Epilepsy in Simplex Autism Pedigrees Is Much Lower Than the Rate in Multiplex Autism Pedigrees

To the Editor:

Epilepsy occurs in 5% to 40% of individuals with autism, whereas the prevalence in the general population is about .7% (1). The variability of rates in autism have been attributed to the heterogeneity of samples with respect to age, sex, intellectual disability (ID), comorbidity, subtype of pervasive developmental disorder, or causes. Another hypothesis is that prevalence rate of epilepsy in autism depends on the genetic background of autism and may therefore differ between simplex or multiplex forms. Indeed, the 12.8% rate of epilepsy in Autism Genetic Research Exchange multiplex autism pedigrees is high (2). The current study aimed to assess the prevalence of epilepsy in the Simons Simplex Collection (SSC) and whether ID and female sex are risk factors of epilepsy in simplex autism.

Data were ascertained from all families participating in SSC ($N = 2644$). A detailed description of procedures used to phenotype this sample is available in Fischbach and Lord (3). We extracted data relevant to epilepsy, full-scale IQ estimates, and Vineland Adaptive Behaviors Scales (VABS) scores to estimate the adaptive functioning level. Data relevant to epilepsy, defined as the occurrence of repeated unprovoked afebrile seizures, were collected through a standardized method combining information from the ADI-R and Medical History Form parents report. It indicates whether a confirmed diagnosis of epilepsy was made, whether the diagnosis was only suspected, or whether there was no evidence for epilepsy. We excluded 184 children: 3 had no data relevant to epilepsy and 181 had likely or possible presence of nonfebrile seizures; 2460 children (age = 9.0 ± 3.6 years) were included.

The prevalence of epilepsy was 58 in 2460 (2.4%). Children with epilepsy tended to be older than children without epilepsy (9.7 ± 3.8 vs. 8.9 ± 3.6 years; $p = .07$). Mean full-scale IQ ($n = 2455$) was 80.1 ± 27.9. Stratification of cases in two categories showed a fivefold increased risk for epilepsy for children with a full-scale IQ less than 70 (39/729; 5.3%) comparing children with a full-scale IQ 70 or higher (19/1726; 1.1%; odds ratio = 5.09; 95% confidence interval: 2.94–9.06; $p = 9.5 \times 10^{-9}$). The more severe the cognitive functioning was impaired, the more prevalent was epilepsy ($p = 6.9 \times 10^{-15}$, Figure 1). Mean overall VABS score was 73.1 ± 12.1. Stratification of cases in two categories (<70, $n = 902$) vs. ≥70, $n = 1558$) showed a fivefold increased risk for epilepsy for children with a low VABS score (43/902 = 4.8% vs. 15/1558 = 0.96%; odds ratio = 5.15; 95% confidence interval: 2.9–9.58; $p = 6.3 \times 10^{-8}$). Among the 324 females, 10 (3.1%) had a form of epilepsy. For the 2,136 male subjects, 48 (2.2%) had an epilepsy. The male/female ratio was 6.6:1 for the children without epilepsy and 4.8:1 for the children with epilepsy ($p = .36$). Considering all the children, girls were found to have a statistically significantly lower IQ than boys when the sample was stratified in two groups (full-scale IQ <70 vs. ≥70; odds ratio = 1.81; $p = 5.1 \times 10^{-7}$). This remains significant in children without epilepsy ($p < 10^{-4}$) but not in children with epilepsy ($p = .35$).

In simplex autism, we found that 2.4% of subjects had epilepsy. This rate is much lower than the prevalence found in Autism Genetic Research Exchange multiplex autism pedigrees (12.8%) but higher than the prevalence of epilepsy in the general population (1). As reported in the literature (4), we also found that the risk for epilepsy was significantly associated with ID. However, we found no significant increase of epilepsy associated with sex. This could reflect 1) that females with autism tend to have more severe ID than their male counterparts and that the mean SSC cognitive level is rather high and 2) that the genetic background differs between simplex or multiplex autism and includes more common risk factors for both epilepsy and autism in multiplex pedigrees. Although the current study was conducted in a large sample, limitations remain. These include that the definition of epilepsy was ascertained through a parent's report, that the young age of the sample may have reduced the prevalence of the late-onset seizures, that cognitive evaluation estimates were made using variable scales, and that there is a possibility of underreporting of epilepsy in SSC. We conclude that genetic factors associated with epilepsy may differ in simplex autism versus multiplex autism.

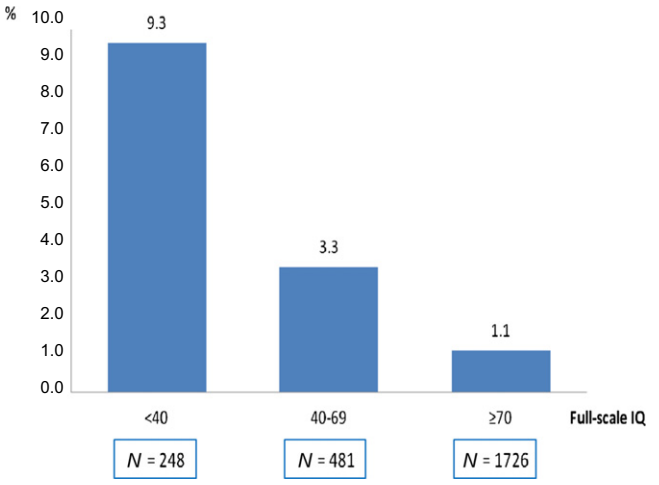

Figure 1. Frequencies of comorbid epilepsy in children with autism from Simons Simplex Collection as function of full-scale IQ (Differential Ability Scales—II, Mullen Scales of Early Learning, Wechsler Abbreviated Scale of Intelligence, or Wechsler Intelligence Scale for Children—IV).

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Approved researchers can obtain the SSC population data set described in this study by applying at https://base.sfari.org.

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