Neurofibromatosis Type 1 and Autism Spectrum Disorder

WHAT’S KNOWN ON THIS SUBJECT: NF1 is the commonest single-gene neurodevelopmental disorder with known neurobiology and developmental impact on attention and cognition. Its impact on social functioning is described but poorly understood, with no population-based study of autism spectrum disorder (ASD) prevalence in the disorder.

WHAT THIS STUDY ADDS: This epidemiological study shows high prevalence of 25% ASD in NF1 not explained by learning difficulties. ASD should be considered during clinical practice with NF1. Further research into NF1 as a single-gene model of ASD is warranted.

OBJECTIVE: To determine the prevalence of autism spectrum disorder (ASD) in Neurofibromatosis Type 1 (NF1).

METHODS: Second-phase population-based epidemiologic study using an allcase NF1 registry in a defined UK 4.1 million population area. A total of 109 (52.7%) of 207 responders from the initial screening phase were grouped by using the parent-rated Social Responsiveness Scale (SRS) as significant ASD (SRS≥76; n = 32), moderate ASD (SRS ≥ 60<76; n = 29), or non-ASD (SRS <60, n = 48). Twenty-three cases from the significant ASD group, 16 from moderate ASD, and 8 from non-ASD (total n = 47), invited proportionately by random selection, were seen for detailed confirmatory ascertainment. Assessments on Autism Diagnostic Interview-Revised, Autism Diagnostic Observation Scale-Generic, and verbal IQ were combined by using standard Collaborative Program for Excellence in Autism criteria into an ASD categorization for each case (ASD, broad ASD with partial features, non-ASD). A preplanned weighted analysis was used to derive prevalence estimates for the whole population.

RESULTS: Fourteen (29.5%) of 47 showed ASD, 13 (27.7%) broad ASD, and 20 (42.5%) non-ASD. The ASD/broad ASD group showed male predominance (1.7:1.0), but did not differ significantly from the non-ASD group on IQ, age, socioeconomic status, inheritance, physical severity, or education. The population prevalence estimate is 24.9% ASD (95% confidence interval 13.1%–42.1%) and 20.8% broad ASD (95% confidence interval 10.0%–38.1%); a total of 45.7% showing some ASD spectrum phenotype.

CONCLUSIONS: Findings indicate high prevalence of ASD in NF1, with implications for clinical practice and further research into NF1 as a single-gene model for autism. Pediatrics 2013;132:e1642–e1648

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KEY WORDS
autism, neurofibromatosis type 1, population, epidemiology

ABBREVIATIONS

ABC—Adaptive Behavior Composite
ADHD—attention-deficit/hyperactivity disorder
ADI-R—Autism Diagnostic Interview-Revised
ADOS-G—Autism Diagnostic Observation Scale-Generic
ASD—autism spectrum disorder
CPEA—Collaborative Program for Excellence in Autism
GSEA—Genetic Environment Score Analysis
NF1—Neurofibromatosis Type 1
Ras—Rat Sarcoma protein
SES—socioeconomic status
SRS—Social Responsiveness Scale
VABS—Vineland Adaptive Behavior Scale
WASI—Wechsler Abbreviated Scale of Intelligence

(Continued on last page)
Autism spectrum disorder (ASD) is a pervasive developmental disorder characterized by impairments in reciprocal social interaction and social communication and restricted interests or rigid, repetitive behaviors, with onset in early childhood. General population prevalence is at least 1% and possibly 1.88, higher in boys.\textsuperscript{1,2} Raised familial recurrence risk and monozygotic twin concordance rates approaching 90% point to high heritability, but there is genetic heterogeneity, with up to 1000 candidate gene sites described; identification of the detailed neuropathology and neurophysiology of the disorder has been equally challenging.\textsuperscript{3} Such difficulties have prompted study of ASD phenotype in cases in which ASD is “symptomatic” from known neuropathology or single-gene abnormality, such as tuberous sclerosis complex or fragile X syndrome, or associated with defined mutations and copy number variations.\textsuperscript{4} Neurofibromatosis type 1 (NF1) has considerable interest in this context. It is a common autosomal dominant genetic disorder with estimated birth incidence of 1:2699 and prevalence of 1:4560.\textsuperscript{5} Fifty percent of cases are inherited; the rest are sporadic due to spontaneous mutation of the \textit{Nf1} tumor suppressor gene at chromosome 17q11.2. Diagnosis of NF1 is based on distinctive physical features, such as café-au-lait spots, skinfold freckling, neurofibromas, and Lisch nodules,\textsuperscript{6} but cognitive and behavioral difficulties in up to 80% of children, including problems with attention, executive function, language, and visual perception,\textsuperscript{7} cause significant morbidity. Study of NF1\textsuperscript{1−7} knockout mice has enabled detailed insight into the cellular biology and neuropathology of NF1 and identified potential rational intervention. The \textit{Nf1} gene encodes for neurofibromin, which regulates the activity of the Rat Sarcoma protein (Ras)-bound intracellular signaling pathway, key in the regulation of cell differentiation, growth, and apoptosis. In knockout mice, loss of neurofibromin is associated with downstream increased Ras pathway activity, Ras/extracellular signal-regulated kinase signaling, and pre-synaptic \textit{γ}-aminobutyric acid; decreased synaptic long-term potentiation; and a pattern of cognitive impairment with similarities to the human phenotype.\textsuperscript{8} Farnesyl transferase inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors block Ras isoprenylation and reduce pathway activation, thus suggesting a potential rational intervention for NF1. Treatment studies with the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor Lovastatin in knockout mice have indeed shown decreased Ras activity, restoration of long-term potentiation, and rescue of the cognitive phenotype;\textsuperscript{9} however, initial statin intervention studies in humans have failed to replicate this effect.\textsuperscript{10}

Some evidence links abnormalities in the Ras pathway to autism.\textsuperscript{11} Fragile X and tuberous sclerosis complex have biochemical links with the Ras pathway and copy number variants with identified links to autism in large genome-wide studies (eg, deletions at 16p11.2, duplications at 7q11.23 and 22q11.2), harbor genes that influence the Ras pathway. \textit{Nf1}\textsuperscript{10} knockout mice show a selective deficit in social learning alongside increased \textit{γ}-aminobutyric acid and impaired long-term potentiation in projection neurons within the amygdala, a key structure implicated in social behavior.\textsuperscript{12}

Study of autism within NF1 may thus be rewarding; however, there is no detailed information to date on the nature and prevalence of ASD symptoms in NF1. Early reports were in the context of autism-referred or assessed populations. Co-occurrence with NF1 was reported in 3 of 51 cases of infantile autism in a birth cohort study (1962–1976)\textsuperscript{13} and in 0.6% of children with autism in another (1976–1985)\textsuperscript{14}; in retrospective clinical case-note studies of autism referrals, NF1 was found in 1 of 341 children between 1960 and 1984\textsuperscript{15} and 3 of 74 between 1984 and 1994.\textsuperscript{16} On the other hand, studies of NF1 cohorts have identified frequent social problems, isolation, and reduced friendships compared with matched controls\textsuperscript{17} and increased difficulties in social information processing and emotional recognition,\textsuperscript{18} but have not assessed for ASD. Retrospective case-note survey from a leading US national NF1 referral center found 13% (7/52) ASD caseness on a standard parent screen for autism, not associated with NF1 disease severity or behavioral disorders.\textsuperscript{19} These studies are suggestive of the presence of ASD-type symptoms in NF1, but are limited by lack of detailed ascertainment and potential sampling biases in terms of studying autism rather than NF1 populations or specialist clinic populations known to impact prevalence estimates.\textsuperscript{20,21} The aim of this present study was therefore to ascertain the prevalence of ASD in NF1 by using a 2-phase population-based epidemiologic design. Following an initial screening phase,\textsuperscript{22} this current report concerns the phase 2 definitive phenotyping and resulting population-based prevalence estimate.

METHODS

The regional genetics service at the Central Manchester University Hospitals Foundation NHS Trust serves 4.1 million people in a geographically defined area of the north west of England, including a full range of urban, rural, and socioeconomic status (SES) variation. A genetic register, maintained since 1989, proactively ascertains all diagnosed NF1 cases and contains a whole population representation with published prevalence rates.\textsuperscript{5,23} For the current study, all registry cases of NF1 aged between 4 and 16 years (\textit{n} = 207) had been invited into an initial
screening phase, and 109 responders (52.7%) stratified based on standardized scores on the parent-rated Social Responsiveness Scale (SRS); 32 cases into the “clinical ASD” range (SRS ≥76), 29 into the borderline range (SRS ≥ 60 < 76), and 48 into the non-ASD range (SRS < 60).22 For the detailed confirmatory ascertainment reported here, cases were invited from each stratum in proportion to the number of their screen-positive cases, by random selection. Twenty-three cases were seen of 31 invited from the significant ASD group, 16 of 21 from the moderate ASD group, and 8 of 15 from the non-ASD group.

Measures

The Autism Diagnostic Interview-Revised (ADI-R)24 is a standardized, investigator-based developmental interview used in the diagnosis of ASD. It is scored within domains of early childhood and current communication, social development, and restricted, repetitive, stereotyped behaviors and interests. Algorithm scores are generated based on behavioral descriptions of the individual at 4 to 5 years for some items and at any time in their lives for other items. There is an established cutoff for childhood autism.

The Autism Diagnostic Observation Schedule-Generic (ADOS-G) is a semi-structured, standardized observational assessment of communication, social interaction, play and imaginative skills, and repetitive behaviors.25 It consists of 4 modules appropriate to different developmental age and expressive language skills. Scores on individual items range from “0” (no evident abnormality) to “3” (marked abnormality) in domains of communication, social interaction, imagination and restricted, repetitive behaviors. Thresholds consistent with ASD diagnosis are obtained from reciprocal social interaction and social communication algorithm scores.

The Vineland Adaptive Behavior Scale (VABS-II)26 assesses child adaptive behavior in communication, socialization, and daily living skills domains and expresses overall functioning in the Adaptive Behavior Composite (ABC) score. It is administered to the parent/caregiver by using a semistructured interview format. Standard and age-equivalent scores obtained on the 3 domains and on the VABS ABC were used in the current analyses.

The Wechsler Abbreviated Scale of Intelligence (WASI)27 is an individually administered measure of intellectual ability appropriate for children and adults aged 6 to 89 years. The vocabulary and similarities subtests of the WASI were used to assess child verbal IQ.

Procedures

The study was approved by the Greater Manchester West Ethics committee (REC 11/NW/0838). Medical notes of all patients were reviewed to confirm the diagnosis of NF1 by using National Institutes of Health diagnostic criteria.5 Rating of physical NF1 phenotype severity used Riccardi’s scale28 modified only to exclude cognitive aspects: “Minimal” was scored in the presence of harmless clinical signs, such as café-au-lait patches without other physical complication; “mild” when there were minor physical complications, such as mild short stature, mild scoliosis, or discrete asymptomatic plexiform neurofibromas; “moderate” when there were complications that might require treatment but without long-term morbidity; or “severe” in cases of malignancy or significant postoperative morbidity. Socioeconomic status was rated from the participants’ postcode by using the census-based Index of Multiple Deprivation, with domains related to income, employment, health, disability, education, housing and services, living environment, and crime.29 Detailed phenotypic ascertainment consisted of parental ADI-R and VABS-II plus child assessment on ADOS-G and WASI verbal IQ. Parent interviews were audiotaped and child assessments videotaped. Interrater reliability on ADOS coding was tested through independent blind double coding of 25% (12/47) of the sample from videotape; kappas for algorithm scores were 0.83 for communication, 0.66 for reciprocal social interaction, and 1.00 for combined socio-communication.

Diagnostic classification used an algorithm for combining ADI-R, ADOS-G, and IQ into categorical diagnostic groups developed by the National Institute of Child Health and Human Development Collaborative Programs of Excellence in Autism (CPEA).30 The CPEA criteria were developed to standardize diagnostic practice across specialist centers and are used in large multisite confirmatory studies of autism diagnosis.31 In these criteria, classification of ASD is equivalent to a diagnosis of idiopathic ASD; classification of broad ASD is given to subjects with a subdiagnostic threshold partial phenotype, although the CPEA consortium consider that “this group is generally accepted to include many individuals who may have met criteria for autism, aspergers, or PDD-NOS if additional data were available.”30,p226

Statistical Analysis

Data were analyzed in SPSS version 17 (IBM SPSS Statistics, IBM Corporation, Chicago, IL) and Stata version 12 (Stata Corp, College Station, TX). Demographic and clinical characteristics of responders were compared with non-responders by using 2-sample t tests and $\chi^2$ tests. Categorical data are presented as percentages (frequency) and compared by using the $\chi^2$ test. A $P < .05$ was considered significant. The means and SDs of the 3 groups (ASD, broad ASD, and non-ASD) were analyzed on the subdomains of the ADI-R, ADOS, VABS, and verbal IQ. Group
comparisons were made across these measures by using nonparametric Kruskal-Wallis tests with post hoc pairwise testing. For other measures, the ASD/broad ASD groups were combined and compared with the non-ASD group by using 2-sample t tests, Mann-Whitney tests, and \( \chi^2 \) tests.

In calculating the population prevalence estimate, we followed a 2-stage weighting procedure. First, the probability of response from registry cases in the initial screening phase was calculated from logistic regression, with response as the dependent variable and gender, age, socioeconomic index, familiarity, and overall severity as predictors. Second, the probability of responding in phase 2 was calculated separately for each SRS stratum as the number of phase 2 responders divided by the number of phase 1 responders. These weights were then multiplied and used as inverse probability weights in a summary analysis to give the population prevalence with associated confidence intervals.

**RESULTS**

Participants were recruited and assessed between February 2012 and July 2012. Forty-seven children received in-depth assessment from 67 invited (70.15%); mean age was 11.7 years (SD 2.89, range 7.2–18.4), and mean verbal IQ was 95.69 (SD 16.82, range 55–135). Responders and nonresponders did not differ in severity of NF1, gender, or SES, but responders were younger (t = 2.61, \( P = .01 \)) and more likely to have familial NF1 (\( \chi^2 = 6.31, P = .01 \)). Neither age nor familiality showed association with ASD status.

Using CPEA criteria, 14 children (28.8%) met criteria for ASD, 13 (27.7%) for broad ASD, and 20 (42.5%) as non-ASD. Table 1 shows the detailed scores on all ascertainment instruments, grouped by diagnostic category. There is no difference in IQ across the 3 groups. Severity of socialization and communication impairment on ADOS-G and the ADI-R and socialization on VABS shows an ordering across the groups. Repetitive behaviors, however, are particularly associated with the ASD group.

The diagnostic groups also vary in relation to everyday functional impairment as measured on the parent-rated VABS (rated independently and not used in the diagnostic classification). The ASD group was most functionally impaired but this was not significantly different from the broad ASD group, other than the socialization domain. VABS scores for internalizing and externalizing behaviors are also ranked by diagnosis, showing the association of these diagnostic groups with functional outcomes.

Comparison of the ASD groups (ASD/broad ASD, \( n = 27 \)) with non-ASD (Table 2) shows no significant difference in age, SES, inheritance, physical severity, verbal IQ, or receipt of Statement of Special Educational Needs, but a relative male preponderance in ASD. Separate ascertainment at the screening stage of this study, using the standard parent-rated Connors questionnaire, had showed 53.8% (57/106) of children with an attention-deficit/hyperactivity disorder (ADHD) index in the clinical range (T-score >65), with 25% (26/104)

### Table 1: Summary of the Assessed Sample by ASD Diagnoses With ADI-R, ADOS-G, VABS, and Verbal IQ

<table>
<thead>
<tr>
<th>ADI-R</th>
<th>ASD, n = 14</th>
<th>Broad ASD, n = 13</th>
<th>Non-ASD, n = 20</th>
<th>KW ( \chi^2 )</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social</td>
<td>21.86 (5.75)</td>
<td>12.31 (4.37)</td>
<td>4.45 (2.76)</td>
<td>34.54</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Comm</td>
<td>14.07 (6.06)</td>
<td>8.54 (4.61)</td>
<td>4.75 (4.41)</td>
<td>19.56</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Rpt Beh</td>
<td>4.86 (3.01)</td>
<td>2.77 (2.71)</td>
<td>1.75 (1.83)</td>
<td>8.82</td>
<td>.01</td>
</tr>
<tr>
<td>ADOS-G</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comm</td>
<td>3.86 (1.46)</td>
<td>2.08 (1.04)</td>
<td>0.8 (0.89)</td>
<td>28.07</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Social</td>
<td>8.36 (3.57)</td>
<td>4.23 (2.86)</td>
<td>1.25 (1.25)</td>
<td>30.14</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>96.42 (12.2)</td>
<td>88.92 (19.47)</td>
<td>100.21 (17.04)</td>
<td>3.62</td>
<td>.16</td>
</tr>
<tr>
<td>Parent VABS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comm</td>
<td>71.57 (9.65)</td>
<td>77.15 (17.78)</td>
<td>85.60 (14.38)</td>
<td>7.19</td>
<td>.03</td>
</tr>
<tr>
<td>DLS</td>
<td>78.79 (15.90)</td>
<td>77.15 (17.80)</td>
<td>91.22 (23.45)</td>
<td>2.91</td>
<td>.23</td>
</tr>
<tr>
<td>Social</td>
<td>62.71 (11.46)</td>
<td>74.38 (10.14)</td>
<td>87.95 (16.0)</td>
<td>18.15</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ABC</td>
<td>69.36 (9.75)</td>
<td>74.77 (12.48)</td>
<td>88.16 (17.86)</td>
<td>9.43</td>
<td>.01</td>
</tr>
<tr>
<td>Int raw score</td>
<td>10.71 (3.55)</td>
<td>8.75 (4.20)</td>
<td>5.30 (5.33)</td>
<td>6.59</td>
<td>.04</td>
</tr>
<tr>
<td>Ext raw score</td>
<td>9.96 (5.08)</td>
<td>7.92 (3.83)</td>
<td>5.90 (13.67)</td>
<td>5.95</td>
<td>.05</td>
</tr>
<tr>
<td>CPRS-R/CTRS-R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent ADHD index</td>
<td>65.31 (13.02)</td>
<td>71.92 (7.92)</td>
<td>67.58 (14.21)</td>
<td>2.268</td>
<td>.32</td>
</tr>
<tr>
<td>Teacher ADHD index</td>
<td>63 (14.53)</td>
<td>62.38 (14.71)</td>
<td>61.64 (19.15)</td>
<td>.410</td>
<td>.81</td>
</tr>
<tr>
<td>Post hoc Pairwise Comparisons (P Values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ASD/bASD*</td>
<td>ASD/non-ASD</td>
<td>bASD*/non-ASD</td>
<td>ASD+bASD*/non-ASD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASD</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bASD</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-ASD</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Teacher data available on only 66% of the sample: ASD \( n = 9 \), broad ASD \( n = 8 \), non-ASD \( n = 14 \).
meeting parent-rated clinical criteria for both autism and ADHD. Co-occurrence of ADHD and ASD was thus further investigated in this phase 2 ascertainment by comparing these parent- and teacher-rated ADHD ratings across the identified diagnostic groups (Table 1). Parent-rated ADHD scores are generally above clinical threshold and teacher-rated ADHD scores below clinical threshold, but equally across groups; there is no link between ASD and differential ADHD symptom severity. The probability of responding to phase 2 was 23/32 in the clinical severity SRS stratum, 16/29 in the borderline/moderate stratum, and 8/48 in the non-ASD stratum. The probabilities of responding to the phase 1 screening phase across all strata, calculated from the general NF1 registry population, ranged from 0.17 to 0.90. These 2 probabilities, when multiplied to produce inverse probability weights, give a whole-population prevalence for ASD of 24.9% (95% confidence interval 13.1%–42.1%) and for broad ASD of 20.8% (95% confidence interval 10.0%–38.1%).

**DISCUSSION**

To our knowledge, this is the first study to systematically estimate the population-based prevalence of ASD in NF1 by using a 2-phase design and standard diagnostic phenotyping. The estimated whole-population prevalence from these data are 24.9% prevalence for ASD in NF1 with a further 20.8% showing partial features; thus, more than 45% with some ASD symptoms. This represents a very substantial prevalence rate, convergent with the findings on parent-rated SRS in the screening phase of the study and higher than previous estimates. The mean verbal IQ of the ASD sample was within the normal range and was not significantly different compared with the broad ASD or non-ASD group, implying that the social and behavioral impairments in NF1 cannot be explained on the basis of cognitive deficit.

How clinically significant are these findings? The NICHD/NIDCD CPEA criteria produce categories equivalent to clinical diagnosis (see the previous section, Procedures), with the broad ASD group containing partial traits that are considered also as having clinical significance. Thus, the quality and severity of ASD identified here in NF1 is equivalent to idiopathic ASD diagnosis. The pattern of disability across diagnostic groups shows features typical of descriptions of ASD and broad ASD in other contexts, with no evidence of a particularly unusual pattern of ASD symptoms within NF1 compared with idiopathic autism. As in idiopathic autism, there is a relative preponderance of boys diagnosed with ASD, compared with no gender imbalance in the NF1 disorder as a whole. Social communicative impairments are most severe in the ASD category with a lesser degree of social impairment, typical of the broader phenotype compared with non-ASD. The core syndrome of ASD, compared with the broader phenotype is distinguished by the presence of stereotyped and repetitive behaviors, in keeping with current diagnostic formulations. In terms of functional impairment, parent ratings of overall impairment and behavioral difficulties on a standard measure of impairment within autism (VABS) show a level of impairment related to these ASD categories that would be typical also in idiopathic autism.

Previously the psychiatric comorbidity most associated with NF1 has been ADHD. Our previous report on the screening phase 1 of this study did indeed show a high rate of parent-rated ADHD in the sample, along with substantive co-occurrence between ADHD and ASD symptoms (although this co-occurrence rate could have been inflated by common-rater biasing, as both symptom questionnaires were completed in parallel by parents). This phase 2 study was designed to minimize confounding due to diagnostic or symptom overshadowing and maximize the specificity of estimation, by using assessor-rated gold standard ascertainment. The resulting data suggest no evidence of a common-symptom–based inflation of our ASD estimate: parents and teachers rate ADHD symptoms uniformly across groups with no increase in the ASD groups compared with non-ASD. This implies a true comorbidity between ADHD and ASD as separable syndromes within NF1; something also found in ADHD comorbidity within idiopathic autism.

**Strengths and limitations**

A strength of this study is the complete sampling approach from a geographically defined whole population register, and prospective gold standard assessments triangulating assessor-rated observational and developmental information by using standard algorithm criteria, a method known to improve the reliability of assignment. Limitations to the data include inevitable response biases at both the screening and the
second-phase stages of the study. These, however, did not involve variables with associations to ASD in this group and the statistical weighting for the final analysis of the population prevalence estimate took these response biases into account. This study’s focus on ASD in NF1 should not lead to a downplaying of the importance of ADHD symptoms in the disorder, which are also prevalent.

Implications for Clinical Practice and Research

Identification of ASD is important in the clinical formulation of developmental and behavioral presentations and has implications for clinical management and educational planning. It is clear that ASD is under-recognized in NF1; in this sample, only 2 participants reported a previous clinical diagnosis of ASD. It is possible that the social difficulties in these children have been previously ascribed to NF1 itself or to ADHD (which has been the focus of much clinical and research literature in the disorder to date; “diagnostic overshadowing” of this kind is a recognized phenomenon.

It is also possible that the high rates of both ASD and ADHD prevalent in NF1 will at times result in a distinctive clinical picture. Our findings do, however, suggest that screening for ASD (along with ADHD), should be undertaken in all children with NF1, with full clinical assessment as indicated: each syndrome has significant and separate implications for treatment and management.

Future research could include investigation of whether ASD cases with NF1 differ on other aspects of the physical phenotype, such as macrocephaly or T2-weighted magnetic resonance findings. Systematic study of ASD prevalence in other Rasopathies is also indicated, as there is preliminary evidence that ASD also may be found in these conditions. NF1 has potential for investigation as a single-gene model of autism pathogenesis, given its identified cellular-level pathophysiology in animal and human models and the possibility for rational intervention into the biochemical pathway by using statins. The prevalence estimate and characterization of ASD within NF1 established in this study offers an empirical platform for this future work.

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Neurofibromatosis Type 1 and Autism Spectrum Disorder
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