Socioeconomic Status and Psychological Function in Children with Chromosome 22q11.2 Deletion Syndrome: Implications for Genetic Counseling

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Abstract:
The purpose of this study is to examine the association between parental socio-economic status (SES) and childhood neurocognition and behavior in children with chromosome 22q11.2 deletion syndrome (22q11DS). Although undoubtedly, the deletion of genes in the 22q11.2 interval is primarily responsible for the psychological manifestations, little is known about the role of the environment in either mitigating or contributing to these problems. We examined the association of parental socio-economic status (SES) with cognition and behavior in children with 22q11DS ($n = 65$) and matched healthy control subjects ($n = 52$), since SES is a component of family resources. We found that in children with 22q11DS, higher SES correlated with better overall functioning ($p < .01$) and social skills ($p < .01$), and less frequent oppositional defiant behavior ($p < .001$). These findings were in contrast to the control subjects in whom SES correlated with cognition and achievement, but not behavior. Our results indicate that environmental factors influence the behavioral phenotype in children with 22q11DS, providing a framework for developing appropriate interventions. As such, genetic counseling for families with 22q11DS may include consideration of family resources and inclusion of other health professionals, such as social workers, to explore with the family available social supports and resources.

Article:
INTRODUCTION
Cognitive/Behavior Impairments in 22q11DS
Chromosome 22q11.2 deletion syndrome (22q11DS), also known as DiGeorge syndrome or velocardiofacial syndrome, occurs in 1 in 1600 to 1 in 2000 live births, making it the most common chromosomal deletion in humans (Shprintzen 2000, 2008). Among the most ubiquitous manifestations of the condition are cognitive deficits, seen in 80–100% of affected individuals; the mean IQ is reported to be 75 and almost 50% will have a diagnosis of mental retardation (Gerdes et al. 1999; Moss et al. 1999; Swillen et al. 1997; Woodin et al. 2001). A complex and distinctive pattern of cognitive impairment occurs, with deficits in visual-spatial processing, executive function, attention, verbal learning, visual-spatial processing and working memory

(Lewandowski et al. 2007), poor arithmetic performance and language, but relative strengths in reading and spelling skills (Golding-Kushner et al. 1985; Swillen et al. 1997). Taken together, these impairments lead to poor school performance and more generally, to lower adaptive skills and functionality.

Behavioral and emotional problems occur in approximately 50% of children with 22q11DS; the most common are social impairments, somatic complaints, attention deficit/hyperactivity (AD/HD), oppositional defiant disorder (ODD) and anxiety problems (Feinstein et al. 2002; Heineman-de Boer et al. 1999; Swillen et al. 1999; Swillen et al. 2000; Wang et al. 2000). Although aggression and other externalizing behavior problems are reported, they tend not to be as frequent as internalizing problems (Feinstein et al. 2002; Jansen et al. 2007). Interestingly, the behavior problems have been reported to not be correlated with intellectual impairment; thus a behavioral phenotype unique to the disorder has been proposed, rather than the behavior being attributed to the intellectual disability (Jansen et al. 2007).

Childhood Functioning and Socioeconomic Status (SES)

Families of children with developmental and/or behavioral disabilities may face unique stressors related to the disorder. Indeed, increased parental stress has been reported in families with a child with 22q11DS (Briegel et al. 2008). Although it is logical to deduce that the cognitive and behavioral problems associated with 22q11DS are caused by the microdeletion of multiple genes, little is known about the role of psychosocial factors that could be either contributing to, or mitigating this psychological phenotype. One study reported that a supportive parenting style was associated with fewer behavioral problems in young children with 22q11DS (Prinzie et al. 2004). Due to the variability of the cognitive deficits and behavioral problems, an examination of modifying factors such as family resources, is indicated. Family resources include many factors inherent to the family including social support, coping strategies, as well as family economics (SES) and education (McCubbin et al. 1996)

In typically developing children, childhood SES is associated with cognition in childhood and persisting into adulthood, underscoring the importance of the childhood environment in cognition throughout life (Fors et al. 2009; Luo and Waite 2005; Zhang et al. 2008). It appears that SES is correlated with language and executive function in typically developing children (reviewed in (Hackman and Farah 2009)) as well as in adults (Singh-Manoux et al. 2005; Turrell et al. *2002*). It is also associated with IQ and academic achievement beginning in early childhood (Turkheimer et al. 2003). Furthermore, SES has been found to modify the heritability of IQ, such that in the families with the highest SES, genetic factors account for most of the variance in IQ, whereas in the lower SES families, environmental influences account for most of the variance in IQ (Turkheimer et al. 2003). In addition to cognition, SES also has an impact upon behavior and emotional functioning; poor social skills, conduct disorders and aggression are associated with lower SES (Holling et al. 2008; Landry et al. 1997; van Oort et al. 2010) as are psychiatric disorders such as depression, anxiety (Lemstra et al. 2008) and even schizophrenia (Werner et al. 2007). The exact causative factors for this relationship between SES, cognition and behavior in typically developing individuals remain unclear, although epigenetic mechanisms (Graff and Mansuy 2008), high levels of stress associated with lower SES (Goodman et al. 2005; Lantz et al. 2005), parenting styles and nutrition all have been postulated to play roles (Guo and Harris 2000).

22q11DS and SES

There has been little exploration of the role of the environment in the neuropsychological and behavioral phenotype of children with 22q11DS, probably due to the fact that the deletion of several genes would be expected to confer cognitive and behavioral problems upon these children. However, cognition, behavior, and psychopathology are complex functions that undoubtedly involve the interplay of genetic and environmental factors. Delineating factors that influence cognition and behavior (other than the deletion itself) in children with 22q11DS is an especially important avenue of research that could lead to the understanding of factors that contribute to causation and resilience, as well the development of effective interventions for these children. Such information should be especially useful for genetic counselors who are uniquely positioned to provide information and treatment recommendations to patients and families.

We undertook an investigation to examine how SES moderates neurocognition and behavior in children with 22q11DS. It is to be noted that children with 22q11DS have an especially high risk of schizophrenia spectrum disorders, bipolar illness and depression in late adolescence (25–40%) (Murphy 2002; Papolos et al. 1996; Shprintzen et al. 1992), and the well established association between schizophrenia and SES in the general population (Werner et al. 2007) raises the question of the role SES could play in schizophrenia associated with 22q11DS. However, this question is beyond the scope of this article, since our subjects are all children and are not in the age range in which psychosis would be expected to manifest. Thus, we restrict the discussion of this article to the relationship between cognition, behavior and SES in nonpsychotic children with 22q11DS and healthy control children.

Research on the relationship between SES and cognition/behavior is controversial and can be viewed as being judgmental; however it is to be noted that SES has been proven to be a useful proxy to assess access to resources and to use this information to construct remedies (Oakes and Rossi 2003). It is in this context that we utilize SES and cognition/behavior correlates in this study. We hypothesized that children with 22q11DS of lower SES would demonstrate more pronounced cognitive and behavioral problems, as compared to those of higher SES; we also predicted similar correlations in the control group, but that the relationship between cognition, behavior and SES would be more robust in the control group, since we expected that the hemizygous deletion would account for more variance in cognition and behavior in the 22q11DS group.

METHODS
The study was approved by the Institutional Review Boards of Duke University Medical Center and Wake Forest University Health Sciences. Informed consent was obtained from the parent/guardian of the children who participated in the study.

Participants included 65 patients with 22q11DS and 52 control subjects. The majority of 22q11DS subjects were enrolled into the study through the genetics clinics at Wake Forest University and Duke Medical Center. Four of the 22q11Ds subjects were recruited through the listing of the study on the Velocardiofacial Syndrome Educational Foundation website. The control subjects were recruited through the local public school systems as well as through local pediatric practices. The patient and control groups did not differ on sex composition (52% and

62% male, respectively), ethnic composition (88% Caucasian, 6% African American, 6% Hispanic, and 84% Caucasian, 12% African American, 4% Hispanic, respectively), or age (M = 10.2, SD = 2.6, and M = 10.4, SD = 2.3, respectively).

Neuropsychological Measures

The participants completed psychological assessments to ascertain IQ, achievement and *a priori* designated aspects of neurocognition. Parental interviews and questionnaires were also administered to ascertain behavioral and emotional problems of the subjects. The tests and questionnaires administered and the domains of function that were assessed are detailed in Table 1. These measures were all selected based upon the recommendations of the NIMH task force on assessing neurocognition in individuals with schizophrenia (Kern et al. 2004); since children with 22q11DS are at high risk of psychoses in later life, we wish to ascertain the domains that are impaired in the childhood period prior to the onset of psychosis to determine the trajectory of neurodevelopment in these children. Note that the number of subjects that we had data on for the Child Behavior Checklist (CBCL) and the Social Skills Rating Scale (SSRS) was less than for the other measures: we had CBCL data on 56 children with 22q11DS and 37 control subjects and SSRS data on 58 children with 22q11Ds and 37 control subjects.

Table 1: Psychological and Psychiatric Measures and Questionnaires Administered to the Subjects in the Study

Test	Function/domain assessed
Global Assessment of Functioning	Ratings of overall function, independent of specific mental health diagnoses
Wechsler Intelligence Scale for Children (WISC-IV)(Wechsler 2008)	Intelligence Quotient
Wechsler Individual Achievement Test (WIAT-II)(Wechsler 2001)	Academic Achievement
Wisconsin Card Sorting Test (WCST)(Chase-Carmichael et al. 1999)	Executive Function
Continuous Performance Test (CPT_IP and AX)(Cornblatt et al. 1988)	Sustained Attention
California Verbal Learning Test for Children (CVLTC)(Delis et al. 1993)	Verbal Learning and Memory
Child Behavior Checklist (CBCL)(Achenbach and Ruffle 2000)	Childhood Social-behavioral Functioning
Social Skills Rating System(Gresham and Elliot 1990)	Childhood Social Skills
Computerized Diagnostic Interview Schedule for Children, Version IV(NIMH-CDISC 2004)	Structured Diagnostic Interview for DSM-IV disorders

SES

Parental SES was ascertained from all participants, by using the Hollingshead and Redlich Scale (A.B. Hollingshead 1975) (A. B. Hollingshead and Redlich 2007). This is a widely used system that computes SES based upon parental occupation and educational levels (years of education and educational degree earned). Lower parental SES scores indicate higher socioeconomic position. SES was rated for each parent or guardian living in the home. If there were two parents or guardians in the home, the lowest score (highest socioeconomic position) was used for the analyses.

Statistical Methods

Using the statistical software SPSS Statistics 17.0, we examined differences between the groups, with simple t-tests, with a focus on the magnitude of the difference between groups using Cohen's d statistic. To examine the relationship between SES and IQ, achievement, neurocognitive, and social-behavioral variables, we employed several strategies. First, we used Pearson correlations to examine associations of parental SES with neurocognitive, behavioral and psychiatric functioning in both the 22q11 and control groups. Second, in order to examine the association of parental SES with the dependent measures and whether the association was

different in the patient and control group (i.e., whether group membership moderated the relations of SES with the dependent measures), a series of regression analyses were computed. Linear regression was used for continuous dependent measures and binary logistic regression was used for dichotomous dependent measures. In each case, age was entered at the first step in order to allow us to examine the effects of SES over-and-above this variable. SES was entered at the second step, group (1 = 22q11DS group, 2 = control group) was entered at the third step, and the Group by SES interaction was entered in the final step. A significant interaction term would indicate that group moderated the relation of SES and the dependent variable and the nature of the moderator effect would be examined using simple slopes analysis. Note that the SES and group variables were centered prior to creating the interaction term.

RESULTS

Our cohort of subjects with 22q11DS was representative of the population of children with the disorder, since they were not ascertained from a specific subspecialty clinic, such as the pediatric cardiology or child psychiatry clinic, with the vast majority being recruited from the genetic clinics, where overall care is provided to these children. We found significant differences in IQ, achievement, neurocognition and behavior in children with 22q11DS, compared to age and gender-matched control subjects (Table 2). These results are similar to our previous report of neurocognitive deficits in children with 22q11DS (Lewandowski et al. 2007).

Table 2: Cognitive and Behavioral Abnormalities in Children with 22q11DS, Compared to Control Subjects

Measure	22q11DS	Control	t-value	Cohen's d
WISC-Full Scale IQ	71.38 (12.17)	102.50 (13.0)	13.22***	>1.0
WISC—Verbal Comprehension	76.7 (12.0)	102.6 (13.6)	11.50***	>1.00
WISC—Perceptual Organizational	74.8 (12.2)	104.3 (14.0)	11.67***	>1.00
WISC—Working Memory	78.1 (14.6)	99.9 (12.3)	8.09***	>1.00
WISC—Processing Speed	78.0 (14.5)	99.2 (13.9)	7.52***	>1.00
WIAT—Broad Reading	83.1 (16.2)	95.0 (16.7)	3.77***	0.72
WIAT—Broad Math	72.5 (18.6)	101.5 (14.5)	8.83***	>1.00
Continuous Performance Test—IP	0.34 (0.47)	1.00 (0.66)	6.07***	>1.00
Continuous Performance Test—AX	1.22 (1.11)	2.54 (1.16)	6.06***	>1.00
Wisconsin Card Sort Perseverative Errors	85.8 (9.9)	103.1 (13.3)	7.89***	>1.00
California Verbal Learning test	−1.32 (1.10)	1.00 (0.66)	6.07***	1.34
Global Assessment of Functioning	62.8 (8.6)	70.6 (10.3)	4.17***	0.82
CBCL—Overall Competence*	36.7 (8.7)	43.3 (10.9)	3.15**	0.66
CBCL—Internalizing*	59.2 (13.6)	50.7 (12.3)	3.07**	0.66
CBCL—Externalizing*	51.9 (9.1)	49.2 (11.7)	1.22	0.26
CBCL—Problem Score*	60.33 (10.03)	49.22 (11.6)	4.5***	0.87
SSRS—Social Skills*	90.3 (18.6)	98.7 (17.9)	2.12*	0.46
SSRS—Social Impairment*	105.3 (15.4)	100.9 (16.1)	1.30	.28
DSM-IV Anxiety Disorders	51%	12%	FET<.000	
DSM-IV AD/HD	41%	41%	FET=1.00	
DSM-IV Oppositional Defiant Disorder	13%	12%	FET=1.00	

*$p < .05$ **$p < .01$ ***$p < .001$
Note. Scores for the WISC, WIAT, WCST and SSRS are reported in standard scores with a mean = 100 ± 15, with higher scores reflecting a better performance; scores for the Continuous Performance Test and the California Verbal Learning Test are reported in z-scores, with mean = 0+1, and higher scores reflecting a more intact performance; scores for the Global Assessment of functioning Scale are reported in raw scores, with higher scores reflecting a more intact performance; CBCL scores are reported in T-score format with a mean = 50 ± 10, with higher scores reflecting more impairment. The number of subjects that data were available for the CBCL was 56 children with 22q11DS and 37 control subjects; for the SSRS, data was available on 58 subjects and 37 control subjects.
Cohen's d effect size: 0.2 = small effect; 0.5 = medium effect; 0.8 = large effect

Neither SES nor group membership was significantly correlated with age (r = −.03 and .04, respectively), ruling out multicolinearity problems with these variables. Likewise, group and SES were uncorrelated (r = −.09). Five subjects with 22q11DS in the present study had a parent

with a 22q11.2 deletion. The mean parental/guardian SES was significantly lower for children who had a parent with 22q11DS, compared to those who did not have an affected parent ($p < 0.001$). However, it is to be noted that two of these five children were being raised by relatives and did not live with the affected parent; the SES of the guardian was used for the analyses and not of the affected parent.

On examination of the correlations between parental SES and neurocognition/behavior in the 22q11DS and control groups separately, we found that in the 22q11DS group, lower SES was associated with more behavior problems and poor social skills, whilst in the control group, parental SES was strongly associated with cognition and not with behavior, although the incidence of some of the behavior problems such as ODD were similar in both groups. For descriptive purposes, the partial correlations of SES with the dependent measures (with age partialed out) are presented in Table 3.

Table 3: Pearson Partial Correlations of SES and Measures of Neurocognition, Behavior, and Clinical Status Separately by Group (Effect Sizes 0.1 = small, 0.3 = medium, 0.5 = large)

Dependent measure	22q11DS Group	Control group
WISC-Full Scale	−.34*	−.39**
WISC—Verbal Comprehension	−.26	−.40***
WISC—Perceptual Organization	−.32*	−.13
WISC—Working Memory	−.32*	−.54***
WISC—Processing Speed	−.15	−.40**
WIAT—Broad Reading	−.19	−.30*
WIAT—Broad Mathematics	−.33*	−.45**
Wisconsin Cart Sort Perseverative Errors	−.12	−.27
Continuous Performance Test—IP	−.19	−.24
California Verbal Learning Test	.03	−.31*
Global Assessment of Functioning	−.39**	−.10
CBCL—Overall Competence	−.61***	−.27
CBCL—Internalizing	−.02	.05
CBCL—Externalizing	.02	.09
CBCL—Problem Score	.01	.14
SSRS—Social Skills	−.37**	−.10
SSRS—Social Impairment	.12	.09
DSM-IV Anxiety Disorder	.13	.22
DSM-IV AD/HD	.08	.07
DSM-IV ODD	.42***	.17

*$p < .05$ **$p < .01$ ***$p < .001$

Partial correlations with age at assessment partialed out. Note that lower parental SES scores reflect higher socioeconomic position and hence a negative correlation means that higher parental SES is associated with better performance on the domain tested.

On linear regression analyses to determine the amount of variance in psychological functioning associated with age, group membership and SES, we found that achievement and neurocognition scores were worse in older children, an expected finding, since with age the gaps in achievement and cognition widen between children with 22q11DS and typically developing children. We also found that parental SES accounts for a significant variance in several cognitive and behavioral measures in our cohort. As expected, we found that group membership also accounted for significant variance in cognition and behavior, with the 22q11DS group performing poorly. We did not find an interaction between group membership and SES, which indicates that the association between SES and cognition/behavior is not worse in one group as opposed to the other. However, SES is associated with different domains of cognition and behavior in the two groups, as noted above and in Table 3. The results and effect sizes (f^2) are for the linear regression analyses are presented in Table 4 and the binary logistic regressions in Table 5.

Table 4: Relationship of SES and Group with Continuous Measures of Neurocognition, Behavior, and Clinical Status

Criterion	Step 1: Age			Step 2: SES			Step 3: Group			Step 4: SESxGroup		
	β	Δ	f^2	β	Δ	f^2	β	Δ	f^2	β	Δ	f^2
GAF	−.14	.020	.02	−.25*	.063	.07	.37***	.136	**.17**	.10	.009	.01
WISC—Verbal	−.08	.006	.01	−.27**	.074	.08	.70***	.491	**1.14**	−.06	.004	.07
Perceptual Org	−.08	.006	.01	−.19*	.036	.04	.75***	.550	**1.35**	.04	.001	.00
Working Memory	−.23*	.053	.06	−.33**	.110	.13	.62***	.378	**.82**	−.07	.005	.01
Processing Speed	−.26**	.067	.07	−.20*	.038	.04	.60***	.354	**.65**	−.13	.015	.03
WIAT Broad Reading	−.35***	.124	.14	−.24**	.58	.07	.34***	.116	.17	−.09	.007	.01
WIAT Broad Math	−21*	.043	.04	−.30**	.092	.11	.65***	.414	**.92**	−.03	.001	.00
WCST_PE	.09	.008	.01	−.16	.025	.03	.59***	.347	**.56**	−.09	.008	.01
CPT-IP	.55***	.306	.44	−.14	.019	.03	.47***	.347	**.47**	−.03	.001	.00
CVLT	−.02	.000	.00	−.08	.015	.02	.55***	.302	**.44**	−.15	.020	.03
CBCL Competency	−.20	.040	.04	−.46***	.213	**.29**	.32***	.098	**.15**	.08	.006	.01
CBCL Internalizing	.19	.034	.04	.01	.000	.00	−.33**	.108	.13	.02	.000	.00
CBCL Externalizing	.20	.040	.04	.04	.002	.00	.−15	.022	.02	.03	.001	.00
SSRS Social Skills	−.11	.012	.01	−.28**	.079	.09	.22*	.047	.05	.13	.015	.02
SSRS Impairment	.11	.011	.01	.10	.011	.01	−.14	.020	.21	−.01	.000	.00

*$p < .05$ **$p < .01$ ***$p < .0001$

Medium and large effect sizes (f^2) are bolded. Positive β at step 2 indicates higher SES is associated with better cognitive performance, at step 3 indicates better cognitive performance in the control group than in the 22q11DS patient group. *Please note that the effect sizes for variance in neuropsychological measures associated with SES (Step 2) may be lower than expected, since SES is mediating different neurocognitive domains in the 22q11DS group compared to the control group*

Table 5: Relationship of SES and Group with Diagnoses

Criterion	Step 1 Age		Step 2 SES		Step 3 Group		Step 4 SESxGroup	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Any Anxiety	1.00	.86–1.18	1.39	.92–2.09	.37***	.22–.61	1.25	.70–2.22
AD/HD	.97	.83–1.13	1.22	.82–1.79	1.01	.69–1.48	1.02	.67–1.55
ODD	.92	.72–1.17	3.00***	1.58–5.67	1.19	.63–2.26	.77	.38–1.53

*$p < .05$ **$p < .01$ ***$p < .001$

Although our analyses were based on *a priori* hypotheses, we applied the Bonferroni correction method for multiple correlations: lowering the α to .002 would still retain the significance of associations between oppositional defiant disorder and the CBCL—overall competence in the 22q11DS group and the correlations between SES and full-scale and verbal IQ and working memory in the control group.

DISCUSSION

Although there is a reasonable body of literature describing the IQ, achievement, neurocognitive and behavior abnormalities in children with 22q11DS, there is a lack of published studies that have assessed the role of the environment in functioning in these domains. We are the first to examine the association of parental SES with cognition and behavior in children with 22q11DS. Our results indicate that in the 22q11DS group, parental SES is mainly associated with variance in behavior problems and less so with cognition. In contrast, control subjects' parental SES was associated with IQ and achievement, but not with behavior problems. We discuss below the possible reasons for these results and the potential utilization of this information.

Oppositional defiant disorder (ODD) and lower parental SES were correlated in the 22q11DS group and not the controls, indicative of the differential relationship between SES and behavior in the two groups. Paralleling this finding, children with 22q11DS from lower SES families had

higher rates of behavior problems on the CBCL scales as evidenced by more problems with overall competency as wells as poor social skills on the SSRS, compared to those from higher SES families. These findings were consistent with our hypothesis that SES impacts upon behavior in children with 22q11DS, but contrary to our postulation it did not correlate as much with cognition. Although we found correlations between working memory and broad mathematics skills and SES in children with 22q11DS, they were not as pronounced as they were in the control group. Higher neurocognitive skills such as sustained attention, executive function and verbal learning and memory also did not correlate with parental SES in the 22q11DS group. Although we and others have found a high incidence of anxiety disorders (∼50%) in children with 22q11DS (Arnold et al. 2001; Swillen et al. 1999), we found no correlation between those and SES in this study. We infer that neurocognitive functions and anxiety disorders are mainly affected by the hemizygous deletion of the 22q11.2 region and that SES may not influence these domains above and beyond the deletion.

The behavioral problems in children with 22q11DS are numerous and include poor social skills, higher rates of internalizing symptoms, anxiety, ODD and inattention (Swillen et al. 1999; Swillen et al. 2000). Their temperament has been described to be moderately difficult (Antshel et al. 2007). All of these would be expected to interfere with the overall functioning of these children and indeed we have reported poor global function in children with 22q11DS (Lewandowski et al. 2007). In this study we found a relationship between overall function (GAF) and SES, in the same direction as the measures of behavior, a likely reflection of the impact of the behavior problems upon their overall functioning. This leads to the logical question as to whether this information could be used in implementing effective interventions in these children taking into account their SES, to improve functionality. Although this question is not as of yet answered, by studying SES within the framework of 22q11DS we have the potential to examine environmental factors that contribute to the neurobehavioral phenotype of these children. Assuming that all of the cognitive and behavior problems are causally related to the deletion deprives us of the opportunity to develop interventions that may be beneficial in improving functionality.

In the typically developing control group, full-scale IQ as well as many of the IQ sub-indices were associated with parental SES, similar to the reports in the literature (Hackman and Farah 2009) and our hypothesis that parental SES is associated with variance in childhood cognition in the general population. However, we did not see significant associations between behavior and parental SES in this group, contrary to reports in the literature. The reasons for this may be our small sample size of control subjects. Since the focus of this article is to examine the relationship between children with 22q11DS and their parental SES, the sample size of the controls is not a detractor. Moreover, the several published studies on SES and cognition/behavior in typically developing children serve as a comparison for children with 22q11DS in our report. However, it is to be noted that in our study, the incidence of some behavioral problems such as ODD was similar in the control population as in the 22q11DS group (Table 2) and thus the lack of correlation between SES and behavior in the control group indicates that behavior is not as associated with SES in the typically developing control children, as it is in the 22q11DS group.

The limitation of our study is that we did not examine other psychosocial factors, such as parenting style and schooling as variables in the environment of children with 22q11DS;

however, as stated above our study represents an important first step in this direction. One or more of these factors as well as phenomena such as epigenetic regulation of gene expression could be underlying the association between SES and behavior in our cohort of children with 22q11DS. Thus, our study does not establish a causal relationship between parental SES and behavior problems in children with 22q11DS, but highlights the need to further examine the contribution of environmental factors to the psychological phenotype in these children.

What utility would this information provide for children with 22q11DS? We are not aware of any study that would answer this question, but there are important parallels to be drawn from studies involving typically developing children. With parental warmth and SES accounting for a significant proportion (2/3) of the shared variance in general cognitive ability in early childhood in typical children (Petrill and Deater-Deckard *2004*), interventions aimed at overcoming the disadvantages of lower SES, have reported encouraging outcomes with gains in language (Fernald et al. 2008) short-term gains in IQ, but more importantly long-term effects upon high-school graduation rate, home ownership and functionality in society (Muennig et al. 2009; Ramey and Ramey 1998; Weikart 1998). These programs focused on improving academic performance by intensive remediation of executive skills, reasoning skills and direct academic content instruction, as well as increasing parental involvement in their children's education. The children in these longitudinal studies showed more self-regulation, discipline and perseverance; it is thought that these behaviors can be taught from a young age and are more predictive of academic performance than IQ alone (Duckworth et al. 2007; Duckworth and Seligman 2005). Implementation of similar interventions for children with 22q11DS may help alleviate the behavior and cognitive problems and thus increase functionality. The high risk of psychosis in these children mandates attention to the behavior and emotional functioning in childhood and raises the question as to whether childhood interventions would have an impact upon the neurocognitive and behavioral abnormalities seen with the onset of psychosis.

Although the current study was not directly designed to test this, SES may an important variable which influences the home and school environment. Families of lower SES may not have the resources required to strongly advocate for accommodations in the school setting; they may have time limitations due to work schedules that affect their availability to tackle academic and behavioral concerns and lower SES may increase stress levels in the family which in turn may influence the child's behavior. These have implications for the genetic counseling setting, as this study has demonstrated a clear correlation between SES and behavior in children with 22q11DS. Our finding of a significantly lower parental SES in children with 22q11DS who had an affected parent ($n = 5$) compared to those that did not have an affected parent could be indicative that having an affected parent can result in socioeconomic difficulties, not surprisingly, since the deletion would be expected to impact upon the level of education of the affected parent and possibly the occupation of that individual. However, since two of the five children were being raised by relatives, the SES of the guardian was used, not that of the affected parent. Due to this and due to the small number of children with 22q11DS who had an affected parent in this study, further research is needed to make inferences about the relationship between SES and having an affected parent.

The traditional model of genetic counseling has been to alleviate the stress of a family with a genetic disorder by providing them information to increase their knowledge of the condition and

their perceptions of it and less so on identifying environmental factors that may be improved to enhance functionality of the child. Contextual models of family stress have identified the availability/lack of resources to be an important factor in mediating stress a family goes through when multiple demands/stressors leads to "pile-up" resulting in maladaptation or a crisis (Boss 1988; McCubbin et al. 1996). Pile-up is defined as the long-term effect of both normative and non-normative stressors on the family and results from demands made on the family that is inclusive of the effects of the family finances, health, and ability to work (McCubbin et al. 1996). Families with a child with 22q11DS who face multiple challenges, not the least of which are behavioral problems which cause parental stress(Briegel et al. 2008), would certainly fit into this model, with families with lower SES likely to have less access to resources. We suggest that genetic counseling for families with a child with 22q11DS include inquiries about access to resources that may mitigate the behavior problems, such as social skills training and referral to appropriate services, especially since behavior problems are well known to be associated with poor functionality (Kushnir and Sadeh 2010; Pitzer et al. 2009).

Genetic counselors are in a unique position to assist families that have limited resources to obtain access to support, by teaching parents how to advocate for additional school services, providing written information specific to school challenges in children with 22q11DS, or writing letters advocating for additional accommodations on the child's behalf, such as social skills training. Genetic counselors in a pediatric setting often have the opportunity to follow families long-term. Long-term follow up allows genetic counselors to partner with the parents to not only provide information, but to also help identify the child and families' needs, provide anticipatory guidance, and to facilitate referrals to appropriate developmental and educational professionals (McConkie-Rosel A 2007). Additionally, these interventions can be tailored according to the age of the child with 22q11DS. They also can involve a social worker to help the parents to navigate federal or state assistance programs, thereby potentially reducing financial stress caused by medical bills. They can emphasize the importance of support groups in providing encouragement and collaboration in facing challenges specific to raising a child with 22q11DS and parental training in learning to manage behavioral problems in the children. It is our duty to consider these and other opportunities to assist our patients and their families, especially in families of lower SES as demonstrated by the results of this study. We wish to emphasize that lower SES alone should not be an indication for recommending specific intervention programs, but that lower SES should prompt the genetic counselor to ask the family about the access to resources and if needed, further referrals as listed above.

Research on SES and cognition is viewed by many as being undesirable, with the suspicion that inferences will be made to indicate that individuals of lower socioeconomic status are inferior or undeserving (Raizada and Kishiyama 2010). On the contrary, we hope that studies that examine environment and psychological functioning in children with 22q11DS will highlight the need for educational and social intervention programs for these children. We are cognizant of the fact that characterizing the complex environment of children, whether they have 22q11DS or are typically developing, involves much more than examining parental SES; other variables that need to be examined include parenting style, schooling, neighborhoods and levels of stress in the child and family members-all of which are potentially modifiable from a treatment perspective. Although genetic counselors and physicians are not in a position to change the SES status of a family, working within the framework of modifying factors that can be changed, such as maximizing the

availability of resources, increasing parental awareness and involvement are means that have the potential to yield positive results. Our study of the relation of parental SES with neurocognition and behavior in children with 22q11DS is an important first step to highlight awareness of the importance of the environment in the neurodevelopmental outcomes for these children. Interventions that could improve these environmental factors would need to be systematically examined; examples of some of these would be to optimize schooling, parenting, social skills training and on a larger scale assess the impact of improving the SES of these families as part of society. Further research in these areas is needed to answer these critically important questions and we are hopeful that our article will stimulate this field, particularly with respect to the role of the genetic counselor working with this population and their families.

DISCLOSURES
The authors have no conflict of interest to declare. The primary author, Vandana Shashi has all the data presented in this manuscript and this data would be available to the journal, if necessary, for examination.

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