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Comorbidity of Intellectual Disability Confounds Ascertainment of Autism: Implications for Genetic Diagnosis

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While recent studies suggest a converging role for genetic factors towards risk for nosologically distinct disorders including autism, intellectual disability (ID), and epilepsy, current estimates of autism prevalence fail to take into account the impact of comorbidity of these disorders on autism diagnosis. We aimed to assess the effect of comorbidity on the diagnosis and prevalence of autism by analyzing 11 years (2000–2010) of special education enrollment data on approximately 6.2 million children per year. We found a 331% increase in the prevalence of autism from 2000 to 2010 within special education, potentially due to a diagnostic recategorization from frequently comorbid features such as ID. The decrease in ID prevalence equaled an average of 64.2% of the increase of autism prevalence for children aged 3–18 years. The proportion of ID cases potentially undergoing recategorization to autism was higher ($P = 0.007$) among older children (75%) than younger children (48%). Some US states showed significant negative correlations between the prevalence of autism compared to that of ID while others did not, suggesting state-specific health policy to be a major factor in categorizing autism. Further, a high frequency of autistic features was observed when individuals with classically defined genetic syndromes were evaluated for autism using standardized instruments. Our results suggest that current ascertainment practices are based on a single facet of autism-specific clinical features and do not consider associated comorbidities that may confound diagnosis. Longitudinal studies with detailed phenotyping and deep molecular genetic analyses are necessary to completely understand the cause of this complex disorder. 2015 Wiley Periodicals, Inc.

Key words: neurodevelopmental disorders; prevalence; microdeletion; syndrome

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INTRODUCTION

Autism is a neurodevelopmental disorder characterized by impairments in social reciprocity, speech and communication, and restricted, repetitive and stereotyped patterns of behavior [American Psychiatric Association, 2000]. Several epidemiological reports have suggested an apparent increase in the prevalence of autism [Shattuck, 2006; King and Bearman, 2009; Autism et al., 2012]. A recent study by the United States Center for Disease Control estimated the prevalence of autism among 8-year-old children, within the autism and developmental disabilities monitoring (ADDM) network sites in 2010, to be one in 68 children [Rice et al., 2007; Baio et al., 2012]. This estimate was a documented 120% increase in prevalence when compared with the data from 2002 (one in 150 children). Another study, based on a population screening of 7–12-year-old elementary school children in a South Korean community in 2006, estimated an overall autism prevalence of one in 38 children [Kim et al., 2011].

While the rise in autism prevalence has been attributed to various factors including increased awareness [Prior, 2003] and broadening of the diagnostic criteria [Shattuck, 2006; King and Bearman, 2009], significant clinical heterogeneity and the non-specific molecular etiology of autism have precluded robust estimates of prevalence [Levy et al., 2009; Lai et al., 2014]. Further,

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there is a documented clinical overlap or comorbidity of nosologically distinct neurodevelopmental disorders [Mitchell, 2011; Coe et al., 2012]. For example, premorbid social impairment or pervasive developmental disorders (PDD) have been observed in 50–87% of individuals with childhood-onset schizophrenia [Sporn et al., 2004; Rapoport et al., 2009; King and Lord, 2011; Gadow, 2012; Cristino et al., 2014]. Similarly, features of intellectual disability (ID) have been reported in as high as 68% of individuals with autism [Yeargin-Allsopp et al., 2003], and epilepsy and attention-deficit hyperactivity disorders (ADHD) have been reported to co-occur in as high as 38.3% and 59%, respectively, of children with autism [Tuchman and Rapin, 2002; Levy et al., 2009; Viscidi et al., 2013]. Accumulating evidence from genomic studies suggests a converging role for genetic factors towards a common molecular etiology for these varied neurodevelopmental disorders [Cristino et al., 2014; Noh et al., 2013; Steinberg and Webber, 2013; Fromer et al., 2014]. Although the epidemiological studies, to date, report statistically significant increases in the prevalence of autism, they fail to take into account the effect of the comorbidity of other disorders on the diagnosis and prevalence of autism. To better understand the effect of comorbid features on autism prevalence, we systematically analyzed 11 years (2000–2010) of epidemiological data on an average of 6.2 million children per year from the United States special education enrollment. We examined the frequency and age-specific prevalence of autism and frequently comorbid clinical features. Our results suggest that comorbidity of ID can significantly impact diagnosis and confound prevalence estimates of autism.

METHODS

Special Education Data

The individuals with disabilities education act (IDEA) is a law originally enacted in 1975 that ensures services to children with disabilities, ascertained by 13 disability categories throughout the United States. We obtained special education enrollment data, i.e., the number of children receiving services under various disability categories, from publicly available databases (IDEA part B) for the 50 US states. The IDEA part B database includes annual state-by-state counts of children aged 3–21 years documented by their age and classification of disorder (Supplementary Figure S1). However, other clinical details (phenotypic scores, gender, etc) were not available. For the current study, we obtained enrollment data on approximately 6.2 million children per year aged 3–21 years over an 11-year period spanning 2000–2010 evaluated by special education and placed under one of the 13 disability categories (Supplementary Table S1). Children recruited under the special education act are ascertained under only one disability category. However, reclassification to a different IDEA category is possible (e.g., an individual originally identified as having ID can be reevaluated and then reclassified into the autism category). Notably, school districts do not always use the *Diagnostic and Statistical Manual of Mental Disorders* criteria for classifying any of these diagnostic categories [Bertrand et al., 2001; Maenner and Durkin, 2010; Boyle et al., 2011]. Further, the Department of Education's legal definitions of disorders under the IDEA categories are generalized allowing for a broader interpretation, and therefore, the ascertainment for each disorder may vary between different states [Shattuck, 2006; Kogan et al., 2009].

Data Analysis

We used the United States intercensal estimates for ages 3–21 years for 2000–2010 to create proportions (number enrolled out of 10,000 children) for each ascertainment category. To assess the impact of comorbid features on autism prevalence, we estimated combined proportions of one or more related diagnostic categories including autism spectrum disorders (ASD), intellectual disability (ID), other health impairment (OHI), emotional disturbance (ED), and specific learning disability (SLD), whose phenotypes have significant comorbidity with autism [Yeargin-Allsopp et al., 2003; Levy et al., 2009; Autism et al., 2012; Lai et al., 2014]. We note that "developmental delay" was included within the intellectual disability category. Throughout the manuscript, the term "autism" is used interchangeably with "ASD." We used simple linear regression to model the relationship between the year and prevalence of the phenotypic category. Using a nominal cut-off of $P < 0.05$, we determined if the slope of each model was statistically significant.

RESULTS

Consistent with recent reports [Yeargin-Allsopp et al., 2003; Autism et al., 2012] we find a significant rise in the prevalence of autism from 1.2 per 1,000 in 2000 to 5.2 per 1,000 in 2010 (331% increase; linear regression, $P = 4.58 \times 10^{-10}$) within the US special education population (Fig. 1). However, significant decrease in prevalence from 8.3 per 1,000 in 2000 to 5.7 per 1,000 in 2010 was observed for ID (31% decrease, $P = 3.1 \times 10^{-10}$). Significant decreases were also seen for categories of emotional disturbance (22%, $P = 6.1 \times 10^{-5}$), and specific learning disability (19%, $P = 4.1 \times 10^{-8}$) (Supplementary Table S2). However, there was no significant change (linear regression, $P = 0.57$) in the overall proportion of children in special education ascertained under IDEA from 2000 to 2010 (Supplementary Figure S1). Based on recent studies suggesting common molecular etiology [Coe et al., 2012] and documented reports of comorbidity of autism and other neurodevelopmental disorders [Lai et al., 2014], we hypothesized that estimates of autism prevalence are confounded by the presence of comorbid phenotypes. We tested the impact of comorbidities on the prevalence of autism by first combining all related neurodevelopmental phenotypes whose prevalence changed significantly over the 11-year period. The combined prevalence of autism, ID, specific learning disability, and other health impairment did not change significantly from 2000 to 2010 (51.0 per 1,000 in 2000 to 50.3 per 1,000 in 2010; $P = 0.19$) suggesting that the prevalence of autism is influenced by related comorbid phenotypes (Supplementary Figure S2).

Interestingly, when only the prevalence estimates of autism and ID were considered together, the combined prevalence increased by 15% (9.5 per 1,000 in 2000 to 10.9 per 1,000 in 2010, $P = 1.7 \times 10^{-6}$) (Fig. 1A). This increase is 22-fold less than the increase seen for autism prevalence alone (331% vs. 15%), suggesting that a potential diagnostic recategorization from ID to autism can account for a

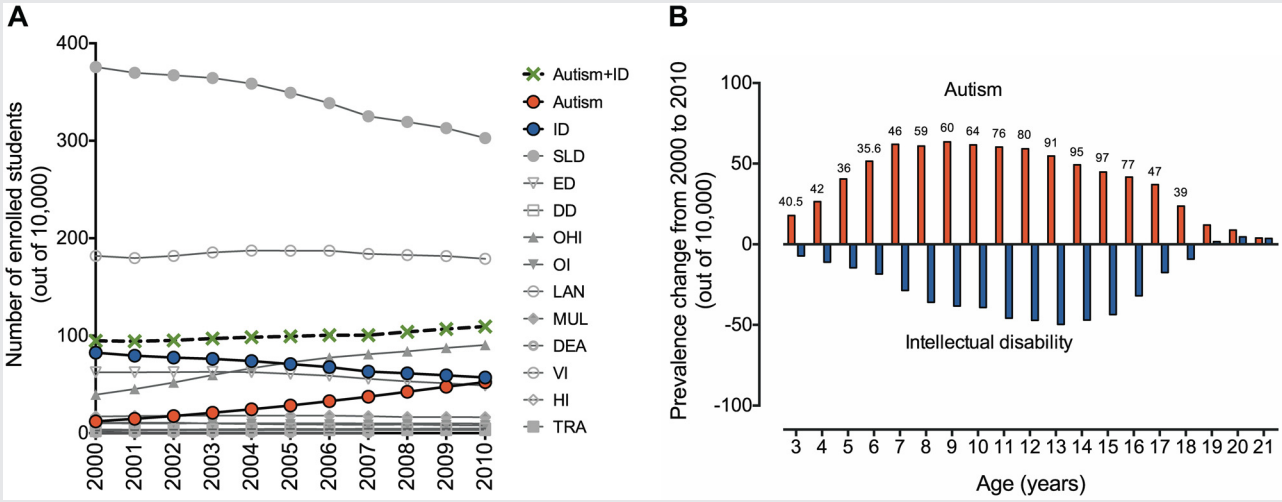

FIG. 1. Prevalence of phenotypes from years 2000 to 2010 ascertained through special education enrollment. (A) Yearly prevalence (out of 10,000) is shown for the 13 special education categories including autism, intellectual disability (ID), specific learning disability (SLD), developmental delay (DD), other health impairments (OHI), emotional disturbance (ED), speech and language impairments (SLD), multiple disorders (MI), traumatic brain injuries (TRA), deaf-blindness (DB), deafness (DEA), orthopedic impairments (OI), hearing impairments (HI), and visual impairments (VI). The combined prevalence of autism and ID (Autism + ID) is also shown. US intercensal estimates for ages between 3 and 21 years were used as denominator in the prevalence calculations. (B) The age-specific changes (2000–2010) in prevalence of autism (red) and ID (blue) are shown from ages 3 to 21 years. Percentage of autism prevalence that can be attributed to diagnostic change from ID to autism is shown for each age as numbers above the red bars.

significant amount of autism prevalence. In order to determine the ages at which these changes were most significant, we analyzed the age-specific changes in prevalence for autism and ID for the ages between 3 and 21 years. We found that an increase in autism prevalence, specifically across ages 3–18 years, corresponded to a decrease in the prevalence of ID (Fig. 1B). These changes in autism prevalence compared to those in ID allowed us to calculate the possible magnitude of diagnostic recategorization from ID to autism. For example, at age 8 years, up to 59% of the increase in autism prevalence could be attributed to a diagnostic recategorization of ID. On an average, between the ages of 3 and 18 years the decrease in ID prevalence equaled 64.2% of the increase of autism prevalence, and these estimates rise to as high as 97% at age 15 years. The magnitude of this change, at age 15 years, from 2000 to 2010 in the observed prevalence of autism is 35-fold greater than that compared to the expected change if autism and ID were combined as a single category (Supplementary Table S3 and Figure S3). Further, older children (ages from 10 to 18 years) with ID were more likely to have a shift of diagnosis towards autism than younger children (ages from 3 to 9 years) (Mann Whitney test, $P = 0.007$) (Supplementary Figure S4). We also found that autism and ID can be distinguished based on age-prevalence. When evaluated by age, the prevalence of autism peaked between ages 7 and 9 years, while the age-specific prevalence for ID peaked between ages 11 and 19 years (Supplementary Figure S5).

To assess if the autism diagnostic criteria are uniform across all US states, we compared the prevalence of autism with the prevalence of other disorders over the 11 year period. We observed positive correlations, at varying degrees, between the prevalence of autism and that of OHI (Pearson's correlation coefficient $r = 0.49$, $P = 0$), OI ($r = 0.097$, $P = 0.02$), ED ($r = 0.19$, $P = 2.38 \times 10^{-15}$), HI ($r = 0.12$, $P = 0.008$), TBI ($r = 0.21$, $P = 2.54 \times 10^{-5}$), and multiple disabilities ($r = 0.15$, $P = 0.001$) (Supplementary Figure S6 and Table S4). Further, negative correlations, at significant levels, were observed between the prevalence of autism compared to that of ID ($r = -0.26$, $P = 1.10 \times 10^{-9}$), and SLD ($r = -0.26$, $P = 1.10 \times 10^{-9}$) when all US states were considered together (Fig. 2, Supplementary Figure S7). Interestingly, the correlation estimates were higher ($r > 0.99$) for some US states than others when prevalence of autism was compared to that of ID (Table I). US states with a higher prevalence rate for ID were more likely (Mann Whitney test, $P = 0.0476$) to show a negative correlation with autism prevalence than those states with a lower prevalence of ID (Supplementary Figure S8). For example, North Dakota, Vermont, and Georgia showed the strongest correlation coefficients (-0.999, -0.998, -0.997, respectively). However, states such as Arizona, New Jersey, and Wyoming showed less strong correlation coefficients (-0.625, -0.621, -0.749, respectively) and certain states, such as California, New Mexico, and Texas, showed no correlation at all. These results potentially reflect differences in state specific policies for ascertainment of children under special education.

DISCUSSION

We analyzed one of the largest cohorts of longitudinal special education population data, through which we observed a 331% increase in the 11-year autism prevalence. Due to the unavailability of standardized phenotypic measures (e.g., IQ scores) to determine

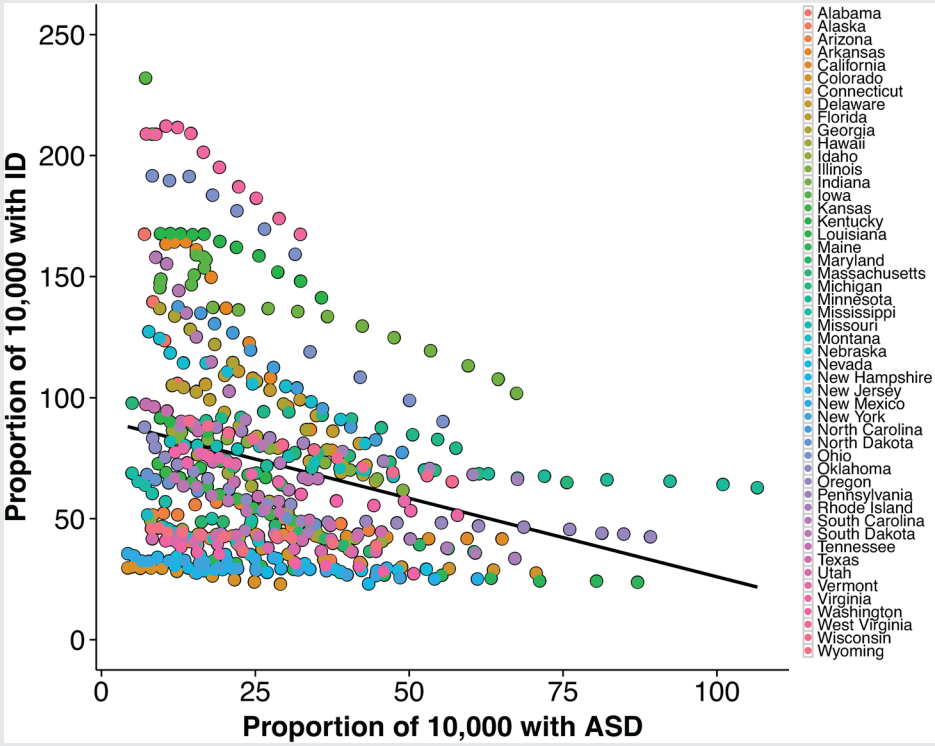

FIG. 2. Negative correlation between the prevalence of autism to that of intellectual disability ($r = -0.26$, $P = 1.10 \times 10^{-9}$). Pearson correlation coefficients were used to assess the relationship between the prevalence of autism and each of the comorbid phenotypic categories within the special education enrollment.

if autistic individuals also showed features of ID, we performed analysis under the premise that individuals manifesting both autism and ID were more likely to be binned into the autism category than that of ID. Nevertheless, the following observations suggest that a diagnostic recategorization towards autism is occurring, potentially confounding estimates of autism prevalence. First, we find no change in the overall proportion of children enrolled in the special education cohort from 2000 to 2010, suggesting that any perceived increase in prevalence within the cohort to be due to a recategorization of ascertainment practices. Second, we find that the increasing trend in autism prevalence disappears when the combined prevalence of autism and related comorbid features were considered (Supplementary Figure S2). Finally, the age-specific changes in prevalence of autism from 2000 to 2010 closely mirrors that of ID, with an average of 64.2% of the increase in prevalence of autism potentially explained by a concomitant decrease in the prevalence of ID. This phenomenon of diagnostic recategorization has been noted previously [Shattuck, 2006; King and Bearman, 2009], however, the magnitude of effect from comorbid features has not been documented. Our study shows a 22-fold drop in prevalence increase when considering the prevalence of a broader neurodevelopmental disorder category including both autism and ID. The proportion of ID cases potentially undergoing diagnostic recategorization to autism was higher among older children (75%) than younger children (48%). These results suggest that comorbid features can confound true prevalence estimates of the autism disorder. We also found that the disability categories within the special education data showed distinct age-specific prevalence rates. For example, prevalence estimates peaked between ages 7 and 9 years for autism and between ages 11 and 18 years for ID. These prevalence peaks suggest distinct developmental trajectories and specific diagnostic windows for certain comorbid phenotypes. Interestingly, one recent study found that older children with autism were more likely to retain their diagnosis than those diagnosed at a younger age suggesting the complexities associated with using one set of identifiable features as diagnostic criteria [Wiggins et al., 2012]. It is likely that older children are more severely affected manifesting intellectual disability and other comorbid phenotypes at a later age. Other disorders in addition to ID can also potentially contribute to a diagnostic recategorization to autism. In fact, a significant negative correlation was observed between the prevalence of autism and that of SLD (Supplementary Figure S7), suggesting SLD as another potential contributor to diagnostic recategorization. Further, we found positive correlations between the prevalence of autism and disorders such as OHI and ED, suggesting that a complex recategorization of disorders is occurring independent of autism. However, we were unable to assess the possible effect of diagnostic recategorization from SLD or OHI as the change in the number of enrolled children within these disorders (469,216 and 420,840 individuals, respectively) over the 11-year period was more than five times that of autism (93,624 individuals).

TABLE I. Pearson's Correlation Coefficients Between the Prevalence of Autism and That of ID for Each of the 50 US States From Years 2000–2010 for Individuals Ages 3–21 Within Special Education

State	ASD prevalence in 2000	ASD prevalence in 2010	ID prevalence in 2000	ID prevalence in 2010	*P*-value	Pearson's r
Alabama	7.02	35.58	167.48	NA	6.58E-03	−0.933
Alaska	11.31	41.99	41.81	31.95	5.62E-04	−0.961
Arizona	8.39	43.41	51.55	45.3	3.96E-02	−0.625
Arkansas	10.5	37.46	163.46	78.28	3.56E-09	−0.991
California	14.32	65.1	40.58	41.65	0.68	−0.143
Colorado	4.3	29.09	29.67	22.98	4.83E-08	−0.984
Connecticut	15.74	70.63	43.21	27.6	7.17E-06	−0.951
Delaware	15.43	43	102.4	72.07	2.93E-04	−0.885
Florida	11.52	44.54	105.05	65.57	2.89E-08	−0.986
Georgia	9.47	42.53	136.7	68.16	6.03E-12	−0.998
Hawaii	11.55	40.28	86.44	37.11	3.46E-11	−0.997
Idaho	8.05	45.64	49.11	40.68	8.88E-04	−0.851
Illinois	12.61	49.01	83.28	61.73	5.47E-07	−0.972
Indiana	18.12	67.46	137.21	101.83	3.26E-06	−0.959
Iowa	8.25	9.66	208.84	148.89	0.09	−0.54
Kansas	9.24	33.99	72.76	47.46	6.90E-10	−0.994
Kentucky	9.61	35.77	167.67	141.23	3.52E-06	−0.958
Louisiana	9.62	29.25	91.65	64.05	1.23E-04	−0.906
Maine	18.3	87.11	32.74	23.77	1.80E-06	−0.964
Maryland	16.28	60.55	48.72	36.36	4.48E-05	−0.925
Massachusetts	5.01	75.65	97.78	64.96	7.54E-03	−0.752
Michigan	17.03	57.59	90.44	79.17	1.97E-03	−0.821
Minnesota	20.25	106.59	74.22	62.81	2.13E-08	−0.987
Mississippi	4.97	28.99	68.83	NA	1.84E-03	−0.937
Missouri	11.24	47.43	81.95	67.49	7.98E-07	−0.97
Montana	7.51	25.57	51.53	40.74	3.15E-03	−0.799
Nebraska	7.7	42.85	127.17	81.11	1.86E-07	−0.978
Nevada	9.11	52.8	34.06	29.16	2.56E-04	−0.889
New Hampshire	11.95	53.6	30.41	NA	7.71E-04	−0.977
New Jersey	15.49	61.1	27.52	25.1	4.16E-02	−0.621
New Mexico	4.3	27.96	35.57	33.91	0.55	−0.201
New York	13.54	48.54	32.66	25.62	1.01E-05	−0.947
North Carolina	12.47	48.89	137.44	77.4	8.82E-11	−0.996
North Dakota	7.4	NA	68.28	44.9	6.49E-09	−0.999
Ohio	8.25	55.51	191.65	90.12	1.87E-06	−0.964
Oklahoma	7	30.77	87.89	55.97	3.15E-06	−0.959
Oregon	32.47	89.22	48.92	42.54	5.81E-06	−0.953
Pennsylvania	12.74	67.61	88.06	66.34	4.66E-10	−0.994
Rhode Island	12.81	67.2	44.17	33.54	5.28E-04	−0.868
South Carolina	8.84	32.83	157.92	67.07	1.26E-08	−0.988
South Dakota	11.88	35.17	66.84	66.54	0.91	−0.04
Tennessee	7.25	37.22	97.3	47.23	1.59E-07	−0.979
Texas	11.46	45.51	41.33	44.53	0.24	0.39
Utah	8.28	44.6	41.68	36.53	2.16E-07	−0.978
Vermont	13.28	56.15	79.25	NA	6.00E-06	−0.998
Virginia	11.94	57.84	77.57	51.43	7.01E-07	−0.971
Washington	10.44	50.73	40.88	27.22	5.81E-06	−0.977
West Virginia	7.32	32.34	208.86	167.39	8.94E-07	−0.969
Wisconsin	14.32	57	90.27	65.27	2.92E-10	−0.995
Wyoming	8.13	44.69	45.88	38.79	8.04E-03	−0.749

NA, data not available for year.

While a negative correlation between the prevalence of autism and that of ID was observed for all the US states as a whole, when assessed individually, not all states showed the same strength of correlation. While the differential rates of autism prevalence reflect differences in ascertainment in special education schools across the US states, documented evidence of inconsistency in ascertainment even among groups following set diagnostic criteria suggests extensive heterogeneity of the disorder [Lord et al., 2012]. In fact, a recent study found the prevalence of autism and ID to be associated with state-related regulatory factors, and even found strong correlations between smaller, county-related factors and autism and ID prevalence [Rzhetsky et al., 2014]. Another report in 2001 found the prevalence of autism within The Brick Township, New Jersey, to be significantly higher than that of the US [Bertrand et al., 2001]. Further, Davidovitch and colleagues found a lower prevalence of autism among an Israeli population compared to the US [Davidovitch et al., 2013]. A recent study in the United Kingdom using the UK General Practice Research Database showed a strikingly similar incidence of autism over a period of 10 years suggesting no apparent increase in prevalence rates [Taylor et al., 2013]. These examples indicate variability in ascertainment of children with neurodevelopmental disorders across different regions, and highlight the need for large-scale studies of autism prevalence to take these health policy variations into account.

Several clinical studies have documented varying percentages of comorbid features suggesting that comorbidity in autism is the norm rather than the exception. Changes in nosology as suggested by revisions to the DSM have certainly contributed to the deviations from the original description of autism. This is reflected by the fact that only 81.2% of children previously diagnosed with autism by DSM-IV met the criteria according to DSM-V [Maenner et al., 2014]. However, studies estimating prevalence of autism seem to focus on one dimension of clinical features, often ignoring other comorbid features. For example, 40.2% of individuals identified with autism by the ADDM network were actually enrolled under eight different special education categories other than autism (Supplementary Figure S9). These rates also varied among states within the ADDM network, further suggesting a major impact by state-specific policies. While it would be important to understand how these comorbidity rates change over time, one limitation of the IDEA dataset was that individuals were only placed into a single diagnostic category.

The relatively high rate of comorbidity within autism may be due to a wide array of common genes implicated in many neurodevelopmental disorders [Pettersson et al., 2013]. Further, core components in autism diagnosis show a documented overlap in clinical features such as language impairments [Taylor et al., 2014]. Interestingly, when individuals with classically defined genetic syndromes were evaluated for autism using standardized instruments, higher frequency of autistic features were observed. In fact, some of these were never thought to be an autism disorder. For example, the frequency of autism in Smith–Magenis syndrome, a

TABLE II. Frequency of Autism Features in Classically Defined Genetic Syndromes

Disorder	Frequency (%)	Reference	Autism diagnosis instrument
22q11.2 deletion syndrome	40	Niklasson et al. [2009]	DSM-IV
Angelman Syndrome	42	Peters et al. [2004]	ADOS/DSM-IV
Beckwith–Wiedemann Syndrome	7	Kent et al. [2008]	Previous diagnosis
Charge Syndrome	28	Hartshorne et al. [2005]	ABC
Chromosome 2q Terminal Deletion	24	Casas et al. [2004]	Previous diagnosis
Cohen Syndrome	79	Howlin et al. [2005]	ADOS
Cornelia De Lange Syndrome	83	Srivastava et al. [2014]	CARS
Cowden Syndrome	53	Varga et al. [2009]	DSM-IV
Down Syndrome	19	Moss et al. [2013]	SCQ
Fragile-X Syndrome	63	Garcia-Nonell et al. [2008]	ADOS-G/DSM-IV
Inverted 8p Deletion Syndrome	75	Fisch et al. [2011]	CARS
Jacobsen Syndrome	47	Akshoomoff et al. [2015]	ADOS
Klinefelter Syndrome	27	Bruining et al. [2009]	ADI-R
Lujan–Fryns Syndrome	63	Lerma-Carrillo et al. [2006]	Unspecified
Moebius Syndrome	40	Johansson et al. [2001]	DSM-3R/ICD-10
Neurofibromatosis Type 1	4	Williams and Hers [1998]	DSM-IV
Phelan–McDermid Syndrome	94	Phelan et al. [2001]	CARS
Potocki–Lupski syndrome	66	Treadwell-Deering et al. [2010]	ADI-R and ADOS
Prader–Willi Syndrome	36	Lo et al. [2013]	DISCO
Smith Magenis Syndrome	90	Laje et al. [2010]	SRS, SCQ
Smith–Lemli–Opitz Syndrome	71–86	Sikora et al. [2006]	ADOS
Sotos Syndrome	68	Zafeiriou et al. [2013]	SCQ
Timothy Syndrome	80	Splawski et al. [2004]	Unspecified
Williams–Beuren Syndrome	93	Klein-Tasman et al. [2009]	ADOS
Wolf–Hirschhorn Syndrome	5	Fisch et al. [2010]	CARS

ADOS, autism diagnostic observation schedule; ADI-R, autism diagnostic interview-revised; ABC, autism behavior checklist; CARS, childhood autism rating scale; DISCO, the diagnostic interview for social and communication; SRS, social responsiveness scale, SCQ, social communication questionnaire; DSM, diagnostic and statistical manual of mental disorders.

disorder characterized by severe intellectual disability/multiple congenital anomalies, was reported to be as high as 90% [Laje et al., 2010] (Table II). About 63% of individuals with Fragile-X syndrome, one of the most common causes of intellectual disability, was reported to show features of autism [Garcia-Nonell et al., 2008]. Further, 93% of individuals with Williams–Beuren Syndrome, a disorder characterized by severe developmental delay, also showed features of autism [Klein-Tasman et al., 2009]. While these studies suggest that autistic features are pervasive in neurodevelopmental disorders, it is possible that many autism diagnosis instruments lose specificity when applied to severe intellectual disability disorders. These factors may create a confounding effect on autism diagnosis.

In conclusion, we propose that nosologically distinct neurodevelopmental phenotypes are not necessarily independent entities and can appear during early or late developmental stages and coexist as comorbid features in an affected individual. Comorbidity of one or more related neurodevelopmental phenotypes with autism may confound the diagnosis and affect the perceived prevalence of autism. This may be due to the emphasis given to the autism component of their diagnoses, as compared to emphasis on the comorbid features in the past years. Further, the differences in the relative severity of each of these comorbid features can complicate definitive diagnosis. Evidently, because these features co-occur to a large extent, they transcend diagnostic boundaries and contribute to the variability and severity as well as confound disease ascertainment. It is therefore clear that the patterns of underlying genetic etiology neither map well onto current disease "models" nor respect the DSM categories [Kendler, 2010; Lichtenstein et al., 2010]. Large-scale longitudinal studies with detailed phenotyping and deep molecular genetic analyses are necessary to completely understand the cause and effect of these "disease models." It is important that future studies of autism prevalence take these factors into account.

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