Developmental Changes in Genetic Relationships Between Traits and Disease: Analyses of Genetic Overlaps Between Social-communication Difficulties, Autism Spectrum Disorders and Schizophrenia

Topic Autism

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SUBMISSION DETAILS

Background The phenotypic overlap between Autism Spectrum Disorders (ASD) and schizophrenia is complex and dates back to Kanner in 1943, including symptomatic similarities such as social withdrawal, communication impairment, and poor eye contact. Recent theories proposed a “continuum of psychosis”, despite differences between disorders, based on shared genetic susceptibility among psychiatric conditions and genetic overlap with milder symptoms in unaffected individuals from the general population. Symptoms of ASD however typically occur during early childhood, whereas the first signs of schizophrenia appear during adolescence and early adulthood. Thus, genetic links with population-based traits may also follow a developmental pattern. Our study was conducted to investigate genetic relationships between social-communication difficulties during childhood and adolescence and both common variation in clinical ASD and schizophrenia.

Methods We studied social-communication difficulties (at ages 8, 11, 14 and 17 years; mother-reported Social and Communication Disorders Checklist) in ≤ 5,553 children from a UK population-based birth cohort (Avon Longitudinal Study of Parents and Children, ALSPAC). Traits were rank transformed to normality, and genome-wide analyses carried out using 1000G imputed data in ALSPAC children. Genetic links between these traits and ASD (5,305 cases, 5,305 pseudocontrols; ASD PGC) as well as schizophrenia (33,640 cases, 43,456 controls; schizophrenia PGC2) were measured with LD Score Regression using genome-wide summary data. In addition, polygenic scores, based on ASD and schizophrenia genome-wide association statistics, were constructed in ALSPAC children and investigated for trait association.

Results Genetic links between social-communication difficulties and ASD common variation in the PGC sample decreased with progressing age. The genetic correlation was strongest at 8 years of age ($r=0.33$, $P=0.027$) and completely attenuated by 17 years of age ($r=0.01$, $P=0.94$). This pattern was replicated for clinical ASD in the Danish iPSYCH sample (7,700 cases, 11,127 controls). In contrast, genetic links between social-communication difficulties and schizophrenia common variation increased during childhood and adolescence. The genetic correlation started to emerge at 8 years of age ($r=0.12$, $P=0.04$) and was strongest at 17 years of age ($r=0.18$, $P=0.003$). Evidence for genetic overlap was supported by polygenic score analysis for the strongest genetic links, i.e. between social-communication difficulties at 8 years and ASD (adjusted-$R2\leq0.12\%$, $P\geq0.005$) and social communication difficulties at 17 years and schizophrenia (adjusted-$R2\leq0.28\%$, $P\geq0.0004$).

Discussion In summary, our findings suggest shared common genetic influences between

social-communication difficulties and both ASD and schizophrenia without implying shared genetic susceptibility between ASD and schizophrenia. We identified disease-specific patterns, which are consistent with the occurrence of clinical symptoms during development and reflect the considerable genetic heterogeneity among social communication difficulties measures over time.

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