at a young age. Both the CARS and M-CHAT have research supporting their use as tools to help identify children with ASD relative to children with other developmental delays. The higher rate of comorbid psychopathology in VCFS+ASD suggests that this subgroup of children with VCFS may be especially in need of more clinical and research focus, since we currently do not know whether ASD-focused behavioral interventions are efficacious in this population. Moreover, with the addition of ASD to the panoply of diagnoses that have been described in VCFS (eg., ADHD, schizophrenia, bipolar disorder, major depressive disorder etc.), VCFS might be considered a genetic model for clinically heterogeneous / comorbid psychiatric illness.

Acknowledgement This work was supported by NIH grants MH64824 and MH65481 to Wendy Kates.

References

Achenbach, T. (1991). *Child behavior checklist*. Burlington, VT: ASEBA.

Amaral, D. G., Bauman, M. D., & Schumann, C. M. (2003). The amygdala and autism: Implications from non-human primate studies. *Genes Brain Behavior, 2*(5),295–302.

AmericanPsychiatricAssociation. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, D.C.: Author.

Antshel, K. M., AbdulSabur, N., Roizen, N., Fremont, W., & Kates, W. R. (2005). Sex differences in cognitive functioning in velocardiofacial syndrome (VCFS). *Developmental Neuropsychology, 28*(3), 849–869.

Antshel, K. M., Fremont, W., Roizen, N. J., Shprintzen, R., Higgins, A. M., Dhamoon, A., et al. (2006). ADHD, major depressive disorder, and simple phobias are prevalent psychiatric conditions in youth with velocardiofacial syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(5), 596–603.

Antshel, K. M., Stallone, K., AbdulSabur, N., Shprintzen, R., Roizen, N., Higgins, A. M., et al. (in press). Temperament in velocardiofacial syndrome. *Journal of Intellectual Disability Research*.

Baron-Cohen, S., Ring, H. A., Bullmore, E. T., Wheelwright, S., Ashwin, C., & Williams, S. C. (2000). The amygdala theory of autism. *Neuroscience and Biobehavioral Reviews, 24*(3), 355–364.

Bearden, C. E., Jawad, A. F., Lynch, D. R., Sokol, S., Kanes, S. J., McDonald-McGinn, D. M., et al. (2004). Effects of a functional COMT polymorphism on prefrontal cognitive function in patients with 22q11.2 deletion syndrome. *American Journal of Psychiatry, 161*(9), 1700–1702.

Bennetto, L., Pennington, B. F., & Rogers, S. J. (1996). Intact and impaired memory functions in autism. *Child Development, 67*(4), 1816–1835.

Boddaert, N., Chabane, N., Gervais, H., Good, C. D., Bourgeois, M., Plumet, M. H., et al. (2004). Superior temporal sulcus anatomical abnormalities in childhood autism: A voxel-based morphometry MRI study. *Neuroimage, 23*(1), 364–369.

Bradley, E. A., Summers, J. A., Wood, H. L., & Bryson, S. E. (2004). Comparing rates of psychiatric and behavior disorders in adolescents and young adults with severe intellectual disability with and without autism. *Journal of Autism Development and Disorder, 34*(2), 151–161.

Brambilla, P., Hardan, A., di Nemi, S. U., Perez, J., Soares, J. C., & Barale, F. (2003). Brain anatomy and development in autism: Review of structural MRI studies. *Brain Research Bulletin, 61*(6), 557–569.

Capone, G. T., Grados, M. A., Kaufmann, W. E., Bernad-Ripoll, S., & Jewell, A. (2005). Down syndrome and comorbid autism-spectrum disorder: Characterization using the aberrant behavior checklist. *American Journal of Medical Genetics A, 134*(4), 373–380.

Chow, E. W., Bassett, A. S., & Weksberg, R. (1994). Velocardio-facial syndrome and psychotic disorders: Implications for psychiatric genetics. *American Jorunal of Medical Genetics, 54*(2), 107–112.

Chudley, A. E., Gutierrez, E., Jocelyn, L. J., & Chodirker, B. N. (1998). Outcomes of genetic evaluation in children with pervasive developmental disorder. *Journal of Developmental and Behavioral Pediatrics, 19*(5), 321–325.

Cohen, D., Pichard, N., Tordjman, S., Baumann, C., Burglen, L., Excoffier, E., et al. (2005). Specific genetic disorders and autism: Clinical contribution towards their identification. *Journal of Autism Development and Disorder, 35*(1), 103–116.

Courchesne, E., Karns, C. M., Davis, H. R., Ziccardi, R., Carper, R. A., Tigue, Z. D., et al. (2001). Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. *Neurology, 57*(2), 245–254.

Critchley, H. D., Daly, E. M., Bullmore, E. T., Williams, S. C., Van Amelsvoort, T., Robertson, D. M., et al. (2000). The functional neuroanatomy of social behaviour: Changes in cerebral blood flow when people with autistic disorder process facial expressions. *Brain, 123*(Pt 11), 2203–2212.

Curatolo, P., Porfirio, M. C., Manzi, B., & Seri, S. (2004). Autism in tuberous sclerosis. *European Journal of Paediatric Neurology, 8*(6), 327–332.

Davis, H. R. (1998). *Colorado assessment tests— visual span test*. Boulder, CO: Colorado Assessment Tests.

Eliez, S. (in press). Letter to the Editor. *Journal of the American Academy of Child and Adolescent Psychiatry*.

Eliez, S., Blasey, C. M., Schmitt, E. J., White, C. D., Hu, D., & Reiss, A. L. (2001). Velocardiofacial syndrome: Are structural changes in the temporal and mesial temporal regions related to schizophrenia? *American Journal of Psychiatry, 158*(3), 447–453.

Eliez, S., Palacio-Espasa, F., Spira, A., Lacroix, M., Pont, C., Luthi, F., et al. (2000). Young children with Velo-Cardio-Facial syndrome (CATCH-22). Psychological and language phenotypes. *European Child and Adolescent Psychiatry, 9*(2), 109–114.

Feinstein, C., Eliez, S., Blasey, C., & Reiss, A. L. (2002). Psychiatric disorders and behavioral problems in children with velocardiofacial syndrome: Usefulness as phenotypic indicators of schizophrenia risk. *Biological Psychiatry, 51*(4), 312–318.

Fine, S. E., Weissman, A., Gerdes, M., Pinto-Martin, J., Zackai, E. H., McDonald-McGinn, D. M. et al. (2005). Autism spectrum disorders and symptoms in children with molecularly confirmed 22q11.2 deletion syndrome. *Journal of Autism and Developmental Disorder, 35*(4), 461–470.

Gerdes, M., Solot, C., Wang, P. P., Moss, E., LaRossa, D., Randall, P., et al. (1999). Cognitive and behavior profile of preschool children with chromosome 22q11.2 deletion. *Americn Journal of Medical Genetics, 85*(2), 127–133.

Gillberg, C. (1992). Subgroups in autism: Are there behavioural phenotypes typical of underlying medical conditions? *Journal of Intellectual Disability Research, 36*(Pt 3), 201–214.

Glaser, B., Mumme, D. L., Blasey, C., Morris, M. A., Dahoun, S. P., Antonarakis, S. E., et al. (2002). Language skills in children with velocardiofacial syndrome (deletion 22q11.2). *Journal of Pediatrcis, 140*(6), 753–758.

Goodlin-Jones, B. L., Tassone, F., Gane, L. W., & Hagerman, R. J. (2004). Autistic spectrum disorder and the fragile X premutation. *Journal of Developmental and Behavioral Pediatrics, 25*(6), 392–398.

Gordon, M., McClure, F. D., & Aylward, G. P. (1989). *Gordon diagnostic system*. Dewitt, NY: Gordon Diagnostic Systems.

Gracious, B. L., Youngstrom, E. A., Findling, R. L., & Calabrese, J. R. (2002). Discriminative validity of a parent version of the Young Mania Rating Scale. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*(11), 1350–1359.

Gur, R., Cowell, P., Latshaw, A., Turetsky, B., Grossman, R., Arnold, S., et al. (2000). Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Archives of General Psychiatry, 57*, 761–768.

Hadjikhani, N., Joseph, R. M., Snyder, J., Chabris, C. F., Clark, J., Steele, S., et al. (2004). Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces. *Neuroimage, 22*(3), 1141–1150.

Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. G., & Curtiss, G. (1993). *Wisconsin card sort test manual: Revised and expanded*. Odessa, FL: Psychological Assessment Resources, Inc.

Hill, E. L. (2004). Executive dysfunction in autism. *Trends in Cognition Science, 8*(1), 26–32.

Howard, M. A., Cowell, P. E., Boucher, J., Broks, P., Mayes, A., Farrant, A., et al. (2000). Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. *Neuroreport, 11*(13), 2931–2935.

IMGSAC. (2001). A genomewide screen for autism: strong evidence for linkage to chromosomes 2q, 7q, and 16p. *American Journal of Human Genetics, 69*(3), 570–581.

Jopp, D. A., & Keys, C. B. (2001). Diagnostic overshadowing reviewed and reconsidered. *American Journal of Mental Retardation, 106*, 416–433.

Joseph, R. M., McGrath, L. M., & Tager-Flusberg, H. (2005). Executive dysfunction and its relation to language ability in verbal school-age children with autism. *Developmental Neuropsycholgy, 27*(3), 361–378.

Kao, A., Mariani, J., McDonald-McGinn, D. M., Maisenbacher, M. K., Brooks-Kayal, A. R., Zackai, E. H., et al. (2004). Increased prevalence of unprovoked seizures in patients with a 22q11.2 deletion. *American Journal of Medical Genetics A, 129*(1), 29–34.

Kaplan, D. M., Liu, A. M., Abrams, M. T., Warsofsky, I. S., Kates, W. R., White, C. D., et al. (1997). Application of an automated parcellation method to the analysis of pediatric brain volumes. *Psychiatry Research, 76*(1), 15–27.

Kates, W. R., Abrams, M. T., Kaufmann, W. E., Breiter, S. N., & Reiss, A. L. (1997). Reliability and validity of MRI measurement of the amygdala and hippocampus in children with fragile X syndrome. *Psychiatry Research, 75*(1), 31–48.

Kates, W. R., Antshel, K., Willhite, R., Bessette, B. A., AbdulSabur, N., & Higgins, A. M. (2005). Gender-moderated dorsolateral prefrontal reductions in 22q11.2 Deletion Syndrome: Implications for risk for schizophrenia. *Child Neuropsychology, 11*(1), 73–85.

Kates, W. R., Burnette, C. P., Eliez, S., Strunge, L. A., Kaplan, D., Landa, R., et al. (2004). Neuroanatomic variation in monozygotic twin pairs discordant for the narrow phenotype for autism. *American Journal of Psychiatry, 161*(3), 539–546.

Kates, W. R., Burnette, C. P., Jabs, E. W., Rutberg, J., Murphy, A. M., Grados, M., et al. (2001). Regional cortical white matter reductions in velocardiofacial syndrome: A volumetric MRI analysis. *Biological Psychiatry, 49*(8), 677–684.

Kates, W. R., Miller, A. M., Abdulsabur, N., Antshel, K. M., Conchelos, J., Fremont, W., et al. (2006). Temporal lobe anatomy and psychiatric symptoms in velocardiofacial syndrome (22q11.2 deletion syndrome). *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(5), 587–595.

Kates, W. R., Mostofsky, S. H., Zimmerman, A. W., Mazzocco, M. M., Landa, R., Warsofsky, I. S., et al. (1998). Neuroanatomical and neurocognitive differences in a pair of monozygous twins discordant for strictly defined autism. *Annals of Neurology, 43*(6), 782–791.

Kau, A. S., Tierney, E., Bukelis, I., Stump, M. H., Kates, W. R., Trescher, W. H., et al. (2004). Social behavior profile in young males with fragile X syndrome: Characteristics and specificity. *American Journal of Medical Genetics A, 126*(1), 9–17.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., et al. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(7), 980–988.

Kaufmann, W. E., Cortell, R., Kau, A. S., Bukelis, I., Tierney, E., Gray, R. M., et al. (2004). Autism spectrum disorder in fragile X syndrome: Communication, social interaction, and specific behaviors. *American Journal of Medical Genetics A, 129*(3), 225–234.

Komoto, J., Usui, S., & Hirata, J. (1984). Infantile autism and affective disorder. *Journal of Autism Development and Disorder, 14*(1), 81–84.

LeDoux, J. E. (1992). Brain mechanisms of emotion and emotional learning. *Current Opinion in Neurobiology, 2*(2), 191–197.

Leyfer, O. T., Folstein, S. E., Bacalman, S., Davis, N. O., Dinh, E., Morgan, J., et al. (2006). Comorbid psychiatric disorders in children with autism: Interview development and rates of disorders. *Journal of Autism Development and Disorder, 36*, 849–861.

Lord, C., Rutter, M., DiLavore, P., & Risi, S. (1999). *Autism diagnostic observation schedule manual*. Los Angeles: Western Psychological Services.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism Development and Disorder, 24*(5), 659–685.

Milner, B. (1971). Interhemispheric differences in the localization of psychological processes in man. *British Medical Bulletin, 27*(3), 272–277.

Muhle, R., Trentacoste, S. V., & Rapin, I. (2004). The genetics of autism. *Pediatrics, 113*(5), e472–e486.

Munson, J., Dawson, G., Abbott, R., Faja, S., Webb, S. J., Friedman, S. D., et al. (2006). Amygdalar volume and behavioral development in autism. *Archives of General Psychiatry, 63*(6), 686–693.

Murphy, K. C., Jones, L. A., & Owen, M. J. (1999). High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Archives of General Psychiatry, 56*(10), 940–945.

Niklasson, L., Rasmussen, P., Oskarsdottir, S., & Gillberg, C. (2001). Neuropsychiatric disorders in the 22q11 deletion syndrome. *Genetic Medicine, 3*(1), 79–84.

Ogilvie, C. M., Moore, J., Daker, M., Palferman, S., & Docherty, Z. (2000). Chromosome 22q11 deletions are not found in autistic patients identified using strict diagnostic criteria. IMGSAC. International Molecular Genetics Study of Autism Consortium. *American Journal of Medical Genetics, 96*(1), 15–17.

Ozonoff, S., & Jensen, J. (1999). Brief report: Specific executive function profiles in three neurodevelopmental disorders. *Journal of Autism Development and Disorder, 29*(2), 171–177.

Ozonoff, S., Pennington, B. F., & Rogers, S. J. (1991). Executive function deficits in high-functioning autistic individuals: Relationship to theory of mind. *Journal of Child Psychology and Psychiatry, 32*(7), 1081–1105.

Ozonoff, S., & Strayer, D. L. (2001). Further evidence of intact working memory in autism. *Journal of Autism Development and Disorder, 31*(3), 257–263.

Papolos, D. F., Faedda, G. L., Veit, S., Goldberg, R., Morrow, B., Kucherlapati, R., et al. (1996). Bipolar spectrum disorders in patients diagnosed with velo-cardio-facial syndrome: Does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? *American Journal of Psychiatry, 153*(12), 1541–1547.

Pelphrey, K., Adolphs, R., & Morris, J. P. (2004). Neuroanatomical substrates of social cognition dysfunction in autism. *Mental Retardation and Developmental Disability Research Reviews, 10*(4), 259–271.

Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry, 37*(1), 51–87.

Philippe, A., Martinez, M., Guilloud-Bataille, M., Gillberg, C., Rastam, M., Sponheim, E., et al. (1999). Genome-wide scan for autism susceptibility genes. Paris Autism Research International Sibpair Study. *Human Molecular Genetcis, 8*(5), 805–812.

Polleux, F., & Lauder, J. M. (2004). Toward a developmental neurobiology of autism. *Mental Retardation and Developmental Disability Research Reviews, 10*(4), 303–317.

Reiss, A. L. (2002). *BrainImage*. Palo Alto, CA: Stanford University School of Medicine.

Reynolds C. R., & Kamphaus R. W. (1992). *Behavioral assessment system for children* Circle Pines, MN: AGS.

Risi, S., Lord, C., Gotham, K., Corsello, C., Chrysler, C., Szatmari, P., et al. (2006). Combining information from multiple sources in the diagnosis of autism spectrum disorders. *Journal of the American Academy of Child Adolescence and Psychiatry, 45*(9), 1094–1103.

Robins, D. L., Fein, D., Barton, M. L., & Green, J. A. (2001). The modified checklist for autism in toddlers: An initial study investigating the early detection of autism and pervasive developmental disorders. *Journal of Autism Development and Disorder, 31*(2), 131–144.

Roubertie, A., Semprino, M., Chaze, A. M., Rivier, F., Humbertclaude, V., Cheminal, R., et al. (2001). Neurological presentation of three patients with 22q11 deletion (CATCH 22 syndrome). *Brain Development, 23*(8), 810–814.

Schopler, E., Reichler, R. J., & Ro, B. (1988). *Childhood autism rating scales (CARS)*. Circle Pines, MN: AGS.

Schultz, R. T., Gauthier, I., Klin, A., Fulbright, R. K., Anderson, A. W., Volkmar, F., et al. (2000). Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. *Archieves in General Psychiatry, 57*(4), 331–340.

Shprintzen, R. J. (2000). Velo-cardio-facial syndrome: A distinctive behavioral phenotype. *Mental Retardation and Developmental Disability Research Reviews, 6*(2), 142–147.

Shprintzen, R. J., Higgins, A. M., Antshel, K., Fremont, W., Roizen, N., & Kates, W. (2005). Velo-cardio-facial syndrome. *Current Opinion in Pediatrics, 17*(6), 725–730.

Smith, T., Groen, A. D., & Wynn, J. W. (2000). Randomized trial of intensive early intervention for children with pervasive developmental disorder. *American Journal of Mental Retardation, 105*(4), 269–285.

Sovner, R. (1989). The use of valproate in the treatment of mentally retarded persons with typical and atypical bipolar disorders. *Journal of Clinical Psychiatry, 50*(Suppl), 40–43.

Sparks, B. F., Friedman, S. D., Shaw, D. W., Aylward, E. H., Echelard, D., Artru, A. A., et al. (2002). Brain structural abnormalities in young children with autism spectrum disorder. *Neurology, 59*(2), 184–192.

Sparrow, S. S., Balla, D. A., & Cichetti, D. V. (1983). *Vineland* Adaptive Behavior Scales. Circle Pines, MN: AGS.

Sverd, J. (2003). Psychiatric disorders in individuals with pervasive developmental disorder. *Journal of Psychiatric Practice, 9*(2), 111–127.

Swillen, A., Devriendt, K., Legius, E., Eyskens, B., Dumoulin, M., Gewillig, M., et al. (1997). Intelligence and psychosocial adjustment in velocardiofacial syndrome: A study of 37 children and adolescents with VCFS. *Journal of Medical Genetics, 34*(6), 453–458.

Swillen, A., Devriendt, K., Legius, E., Prinzie, P., Vogels, A., Ghesquiere, P., et al. (1999). The behavioural phenotype in velo-cardio-facial syndrome (VCFS): From infancy to adolescence. *Genetic Counseling, 10*(1), 79–88.

Swillen, A., Vandeputte, L., Cracco, J., Maes, B., Ghesquiere, P., Devriendt, K., et al. (1999). Neuropsychological, learning and psychosocial profile of primary school aged children with the velo-cardio-facial syndrome (22q11 deletion): Evidence for a nonverbal learning disability? *Child Neuropsychology, 5*(4), 230–241.

Turner, L. M., Stone, W. L., Pozdol, S. L., & Coonrod, E. E. (2006). Follow-up of children with autism spectrum disorders from age 2 to age 9. *Autism, 10*(3), 243–265.

van Amelsvoort, T., Daly, E., Henry, J., Robertson, D., Ng, V., Owen, M., et al. (2004). Brain anatomy in adults with velocardiofacial syndrome with and without schizophrenia: Preliminary results of a structural magnetic resonance imaging study. *Archieves in General Psychiatry, 61*(11), 1085–1096.

Veenstra-VanderWeele, J., & Cook, E. H., Jr. (2004). Molecular genetics of autism spectrum disorder. *Molecular Psychiatry, 9*(9), 819–832.

Vorstman, J. A., Morcus, M. E., Duijff, S. N., Klaassen, P. W., Heineman-de Boer, J. A., Beemer, F. A., et al. (2006). The 22q11.2 deletion in children: High rate of autistic disorders and early onset of psychotic symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(9), 1104–1113.

Vorstman, J. A., Staal, W. G., van Daalen, E., van Engeland, H., Hochstenbach, P. F., & Franke, L. (2006). Identification of novel autism candidate regions through analysis of reported cytogenetic abnormalities associated with autism. *Molecular Psychiatry, 11*(1), 1, 18–28.

Walker, D. R., Thompson, A., Zwaigenbaum, L., Goldberg, J., Bryson, S. E., Mahoney, W. J., et al. (2004). Specifying PDD-NOS: A comparison of PDD-NOS, Asperger syndrome, and autism. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*(2), 172–180.

Wang, A. T., Dapretto, M., Hariri, A. R., Sigman, M., & Bookheimer, S. Y. (2004). Neural correlates of facial affect processing in children and adolescents with autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*(4), 481–490.

Wechsler, D. (1991). *Wechsler intelligence scale for children* (3rd ed.). San Antonio, TX: Psychological Corporation.

Weisbrot, D. M., Gadow, K. D., DeVincent, C. J., & Pomeroy, J. (2005). The presentation of anxiety in children with pervasive developmental disorders. *Journal of Child Adolescent and Psychopharmacology, 15*(3), 477–496.

Wing, L. (1997). *Syndromes of autism and atypical development*. (2nd ed.). New York: Wiley Press.

Wozniak, J., Biederman, J., Faraone, S. V., Frazier, J., Kim, J., Millstein, R., et al. (1997). Mania in children with pervasive developmental disorder revisited. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(11), 1552–1559; discussion 1559–1560.

Ylisaukko-oja, T., Alarcon, M., Cantor, R. M., Auranen, M., Vanhala, R., Kempas, E., et al. (2006). Search for autism loci