Archival Report

Heritable Variation, With Little or No Maternal Effect, Accounts for Recurrence Risk to Autism Spectrum Disorder in Sweden

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ABSTRACT

BACKGROUND: Autism spectrum disorder (ASD) has both genetic and environmental origins, including potentially maternal effects. Maternal effects describe association of one or more maternal phenotypes with liability to ASD in progeny that are independent of maternally transmitted risk alleles. While maternal effects could play an important role, consistent with association to maternal traits such as immune status, no study has estimated maternal, additive genetic, and environmental effects in ASD.

METHODS: Using a population-based sample consisting of all children born in Sweden from 1998 to 2007 and their relatives, we fitted statistical models to family data to estimate the variance in ASD liability originating from maternal, additive genetic, and shared environmental effects. We calculated sibling and cousin family recurrence risk ratio as a direct measure of familial, genetic, and environmental risk factors and repeated the calculations on diagnostic subgroups, specifically autistic disorder (AD) and spectrum disorder (SD), which included Asperger's syndrome and/or pervasive developmental disorder not otherwise specified.

RESULTS: The sample consisted of 776,212 children of whom 11,231 had a diagnosis of ASD: 4554 with AD, 6677 with SD. We found support for large additive genetic contribution to liability; heritability (95% confidence interval [CI]) was estimated to 84.8% (95% CI: 73.1–87.3) for ASD, 79.6% (95% CI: 61.2–85.1) for AD, and 76.4% (95% CI: 63.0–82.5) for SD.

CONCLUSIONS: There was modest, if any, contribution of maternal effects to liability for ASD, including subtypes AD and SD, and there was no support for shared environmental effects. These results show liability to ASD arises largely from additive genetic variation.

Keywords: Autism, Epidemiology, Genetics, Heritability, Population-based, Psychiatry

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Autism spectrum disorder (ASD), a neurodevelopment disorder with significant social, communication, and behavioral challenges (1), has both genetic and environmental origins. Research into its genetic origins has consistently implicated rare and common inherited variation, as well de novo mutation (2–5). Most (6–12) but not all estimates of ASD heritability derive from twin studies, and the remainder derive from direct (2,3) or indirect (13–15) assessments of extended pedigrees. For environmental variation, some of the most consistent findings center on factors of maternal origin or maternal effects. Maternal obesity, hypertension, diabetes, prepregnancy body mass index, polycystic ovary syndrome, hypertensive disorders of pregnancy, and gestational diabetes all have some support for conferring risk for ASD in offspring (16–24). In addition, maternal immune status has been associated with ASD, and altered immune status is quite frequent in studies of mothers and ASD, estimated at >15% for autoimmune diseases and asthma, and 50% for allergies (25).

Here we use "maternal effect" to describe the association of a maternal phenotype with ASD in offspring. That association is assumed to be independent of genetic inheritance of ASD risk alleles from mother to offspring. Quantitative geneticists have long recognized that maternal effects can account for a substantial portion of population variability in an offspring trait (26). Like the offspring trait, the maternal phenotype can itself have both environmental and genetic origins; however, teasing apart these origins requires either carefully designed genetic crosses or extensive and deep pedigree data.

If maternal phenotypes, such as those described above, were a substantial source of liability for ASD, we reasoned that a portion of their impact on liability should be detectable as a maternal effect on ASD. By evaluating full sibling, half-sibling, and cousin relationships, we would predict that maternal effects could account for a substantial portion of the variability of ASD in such a sample. Pawitan et al. (27) proposed a statistical method to estimate the contribution to the variances in

liability originating from maternal effects, together with variance due to additive genetic effects and shared environmental effects on binary traits using family data. This method has been applied to preterm birth (28), preeclampsia (29), and schizophrenia and bipolar disorder (30,31). The magnitude of maternal effects for ASD, however, is not yet known, and so far no study has been conducted to separate the maternal effects and additive genetic effects from environmental effects. This is an important gap in our knowledge: if maternal effects were linked to increased ASD risk, investigating their nature is relatively straightforward and such investigations could lead to insights into the etiology of ASD. Moreover, genetically, the presence of maternal effects can bias heritability estimates derived from extended pedigrees because of the (unmodeled) increase of similarity among maternal relatives.

Maternal effects are not estimable from the standard twin design. Monozygotic and dizygotic twins presumably have similar maternal influences on the trait of interest, unless placentation is critical, yet they differ by additive and potentially dominant genetic effects on the trait. Twins also are relatively uncommon in the population and experience disproportionately elevated rates of obstetric complications, such as low birth weight and prematurity. Contrary to twins, contrasts of maternal versus paternal lineages from half-siblings and cousins are informative for maternal effects because additive genetic contributions are predictable and dominant effects should be largely absent, while shared environmental effects should be minimized and are assumed to be zero in our models for cousins. Therefore, differences in recurrence risk between equivalent maternal and paternal lineages should yield legitimate estimates of maternal effects.

In this study, we estimated maternal effects, together with additive genetic and shared environmental effects, for ASD using Swedish family data of nontwin (or singleton) births between the years 1998 to 2007. We also separated ASD into two diagnostic types relevant to that birth cohort, namely DSM-IV autistic disorder (AD), which captures more severely affected individuals, and individuals who have a diagnosis of ASD not as severe as AD, which we term spectrum disorder (SD). AD and SD are known to differ in the distribution of intellectual function, as well as ASD severity; in particular a greater fraction of AD subjects also have comorbid intellectual disability (32,33). Thus, this partition could also be meaningful for maternal effects.

METHODS AND MATERIALS

Study Population and Family Structure

Using the Swedish Medical Birth Register (34), we created a cohort consisting of all singletons who were born in Sweden between 1998 and 2007 and lived beyond 2 years of age. Note that children born in 2007 were 8 years old in 2014, the close of follow-up. The Swedish Multi-generation Register (35), which consists of all children born in Sweden since 1932 (and alive in 1961) and their parents, was used to identify parents and grandparents of eligible children and construct seven family types. We first identified cousin pairs: those related through mothers who were sisters were maternal parallel cousins (mPCs); those related through fathers who were brothers were paternal parallel cousins (pPCs); and cousins of other

relationships were cross-cousins (CCs). Of the families that remained, the next pairings were families with half-siblings (HSs), of either maternal (mHS) or paternal origin (pHS); note that these families could also contain full siblings. Finally, we formed "nonpaired families," consisting of full siblings. If there were more than two eligible pairings per family, say mPCs and CCs, then only eligible children of the oldest two siblings formed the paired family; we also limited families to a maximum of six children.

Outcome Variables

ASD, AD, and SD were ascertained using the Swedish National Patient Register. In addition to routine medical and developmental screening, all children had mandatory developmental assessment at 4 years of age, consisting of motor, language, cognitive, and social development. Children with a suspected developmental disorder were referred for further assessment to a specialized team. Diagnostic information was reported to the National Patient Register using the ICD-10: AD (ICD-10: F84.0); SD, (ICD-10: F84.5 "Asperger's syndrome"), and/or pervasive developmental disorder not otherwise specified (ICD-10: F84.9). See the Supplement for more details regarding diagnosis.

Statistical Methods

All analyses are conducted using R version 3.2.29 (36). To compare ASD risk in families of different relatedness, we calculated the recurrence risk and family recurrence risk ratio (FRR). The two measures are expected to vary across paired families in the presence of a true underlying maternal effect; for instance, first, the FRR should be greater for mPCs than pPCs. Second, we fitted variance component models to estimate the contribution of maternal, additive, and environmental effects, and we repeated those analyses separately for AD and SD. FRR is calculated as the ratio of family/sibling recurrence risk and the population prevalence (37). To estimate the recurrence risk, we identified all index cases and calculated the proportion of individuals diagnosed among their full siblings, half-siblings, and cousins of this proband. Then, for each family type, we defined the recurrence risk as the proportion of affected individuals among all siblings/cousins of those affected and defined FRR as this proportion divided by the prevalence. Confidence intervals were calculated by assuming a binomial distribution (38). For the severity subtypes, we require the proband and relative pairs to be of the same diagnostic subtype.

Liability Modeling. Maternal, additive genetic, and shared environmental effects can be estimated because the strength of genetically induced correlation of a trait varies by degree of relatedness between pairs. A residual term, which is commonly interpreted as unshared environmental effects, can also be estimated, although, in reality, it could be influenced by unmodeled genetic effects as well.

We assume a genetic coefficient of relationship of 0.5 for full siblings, 0.25 for half-siblings, and 0.125 for cousins (27,39). Maternal effect coefficients are assumed to be 1 for full siblings and mHSs, 0.5 for mPCs, and 0 for other relative pairs. Shared environment is unique to maternal families assumed to be