ORIGINAL ARTICLE

Autism Spectrum Disorders and Autisticlike Traits

Similar Etiology in the Extreme End and the Normal Variation

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Context: Autism spectrum disorders (ASDs) have been suggested to represent the extreme end of a normal distribution of autisticlike traits (ALTs). However, the evidence of this notion is inconclusive.

Objective: To study whether there are similar genetic and/or environmental etiologies behind ASDs and ALTs.

Design: A nationwide twin study.

Participants: Consenting parents of all Swedish twins aged 9 and 12 years, born between July 1, 1992, and December 31, 2001 (n=19 208), were interviewed by telephone to screen for child psychiatric conditions, including ASDs.

Main Outcome Measures: Two validated cutoffs for ASDs, 2 cutoffs encompassing the normal variation, and 1 continuous measure of ALTs were used with DeFries-Fulker extreme-end analyses and standard twin study methods.

Results: We discerned a strong correlation between the 4 cutoffs and the full variation of ALTs. The correlation was primarily affected by genes. We also found that the heritability for the 4 cutoffs was similar.

Conclusion: We demonstrate an etiological similarity between ASDs and ALTs in the normal variation and, with results from previous studies, our data suggest that ASDs and ALTs are etiologically linked.

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Autism spectrum disorders (ASDs; ie, autistic disorder, Asperger's disorder, and pervasive developmental disorders) are characterized by deficits in social interaction, communication, and behavioral flexibility[1] and affect about 1% of the population.[2] Population-based studies have found that, in addition to the individuals with ASD, many others exhibit subthreshold autistic or autisticlike traits (ALTs), that is, problems or peculiarities in sociocommunicative behavior, perception of others and self, and adaptation to the environment that do not meet formal criteria for an ASD.[3,4] It is important for clinicians and researchers to understand whether ASDs and ALTs are different manifestations of the same underlying susceptibility or whether they have differing etiologies.

Several authors[3,5,6] have suggested that ASDs should be conceptualized as conditions arising in individuals found in the lowermost extreme end of a normal distribution of abilities for social adaptation and communication because they cannot deal with the demands made on social interaction in society. In such a model, the persons with ASDs would indeed have problems in common with the persons in the lower end of the proposed distribution who do not meet formal criteria for a mental disorder. There are several strands of evidence for this notion; factor analytic approaches have failed to show discontinuities between ASDs and ALTs.[7] Furthermore, ALTs and ASDs have convergent patterns of comorbidity; for example, ALTs and ASDs are strongly associated with attention-deficit/hyperactivity disorder (ADHD) and conduct problems.[8,9] Autisticlike traits were first noted as phenomena in relatives of individuals with ASDs,[10] and more recent studies have found subtle and severe communicative and social impairments in the parents and siblings of individuals with ASDs at rates higher than those expected by chance alone.[11-14] Finally, known risk factors for ASDs (eg, paternal age at birth) have been shown to influence ALTs,[15] and a recent (yet unreplicated) study[16] has shown that 1 high-risk autism locus (5p14.1) also was associated with normal variation of social communication.

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However, others have suggested that ASDs have distinct causes (above all, mutations and chromosomal changes)[17-19] and that the ASDs are best characterized as a category distinct from ALTs.[20] In agreement with this idea, one genome-wide association study[21] failed to identify any single-nucleotide polymorphisms associated with ALTs and ASDs, and studies[22] investigating the contribution of common genetic variation have not been particularly fruitful in capturing a substantial proportion of the variance related to the ASD phenotype. Although known genetic variants (eg, de novo copy number variants and genetic syndromes) only account for a small proportion of individuals with ASDs,[17] little is known about small-scale rare variations and highly penetrant but unknown rare variants.

One way to study whether the ASDs are best viewed as a continuum at the extreme end of normal behavior or as a distinct category is by using twin study methods. In a sample of 3400 twin pairs, no genetic or environmental thresholds could be discerned, indicating a continuity between ALTs and ASDs.[23] Still, the relatively small sample size and the lack of clinically validated cutoffs preclude conclusions on the basis of this single study.

To resolve the question of similar genetic and/or environmental causes behind ASDs and ALTs, we used DeFries-Fulker extreme-end analyses[24] in a population cohort of 19 208 twins aged 9 and 12 years who were interviewed by telephone using an instrument with 2 specifically validated clinical cutoffs and 2 statistically established cutoffs delineating ALTs at or below the 10th and 15th percentiles of the normal variation.

METHODS

PARTICIPANTS

This study was based on the nationwide cohorts of twins born between July 1, 1992, and December 31, 2001, and included in the ongoing Child and Adolescent Twin Study in Sweden (CATSS).[25-27] Parents of all twins in Sweden were contacted when their twins turned 9 (for twins born between July 1, 1995, and December 31, 2001) or 12 (for twins born between July 1, 1992, and June 30, 1995) years and asked to participate in a telephone interview that included, among other instruments, the inventory of autism tics, ADHD, and other comorbidities (A-TAC).[28,29] The CATSS has a response rate of 80% and consists of 28% monozygotic (MZ) twins, 36% dizygotic (DZ) same-sex twins, 34% DZ opposite-sex twins, and 2% twins with unknown zygosity (DZ opposite-sex twins and twins with unknown zygosity were excluded from the analyses). In total, 178 twins with brain damage, such as cerebral palsy, or known chromosomal syndromes, such as Down syndrome and fragile X syndrome, were excluded from the analyses. Zygosity was determined by a validated algorithm with a greater than 95% predictive value compared with DNA testing.[26] Boys constituted 51.2% of the sample. Informed consent and ethical approval were appropriately obtained (the CATSS study has ethical approval from the Karolinska Institute Ethical Review Board under contracts Dnr 03-672 and 2010/507-31/1).

MEASURES

The ASD-related symptoms were measured by 17 items in the A-TAC, including 12 questions specifically addressing the *DSM-IV* symptom criteria for autistic disorder (299.00), which predicted clinical expert ASD diagnoses according to the *DSM-IV* criteria for pervasive developmental disorders with an area under a receiver operating characteristic curve of 0.96.[29] The A-TAC is freely available from the Web as an appendix to the study by Larson et al.[29] Of the 17 items in the ASD gate score, 6 correspond to the language domain, 6 to the social interaction domain, and 5 to the restricted and repetitive behavior domain. The items were scored 1 for yes, 0.5 for yes to some extent, and 0 for no. For continuous univariate twin analysis, a sum score ranging from 0 to 17 was used.

To perform the extreme analyses, the following 4 dichotomous cutoffs were used: (1) a high cutoff (HiC) of 8.5, with a sensitivity and specificity of 0.71 and 0.95, respectively, and with a prevalence of 0.8% (used as a validated proxy for clinical diagnoses of ASDs[29]); (2) a lower cutoff (LoC) of 4.5, yielding a sensitivity and specificity of 0.96 and 0.88, respectively, with a prevalence of 3.0%,[25] thus corresponding to the notion of a broader autistic or autisticlike phenotype; and (3) 2 cutoffs aimed to capture the wider variation of ALTs (10C and 15C) as close to the 10th and 15th percentiles, respectively, as possible, yielding a prevalence of 8.7% and 12.4%, respectively. Because these cutoffs were not aimed at identifying a clinical condition, sensitivity and specificity were not calculated.

ANALYSES

Twin methodology relies on the genetic relatedness of MZ vs DZ twins. The MZ twins are genetically identical, whereas DZ twins, just like any full siblings, on average share 50% of their segregating alleles. If a trait is influenced by genes, there will be a higher twin similarity within MZ twin pairs than within DZ twin pairs. Twin similarity is measured by the intraclass correlation for continuous traits and by tetrachoric correlations for dichotomous outcomes. A higher correlation for MZ twins than for DZ twins implies genetic effects on the measured trait. Tetrachoric cross-twin cross-cutoff correlations were used to determine the relationship between various cutoffs.[30] A high correlation coefficient indicates that the cutoffs are different degrees of the same underlying process. In addition, a higher correlation coefficient for MZ twins compared with DZ twins suggests shared genetic influences across the cutoffs.

Twin analyses can be used to estimate the relative importance of genetic and environmental effects. The variation in a phenotype is decomposed in the following 3 factors: additive genetic factors, shared environmental factors (ie, factors that make the 2 twins in a pair alike), and nonshared environmental factors (ie, factors that make the 2 twins in a pair dissimilar).[31] In the present article, standard continuous (ie, individual differences analyses) and categorical (ie, threshold models) univariate twin analyses were used to estimate heritability.[32] We did not attempt to reduce the univariate models because this can lead to biases and inaccuracy in the observed estimates.[33] Because ASDs have markedly different prevalences across sexes, sex-specific analyses were first attempted. Because separate analyzes for girls were not feasible owing to insufficient statistical power, analyses were conducted for both sexes collapsed and for boys separately. A total of 5028 MZ and 6507 same-sex DZ twins were included in the individual differences and threshold models analyses, of whom 2442 and 3466, respectively, were boys.

EXTREMES ANALYSES

DeFries and Fulker[24] proposed a model (DeFries-Fulker analyses) to analyze twin data in extreme scoring groups to assess the heritability for an extreme trait. Briefly, in DeFries-Fulker analyses, probands are identified and the continuous score of the co-twin is used to obtain heritability estimates. A mean stan-

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Table 1. Descriptive Statistics

Group	Total Sample, No.	Autism Score, Mean (SD)	Pair Prevalence by Cutoff, No. (%)				Proband Mean				Co-twin Mean			
			HiC	LoC	10C	15C	HiC	LoC	10C	15C	HiC	LoC	10C	15C
All	**11 535**	0.7 (1.5)	**96** (0.8)	**350** (3.0)	**1003** (8.7)	**1440** (12.5)	10.6	7.1	4.5	3.7	4.4	3.1	2.3	2.1
Boys	5908	0.9 (1.7)	76 (1.3)	251 (4.2)	648 (11.1)	909 (15.4)	10.7	7.3	4.7	3.9	4.7	3.3	2.5	2.3
Girls	5627	0.6 (1.2)	20 (0.4)	99 (1.8)	355 (6.3)	531 (9.4)	10.5	7.0	4.1	3.4	3.2	2.6	1.9	1.7
Twins														
MZ	5028	0.7 (1.3)	38 (0.8)	114 (2.3)	378 (7.5)	558 (11.1)	10.1	7.3	4.3	3.6	6.2	5.1	3.1	2.6
DZ	6507	0.8 (1.6)	58 (0.9)	236 (3.6)	625 (9.6)	882 (13.6)	10.9	7.1	4.6	3.8	3.2	2.2	1.8	1.7
Male														
MZ	2442	0.8 (1.6)	30 (1.2)	85 (3.5)	241 (9.9)	348 (14.3)	10.2	7.3	4.6	3.8	7.0	5.4	3.5	2.9
DZ	3466	1.0 (1.8)	46 (1.3)	166 (4.8)	407 (11.7)	561 (16.2)	11.0	7.3	4.8	4.0	3.2	2.2	1.9	1.8
Female														
MZ	2586	0.5 (1.0)	8 (0.3)	29 (1.1)	137 (5.3)	210 (8.1)	9.9	7.2	3.9	3.2	3.1	4.0	2.3	2.0
DZ	3041	0.7 (1.3)	12 (0.4)	70 (2.3)	218 (7.2)	321 (10.5)	10.8	6.5	4.2	3.5	3.3	2.0	1.7	1.5

Abbreviations: DZ, dizygotic; 15C, 15th percentile cutoff; HiC, high cutoff; LoC, low cutoff; MZ, monozygotic; 10C, 10th percentile cutoff.

dardized quantitative trait score (represented as sq) was calculated via the following equation:

$$sq = a - \bar{x} \,/\, \bar{y} - \bar{x},$$

where a is the quantitative trait of the co-twin; $\bar{x}$, the population mean; and $\bar{y}$, the proband mean. This score ranges from 0.00 to 1.00; 0.00 is the population mean and 1.00 is the proband mean. This estimate is basically a correlation coefficient between the full variation of a quantitative trait in the co-twin to a proband and the narrowly defined extreme-end condition in the proband. These correlations in MZ and DZ twins can then be used to estimate genetic (commonly called *group heritability*) and environmental contributions in the same fashion as for any quantitative trait. To estimate the group heritability, a regression model predicting the score of the co-twin can be used.[34] The regression can be expressed as follows:

$$C = B1P + B2R + D,$$

where C is the co-twin score; P, the proband score; R, the genetic relatedness (1.0 for MZ and 0.5 for DZ twins); $B1$, the partial regression of the co-twin's score on the proband's score and a measure of twin resemblance,independent of zygosity; $B2$, a regression coefficient estimating the group heritability; and D, a regression constant. If the effect is due solely to nonshared environmental influences, then the co-twin shares none of these etiological influences with the proband. Therefore, the means of MZ and DZ co-twins should regress equally to the population mean. However, if the trait is affected by genetic factors, the co-twin mean of the MZ twins should regress less toward the population mean than the co-twin mean of the DZ twins. The genetic estimation accounts for all possible genetic contributions (eg, dominance, epistasis, or additive effects) shared between the extreme-end condition and the variance in the quantitative trait. Therefore, if the extreme group correlations show a pattern of dominance (ie, a MZ correlation more than twice as high as the DZ correlation), group heritability is to be restrained to the value of the MZ correlation. Probandwise concordance rates (ie, the risk for a co-twin receiving the same diagnosis as the proband) were calculated across the 4 cutoffs. All analyses were conducted using commercially available statistical software (SAS, version 9.2 [SAS Institute, Inc, Cary, North Carolina] or Mx[32]).

RESULTS

Descriptive statistics for all cutoffs and zygosities are provided in **Table 1**. Mean (SD) continuous autism score for boys was 0.9 (1.7) with a prevalence of 1.3% for the proxy for a clinical diagnosis (HiC). For girls, the mean autism score was 0.6 (1.2) and the HiC prevalence was 0.4%. The male to female ratio regardless of zygosity was 4:1 in the HiC. Table 1 also provides the mean continuous autism score for the co-twins of probands by the different cutoffs.

INDIVIDUAL DIFFERENCES AND THRESHOLD MODELS

Twin similarity, as measured by intraclass correlations and tetrachoric correlations (**Table 2**), was higher for MZ twins than for DZ twins in the collapsed analyses and for boys only. This was verified by the model-fitting analyses, which yielded a heritability estimate of 0.71 (95% CI, 0.69-0.73) for the entire sample and 0.75 for boys when using the continuous ASD measure, as well as by the threshold models, in which the heritability estimates for ASDs using the HiC were 0.59 (95% CI, 0.08-0.91) for the entire sample and 0.77 (0.21-0.95) for boys (**Table 3**). The cross-twin cross-cutoff correlations were consistently around 0.70 to 0.80 and higher for MZ twins than for DZ twins; between the HiC and the 10C, the correlations were 0.72 (0.60-0.84) and 0.41 (0.24-0.57), respectively (Table 2). In addition, the proband-wise concordance rates were higher for MZ twins than for DZ twins (**Table 4**).

EXTREMES ANALYSIS

The correlation coefficient between the full variation of ALTs and the HiC for MZ twins in the entire sample was 0.59, whereas this correlation for DZ twins was 0.24 (**Table 5**). This corresponded to a "group heritability" of 0.59 (95% CI, 0.44-0.74), indicating that 59% of the correlation between the full variation of ALT and caseness was accounted for by genetic effects (**Table 6**). For the LoC, 10C, and 15C, the genetic contribution to the correlation was about 66%, and the contribution from nonshared environmental factors was around 34% (Table 6). The analyses conducted for boys alone revealed a higher degree of genetic influence, where roughly 70% of the correlation could be attributed to genetic ef-

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Table 2. Twin Similarity for Dichotomous Outcomes and Cross-Twin Cross-Cutoff Correlations for the Entire Sample and for Boys Only[a]

Twin Cutoff	Tetrachoric Correlation and Cross-Twin Cross-Cutoff (95% CI)							
	All				Boys Only			
	HiC	LoC	10C	15C	HiC	LoC	10C	15C
MZ								
HiC	**0.83 (0.70-0.96)**	0.84 (0.75-0.93)	0.72 (0.60-0.84)	0.68 (0.55-0.80)	**0.86 (0.73-0.99)**	0.86 (0.75-0.96)	0.79 (0.66-0.92)	0.72 (0.58-0.88)
LoC	0.70 (0.53-0.87)	**0.87 (0.80-0.94)**	0.83 (0.77-0.90)	0.78 (0.71-0.85)	0.70 (0.52-0.89)	**0.86 (0.79-0.94)**	0.86 (0.79-0.93)	0.80 (0.72-0.89)
10C	0.72 (0.56-0.88)	0.82 (0.75-0.90)	**0.80 (0.75-0.85)**	0.79 (0.74-0.84)	0.73 (0.56-0.90)	0.82 (0.73-0.90)	**0.84 (0.78-0.89)**	0.83 (0.77-0.89)
15C	0.74 (0.57-0.90)	0.81 (0.73-0.89)	0.80 (0.75-0.84)	**0.78 (0.73-0.83)**	0.75 (0.57-0.92)	0.80 (0.70-0.89)	0.79 (0.73-0.86)	**0.80 (0.75-0.86)**
DZ								
HiC	**0.54 (0.37-0.70)**	0.44 (0.28-0.61)	0.41 (0.24-0.57)	0.54 (0.37-0.70)	**0.33 (0.29-0.37)**	0.53 (0.34-0.72)	0.45 (0.26-0.63)	0.43 (0.24-0.61)
LoC	0.38 (0.25-0.51)	**0.41 (0.31-0.52)**	0.40 (0.30-0.50)	0.38 (0.25-0.51)	0.36 (0.13-0.58)	**0.47 (0.20-0.74)**	0.35 (0.22-0.49)	0.35 (0.22-0.48)
10C	0.34 (0.23-0.45)	0.42 (0.34-0.50)	**0.41 (0.34-0.49)**	0.34 (0.23-0.45)	0.24 (0.02-0.44)	0.32 (0.18-0.45)	**0.31 (0.15-0.48)**	0.39 (0.29-0.48)
15C	0.35 (0.25-0.52)	0.44 (0.37-0.51)	0.45 (0.38-0.52)	**0.35 (0.25-0.52)**	0.18 (0.01-0.40)	0.33 (0.21-0.45)	0.42 (0.33-0.51)	**0.43 (0.34-0.52)**

Abbreviations: DZ, dizygotic; 15C, 15th percentile cutoff; HiC, high cutoff; LoC, low cutoff; MZ, monozygotic; 10C, 10th percentile cutoff.
[a]For continuous outcomes, intraclass correlations (95% CI) for all MZ twins were 0.68 (0.66-0.70); for all DZ twins, 0.36 (0.33-0.39); for male MZ twins, 0.71 (0.68-0.74); and for male DZ twins, 0.33 (0.29-0.37). Tetrachoric correlations on the diagonal are given in boldface.

Table 3. Estimates of Genetic and Environmental Effects for the 4 Cutoffs

Outcome	Genetic and Environmental Effect (95% CI)					
	All			Boys Only		
	A	C	E	A	C	E
Continuous	0.71 (0.69-0.73)	0.00 (0.00-0.00)	0.29 (0.28-0.31)	0.75 (0.72-0.77)	0.00 (0.00-0.00)	0.25 (0.25-0.28)
Dichotomous						
HiC	0.59 (0.08-0.91)	0.23 (0.00-0.64)	0.18 (0.08-0.36)	0.77 (0.21-0.95)	0.08 (0.00-0.57)	0.14 (0.05-0.32)
LoC	0.88 (0.71-0.93)	0.00 (0.00-0.15)	0.12 (0.07-0.20)	0.86 (0.69-0.93)	0.00 (0.00-0.14)	0.14 (0.07-0.23)
10C	0.76 (0.57-0.84)	0.03 (0.00-0.19)	0.21 (0.16-0.27)	0.82 (0.62-0.87)	0.00 (0.00-0.18)	0.18 (0.13-0.25)
15C	0.66 (0.49-0.81)	0.11 (0.00-0.25)	0.23 (0.19-0.28)	0.74 (0.53-0.85)	0.05 (0.00-0.23)	0.21 (0.15-0.27)

Abbreviations: A, additive genetic factors; C, shared environmental factors; E, nonshared environmental factors; 15C, 15th percentile cutoff; HiC, high cutoff; LoC, low cutoff; 10C, 10th percentile cutoff.

Table 4. Estimates of Proband-wise Concordance Rates for the 4 Cutoffs

Cutoff	Proband-wise Concordance Rate (95% CI)			
	All		Boys Only	
	MZ	DZ	MZ	DZ
HiC	0.36 (0.18-0.58)	0.14 (0.04-0.31)	0.47 (0.23-0.69)	0.13 (0.03-0.32)
LoC	0.51 (0.40-0.63)	0.15 (0.09-0.23)	0.55 (0.41-0.68)	0.14 (0.08-0.23)
10C	0.51 (0.44-0.57)	0.32 (0.27-0.37)	0.57 (0.50-0.65)	0.29 (0.23-0.35)
15C	0.53 (0.48-0.58)	0.34 (0.30-0.38)	0.58 (0.52-0.65)	0.36 (0.30-0.41)

Abbreviations: See Table 2.

fects and 30% to nonshared environmental factors in all 3 cutoffs. Nonshared environmental effects could be discerned for the entire sample and for the boys only. Because highly skewed data may alter the DeFries-Fulker estimates,[35] we log-transformed the data and detected no differences in the results between the raw data and the log-transformed data (data not shown).

COMMENT

The analyses presented herein show a strong correlation between narrowly defined extreme-end conditions and the full variation of ALTs and that this correlation predominantly is affected by genetic factors. Also, the DeFries-Fulker analyses yielded similar group heritability estimates for the different cutoff levels, which is in agreement with the results reported by Ronald et al,[23] who also used DeFries-Fulker analyses. Taken together, the results suggest that ASDs and ALTs are related to the same genetic susceptibilities and that ASDs may represent the extreme end of a continuous distribution of ALTs in the population, as previously suggested by several research groups.[3,5,25] We found high cross-twin cross-cutoff correlations between the 4 cutoffs and group heritability es-

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Table 5. Extreme Group Correlations

	Extreme Group Correlation (No. of Probands)			
	All		Boys Only	
Cutoff	MZ	DZ	MZ	DZ
HiC	0.59 (38)	0.24 (58)	0.66 (30)	0.23 (46)
LoC	0.66 (114)	0.22 (236)	0.71 (85)	0.20 (166)
10C	0.67 (378)	0.27 (625)	0.71 (241)	0.26 (407)
15C	0.66 (558)	0.31 (882)	0.71 (348)	0.29 (561)

Abbreviations: See Table 2.

Table 6. DeFries-Fulker Estimates

	Group Estimate (95% CI)[a]			
	All		Boys Only	
Cutoff	A	E	A	E
HiC	0.59 (0.44-0.74)	0.41 (0.26-0.56)	0.66 (0.49-0.83)	0.34 (0.17-0.51)
LoC	0.66 (0.57-0.76)	0.34 (0.24-0.43)	0.71 (0.60-0.83)	0.29 (0.17-0.40)
10C	0.67 (0.59-0.74)	0.33 (0.26-0.41)	0.71 (0.61-0.81)	0.29 (0.19-0.39)
15C	0.66 (0.59-0.73)	0.34 (0.27-0.41)	0.71 (0.61-0.81)	0.29 (0.19-0.39)

Abbreviations: See Table 3.
[a] No shared environmental effect was discerned.

timates of 0.59, 0.66, 0.67, and 0.66 for the HiC, LoC, 10C, and 15C, respectively (Table 6). This suggests that the set of genes influencing our clinical proxies of ASDs to a high degree also affects ALTs. If different genes had been responsible for the most extreme ends, lower correlations and group heritabilities for the most narrow cutoffs would have been noted. Our results are in agreement with the only other twin study using this method,[23] in which a group heritability of 0.66 for its equivalence of our highest cutoff was found. In addition, we used 4 different cutoffs to study whether there were marked differences in group heritability depending on how strictly we defined caseness. Again, the group heritability was very similar across the 4 cutoffs, and these results are also in accordance with those reported by Ronald et al,[23] providing no evidence of a clear distinction between ASDs and normal variation in the trait.

Our results question a distinct boundary between pathologic changes and normality and have implications for future versions of diagnostic classification systems. For instance, Kendell and Jablensky[36] suggested that diagnostic categories are valid only if they can be viewed as discrete entities with natural boundaries, and Robins and Guze[37] and Kendler[38] emphasized that valid mental disorders should show unique genetic correlates and diagnostic consistency over time. Today, the ASDs fall short of these suggestions,[39] and our results provide no support for an overall different etiology in terms of the overall importance of genetic vs environmental effects between ASDs and ALTs. Instead, the findings reported herein align with the quantitative trait locus theory,[31] which hypothesizes that many genes, each with a small effect size, influence the whole phenotypic variation, that is, the genetic effects on ASDs may also give rise to ALTs and vice versa. Such effects could include a large number of functional polymorphisms but also larger structural changes, including so-called copy number variants. At present, the effect sizes of known genetic variations (eg, de novo copy number variants and genetic syndromes) are modest, with no cause explaining more than 2% of ASD cases, and together they account for, at most, 20% of ASD cases.[17] Further studies are needed to evaluate whether these genetic variations are important for ALTs also. Genome-wide association studies are likely to benefit from including the entire variation of ALTs,[40] or even the full population variance in sociocommunicative abilities or social personality traits, rather than being limited to narrowly defined cases diagnosed with classic forms of autism. Consensus on what the ALTs are and how to measure them properly would facilitate this approach. Today, definitions and measures vary considerably across studies, and there is no consensus with respect to what best reflects autism-related phenomena compared with autisticlike personality traits or variations in cognitive-emotional functions (eg, social responsivity and empathy[3,41,42]).

In our study, nonshared environmental factors had a modest effect on the correlation between the full variation of ALTs and the extreme ends. Nonshared environment has been identified in studies examining ASDs[26] and ALTs,[3] and possible explanations may include de novo mutations[19] and prenatal factors.[43] However, it is important to recognize that the nonshared environmental estimate also entails measurement errors.

The ASDs are heterogeneous conditions in which 2 individuals diagnosed as having the disorder do not necessarily share a single symptom.[1] Some studies have pointed to the possibility of etiological differences be-

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tween the core symptoms in ASD.[17,23] Future studies should therefore investigate whether the results reported herein are also applicable to social communication deficits on one hand and stereotyped and repetitive behaviors on the other. In addition, taxometric and latent variables models used in a genetically sensitive design may identify new latent categories within the ASDs.[20]

Our study has 2 main strengths. First, it includes a large nationwide cohort with a high response rate (80%). Second, it has access to clinically validated cutoff levels with detailed psychometric data. The results, however, also have to be interpreted in light of the limitations. First, although, at this time, ours is the largest twin study of child psychiatric conditions in the world, only 20 girls met the criteria for the HiC (ie, the proxy for a clinical diagnosis), which did not allow sex-specific analysis for girls. This will have to be postponed until an even larger group has been collected. Second, ASDs are developmental disorders and should optimally be studied over a longer period with repeated clinical assessments. However, this is rarely feasible in large epidemiological twin studies.[3,44,45] Instead, we have conducted 2 validation studies for the A-TAC, both of which demonstrated good psychometric properties,[28,29] to provide research proxies for clinical diagnoses of ASDs. Recently, the A-TAC has also been used as a dimensional measure of ALTs.[45] Third, because ASDs are rare conditions, even instruments with excellent predictive properties and specificities will identify false positives. Fourth, it is important to underscore that our material does not allow us to consider subtypes of autism related to specific causes, such as intrauterine exposure to environmental toxins (eg, thalidomide and valproate). However, there are no empirical data to delineate such specific causes in subgroups of ASDs from cases owing to tail-end exaggerations of ALTs. Because the present study includes the full variation of ASDs and ALTs (besides early brain damage and chromosomal syndromes), environmental and submicroscopic genetic variants have influenced the results. Fifth, it is possible that the underlying reasons for the similar genetic correlation across the 4 cutoffs differ; for instance, polymorphisms altering normal variation (10C and 15C) may be different from polymorphisms altering the extreme ends (HiC and LoC) but have a similar impact in terms of degree of genetic correlation. However, the results from the cross-twin cross-cutoff models speak against that notion and imply a continuum,[30] and although some such rare effects indeed exist in limited numbers of cases (but possibly with large effects in these cases[46]), it seems far-fetched that a large proportion of the genetic effects influencing the full variation of ALTs would not influence the extreme end. For example, an unreplicated novel molecular genetic study has indicated that common variation in a high-risk autism locus (5p14.1)[30] is also associated with social communication in the general population,[16] and shared pathways between specific language disorders and ASDs have been demonstrated.[47]

CONCLUSIONS

We have demonstrated etiological similarity across ASDs and ALTs in the general population. Taken together with the results of previous studies,[7,13,16,23,47] our data suggest that ASDs and ALTs are etiologically linked. In addition, it seems reasonable to assume that ASDs and ALTs differ from each other in means of severity and/or degrees of functional impairment. In the clinical setting, the findings call for reconsideration of the value of categorical diagnoses and open up the possibility that individuals may move in and out of the autism spectrum on the basis of their overall adaptation. Indeed, it is known that diagnostic stability is greater in classic autism and in the presence of mental retardation compared with Asperger's disorder in the presence of normal or high intelligence.[48] In the context of research, attention is drawn to the possibility of factors mediating the differentiation between ASDs and ALTs, such as perinatal suboptimality,[49] or gene-environment interactions.[50]

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