Published in final edited form as:

J Autism Dev Disord. 2008 July ; 38(6): 1019–1027. doi:10.1007/s10803-007-0476-z.

Level of Functioning in Autism Spectrum Disorders: Phenotypic Congruence Among Affected Siblings

Robin P. Goin-Kochel,

Molecular and Human Genetics, Baylor College of Medicine, Texas Children's Hospital, 6621 Fannin Street, CC1560, Houston, TX 77030, USA

Carla A. Mazefsky, and

Departments of Pediatrics and Psychiatry, University of Pittsburgh, PA, USA

Brien P. Riley

Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA

Robin P. Goin-Kochel: kochel@bcm.tmc.edu

Abstract

Little evidence supports that siblings with autism exhibit the same behaviors; however, some findings suggest that level of functioning shows familial aggregation. We tested this notion among multiplex families participating with the Autism Genetic Resource Exchange (AGRE) Consortium, using scores on the *Peabody Picture Vocabulary Test—Third Edition* ($N = 204$ families), the *Ravens Colored Progressive Matrices* ($N = 226$ families), and the *Vineland Adaptive Behavior Scales* ($N = 348$ families). Intraclass Correlation Coefficients revealed that siblings with autism/autism spectrum disorders (ASD) were more similar on measures of verbal and nonverbal IQ and adaptive functioning than were unrelated children with autism/ASD. Preliminary twin correlations indicated strong genetic effects for some skill domains and the influence of shared environmental factors for others.

Keywords

AGRE; Broad spectrum; Twins; IQ; Adaptive behavior

Individuals with autism spectrum disorders (ASD) present with tremendously varying degrees of severity, and this clinical heterogeneity has likely made the task of locating etiologically relevant genes more difficult. Identifying genetically homogenous subsets of individuals with ASD to participate in molecular genetic studies may increase the likelihood of detecting such genes; this effort is already reflected in the development of datasets involving families with two or more affected individuals, such as the Autism Genetic Resource Exchange (AGRE). However, few studies have examined the degree to which individual differences in level of overall functioning can be explained by genetic versus

environmental factors. If variance in the ASD phenotype is largely the result of genetic influences, then it may be possible to identify specific domains of functioning (e.g., IQ, social skills, communication skills) on which samples can be further stratified for molecular-genetic analyses.

The earliest study to investigate concordance for indices of functioning between siblings with autism was Folstein and Rutter (1977). Looking at twin pairs concordant for autism, 50% appeared phenotypically congruent in terms of cognitive and language skills. However, when the authors examined concordance for cognitive and social impairments among the twins *discordant* for autism (i.e., one twin had autism, but the other did not meet criteria according to the authors' definition), they discovered that 9 of the 11 monozygotic (MZ) twin pairs (82%) and one of the dizygotic (DZ) twin pairs (10%) were concordant for cognitive disabilities, usually related to language impairments. In a follow-up study using an expanded twin sample, the authors revealed that 92% of MZ twins and 10% of DZ twins were concordant for cognitive and/or social deficits; because these numbers included pairs that were discordant for autism, the authors concluded that these data suggested considerable genetic effects for a broader autism phenotype (Bailey et al. 1995).

Subsequent research focusing on sibling concordance for level of functioning in autism, however, has generated mixed results. For example, Spiker et al. (1994) found little to no evidence for familial aggregation of IQ, verbal ability, or specific behaviors, with the exception of ritualistic and repetitive actions, among their sample of 37 multiplex families (i.e., two or more children affected with autism or ASD). A second study 2 years later examined the same phenomenon among MZ twins, reporting significant sibling concordance only for nonverbal IQ and verbal versus nonverbal status (Le Couteur et al. 1996). Essentially, these latter reports suggested that twins and siblings with autism were phenotypically more *dissimilar* for most characteristics than were unrelated individuals with autism. Other researchers, though, found just the opposite. Szatmari et al. (1996) compared measures of intelligence, social and communication skills, and autism characteristics among 23 multiplex families using Intraclass Correlation Coefficients (ICCs) to determine the extent to which there was variability within sibships *relative to* variability between sibships. Significantly high ICCs were noted for virtually all domains measured, indicating that familial factors accounted for the greatest proportion of phenotypic variance among children with autism/PDD from different families. The authors concluded that, "Severity of impairment in measures of social-communication development, nonverbal IQ, and autistic symptoms appears to be genetically determined" (p. 359).

It is possible that these discrepant findings could be attributed to differences between small samples and the fact that some comparisons were made between siblings concordant for autism and others were between siblings discordant for autism/ASD. Subsequent investigations that utilized larger samples of multiplex families found familial resemblance for the majority of domains assessed. For example, MacLean et al. (1999) conducted a study similar to Szatmari et al. (1996) using data from 46 families, further analyzing data by sibships meeting strict criteria for autism versus those meeting criteria for any ASD (i.e., autism, Asperger's syndrome, atypical autism, disintegrative disorder). IQ and adaptive behaviors in socialization and communication showed significant familial aggregation in

both the autism-only and any-ASD groups (MacLean et al. 1999). The authors further examined phenotypic similarity for domains on the *Autism Diagnostic Interview—Revised* (ADI-R; Lord et al. 1994); only the nonverbal communication domain and verbal/nonverbal status of the children showed significant aggregation within families.

More recently, Silverman et al. (2002) investigated familial effects for ASD using the ADI-R domains and select item scores among 212 sibships. They reported significantly reduced variance within sibships for the, “severity of repetitive behaviors, the level of deficits in nonverbal communication, the presence of phrase speech, and the age at phrase speech” (p. 69). These findings corroborate MacLean et al. (1999) with respect to two of these areas (nonverbal communication and verbal/nonverbal status), demonstrating this phenomenon in a much larger sample. However, further comparisons were impossible because the authors did not investigate additional measures of functioning (e.g., IQ, adaptive behaviors). In a subsequent study focusing just on 16 families with MZ twins who were concordant for autism, the same group again used the ADI-R domains, including select individual-item scores, to examine intrafamily variation in features of autism (Kolevzon et al. 2004). Significant familial aggregation was noted for impairments in communication and social interactions but not behavior. Cuccaro et al. (2003) also used domain scores from the ADI-R to assess clinical heterogeneity among children with autism from multiplex or simplex families (i.e., only one child affected with no family history of ASD). They found no differences between groups on any ADI-R domain, which lead them to conclude that, “... clinical features of [autism] alone are insufficient in stratification for examination of complex genetic mechanisms (Szatmari 1999). Variables such as level of functioning and socialization need to be studied in more comprehensive ways” (p. 90).

It is clear that the most powerful results on familial similarity in the autism/ASD phenotype are based on data from the ADI-R. While this instrument captures information on *specific characteristics* indicative of autism and is appropriate for examining phenotypic similarities for autistic symptoms, it is not appropriate for examining phenotypic congruence for *level of functioning*. Only Szatmari et al. (1996) and MacLean et al. (1999) extended their foci to include measures of cognition and adaptive behaviors, which are generally accepted as better indications of level of functioning in ASD relative to the ADI-R. However, their results are based on relatively small samples. The main purpose of the current project, then, was to extend Szatmari et al.'s (1996) and MacLean et al.'s (1999) work on phenotypic congruence among siblings with autism/ASD with respect to level of functioning using a substantially larger, well-characterized sample of multiplex families with autism/ASD. Our second aim was to present what is, to our knowledge, the only adaptive-behavior data on MZ and dizygotic (DZ) twins with autism/ASD. We hypothesized that our findings would be comparable to those of Szatmari et al. (1996) and MacLean et al. (1999) in that siblings with autism/ASD would appear more similar on measures of cognition and adaptive functioning than unrelated individuals with autism/ASD. Additionally, we expected that twin correlations would be higher between MZ than DZ twins, suggesting that genetic effects explain the largest proportions of variance in cognitive skills and adaptive behaviors. If our hypotheses hold true, then results could suggest specific domains of functioning (e.g., cognition, communication, socialization) on which autism/ASD samples may be further

stratified for molecular-genetic studies. This action would create more phenotypically homogenous subgroups for the identification of etiologically relevant genes.

Methods

Participants

Data were ascertained on all multiplex families participating in the Autism Genetic Resource Exchange (AGRE) who had complete data for at least two full siblings on select instruments (see Table 1 for exact numbers and specific demographics available for each measure). Initial family contact is made by an AGRE family recruiter through advertisements at autism-related meetings, on the website, or by referral. Once a family indicates interest, an AGRE packet and questionnaire are distributed to them, with follow-up contacts to encourage participation and monitor return of the questionnaire. A family is registered with AGRE upon receipt of their completed questionnaire; subsequently, arrangements are made for AGRE staff to begin administering the battery of assessments in the AGRE protocol, which includes confirmation of the autism diagnoses through assessments with the *Autism Diagnostic Interview—Revised* (ADI-R; Lord et al. 1994) and the *Autism Diagnostic Observation Schedule* (ADOS; Lord et al. 2000). Because data are collected from these families in stages, the sample sizes varied for each measure.

The AGRE staff administer their battery of standardized instruments only to individuals who meet criteria, per the ADI-R algorithm, for diagnoses in the autism spectrum. They developed three computer-scored, affected-status categories based on ADI-R results: autism, Not Quite Autism (NQA), and Broad Spectrum (BS; AGRE 2006). To meet criteria for autism, the individual must exceed the ADI-R cutoff for autism in all domains. To meet criteria for NQA, the individual (a) must meet cutoff scores for autism on the three content domains (i.e., social, communication, behavior) but not on the age-of-onset domain or (b) must be no more than one point below the cutoff score on any of the three content domains while also meeting the cutoff for the age-of-onset domain. To meet criteria for BS, the individual must not meet criteria for autism or NQA as described previously. In addition, he/she must (a) show a severe deficit in at least one domain, (b) show moderate deficits in at least two domains, and/or (c) show only minimal deficits in all three domains (see <http://www.agre.org> for more specifics).

Instrumentation

While data are available on a range of instruments for families participating with AGRE, we were interested in measures of cognition and adaptive behaviors that would provide data on individuals' overall level of functioning. Additionally, we sought measures that would be comparable to those used in Szatmari et al. (1996) and MacLean et al. (1999) so that we would be able to make comparisons between our findings and theirs.

Peabody Picture Vocabulary Test—Third Edition (PPVT-III)—The PPVT-III is an individually administered, norm-referenced assessment of receptive vocabulary. It requires participants to point the correct picture of a possible four that correctly matches a spoken vocabulary word. The PPVT-III provides one total, standard score, with a mean of 100 and a

standard deviation of 15, and has a correlation of .91 with the *Wechsler Individual Test of Intelligence for Children-III Verbal IQ* (Dunn and Dunn 1997). With the exception of a full intelligence test, the PPVT-III is the most widely used measure to estimate *verbal* ability for matching in studies of individuals with ASD (Motttron 2004). For the current project, we deemed the PPVT-III as providing evidence of verbal IQ.

Ravens Colored Progressive Matrices (Ravens)—The Ravens is an individually administered, norm-referenced assessment of nonverbal processing, including the ability to discern perceptual relations and reason by analogy, that requires the participant to identify the missing piece in a visual pattern (Raven 1947, 1995). Again, with the exception of a full intelligence test, the Ravens is the most widely used measure to estimate *nonverbal* cognitive ability for matching in studies of individuals with ASD (Motttron 2004). For the current project, we deemed the Ravens as providing evidence of nonverbal IQ; raw total scores were used in the analyses, as some children's estimates for nonverbal IQ were either above or below age-specific test norms.

Vineland Adaptive Behavior Scales (VABS)—The VABS is a parental rating of how many age-appropriate, socially adaptive behaviors a child exhibits (Sparrow et al. 1984). It is a well-recognized instrument in the child development literature, with demonstrable reliability and validity both for children who are typically developing and those with disabilities. It is also the preeminent measure for the assessment of adaptive functioning in children with autism (Newsom and Hovanitz 1997). The VABS provides standard scores ($M = 100$, $SD = 15$) for four skill domains: communication, daily-living, socialization, and motor; and higher scores indicate better functioning. Supplementary norms for individuals with autism are now available for the VABS; Carter et al. (1998) reported the following average scores per skill domain for verbal children with autism under age 10 ($n = 141$): communication—62.64 ($SD = 19.8$), daily living—55.35 ($SD = 19.3$), socialization—59.73 ($SD = 12.7$), and composite—55.00 ($SD = 15.9$).¹

Procedure

Permission was granted to access the AGRE database. Data for the selected instruments, along with the AGRE pedigree file, were downloaded and converted into SAS® files. Because participants in the AGRE system are given person numbers that correspond to their (a) status as parent, grandparent, child, or other relative and (b) birth order among children, we gave each sibling with ASD an additional number—a sibling identification number—indicating which *affected* child he/she was in that family. This arrangement preserved the birth order and allowed us to appropriately organize the data for full siblings with ASD on whom complete data were available.

Analyses—Descriptive statistics were first run to characterize the samples and illustrate potential variation in individual scores. The extent to which level of functioning varied within versus between sibships was investigated using Intraclass Correlation Coefficients (ICCs). ICCs were calculated using estimates for the covariance parameters generated from

¹This information was not provided for the motor-skills domain.

Hierarchical Linear Modeling (HLM). HLM is particularly appropriate for analyzing “clustered” variables (i.e., siblings within families) and can effectively incorporate families with more than two affected children into the analysis (Boyle and Willms 2001). The corresponding ICCs represent the amount of variance at the family level, given the relationship between scores for any two randomly selected children within a given family (Hox 2002); significantly high ICCs indicate greater similarity for a given skill domain *within* families than *between* families. Conversely, low ICCs suggest greater phenotypic similarity *between* unrelated individuals than *within* sibships. For the current project, ICCs were computed for all measures, including each domain on the VABS, for both (a) siblings with any ASD (i.e., autism, NQA, or BS) and (b) just siblings who met strict criteria for autism. Like MacLean et al. (1999), we thought that associations may be stronger between siblings who each/all met criteria for autism; these separate analyses would provide further insight as to whether the adaptive-functioning domains of interest show familial aggregation *despite* the specific ASD diagnosis (e.g., autism versus BS) or more so *because* of diagnostic grouping (e.g., autism only).

Additionally, twin correlations were calculated for all MZ and dizygotic (DZ) twins on whom data were available for each measure of interest. Because identical twins share 100% of their genes and fraternal twins share approximately 50% of their genes, MZ correlations that are greater than DZ correlations suggest evidence of additive genetic effects. Conversely, DZ correlations higher than one half the MZ correlations implicate the influence of shared environmental factors. Non-shared environmental effects are reflected in the difference between unity and the MZ correlation. As with the ICCs, twin correlations were calculated for both the any-ASD and the autism-only groups. All analyses were performed with SPSS® and SAS® software programs.

Results

Great variability existed among scores on the PPVT-III, Ravens, and VABS, as can be seen in Table 2.

ICC results suggested that familial factors explained the bulk of this variance, as significantly high ICCs were noted across all measures, including all domains of the VABS (see Table 3).

ICCs for most skills were only marginally higher for the autism-only siblings versus those with any ASD; the only exception to this was a slightly higher ICC for the Ravens among the any-ASD group. One-way analyses of variance (ANOVAs) indicated that there were no birth-order effects for the PPVT-III; however, birth-order effects were evidenced on the Ravens for both the any-ASD group ($F[3, 467] = 6.199, p < .001$) and the AD-only group ($F[2, 351] = 8.743, p < .001$). Among the any-ASD group, first siblings ($M = 25.35, SD = 8.51$) had significantly higher scores on the Ravens compared with second siblings ($M = 22.19, SD = 8.51, p = .001$); among the AD-only group, first siblings ($M = 25.06, SD = 8.71$) scored higher than both second siblings ($M = 21.68, SD = 8.75, p = .001$) and third siblings ($M = 18.14, SD = 9.44, p = .013$), but the latter two were not significantly different from one another. On the VABS, birth-order effects were only evidenced on the socialization domain

among the any-ASD group ($F[4, 735] = 3.390, p = .009$). Here, first siblings ($M = 53.51, SD = 19.48$) scored significantly lower than third siblings ($M = 62.50, SD = 17.21, p = .022$), but neither scored significantly different than second siblings.

The twin correlations provided evidence for strong genetic influences in some areas of functioning, as MZ correlations were almost always higher than DZ correlations (see Table 4). Genetic effects were most pronounced for verbal IQ as measured with the PPVT-III and the VABS daily living skills among siblings with any ASD, as well as for nonverbal IQ as measured with the Ravens among autism-only siblings. However, many DZ correlations were greater than one half the MZ correlations, suggesting the influence of common (shared) environmental factors. This was particularly evident across all VABS domains for the autism-only group.

Discussion

Our results indicated that siblings with autism/ASD are more similar on measures of verbal and nonverbal IQ and adaptive functioning than are affected non-siblings. Relative to ICCs reported in prior studies, our results are similar for measures of verbal IQ but lower for indices of nonverbal IQ, social skills, and communication skills. For example, Szatmari et al. (1996) noted an ICC of .37 for verbal IQ, as measured with the Wechsler intelligence tests (Wechsler 1967, 1974, 1981), compared with our ICCs of .34 (any ASD) and .42 (autism only) on the PPVT-III. However, Szatmari et al. reported an ICC of .62 and MacLean et al. (1999), ICCs of .42 (any ASD) and .44 (autism only) for nonverbal IQ as measured with the Leiter Performance Scales (Levine 1986), compared with our ICCs of .39 (any ASD) and .37 (autism only) on the Ravens. Similarly, VABS ICCs for (a) socialization were .62 in Szatmari et al. and .40 (any ASD) and .49 (autism only) in MacLean et al. and (b) communication were .54 in Szatmari et al. and .50 (any ASD) and .51 (autism only) in MacLean et al.; our ICCs were .22 (any ASD) and .28 (autism only) for socialization and .19 (any ASD) and .21 (autism only) for communication. Some of these discrepancies, particularly those seen for IQ, could arise from differences in instrumentation. However, it is interesting to note that ICCs for levels of functioning have tended to decrease from Szatmari et al.'s original estimates with 23 families as sample sizes have increased; this was demonstrated with the expanded sample in MacLean et al. (46 families) and again with our significantly larger AGRE sample (204–348 families, depending on the measure). Although our correlations tended to be smaller, we would argue that they illustrate considerable sibling resemblance, nonetheless. The vast majority of sibships were not MZ twins; therefore, we would not expect the same degree of concordance among DZ twins or, more common in this sample, non-twin siblings who share, on average, half as many genes. Moreover, significant correlations in the ranges that we obtained illustrated the strength of familial effects against the backdrop of between-group (interfamilial) differences.

With the exception of the Ravens, ICCs across measures were only slightly higher for the autism-only group than for the any-ASD group. This is a similar finding compared with MacLean et al. (1999), who noted ICCs for the autism-only group on the order of 0.01–0.09 greater than those for the any ASD group, specifically for IQ and VABS measures. It further implies comparable levels of functioning within sibships of different ASD diagnoses,

suggesting that their *degree* of impairment is similar even when the *number* of autism characteristics exhibited is not. However, it should be noted that individuals who met strict criteria for autism comprised approximately 85% of the any-ASD group. Thus, most sibships in this broader category included children meeting strict criteria for autism. Different results might be obtained when (a) the focus is limited to sibships where only one child meets strict criteria for autism and remaining children are categorized as NQA or BS or (b) those meeting criteria for strict autism are excluded and the focus is on sibships where all children are categorized as NQA or BS.

The twin correlations should be interpreted with caution and considered preliminary, as the sample sizes become extremely small when the data are divided by zygosity. This was particularly true for the autism-only group, where the numbers of MZ pairs were always 18 and the numbers of DZ pairs, 9. Here, correlations for all domains on the VABS indicated some degree of influence for the common environment; however, among the any-ASD group, there was less evidence for common-environment effects and stronger evidence for additive-genetic effects across all domains, with the exception of the VABS socialization scores. This specific finding is not easy to explain, as social-skill deficits are the predominant feature of this very heritable disorder. The relatively low MZ correlation ($r = .41$, $DZ r = .45$) further suggests pronounced effects for unique-environmental factors, in addition to potential common-environment effects. This is in keeping with our recent finding that, within the AGRE sample, 72% of the variance in socialization skills as measured with the ADI-R was accounted for by unique environmental factors (Mazefsky et al. 2007). Better clarification with the VABS data would come using structural equation modeling (SEM) within the classic twin-study paradigm, which would more precisely measure the proportions of covariance in each phenotypic measure that are explained by additive-genetic, common-environmental, and unique-environmental influences. However, such analyses would require a much larger MZ twin sample than AGRE currently contains to yield meaningful results.

Overall, our findings support the notion that the success of molecular-genetic tests aimed at locating etiologically relevant genes in autism may be heightened by first stratifying samples of related individuals with ASD by level of functioning. In particular, measures of verbal and nonverbal IQ with the PPVT-III and Ravens, respectively, and the VABS motor skills domain—an area not previously reported as showing familial aggregation—surfaced as indicators of the strongest sibling resemblance. While it may seem prudent to consider (at least among autism-only samples) stratification by socialization skills and daily living skills, we believe it is important to consider the possibility that the familial aggregation we see across skills, particularly the adaptive-functioning behaviors, may be only *partially* explained by genetic factors—not wholly explained by genetic factors, as was suggested by Szatmari et al. (1996). Consequently, there does not seem much logic in stratifying samples for molecular-genetic studies based on a phenotypic measure that appears to be heavily influenced by environmental factors.

Limitation

Many children with ASD receive some sort of intervention—often multiple treatments simultaneously (Goin-Kochel et al. 2006)—and their outcomes following intervention can range dramatically. While IQ has often been examined as an index of change during and after treatment, cognitive gains tend to be less pronounced than adaptive-behavior gains, such as communication, social skills, and self-help skills, because the latter is generally easier to modify (Carter et al. 1998; Kraijer 2000). Thus, it seems possible that treatment effects could have impacted VABS scores for some children in the current sample, and this may have influenced the degree to which siblings appeared more or less similar on the adaptive-behavior domains. This notion might explain the relatively strong environmental effects indicated for the socialization domain and further account for our finding of a higher DZ than MZ correlation for the VABS socialization data. For example, siblings may have had highly correlated scores on one or more domains pre-treatment but very uncorrelated scores post-treatment, suggesting that genes that influence level of functioning may be different from those that influence responsiveness to treatment. Similarly, a pair of siblings may have had uncorrelated pretreatment scores, but because one received an intense form of behavior therapy, their scores are now highly correlated. Again, though, this explanation is only speculative, as the AGRE data available to us did not contain information about children's therapies, and we have no way of knowing how many children are/were participating in treatment and for whom the VABS data reflect pretreatment level of functioning.

Future Directions

It would be interesting to replicate the current project using a different, yet equally large sample of siblings with autism/ASD, particularly one containing a greater number of twins, which would enhance confidence in the validity of the MZ/DZ correlations. Considering the difficulty in ascertaining large, well-characterized samples among this population, it may be more feasible to conduct this type of study in countries other than the U.S. where medical information is collected on a population-wide basis. Such a project could also examine cognitive and adaptive-functioning data on a control sample of siblings/twins *without* autism/ASD, as this would allow comparisons of the degree to which these traits are more or less heritable in the context of disability.

Given our aforementioned concern over potential treatment effects within the AGRE population, further work on this topic that involves the collection of new data should take into consideration the potential influence of treatment on measures of adaptive functioning. Ideally, ascertainment of cognitive and adaptive-functioning data from twins/siblings with autism/ASD would occur at the earliest ages possible, following an ASD diagnosis and before any therapies have been initiated. Given an adequate sample size, behavior-genetic analyses using SEM could then provide more precise estimates of the proportions of covariance in various domains of functioning that are explained by genetic and environmental factors (both shared and unique), using data that are not colored by the potential influences of various treatments.

Keeping with the focus on treatment for children with ASD, our current results also have implications for research on behavioral interventions for children with ASD. It is well documented that pretreatment levels of functioning, particularly IQ and adaptive behaviors, predict outcomes following early intensive behavioral intervention (IBI) (e.g., Bibby et al. 2002; Eikeseth et al. 2002; Goldstein 2002; Newsom and Rincover 1989; Schopler et al. 1989). Understanding which skill domains are most heavily influenced by genetic factors (e.g., IQ) could help explain why environmental efforts, such as intensive behavioral intervention (IBI), rarely incite substantive changes in these areas. Likewise, knowing which skill domains are more amenable to environmental influences could explain the improvements in adaptive functioning that we see in many children with ASD who participate in IBI. Future studies in this arena could identify those adaptive behaviors that are more amenable to environmental influences and which, if any, genotypes indicate a greater degree of responsiveness to IBI; such results could vastly alter the patterns of treatment delivery and to whom IBI treatment is targeted.

Acknowledgments

We gratefully acknowledge the resources provided by the Autism Genetic Resource Exchange (AGRE) Consortium² and the participating AGRE families. The Autism Genetic Resource Exchange is a program of Cure Autism Now and is supported, in part, by grant MH64547 from the National Institute of Mental Health to Daniel H. Geschwind (PI). Dr. Goin-Kochel was supported by an NIH Institutional Training Grant, T32NS-43124 (PI JW Swann); Dr. Mazefsky was supported by a National Research Service Award from the NIH, T32MH-20030 (PI MC Neale). We would also like to thank Eric Duku at the Offord Centre for Child Studies for his assistance with statistical analyses.

References

- Autism Genetic Resource Exchange Consortium. AGRE affected status categories. 2006. Retrieved December 12, 2006, from <http://agre.org/agrecatalog/algorithm.cfm>
- Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, Rutter M. Autism as a strongly genetic disorder: Evidence from a British twin study. *Psychological Medicine*. 1995; 25:63–77. [PubMed: 7792363]
- Bibby P, Eikeseth S, Martin NT, Mudford OC, Reeves D. Progress and outcomes for children with autism receiving parent-managed intensive interventions. *Research in Developmental Disabilities*. 2002; 23(1):81–104. [PubMed: 12071397]
- Boyle MH, Willms JD. Multilevel modelling of hierarchical data in developmental studies. *Journal of Child Psychology and Psychiatry*. 2001; 42(1):141–162. [PubMed: 11205622]
- Carter AS, Volkmar FR, Sparrow SS, Wang J, Lord C, Dawson G, Fombonne E, Loveland K, Mesibov G, Schopler E. The Vineland Adaptive Behavior Scales: Supplementary norms for individuals with autism. *Journal of Autism and Developmental Disorders*. 1998; 28(4):287–302. [PubMed: 9711485]
- Cuccaro ML, Shao Y, Bass MP, Abramson RK, Ravan SA, Wright HH, Wolpert CM, Donnelly SL, Pericak-Vance MA. Behavioral comparisons in autistic individuals from multiplex and singleton families. *Journal of Autism and Developmental Disorders*. 2003; 33(1):87–91. [PubMed: 12708583]

²The AGRE Consortium includes: Dan Geschwind, M.D., Ph.D., UCLA, Los Angeles, CA, USA; Maja Bucan, Ph.D., University of Pennsylvania, Philadelphia, PA, USA; W. Ted Brown, M.D., Ph.D., F.A.C.M.G., N.Y.S. Institute for Basic Research in Developmental Disabilities, Long Island, NY, USA; Rita M. Cantor, Ph.D., UCLA School of Medicine, Los Angeles, CA, USA; John N. Constantino, M.D., Washington University School of Medicine, St. Louis, MO, USA; T. Conrad Gilliam, Ph.D., University of Chicago, Chicago, IL, USA; Clara Lajonchere, Ph.D., Cure Autism Now, Los Angeles, CA; David H. Ledbetter, Ph.D., Emory University, Atlanta, GA; Christa Lese-Martin, Ph.D., Emory University, Atlanta, GA; Janet Miller, J.D., Ph.D., Cure Autism Now, Los Angeles, CA; Stanley F. Nelson, M.D., UCLA School of Medicine, Los Angeles, CA, USA; Gerard D. Schellenberg, Ph.D., University of Washington, Seattle, WA; Carol A. Samango-Sprouse, Ed.D., George Washington University, Washington, D.C.; Sarah Spence, M.D., Ph.D., UCLA, Los Angeles, CA, USA; Matthew State, M.D., Ph.D., Yale University, New Haven, CT, USA; Rudolph E. Tanzi, Ph.D., Massachusetts General Hospital, Boston, MA, USA.

- Dunn, LM.; Dunn, LM. Peabody Picture Vocabulary Tests. 3rd. Circle Pines: American Guidance Service; 1997.
- Eikeseth S, Smith T, Jahr E, Eldevik S. Intensive behavioral treatment at school for 4- to 7-year-old children with autism. A 1-year comparison controlled study. *Behavior Modification*. 2002; 26(1): 49–68. [PubMed: 11799654]
- Folstein S, Rutter M. Infantile autism: A genetic study of 21 twin pairs. *Journal of Child Psychology and Psychiatry*. 1977; 18:297–321. [PubMed: 562353]
- Goin-Kochel RP, Myers BJ, Mackintosh VH. Parental reports on the use of treatments and therapies for children with autism spectrum disorders. *Research in Autism Spectrum Disorders*. 2006; 10.1016/j.rasd.2006.08.006
- Goldstein H. Communication intervention for children with autism: A review of treatment efficacy. *Journal of Autism and Developmental Disorders*. 2002; 32(5):373–396. [PubMed: 12463516]
- Hox, J. Multilevel analysis: Techniques and applications. New Jersey: Lawrence Erlbaum Associates; 2002.
- Kolevzon A, Smith CJ, Schmeidler J, Buxbaum JD, Silverman JM. Familial symptom domains in monozygotic siblings with autism. *American Journal of Medical Genetics. Part B Neuropsychiatric Genetics*. 2004; 129(1):76–81.
- Kraijer D. Review of adaptive behavior studies in mentally retarded persons with autism/pervasive developmental disorder. *Journal of Autism and Developmental Disorders*. 2000; 30(1):39–47. [PubMed: 10819119]
- Le Couteur A, Bailey A, Goode S, Pickles A, Robertson S, Gottesman I, et al. A broader phenotype of autism: The clinical spectrum in twins. *Journal of Child Psychology and Psychiatry*. 1996; 37(7): 785–801. [PubMed: 8923222]
- Levine, MN. *Leiter International Performance Scale: A handbook “Arthur Adaptation of the Leiter International Performance Scale: A Handbook”*. Los Angeles: Western Psychological Services; 1986.
- Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, et al. The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders*. 2000; 30(3):205–223. [PubMed: 11055457]
- Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*. 1994; 24(5):659–685. [PubMed: 7814313]
- MacLean JE, Szatmari P, Jones MB, Bryson SE, Mahoney WJ, Bartolucci G, et al. Familial factors influence level of functioning in pervasive developmental disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1999; 38(6):746–753. [PubMed: 10361794]
- Mazefsky CA, Goin-Kochel RP, Riley BP, Maes HH. The Autism Genetic Resource Exchange Consortium. Genetic and environmental influences on symptom domains in twins and siblings with autism. *Research in Autism Spectrum Disorders*. 2007; 10.1016/j.rasd.2007.08.002
- Mottron L. Matching strategies in cognitive research with individuals with high-functioning autism: Current practices, instrument biases, and recommendations. *Journal of Autism and Developmental Disorders*. 2004; 34(1):19–27. [PubMed: 15098953]
- Newsom, C.; Hovanitz, CA. Autistic disorder. In: Mash, EJ.; Terdal, LG., editors. *Assessment of childhood disorders*. 3rd. New York: Guilford; 1997. p. 408-452.
- Newsom, C.; Rincover, A. Autism. In: Mash, EJ.; Barkley, RA., editors. *Treatment of childhood disorders*. New York: Guilford; 1989. p. 286-346.
- Raven, JC. *Colored progressive matrices: Sets I and II*. Oxford: Oxford Psychologists Press Ltd; 1947, 1995.
- Schopler E, Short A, Mesibov G. Relation of behavioral treatment to “normal functioning”: Comment on Lovaas. *Journal of Consulting and Clinical Psychology*. 1989; 57(1):162–164. [PubMed: 2925968]
- Silverman JM, Smith CJ, Schmeidler J, Hollander E, Lawlor BA, Fitzgerald M, Buxbaum JD, Delaney K, Galvin P. Autism Genetic Research Exchange Consortium. Symptom domains in autism and

- related conditions: Evidence for familiarity. *American Journal of Medical Genetics. Part B Neuropsychiatric Genetics*. 2002; 114:64–73.
- Sparrow, SS.; Balla, DA.; Cicchetti, DV. *Vineland adaptive behavior scales*. Circle Pines: American Guidance Service; 1984.
- Spiker D, Lotspeich L, Kraemer HC, Hallmayer J, McMahon W, Petersen PB, et al. Genetics of autism: Characteristics of affected and unaffected children from 37 multiplex families. *American Journal of Medical Genetics*. 1994; 54(1):27–35. [PubMed: 8178836]
- Szatmari P. Heterogeneity and the genetics of autism. *Journal of Psychiatry & Neuroscience*. 1999; 24(2):159–165. [PubMed: 10212560]
- Szatmari P, Jones MB, Holden J, Bryson S, Mahoney W, Tuff L, MacLean J, White B, Bartolucci G, Schutz C, Robinson P, Hoult L. High phenotypic correlations among siblings with autism and pervasive developmental disorders. *American Journal of Medical Genetics. Part B Neuropsychiatric Genetics*. 1996; 67:354–360.
- Wechsler, D. *Manual for the Wechsler preschool and primary scale of intelligence*. New York: The Psychological Corporation; 1967.
- Wechsler, D. *Manual for the Wechsler intelligence scale for children–revised*. New York: The Psychological Corporation; 1974.
- Wechsler, D. *WAIS-R manual Wechsler Adult Intelligence Scale-Revised*. New York: The Psychological Corporation. Harcourt Brace Jovanovich Publishers; 1981.

Table 1

Demographic information by instrument

Instrument	N	Age <i>M</i> (<i>SD</i>)	% Male	ASD diagnosis		Frequencies of families with a given number of affected siblings ^a				
				Autism	BS	NQA	Two sibs	Three sibs	Four sibs	Five sibs
PPVT-III	427	9.3 (3.8)	78.0	362 (84.8%)	45 (10.5%)	20 (4.7%)	185 (90.7%)	16 (7.8%)	3 (1.5%)	0 (0%)
Ravens	471	9.2 (3.7)	79.2	402 (85.4%)	50 (10.6%)	19 (4.0%)	207 (91.6%)	17 (7.5%)	2 (0.9%)	0 (0%)
VABS	740	9.4 (4.8)	79.6	644 (87.0%)	68 (9.2%)	28 (3.8%)	304 (87.4%)	40 (11.5%)	3 (0.9%)	1 (0.3%)

PPVT-III = Peabody Picture Vocabulary Test (verbal IQ); Ravens = Ravens Colored Progressive Matrices (nonverbal IQ); VABS = Vineland Adaptive Behavior Scales. BS = Broad Spectrum; NQA = Not Quite Autism

^aThese percentages were calculated based on the numbers of families—not individuals—with available data on select measures: PPVT-III = 204 families, Ravens = 226 families, VABS = 348 families

Table 2
Means, standard deviations, and score ranges for the PPVT-III, Ravens, and VABS

Measure	Any-ASD siblings		Autism-only siblings	
	<i>n</i>	<i>M</i> (<i>SD</i>); Range	<i>n</i>	<i>M</i> (<i>SD</i>); Range
PPVT-III	427	83.3 (28.1); 20–144	362	80.6 (28.6); 20–140
Ravens	471	23.6 (8.7); 0–36	402	23.3 (8.8); 0–36
VABS				
Communication	740	59.5 (26.7); 20–134	644	56.5 (25.6); 20–134
Daily living	665	46.2 (22.6); 20–116	585	44.2 (21.6); 20–114
Social	740	55.0 (18.9); 20–133	644	52.9 (17.8); 20–117
Motor	665	77.9 (22.9); 20–119	585	76.5 (22.9); 20–113
AB Composite	740	50.1 (20.2); 20–124	644	47.6 (18.8); 20–116

PPVT-III = Peabody Picture Vocabulary Test (verbal IQ); Ravens = Ravens Colored Progressive Matrices (nonverbal IQ); VABS = Vineland Adaptive Behavior Scales; AB Composite = Adaptive Behavior Composite

Table 3
Intraclass Correlation Coefficients (ICCs) for any-ASD families and AD-only families

Measure	Any-ASD families		Autism-only families	
	ICC	F (df)	ICC	F (df)
PPVT-III	.34*	2710.08 (1, 198.53)	.42*	1815.16 (1, 150.42)
Ravens	.39*	2412.54 (1, 222.87)	.37*	1709.73 (1, 169.96)
VABS				
Communication	.19*	2995.75 (1, 337.07)	.21*	2368.55 (1, 269.77)
Daily living	.22*	2336.71 (1, 337.36)	.25*	1883.75 (1, 271.40)
Social	.22*	4949.97 (1, 333.93)	.28*	4065.27 (1, 266.55)
Motor	.56*	2109.06 (1, 343.69)	.58*	1878.41 (1, 275.15)
AB Composite	.20*	3663.00 (1, 335.20)	.23*	3076.07 (1, 267.23)

PPVT-III = Peabody Picture Vocabulary Test (verbal IQ); Ravens = Ravens Colored Progressive Matrices (nonverbal IQ); VABS = Vineland Adaptive Behavior Scales; AB Composite = Adaptive Behavior Composite

*
 $p < .001$

Table 4
Twin correlations for siblings with any ASD and AD-only siblings

Measure	Any-ASD pairs			Autism-only pairs		
	Twin <i>r</i> by zygosity			Twin <i>r</i> by zygosity		
	MZ	<i>n</i> Pairs	DZ	MZ	<i>n</i> Pairs	DZ
PPVT-III	.50*	17	.09	.71**	15	–
Ravens	.67**	19	.48	.72**	16	.25
VABS						
Communication	.51*	23	.30	.72**	18	.43
Daily living	.71**	23	.31	.80***	18	.50
Social	.41*	23	.45	.61**	18	.54
Motor	.79***	19	.42	.84***	14	.79*
AB Composite	.55**	23	.33	.76**	18	.56

PPVT-III = Peabody Picture Vocabulary Test (verbal IQ); Ravens = Ravens Colored Progressive Matrices (nonverbal IQ); VABS = Vineland Adaptive Behavior Scales; AB Composite = Adaptive Behavior Composite

* $p < .05$;

** $p < .008$;

*** $p < .0001$