Associations between parental broader autism phenotype and child autism spectrum disorder phenotype in the Study to Explore Early Development

Eric Rubenstein[1], **Lisa D Wiggins**[2], **Laura A Schieve**[2], **Chyrise Bradley**[1], **Carolyn DiGuiseppi**[3], **Eric Moody**[3], **Juhi Pandey**[4], **Rebecca Edmondson Pretzel**[1], **Annie Green Howard**[1], **Andrew F Olshan**[1], **Brian W Pence**[1], and **Julie Daniels**[1]

[1]University of North Carolina at Chapel Hill, USA

[2]Centers for Disease Control and Prevention, USA

[3]University of Colorado-Anschutz Medical Campus, USA

[4]Children's Hospital of Philadelphia, USA

Abstract

The autism spectrum disorder phenotype varies by social and communication ability and co-occurring developmental, behavioral, and medical conditions. Etiology is also diverse, with myriad potential genetic origins and environmental risk factors. Examining the influence of parental broader autism phenotype—a set of sub-clinical characteristics of autism spectrum disorder—on child autism spectrum disorder phenotypes may help reduce heterogeneity in potential genetic predisposition for autism spectrum disorder. We assessed the associations between parental broader autism phenotype and child phenotype among children of age 30–68 months enrolled in the Study to Explore Early Development (N = 707). Child autism spectrum disorder phenotype was defined by a replication of latent classes derived from multiple developmental and behavioral measures: *Mild Language Delay with Cognitive Rigidity, Mild Language and Motor Delay with Dysregulation* (e.g. anxiety/depression), *General Developmental Delay*, and *Significant Developmental Delay with Repetitive Motor Behaviors*. Scores on the Social Responsiveness Scale-Adult measured parent broader autism phenotype. Broader autism phenotype in at least one parent was associated with a child having increased odds of being classified as mild language and motor delay with dysregulation compared to significant developmental delay with repetitive motor behaviors (odds ratio: 2.44; 95% confidence interval: 1.16, 5.09). Children of parents with broader autism phenotype were more likely to have a phenotype qualitatively similar to broader autism phenotype presentation; this may have implications for etiologic research.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Keywords

autism spectrum disorder; broader autism phenotype; endophenotypes; subgrouping

---

Autism spectrum disorder (ASD), defined by impairment in social communication and social interaction as well as repetitive and restricted behaviors and interests (American Psychiatric Association, 2013), is heterogeneous in phenotype and genotype (American Psychiatric Association, 2013; An and Claudianos, 2016; Lai et al., 2014; Miles, 2011). Individuals with ASD have a broad range of adaptive functioning, intellectual development, verbal ability, co-occurring conditions, and varying presentation of other diagnostic or associated features (American Psychiatric Association, 2013; Lai et al., 2014; Levy et al., 2010). Potential genetic contributions explain up to 83% of the variance in ASD in the population with potential genetic mechanisms including chromosomal abnormalities, rare inherited genes, copy number variants, and rare penetrant genes (De la Torre-Ubieta et al., 2016; Gaugler et al., 2014; Sandin et al., 2017). Other potential etiologic mechanisms for ASD include epigenetic changes, environmental factors like preterm birth or air pollution, and combined effects of genetic and environmental factors (Lyall et al., 2016). The myriad potential causes and presentations of ASD create challenges when trying to understand how etiologic origin is associated with the development and presentation of ASD (An and Claudianos, 2016; Georgiades et al., 2013; Koegel et al., 2014; Lai et al., 2013; Miles, 2011).

Defining and assessing distinct homogeneous ASD phenotypic subgroups, rather than simply assessing all ASD cases as a single outcome, might enhance the ability to detect etiologic associations and elucidate developmental trajectories (Lai et al., 2013; Landa et al., 2012; Veatch et al., 2014). Data-driven techniques like cluster analysis and latent class analysis (LCA) partition children into meaningful subgroups based on similar responses to observed data and allow different types of variables to be included in analytic models. Thus, data-driven techniques might enhance subgrouping to include a broader range of variables that help define phenotypic groups (Cholemkery et al., 2016; Georgiades et al., 2013, 2014; Munson et al., 2008; Veatch et al., 2014). Indeed, using LCA generated from a variety of behavioral, developmental, and medical symptoms, Wiggins et al. (2017) found four distinct classes of preschool children with ASD that highlighted the influence of co-occurring conditions on phenotypic presentation. The presence of these conditions *within* the autism spectrum may be a better indicator of shared etiology and brain dysfunction than assessing core ASD domains alone (Lai et al., 2013; Waterhouse and Gillberg, 2014; Wiggins et al., 2017).

Since a large portion of ASD genetic liability in the population can be attributed to both common variation (minor allele frequencies of genetic variants present in >5% of a population; Guthery et al., 2007) and intergenerational transmission (Gaugler et al., 2014; Sandin et al., 2017; Yip et al., 2017), exploring how autism traits congregate in families may improve our ability to identify specific causal genetic mechanisms. In families of children with ASD, the presence of sub-clinical ASD characteristics is commonly referred to as the broader autism phenotype (BAP; Bolton et al., 1994). Common features of BAP include

pragmatic difficulties, broadly defined communication difficulties, poor social skills, cognitive rigidity, anxiety, and aloofness (Sucksmith et al., 2011). This congregation of ASD-like traits is significantly more prevalent among parents and relatives of probands with ASD compared to families of typically developing children or families of children with Down's syndrome (Bolton et al., 1994; Bora et al., 2016; De la Marche et al., 2012; Lyall et al., 2014; Maxwell et al., 2013; Piven et al., 1994; Sasson et al., 2014, 2013b; Schwichtenberg et al., 2010; Seidman et al., 2012). In addition, BAP is heritable (Sucksmith et al., 2011), with a study by Robinson et al. (2011) finding sub-diagnostic autism traits to have a similar level of heritability as ASD. Features of BAP may therefore represent an endophenotype: a measurable phenotypic trait that is heritable, state independent, co-segregates in families, and found in higher rates in relatives of probands than in the general population (Gottesman and Gould, 2003; Gould and Gottesman, 2006). As such, considering BAP as an endophenotype in etiologic research may increase the efficiency of linkage analyses, genome-wide association studies, or other techniques that look for specific causal genes, common variants, and single nucleotide polymorphisms (Alarcon et al., 2005; Butler et al., 2005; Connolly et al., 2013; Flint and Munafo, 2007; Francis et al., 2016; Hall and Smoller, 2010; Liu et al., 2008; Losh and Piven, 2007; Lowe et al., 2015). Furthermore, evaluating the association between BAP and empirically derived phenotypic subgroups of ASD may further our ability to find meaningful endophenotypes through reducing heterogeneity in phenotype, which will allow for improved efficiency when exploring potentially causal common genetic variants.

We evaluated the association between parental BAP and child ASD phenotype subgroups defined by multiple behavioral and health-related constructs using a large US community-based study. In addition, we explored whether these associations differed by which parent had BAP and whether the child's sex affected the relationship between parental BAP and child class.

Methods

This study used data from Phase 1 of the Study to Explore Early Development (SEED), a community-based case-control study designed to better understand ASD etiology and phenotypic presentation (Schendel et al., 2012). Six sites (California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania) collected data on maternal pregnancy and health history, child developmental history, and other familial data for children between the ages of 30 and 68 months between 2007 and 2012. Children had to have been born in a study catchment area, lived there at time of first enrollment, and had a caregiver who could provide legal consent for participation (Schendel et al., 2012). Children were identified and recruited through educational or medical providers who served children with ASD and other developmental disorders or delays. A population comparison group was recruited through random sampling of birth certificates. This analysis was restricted to children with confirmed ASD. Each study sites Institutional Review Board approved data collection, and the University of North Carolina Institutional Review Board approved this secondary analysis.

ASD confirmation

Children were screened for ASD using the Social Communication Questionnaire upon study entry. If a child screened positive (scored 11 to maximize case finding (Wiggins et al., 2007)), had a past diagnosis of ASD, or was suspected by a study clinician to have ASD during the initial developmental assessment, the child underwent a full ASD evaluation. Clinicians who had established research reliability evaluated the child for ASD using the Autism Diagnostic Observation Schedule-2 (ADOS) (Lord et al., 2012) and completed the Autism Diagnostic Interview-Revised (ADI-R) (Rutter et al., 2003) with the caregiver. Final case status was determined through a SEED-derived algorithm using scores from the ADOS and the ADI-R (Wiggins et al., 2015). SEED clinicians also administered the Mullen Scales of Early Learning (Mullen, 1995), which provided information on expressive and receptive language, visual reception, and motor development. Additional phenotypic and demographic descriptions were provided through the caregiver's completion of the Child Behavior Checklist (Achenbach, 1992), other questionnaires and interviews, and the child's birth certificate.

For this analysis, siblings of children who were already enrolled were excluded because their inclusion may introduce violation of our assumption of independence between observations. When evaluating associations with parental BAP, our inferences are only applicable to children who had BAP measures completed for their biological mother and father.

Parent BAP measurement

BAP was measured using the informant-reported Social Responsiveness Scale-Adult (SRS-A), a 65-item Likert-type scale questionnaire (Constantino and Todd, 2005). Although not specifically designed to measure BAP, the SRS-A has shown good consistency with other BAP and quantitative autistic trait measures and is commonly used to measure BAP in adults (Gerdts and Bernier, 2011; Ingersoll et al., 2011; Nishiyama et al., 2014). The SRS-A has strong internal validity, exhibiting a Cronbach's alpha internal consistency coefficient of 0.95 (Constantino and Todd, 2005; Ingersoll et al., 2011) and has been shown to be independent of the subject's IQ and age, and not impacted by the informant's education level (Constantino, 2002; Constantino et al., 2009, 2015; Constantino and Todd, 2005). In addition, results on the SRS-A are not associated with the subject's race or ethnicity, or the identity of the informant (Constantino and Gruber, 2012).

Each parent was asked to have a friend, spouse, or relative complete the SRS-A on the parent and then return it to SEED. Scores were tabulated based on whether responses indicated social abnormality, with higher scores indicating greater social abnormality. These overall scores were standardized to create T-scores, which were normed using a standard population to have a mean of 50 and a standard deviation of 10. For this study, we used the standard "mild range" recommendation of a T-score 60 to classify a parent as having BAP (BAP+) (Constantino, 2002). In addition, we categorized BAP by parental combination: mother and father were BAP+, father only was BAP+, mother only was BAP+, or both parents did not have BAP (BAP−).

Creating child phenotypic classes

We first used an extended LCA to create ASD phenotypic classes based on all ASD cases in SEED, replicating the work of Wiggins et al. (2017) who previously created latent classes in these data using the same methodology. LCA assumes that there are unobservable subpopulations, often associated with certain patterns of observable data, within the larger study population (Hagenaars and McCutcheon, 2002). For each individual, an LCA model provides probabilities of being in each class based on their observed outcome variables. While standard LCA models use only categorical observed variables, an extended LCA model allows for use of continuous, dichotomous, and categorical variables to estimate and explore any potential underlying latent classes.

LCA results are highly dependent upon the indicator variables used to generate latent classes. In total, 25 indicators were chosen for the model, as selected by Wiggins et al. (2017). The first step in choosing these indicators was a careful review of studies that classified children with ASD into subgroups, with specific focus on identifying behavioral, developmental medical features that defined subgroups. In the second step, a group of experts, that included psychologists, pediatricians, and epidemiologists, discussed other variables that could be used to describe ASD phenotypes and differentiate subgroups of children within the autism spectrum. Indicators chosen for LCA were those identified by the process noted above and quantified by SEED data collection instruments (Table 1).

Results found that a four-class model best fit the data based on a lower Bayesian information criterion than the three class model, Lo–Mendel–Rubin Likelihood Ratio Tests (LMR-LRT) that found that the four-class model improved on fit compared to the three class model with no additional improvement in a five class model, and an entropy estimate of 0.92 (entropy ranges from 0 to 1 with higher entropy indicating higher precision of latent classification) (Wiggins et al., 2017). The four classes generated from our analysis were identical to those found in the earlier analysis of the same data and represent children with *Mild Language Delay with Cognitive Rigidity, Mild Language and Motor Delay with Dysregulation* (e.g. anxiety/depression, attention problems, and sleep problems), *General Developmental Delay*, and *Significant Developmental Delay with Repetitive Motor Behaviors* (Table 2). Table 1 presents the item response probabilities (the probability that a member of a class has the given trait) and means scores for continuous indicator by class. Further details on this LCA method in SEED are provided in Wiggins et al. (2017).

Analytic approach

Having confirmed our classes using the extended LCA, we regenerated our classes using an inclusive extended LCA approach to generate odds ratios (ORs) that compare phenotypic class membership by presence of parental BAP. In this method, we reran our LCA described above to include, as predictors of class membership, our BAP covariate and an indicator for missing SRS-A data. This model then calculated ORs using multinomial logistic regression that estimated model posterior probabilities for the inclusive classes. This inclusive model improves validity of effect estimates since it allows for a child to have a probability of being in multiple classes, rather than assigning them to one class and assuming no classification error. In addition, an inclusive LCA accounts for the potential effect of the covariate in

deriving latent classes (Bray et al., 2015). A disadvantage of this approach is that estimated posterior probability for class membership is slightly different than our original model without covariates or when models contain different covariates. To address these issues, we compared our inclusive approach with a "three-step approach" (which assigns each individual a class then weights for classification error) (Vermunt, 2010) as a sensitivity analysis.

Parental BAP data were missing for approximately 17% of children with ASD in SEED. In order to use data on all cases, we included an indicator for missing BAP in our analyses. Past work has shown that for LCA, using an indicator is less biased than restricting to those with complete data (Formann, 2007). A model with missing indicators creates class distributions for both observed and missing data, which provides information on missing data mechanisms (Formann, 2007). In most cases, a missing indicator approach is biased in epidemiological analyses because it removes the effects covariates have on one another, preventing adequate control of confounding (Groenwold et al., 2012; Jones, 1996). However, there were no confounders in our analysis, and our dependent variables (whether dichotomous BAP or BAP by parent type) were exclusive, eliminating the issue of covariance. We ran additional sensitivity analyses to assess the effect of using inverse probability weights to account for missing SRS-As.

We evaluated the effects of which parent or parents had BAP by rerunning our inclusive LCA with indicators for parental BAP combinations (father only, mother only, and both). In addition, we aimed to present data on differences between child sexes. To do this, we added a child sex covariate, a child sex by BAP interaction term, and a child sex by missing SRS-A interaction term to our LCA model in order to stratify estimates by child sex. Child sex was not associated with missing SRS-As (χ^2 p-value = 0.2); therefore, we believe the missing indicator approach is still unbiased (Groenwold et al., 2012). Since the sample size of girls was low, we did not statistically test differences between sexes since our LCA model could not calculate exact statistics. Therefore, we present ORs and confidence intervals (CIs) for each sex and compare qualitatively. For all models, we chose the *Significant Developmental Delay with Repetitive Motor Behaviors* class (class 2) to be the referent class because it was the most distinct class in terms of cognitive impairment and social and communicative deficits.

As a construct, BAP is theorized to be independent of IQ, age, and race (Constantino and Todd, 2005). Factors like socioeconomic status, parental education, child age at diagnosis, and child service usage are potential mediators because they may be caused by BAP and affect child phenotype; these analyses are beyond the scope of this article. For these reasons, we did not add any additional demographic covariates to our models in these analyses, which is consistent with past work that has assessed the relationship between parental autism-like traits and child phenotype (De la Marche et al., 2012; Duvekot et al., 2016; Schwichtenberg et al., 2010).

Analyses were conducted in SAS Institute Inc. (version 9.3; 2011) and Mplus 7 (Muthen and Muthen, 1998–2012).

Results

Of 707 children with ASD in our sample, 524 children had SRS-A data from both parents of which 100 had at least one parent who was BAP+. Table 3 presents demographics by BAP status (either/both parents BAP+, both BAP−, or BAP missing). For mothers, of those in the BAP+ group, 17.8% were black, 16.2% were of Hispanic ethnicity, and 24.2% had less than 12 years of education. For those in the BAP− group, 13.4% were black and 11.0% were of Hispanic ethnicity, while 12.7% had less than 12 years of education. Demographics for the fathers were similar to those of the mothers (data not shown). When SRS-A data were missing (either on the mother only (n = 43), father only (n = 70), or both (n = 70)), 39.7% of mothers were black, 12.5% were of Hispanic ethnicity, and 6.6% had less than 12 years of education.

When at least one parent was BAP+, the odds of the child being in the *Mild Language and Motor Delay with Dysregulation* class (class 4) compared to the *Significant Developmental Delay with Repetitive Motor Behaviors* class (class 2) were 2.44 times that then when both parents were BAP− (95% CI: 1.16, 5.09) (Figure 1). Compared to class 2, neither the *Mild Language Delay with Cognitive Rigidity* class (class 1) OR: 0.73; 95% CI: 0.36, 1.48), nor the *General Developmental Delay* class (class 3) (OR: 0.86; 95% CI: 0.44, 1.66) was associated with parental BAP status. The results were robust to alternative LCA methods (three-step LCA) and missing data approaches (inverse probability for missing weights) (Supplement 1). Our inclusive LCA approach shifted class distribution by 0.5% compared to our classes without covariates, indicating no difference in class interpretation. Missing SRS-A data (compared to not missing data) were not statistically associated with increased odds of being in a certain class (p > 0.05 for missing indicators). Children with any BAP+ parent in class 4 had the highest scores in anxiety/depression, aggressive behaviors, and sleep problems relative to any other BAP class combination (Supplement 2). In post hoc analyses, parental BAP was statistically associated with the child having history of regression, later age at social smile, and more restricted interests, aggressive behavior, anxiety/depression, emotional reactivity, sleep problems, somatic complaints, and withdrawn behavior.

Compared to both parents being BAP−, both parents being BAP+ had an elevated but imprecise association with child's membership in class 4 versus class 2 (OR: 2.40; 95% CI: 0.54, 10.57) (Table 4). When only mothers were BAP+ (N = 20), there were no significant associations between classes and maternal BAP, but estimates were imprecise. Fathers alone being BAP+ (N = 64) compared to both parents being BAP− was associated with a child being in class 4 compared to class 2 (OR: 2.71; 95% CI: 1.09, 6.77). We saw no significant associations between any of the parental BAP categories and the child being in class 1 or class 3 as compared to class 2. Because we used an inclusive LCA model, the model-estimated posterior probabilities of class distribution were 0.1% different than when we did not include covariates; therefore, there is no difference in interpretation for what each class represents.

After stratification by child sex, results were similar for boys and girls. Among boys, the relationship between any parent being BAP+ and phenotypic class was similar to overall results, as there was a significant effect comparing class 4 to class 2 (OR: 2.68; 95% CI:

1.06, 6.79) (Table 5). Results for girls were imprecise due to small sample size (N = 20), but ORs for any parent being BAP+ were elevated for the child being in class 4 compared to class 2 (OR: 3.92; 95% CI: 0.74, 20.76). Adding child sex and the interaction term into the LCA model shifted the model-estimated posterior probability by 0.5% from the LCA without covariates, again indicating that our classes have the same interpretation as our model without covariates.

Discussion

In a study of children aged 30–68 months with ASD, having a BAP+ parent was associated with increased odds of being in the *Mild Language and Motor Delay with Dysregulation* class, marked by average nonverbal abilities, mild language and motor delays, average non-verbal abilities, and an increased propensity for co-occurring conditions like anxiety, depression, aggression, and attention problems, compared to the *Significant Developmental Delay with Repetitive Motor Behaviors* class, defined by increased cognitive impairment and repetitive motor behaviors. Our other phenotypic class comparisons were not statistically significantly associated with parental BAP, suggesting that the association with BAP is distinct to the ASD phenotype with more co-occurring conditions and not inversely associated with the phenotype marked by considerable cognitive impairment. In addition, this association with an ASD phenotype class with more co-occurring conditions was statistically significant if fathers alone were BAP+ and had elevated but imprecise ORs if both parents were BAP+ or if mother alone was BAP+. The relationship between parental BAP and child phenotypic class was qualitatively similar for boys and girls.

Past work has found that having a parent with BAP is associated with a child's ASD presentation, finding that increased scores on a measure of BAP in a parent was related to increased scores on a measure of the child's ASD or other developmental traits (De la Marche et al., 2015; Hasegawa et al., 2015; Maxwell et al., 2013; Mazefsky et al., 2008; Sasson et al., 2013b; Schwichtenberg et al., 2010; Smith et al., 2009). These studies relied on one standardized measure of child ASD traits. We extend this prior work by defining child ASD phenotype using latent classes derived from multiple instruments and data sources (caregiver interview, developmental questionnaires, and clinician observation), which improves phenotypic classification by enabling a wider description of ASD presentation that considers co-occurring conditions and associated features. This approach is also less reliant on one informant or one instrument, reducing risk of bias due to informant effects or measurement error.

The moderately strong association between parental BAP and a child phenotype defined by average nonverbal skills, mild language and motor delays, mild ASD symptom severity, and more co-occurring conditions may support that this ASD presentation is more likely to be hereditary (Constantino and Todd, 2005; Gaugler et al., 2014). Qualitatively, BAP is similar to this class since BAP also presents with average cognitive functioning and high levels of anxiety, depression, and attention issues (Gerdts and Bernier, 2011). Our results align with other studies that have found that anxiety (Duvekot et al., 2016) and general social ability (Sasson et al., 2013b) present more similarly between parents with BAP and their children with ASD as compared to parents without BAP and their children with ASD.

This result has implication for the study of ASD genetics. Past work has assessed de novo copy number variants (CNVs) as potential causal mechanisms for ASD (Shishido et al., 2014). CNVs can be strongly associated with ASD but are rare (<5% prevalence). Although rare, these CNVs are more common in simplex families (families with only one child with ASD) as compared to multiplex families (families with multiple children with ASD) (Gerdts et al., 2013; Leppa et al., 2016; Sasson et al., 2013b). Multiplex ASD is highly associated with BAP in relatives (Gerdts et al., 2013; Losh et al., 2008; Virkud et al., 2009) and thus it is unlikely these CNV mutations explain the intergenerational autistic traits seen when parents have BAP and the child has ASD (Sasson et al., 2013b). The associations that we see between parental BAP and the *Mild Language and Motor Delay with Dysregulation* class may suggest at least partial inheritance of common genetic variants in this group of parents and children. Common genetic variants are prevalent (>5% prevalence in the population), but do not have a large enough effect to be considered causal for ASD (Geschwind, 2011). However, Klei et al. (2012) found that a combination of these common variants lead to an additive effect on ASD risk with even higher effects among multiplex families. Yip et al. (2017) also found that additive genetic variability explains a large amount of ASD liability in a population-based sample from Sweden. Therefore, shared genetic variability may be the plausible pathway for familial transmission of traits common among parental BAP and child *Mild Language and Motor Delay with Dysregulation* class.

With the complexity and heterogeneity of ASD genetics, it is important to utilize the unique intergenerational aspects of BAP and ASD to improve the search for risk factors and learn how these factors manifest into the ASD presentation. In studies aimed at evaluating genetic risk associated with ASD, identifying parents with BAP and their phenotypically similar children would reduce heterogeneity in both phenotype and genotype, thus increasing the likelihood of meaningful genetic findings and discovery of etiologic mechanisms for specific ASD traits. In contrast, utilizing a study sample of children with ASD and no family history of ASD or BAP may improve power to find sporadic mutations and other non-heritable ASD etiologies.

There was an elevated but imprecise association between both parents having BAP and a child being in the *Mild Language and Motor Delay with Dysregulation* class compared to the *Significant Developmental Delay with Repetitive Motor Behaviors* class. The prevalence of BAP for any parent in our study was 19.0%, which is consistent with the literature that estimates prevalence between 10% and 50% (Dawson et al., 2007; Gerdts and Bernier, 2011; Lainhart et al., 2002; Lyall et al., 2014; Maxwell et al., 2013; Sasson et al., 2013a; Seidman et al., 2012) with lower prevalence among mothers of children with BAP (Gerdts and Bernier, 2011) (6.9% in our sample); consequently, statistical power is an issue when trying to assess the combined effects of having two parents with BAP. Our results for mothers alone being BAP+ compared to both parents being BAP−, which were imprecise, were similar in direction, but smaller in magnitude than results when fathers alone or both parents were BAP+. This result is in line with previous studies that found no or much weaker associations between maternal BAP and child scores on ASD measures of symptomatology relative to associations with paternal BAP (De la Marche et al., 2015; Losh et al., 2012; Maxwell et al., 2013; Schwichtenberg et al., 2010; Smith et al., 2009). This difference between parents with BAP could be a result of our limited sample size, or a reflection of

differing etiologic mechanisms based on parent of origin. Parents may transmit genes or epigenetic dysregulation that cause ASD through sex-specific pathways (Flashner et al., 2013; Gerdts and Bernier, 2011; Keverne, 1997). A population-based study found that heritable effects from the mother explained neither ASD liability nor ASD subtype; while in contrast, overall additive genetic variable accounted for a large proportion of ASD variability (Yip et al., 2017). Future work with a larger sample of mothers with BAP will allow us to better assess the sex-related genetic effects of BAP as an endophenotype.

In the full SEED sample, there was no statistically significant difference in class distribution between boys and girls (Wiggins et al., 2017), and qualitatively, our results did not show modification of the association between parental BAP and child ASD phenotype by child sex. Child sex may play a role in ASD etiology, based on a "female protective effect" (Jacquemont et al., 2014) or differences related to diagnostic practice and under-identification of ASD in females (Begeer et al., 2013). However, our results suggest that pathways associated with parental BAP do not drive sex differences in ASD. Caution is warranted given the imprecision of our findings because of limited sample size. Further work should explore how parental BAP relates to the biological mechanisms that lead to female ASD in a larger sample of girls.

Our ability to investigate whether the paternal versus maternal BAP was more strongly associated with the child's phenotype was limited by the low prevalence of having both parents BAP+ or only mothers that were BAP+. The ability to investigate whether the associations differed by child's sex was also limited by the small number of girls. We aim to statistically assess these associations with larger samples in the future. In this work, 183 children were missing parental SRS-A data. Sensitivity analyses that weighted for this missingness had results similar to the full sample missing indicator approach. We did not know who acted as the informant on the SRS-A for 37.5% of fathers and 75.7% of mothers. It is likely that some mothers and fathers filled out SRS-As on themselves and this could affect accuracy in reporting BAP (De la Marche et al., 2015; Sasson et al., 2014). The effect of this self-reporting on the SRS-A in our study would likely lead to non-differential misclassification, since reporting method would not be associated with BAP status or child phenotype (Constantino and Gruber, 2012; De la Marche et al., 2015).

Although SEED was community-based, the sample is comprised six sites that may not fully represent other geographic areas with differing socioeconomic and demographic distributions. In addition, the results of LCA are dependent on the variables used to generate latent classes and characteristics of the sample. Replication studies are needed to demonstrate the stability of our subgroups in other samples of children, in similar and different age ranges and over time. In addition, this work should be replicated using results when using other methods, such as semi-structured interviews, observations, self-reports, and other tools to measure BAP to ensure there are no residual effects of using the SRS-A. In past work with these data, we found mothers with BAP may report differently on child ASD traits (Rubenstein et al., 2017); this may have affected reporting on indicators taken from maternal report measures. However, since we used indicators from a wide range of instruments with both maternal and clinician informants, this is unlikely to have substantially biased our results. Based on the conceptual framework of our study, we did not

believe that it was necessary to statistically adjust for demographic characteristics. Nonetheless, with more data, we hope to validate latent classes after stratification by race or parental age and then assess relationships between parental BAP.

An important strength of this study is SEED's large community-based sample of children with ASD. These children had a broad range of symptoms and symptom severity, yet were confirmed to have ASD by a comprehensive in-person evaluation with research reliable clinicians. The inclusion of children with a diverse range of symptoms increased the generalizability of the observed associations with parental BAP compared to observations from potentially more severe clinic-based samples. In addition, SEED collected extensive data on behavior and co-occurring conditions that allowed us to better describe child ASD phenotypic subgroups. Although sample size was limited for some groups, we were able to explore effects of which parent was BAP+ and interaction by child sex, highlighting avenues for future research.

Conclusion

BAP in parents of children with ASD was significantly associated with the child being in a phenotypic class that presented with average nonverbal abilities, mild language and motor delays, and more co-occurring conditions like anxiety, depression, and sleep problems. Children in this class have a presentation that includes traits qualitatively similar to BAP in adults. Future work should continue to better define and identify ASD subgroups using characteristics like BAP in parents and then use these groups to explore endophenotypes that can identify hereditary genetic mechanisms to for certain ASD characteristics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

Achenbach, BS. Child Behavior Checklist. Burlington, VT: Achenbach System of Empirically Based Assessment; 1992.

Alarcon M, Yonan AL, Gilliam TC, et al. 2005; Quantitative genome scan and Ordered-Subsets Analysis of autism endophenotypes support language QTLs. Molecular Psychiatry. 10:747–757. [PubMed: 15824743]

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5. Arlington, TX: American Psychiatric Publishing; 2013.

An JY, Claudianos C. 2016; Genetic heterogeneity in autism: From single gene to a pathway perspective. Neuroscience and Biobehavioral Reviews. 68:442–453. [PubMed: 27317861]

Begeer S, Mandell D, Wijnker-Holmes B, et al. 2013; Sex differences in the timing of identification among children and adults with autism spectrum disorders. Journal of Autism and Developmental Disorders. 43:1151–1156. [PubMed: 23001766]

Bolton P, Macdonald H, Pickles A, et al. 1994; A case-control family history study of autism. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 35:877–900.

Bora E, Aydin A, Sarac T, et al. 2016; Heterogeneity of subclinical autistic traits among parents of children with autism spectrum disorder: identifying the broader autism phenotype with a data-driven method. Autism Research. 10:321–326. [PubMed: 27383033]

Bray BC, Lanza ST, Tan X. 2015; Eliminating bias in classify-analyze approaches for latent class analysis. Structural Equation Modeling. 22:1–11. [PubMed: 25614730]

Butler MG, Dasouki MJ, Zhou XP, et al. 2005; Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. Journal of Medical Genetics. 42:318–321. [PubMed: 15805158]

Cholemkery H, Medda J, Lempp T, et al. 2016; Classifying autism spectrum disorders by ADI-R: subtypes or severity gradient? Journal of Autism and Developmental Disorders. 46:2327–2339. [PubMed: 26956715]

Connolly JJ, Glessner JT, Hakonarson H. 2013; A genome-wide association study of autism incorporating autism diagnostic interview-revised, autism diagnostic observation schedule, and social responsiveness scale. Child Development. 84:17–33. [PubMed: 22935194]

Constantino, JN. Social Responsiveness Scale. Los Angeles, CA: Western Psychological Services; 2002.

Constantino JN, Abbacchi AM, Lavesser PD, et al. 2009; Developmental course of autistic social impairment in males. Development and Psychopathology. 21:127–138. [PubMed: 19144226]

Constantino, JN, Gruber, CP. Social Responsiveness Scale. 2. Los Angeles, CA: Western Psychological Services; 2012.

Constantino JN, Todd RD. 2005; Intergenerational transmission of subthreshold autistic traits in the general population. Biological Psychiatry. 57:655–660. [PubMed: 15780853]

Constantino JN, Zhang Y, Holzhauer K, et al. 2015; Distribution and within-family specificity of quantitative autistic traits in patients with neurofibromatosis type I. Journal of Pediatrics. 167:621–626. [PubMed: 26051969]

Dawson G, Estes A, Munson J, et al. 2007; Quantitative assessment of autism symptom-related traits in probands and parents: broader phenotype autism symptom scale. Journal of Autism and Developmental Disorders. 37:523–536. [PubMed: 16868845]

De la Marche W, Noens I, Kuppens S, et al. 2015; Measuring quantitative autism traits in families: informant effect or intergenerational transmission? European Child and Adolescent Psychiatry. 24:385–395. [PubMed: 25086652]

De la Marche W, Noens I, Luts J, et al. 2012; Quantitative autism traits in first degree relatives: evidence for the broader autism phenotype in fathers, but not in mothers and siblings. Autism. 16:247–260. [PubMed: 21949002]

De la Torre-Ubieta L, Won H, Stein JL, et al. 2016; Advancing the understanding of autism disease mechanisms through genetics. Nature Medicine. 22:345–361.

Duvekot J, Van der Ende J, Constantino JN, et al. 2016; Symptoms of autism spectrum disorder and anxiety: shared familial transmission and cross-assortative mating. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 57:759–769.

Flashner BM, Russo ME, Boileau JE, et al. 2013; Epigenetic factors and autism spectrum disorders. Neuromolecular Medicine. 15:339–350. [PubMed: 23468062]

Flint J, Munafo MR. 2007; The endophenotype concept in psychiatric genetics. Psychological Medicine. 37:163–180. [PubMed: 16978446]

Formann AK. 2007; Mixture analysis of multivariate categorical data with covariates and missing entries. Computational Statistics & Data Analysis. 51:5236–5246.

Francis SM, Kistner-Griffin E, Yan Z, et al. 2016; Variants in adjacent oxytocin/vasopressin gene region and associations with ASD diagnosis and other autism related endophenotypes. Frontiers in Neuroscience. 10:195. [PubMed: 27242401]

Gaugler T, Klei L, Sanders SJ, et al. 2014; Most genetic risk for autism resides with common variation. Nature Genetics. 46:881–885. [PubMed: 25038753]

Georgiades S, Boyle M, Szatmari P, et al. 2014; Modeling the phenotypic architecture of autism symptoms from time of diagnosis to age 6. Journal of Autism and Developmental Disorders. 44:3045–3055. [PubMed: 24958435]

Georgiades S, Szatmari P, Boyle M, et al. 2013; Investigating phenotypic heterogeneity in children with autism spectrum disorder: a factor mixture modeling approach. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 54:206–215.

Gerdts J, Bernier R. 2011; The broader autism phenotype and its implications on the etiology and treatment of autism spectrum disorders. Autism Research and Treatment. 2011:545901. [PubMed: 22937250]

Gerdts J, Bernier R, Dawson G, et al. 2013; The broader autism phenotype in simplex and multiplex families. Journal of Autism and Developmental Disorders. 43:1597–1605. [PubMed: 23117424]

Geschwind DH. 2011; Genetics of autism spectrum disorders. Trends in Cognitive Sciences. 15:409–416. [PubMed: 21855394]

Gottesman II, Gould TD. 2003; The endophenotype concept in psychiatry: etymology and strategic intentions. American Journal of Psychiatry. 160:636–645. [PubMed: 12668349]

Gould TD, Gottesman II. 2006; Psychiatric endophenotypes and the development of valid animal models. Genes, Brain, and Behavior. 5:113–119.

Groenwold RHH, White IR, Donders ART, et al. 2012; Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. Canadian Medical Association Journal. 184:1265–1269. [PubMed: 22371511]

Guthery SL, Salisbury BA, Pungliya MS, et al. 2007; The structure of common genetic variation in United States populations. American Journal of Human Genetics. 81:1221–1231. [PubMed: 17999361]

Hagenaars, JA, McCutcheon, AL. Applied Latent Class Analysis. Cambridge; New York: Cambridge University Press; 2002.

Hall MH, Smoller JW. 2010; A new role for endophenotypes in the GWAS era: functional characterization of risk variants. Harvard Review of Psychiatry. 18:67–74. [PubMed: 20047462]

Hasegawa C, Kikuchi M, Yoshimura Y, et al. 2015; Broader autism phenotype in mothers predicts social responsiveness in young children with autism spectrum disorders. Psychiatry and Clinical Neurosciences. 69:136–144. [PubMed: 24902617]

Ingersoll B, Hopwood CJ, Wainer A, et al. 2011; A comparison of three self-report measures of the broader autism phenotype in a non-clinical sample. Journal of Autism and Developmental Disorders. 41:1646–1657. [PubMed: 21331821]

Jacquemont S, Coe BP, Hersch M, et al. 2014; A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders. American Journal of Human Genetics. 94:415–425. [PubMed: 24581740]

Jones MP. 1996; Indicator and stratification methods for missing explanatory variables in multiple linear regression. Journal of the American Statistical Association. 91:222–230.

Keverne EB. 1997; Genomic imprinting in the brain. Current Opinion in Neurobiology. 7:463–468. [PubMed: 9287207]

Klei L, Sanders SJ, Murtha MT, et al. 2012; Common genetic variants, acting additively, are a major source of risk for autism. Molecular Autism. 3:9. [PubMed: 23067556]

Koegel LK, Koegel RL, Ashbaugh K, et al. 2014; The importance of early identification and intervention for children with or at risk for autism spectrum disorders. International Journal of Speech-language Pathology. 16:50–56. [PubMed: 24328352]

Lai MC, Lombardo MV, Baron-Cohen S. 2014; Autism. Lancet. 383:896–910. [PubMed: 24074734]

Lai MC, Lombardo MV, Chakrabarti B, et al. 2013; Subgrouping the autism "spectrum": reflections on DSM-5. PLoS Biology. 11:e1001544. [PubMed: 23630456]

Lainhart JE, Ozonoff S, Coon H, et al. 2002; Autism, regression, and the broader autism phenotype. American Journal of Medical Genetics. 113:231–237. [PubMed: 12439889]

Landa RJ, Gross AL, Stuart EA, et al. 2012; Latent class analysis of early developmental trajectory in baby siblings of children with autism. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 53:986–996.

Leppa VM, Kravitz SN, Martin CL, et al. 2016; Rare inherited and De novo CNVs reveal complex contributions to ASD risk in multiplex families. American Journal of Human Genetics. 99:540–554. [PubMed: 27569545]

Levy SE, Giarelli E, Lee LC, et al. 2010; Autism spectrum disorder and co-occurring developmental, psychiatric, and medical conditions among children in multiple populations of the United States. Journal of Developmental and Behavioral Pediatrics. 31:267–275. [PubMed: 20431403]

Liu XQ, Paterson AD, Szatmari P, et al. 2008; Genome-wide linkage analyses of quantitative and categorical autism sub-phenotypes. Biological Psychiatry. 64:561–570. [PubMed: 18632090]

Lord, C, Rutter, M, DiLavore, PC. , et al. Autism Diagnostic Observation Schedule. 2. Torrance, CA: Western Psychological Services; 2012.

Losh M, Piven J. 2007; Social-cognition and the broad autism phenotype: identifying genetically meaningful phenotypes. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 48:105–112.

Losh M, Childress D, Lam K, et al. 2008; Defining key features of the broad autism phenotype: a comparison across parents of multiple- and single-incidence autism families. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 147:424–433.

Losh M, Klusek J, Martin GE, et al. 2012; Defining genetically meaningful language and personality traits in relatives of individuals with fragile X syndrome and relatives of individuals with autism. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 159:660–668.

Lowe JK, Werling DM, Constantino JN, et al. 2015; Social responsiveness, an autism endophenotype: genomewide significant linkage to two regions on chromosome 8. American Journal of Psychiatry. 172:266–275. [PubMed: 25727539]

Lyall K, Constantino JN, Weisskopf MG, et al. 2014; Parental social responsiveness and risk of autism spectrum disorder in offspring. JAMA Psychiatry. 71:936–942. [PubMed: 25100167]

Lyall K, Croen L, Daniels J, et al. 2016; The changing epidemiology of autism spectrum disorders. Annual Review of Public Health. 38:81–102.

Maxwell CR, Parish-Morris J, Hsin O, et al. 2013; The broad autism phenotype predicts child functioning in autism spectrum disorders. Journal of Neurodevelopmental Disorders. 5:25. [PubMed: 24053506]

Mazefsky CA, Williams DL, Minshew NJ. 2008; Variability in adaptive behavior in autism: evidence for the importance of family history. Journal of Abnormal Child Psychology. 36:591–599. [PubMed: 18188537]

Miles JH. 2011; Autism spectrum disorders–a genetics review. Genetics in Medicine. 13:278–294. [PubMed: 21358411]

Mullen, E. Mullen Scales of Early Learning. San Antonio, TX: Pearson; 1995.

Munson J, Dawson G, Sterling L, et al. 2008; Evidence for latent classes of IQ in young children with autism spectrum disorder. American Journal of Mental Retardation. 113:439–452. [PubMed: 19127655]

Muthen, LK, Muthen, BO. Mplus User's Guide. Los Angeles, CA: Muthen & Muthen; 1998–2012.

Nishiyama T, Suzuki M, Adachi K, et al. 2014; Comprehensive comparison of self-administered questionnaires for measuring quantitative autistic traits in adults. Journal of Autism and Developmental Disorders. 44:993–1007. [PubMed: 24342972]

Piven J, Wzorek M, Landa R, et al. 1994; Personality characteristics of the parents of autistic individuals. Psychological Medicine. 24:783–795. [PubMed: 7991760]

Robinson EB, Koenen KC, McCormick MC, et al. 2011; Evidence that autistic traits show the same etiology in the general population and at the quantitative extremes (5%, 2.5%, and 1%). Archives of General Psychiatry. 68:1113–1121. [PubMed: 22065527]

Rubenstein E, Edmondson Pretzel R, Windham GC, et al. 2017; The broader autism phenotype in mothers is associated with increased discordance between maternal-reported and clinician-

observed instruments that measure child autism spectrum disorder. Journal of Autism and Developmental Disorders. 47:3253–3266. [PubMed: 28748335]

Rutter, M; Le Couteur, A; Lord, C. ADI-R: Autism Diagnostic Interview-Revised. 2003. Available at: https://www.wpspublish.com/store/p/2645/adi-r-autism-diagnostic-interview-revised

Sandin S, Lichtenstein P, Kuja-Halkola R, et al. 2017; The heritability of autism spectrum disorder. JAMA. 318:1182–1184. [PubMed: 28973605]

SAS Institute Inc. SAS/STAT Software, Version 9.3. Cary, NC: SAS Institute Inc; 2011.

Sasson NJ, Faso DJ, Parlier M, et al. 2014; When father doesn't know best: selective disagreement between self-report and informant report of the broad autism phenotype in parents of a child with autism. Autism Research. 7:731–739. [PubMed: 25339495]

Sasson NJ, Lam KS, Childress D, et al. 2013a; The broad autism phenotype questionnaire: prevalence and diagnostic classification. Autism Research. 6:134–143. [PubMed: 23427091]

Sasson NJ, Lam KS, Parlier M, et al. 2013b; Autism and the broad autism phenotype: familial patterns and intergenerational transmission. Journal of Neurodevelopmental Disorders. 5:11. [PubMed: 23639131]

Schendel DE, Diguiseppi C, Croen LA, et al. 2012; The Study to Explore Early Development (SEED): a multisite epidemiologic study of autism by the centers for autism and developmental disabilities research and epidemiology (CADDRE) network. Journal of Autism and Developmental Disorders. 42:2121–2140. [PubMed: 22350336]

Schwichtenberg AJ, Young GS, Sigman M, et al. 2010; Can family affectedness inform infant sibling outcomes of autism spectrum disorders? Journal of Child Psychology and Psychiatry, and Allied Disciplines. 51:1021–1030.

Seidman I, Yirmiya N, Milshtein S, et al. 2012; The broad autism phenotype questionnaire: mothers versus fathers of children with an autism spectrum disorder. Journal of Autism and Developmental Disorders. 42:837–846. [PubMed: 21706249]

Shishido E, Aleksic B, Ozaki N. 2014; Copy-number variation in the pathogenesis of autism spectrum disorder. Psychiatry and Clinical Neurosciences. 68:85–95. [PubMed: 24372918]

Smith CJ, Lang CM, Kryzak L, et al. 2009; Familial associations of intense preoccupations, an empirical factor of the restricted, repetitive behaviors and interests domain of autism. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 50:982–990.

Sucksmith E, Roth I, Hoekstra RA. 2011; Autistic traits below the clinical threshold: re-examining the broader autism phenotype in the 21st century. Neuropsychology Review. 21:360–389. [PubMed: 21989834]

Veatch OJ, Veenstra-Vanderweele J, Potter M, et al. 2014; Genetically meaningful phenotypic subgroups in autism spectrum disorders. Genes, Brain, and Behavior. 13:276–285.

Vermunt JK. 2010; Latent class modeling with covariates: two improved three-step approaches. Political Analysis. 18:450–469.

Virkud YV, Todd RD, Abbacchi AM, et al. 2009; Familial aggregation of quantitative autistic traits in multiplex versus simplex autism. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 150:328–334.

Waterhouse L, Gillberg C. 2014; Why autism must be taken apart. Journal of Autism and Developmental Disorders. 44:1788–1792. [PubMed: 24390538]

Wiggins LD, Bakeman R, Adamson LB, et al. 2007; The utility of the Social Communication Questionnaire in screening for autism in children referred for early intervention. Focus on Autism and Other Developmental Disabilities. 22:33–38.

Wiggins LD, Reynolds A, Rice CE, et al. 2015; Using standardized diagnostic instruments to classify children with autism in the study to explore early development. Journal of Autism and Developmental Disorders. 45:1271–1280. [PubMed: 25348175]

Wiggins LD, Tian LH, Levy SE, et al. 2017; Homogeneous subgroups of young children with autism improve phenotypic characterization in the study to explore early development. Journal of Autism and Developmental Disorders. 47:3634–3645. [PubMed: 28879490]

Yip BHK, Bai D, Mahjani B, et al. 2017Heritable variation, with little or no maternal effect, accounts for recurrence risk to autism spectrum disorder in Sweden. Biological Psychiatry.
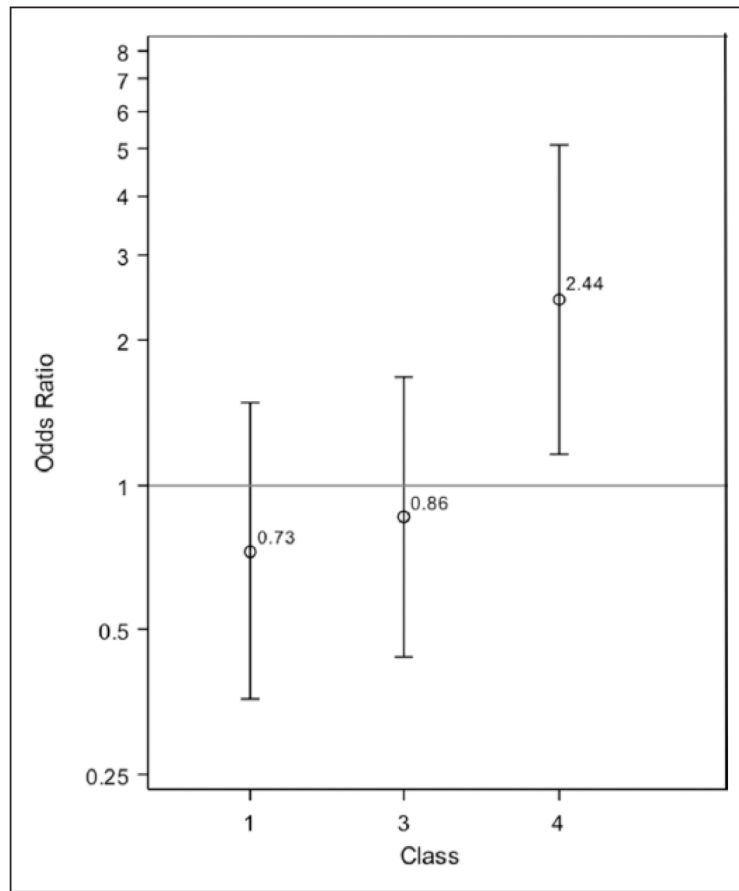
Figure 1.
Odds ratios and 95% confidence intervals comparing child autism spectrum disorder phenotypic classes by parental broader autism phenotype in the Study to Explore Early Development.

Class 2 and neither parent having the broader autism phenotype is the referent class.

Class 1: Mild Language Delay with Cognitive Rigidity. Class 2: Significant Developmental Delay with Repetitive Motor Behaviors. Class 3: General Developmental Delay. Class 4: Mild Language and Motor Delay with Dysregulation (e.g. anxiety/depression).

Table 1

Indicator variables and item response probabilities or means for children with autism spectrum disorder in the Study to Explore Early Development, using an inclusive latent class analysis approach.

	Source	Variable type (range)	Direction of score indicating impairment	Item response probability/mean by class			
				1	2	3	4
Categorical variables (response probabilities)							
Current diet restrictions	GIQ	Yes/No	Higher	0.26	0.36	0.30	0.40
Early recognition of epilepsy/ seizure disorder	Caregiver interview	Yes/No	Higher	0.00	0.13	0.02	0.05
History of regression	ADI-R	Yes/No	Higher	0.16	0.34	0.29	0.27
Insistence on sameness	ADI-R	Yes/No	Higher	0.72	0.63	0.66	0.90
Problems with age at first social smile	EDQ	Yes/No	Higher	0.13	0.24	0.15	0.31
Repetitive behavior with objects	ADI-R	Yes/No	Higher	0.77	0.94	0.82	0.96
Repetitive motor mannerisms	ADI-R	Yes/No	Higher	0.74	0.96	0.78	0.83
Restricted interests	ADI-R	Yes/No	Higher	0.85	0.73	0.81	0.92
Self-injurious behaviors	ADI-R	Yes/No	Higher	0.38	0.58	0.37	0.79
Unusual sensory response	ADI-R	Yes/No	Higher	0.91	0.97	0.94	0.97
Continuous variables (response means)							
Age at verbal language development	ADI-R	Months	Higher	19.92	30.57	25.14	24.25
Age at walking	ADI-R	Months	Higher	13.69	16.32	14.11	13.58
Aggressive behaviors	CBCL	T-scores	Higher	55.92	61.96	57.93	76.07
Anxiety/depression	CBCL	T-scores	Higher	53.58	56.24	53.38	69.37
Attention problems	CBCL	T-scores	Higher	59.03	67.12	61.59	70.90
Autism severity	ADOS	Total severity scores (1–10)	Higher	6.73	7.88	7.21	6.46
Emotionally reactive	CBCL	T-scores	Higher	57.93	61.74	57.35	77.67
Expressive language skills	MSEL	Age equivalent scores (2–70)	Lower	50.77	14.50	34.03	46.10
Fine motor skills	MSEL	Age equivalent scores (4–68)	Lower	54.52	23.08	37.57	49.89
Receptive language skills	MSEL	Age equivalent score (1–69)	Lower	56.98	15.22	34.33	48.24
Sleep problems	Sleep Habit Questionnaire	Total problem score	Higher	47.38	53.87	49.34	59.65
Social communication abilities	SCQ	Total score (1–35)	Higher	13.04	20.97	16.93	20.53
Somatic complaints	CBCL	Total score (0–91)	Higher	57.18	60.80	58.14	67.70
Visual reception skills	MSEL	Age equivalent score (5–69)	Higher	61.33	23.13	40.50	53.68

| Source | Variable type (range) | Direction of score indicating impairment | Item response probability/mean by class | | | |
			1	2	3	4
Withdrawn behaviors	CBCL	T-scores	Higher	64.89	76.37	67.00	76.54

ADI-R: Autism Diagnostic Interview-Revised; EDQ: Early Development Questionnaire; ADOS: Autism diagnostic observation schedule-2; CBCL: Child Behavior Checklist; MSEL: Mullen Scale of Early Learning; SCQ: Social Communication Questionnaire.

Based on variables selected by Wiggins et al. (2017).

Table 2

Phenotypic subgroups in the Study to Explore Early Development, derived using latent class analysis.

Class	Percentage[a]	Description
1	28.1	*Mild Language Delay with Cognitive Rigidity*: children in this group had the least impairment in terms of cognitive functioning and the youngest age of language development. They were less likely to have developmental regression than children in other classes. This class had high rates of restricted interests and unusual sensory responses
2	26.6	*Significant Developmental Delay with Repetitive Motor Behaviors*: children in this group had the most impairment in cognitive functioning. Members of this group acquired language at later ages (if at all) and were latest to walk unsupported. This group had the highest rate of seizures, unusual sensory responses, and more repetitive motor mannerisms
3	33.3	*General Developmental Delay*: children in this group had significant impairments in cognitive functioning and were similar to class 1 except that they had more reported developmental regression and delayed language development. This group also had high levels of unusual sensory response.
4	12.0	*Mild Language and Motor Delay with Dysregulation*: children in this group had average nonverbal functioning and mild language and motor delays. This class had high rates of cognitive rigidity, and relatively higher rates of aggressive behaviors, anxiety/depression, attention problems, emotional reactivity, self-injurious behaviors, sleep problems, and somatic complaints than other groups. This group also had high levels of unusual sensory response.

[a] Percentage is from a latent class model that included our broader autism phenotype covariate.

Table 3

Demographic characteristics by parent's broader autism phenotype status in the Study to Explore Early Development.

	One or both parents BAP+a		Both parents BAP–		Missing BAP[b]	
	N=100		N=424		N=183	
	n	%	n	%	n	%
Child sex						
Male	80	80.0	355	83.7	144	78.7
Female	20	20.0	69	16.3	39	21.3
Maternal race						
White	64	63.4	290	68.4	88	48.1
Black	18	17.8	57	13.4	68	37.2
Asian	9	8.9	43	10.1	8	4.4
Other	6	5.9	18	4.2	9	4.9
Multi-racial	4	4.0	16	3.8	10	5.5
Paternal race						
White	62	62.0	289	68.2	91	52.3
Black	19	19.0	65	15.3	69	39.7
Asian	7	7.0	39	9.2	8	4.6
Other	9	9.0	19	4.5	6	3.4
Multi-racial	3	3.0	12	2.8	3	1.7
Missing					7	
Maternal ethnicity						
Hispanic	16	16.2	46	11.0	23	12.6
Not-Hispanic	84	83.8	378	89.0	160	87.4
Paternal ethnicity						
Hispanic	19	19.4	40	9.5	22	12.6
Not-Hispanic	79	80.6	383	90.5	153	87.4
Missing	2		1		8	
Maternal education (years)						
<12	24	24.2	54	12.7	12	6.6

	One or both parents BAP+[a] N=100		Both parents BAP– N=424		Missing BAP[b] N=183	
	n	%	n	%	n	%
12 to <16	58	58.6	266	62.7	101	55.2
>=16	17	17.2	104	24.5	70	38.3
Missing	1					
Paternal education (years)						
<12	33	33.3	88	20.5	21	12.1
12 to <16	43	43.4	235	54.7	95	54.6
>=16	23	23.2	107	24.9	58	33.3
Missing	1				9	
Site						
California	18	18.0	76	17.9	18	9.8
Colorado	19	19.0	85	20.0	38	20.8
Georgia	18	18.0	81	19.1	39	21.3
Maryland	19	19.0	48	11.3	41	22.4
North Carolina	12	12.0	77	18.2	15	8.2
Pennsylvania	14	14.0	57	13.4	32	17.5
Phenotypic class[c]						
1	26	26.0	106	25.0	56	30.6
2	22	22.0	134	31.6	43	23.5
3	30	30.0	144	34.0	59	32.2
4	22	22.0	38	9.0	25	13.7

BAP: broader autism phenotype.

[a]BAP+ defined as a Social Responsiveness-Adult T-score 60.

[b]Missing SRS-A includes missing data for mother SRS-A only (N = 43), father SRS-A only (N = 70), or both missing SRS-A (N = 70).

[c]Phenotypic classes were from the inclusive latent class model with any parent BAP+. Classes are assigned by highest posterior probability (analyses did not assign children to classes but used estimated model probabilities).

Table 4

Odds ratios comparing child autism spectrum disorder phenotype class by which parent presented with broader autism phenotype in the Study to Explore Early Development.

Class	Both parents BAP+ (N=16)			Mother only BAP+ (N=20)			Father only BAP+ (N=64)		
	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI
1	2	0.34	0.06, 1.87	9	0.28	0.05, 1.54	19	1.07	0.47, 2.45
2	5	REF		6	REF		15	REF	
3	5	0.77	0.20, 2.94	2	1.06	0.33, 3.46	17	0.82	0.21, 3.12
4	4	2.40	0.54, 10.57	3	1.63	0.34, 7.68	13	2.71	1.09, 6.77

BAP: broader autism phenotype; OR: odds ratio; CI: confidence interval.

Neither parent having BAP (n = 424). Ns were derived using classes assigned by posterior probabilities while analyses used model-estimated probabilities.

Class 1: *Mild Language Delay with Cognitive Rigidity*. Class 2: *Significant Developmental Delay with Repetitive Motor Behaviors*. Class 3: *General Developmental Delay*. Class 4: *Mild Language and Motor Delay with Dysregulation* (e.g. anxiety/depression).

Bold indicates statistical significance at an α = 0.05 level.

Table 5

Odds ratios comparing child autism spectrum disorder phenotype classes by parental broader autism phenotype (any parent BAP+ vs both parents BAP−) separately by child's sex in the Study to Explore Early Development.

Class	Boys with any parent BAP+ (N=80)			Girls with any parent BAP+ (N=20)		
	N	OR	95% CI	N	OR	95% CI
1	20	1.22	0.56, 2.65	6	0.50	0.11, 2.34
2	20	REF		3	REF	
3	25	1.23	0.57, 2.61	5	0.44	0.08, 2.41
4	15	2.69	1.06, 6.79	6	3.92	0.74, 20.76

BAP: broader autism phenotype; OR: odds ratio; CI: confidence interval.

Neither parent having BAP is the referent. Ns were derived using classes assigned by posterior probabilities while analyses used model-estimated probabilities.

Class 1: *Mild Language Delay with Cognitive Rigidity.* Class 2: *Significant Developmental Delay with Repetitive Motor Behaviors.* Class 3: *General Developmental Delay.* Class 4: *Mild Language and Motor Delay with Dysregulation* (e.g. anxiety/depression).

Bold indicates statistical significance at an α = 0.05 level.