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COMMENTARY

Contemplating syndromic autism

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Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopmental conditions that share core phenotypic characteristics of impairments in social communicative functioning and the presence of restricted and/or repetitive behaviors.[1] During the past 2 decades, there has been substantial progress in our understanding of the genetic contribution to ASD, generating important opportunities for clinical translation.[2] One corollary of these genetic advances is the widespread use of the term "Syndromic Autism" to designate a subset of individuals with ASD, as well as a subset of genes putatively associated with ASD. Here, we examine the history and denotation of the concept and discuss observations that indicate that the underlying assumption of the concept is flawed.

From the syndrome of autism to syndromic autism

Ever since the first recognition of autism as a clinical entity, both clinicians and researchers have used notions such as "the syndrome of (childhood) autism" or "Kanner's syndrome" interchangeably with the term Autism.[3-5] During the early 1980s, the expression "Asperger's syndrome" was added to the list of clinical constructs, which subsequently merged into the unifying concept of ASD.[6] In this historical context, the meaning of the concept syndrome in its various combinations, is exclusively phenotypic in that it denotes a cluster of co-occurring developmental and behavioral symptoms observed in individuals. This specific phenotypic meaning of the word syndrome continues to be used in current ASD research.[7-9] However, advances in genetic studies have introduced an entirely different denotation of syndrome and syndromic in the context of ASD. Although these terms originally referred to the behavioral characteristics of the condition, their novel denotation indicates either the presence of comorbid features or a (putative) genetic etiology with which the occurrence of ASD is associated. Hence, the first challenge related to the usage of syndromic ASD is the conflation of 2 essentially different meanings. However, there are more fundamental reasons why the

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concept syndromic ASD has become increasingly problematic.

No consensus on the definition of syndromic autism

Even when restricting the focus on syndromic ASD in its more recent meaning, a quick review of literature will show a surprising diversity of definitions. The construct is understood by some to imply the presence of additional symptoms,[10] the latter sometimes specified as "neurological disorders,"[11] "dysmorphic features typically associated with genetic variants,"[12] or as "major anomalies, suggesting malformation."[13] Although all these definitions can, with some goodwill, be grouped as "ASD with additional phenotypes," another usage of the concept syndromic autism hinges on the presumed genetic etiology as its core defining feature. Here, the concept is predicated on the presence, or presumed presence, of an identifiable genetic disorder in individuals with ASD or significant autistic traits.[14] Lastly, it is important to note that the term implies the existence of its antonym, nonsyndromic ASD, which indeed is frequently used.[15-17] Logically, clarity of this counterpart term is directly dependent on the degree of unambiguity of the primary construct. Generally, it is understood to refer to individuals with ASD without additional associated phenotypic features.[18]

This review of relatively recent literature suggests 2 main components of the different definitions of syndromic autism, respectively, phenotypic comorbidity and genetic etiology. Regarding the first, there is no consensus as to which phenotypes (dysmorphic features,[19] congenital malformations,[20] intellectual disability (ID),[21] etc) define comorbidity. A similar lack of clarity exists regarding genetic etiology, which by some is defined as monogenic or related to a single gene, whereas others include chromosomal and structural genomic abnormalities such as copy number variants in this definition.

However, even if a clearer consensus could be achieved on the definitions of both components, a fundamental issue remains. A necessary assumption underlying syndromic autism is that the 2 components can be conceptualized along one and the same axis (Figure 1A). Therein lies a fundamental problem because this assumption is flawed and not corroborated by current evidence. In fact, there are patients whose ASD can be related to a single genetic cause but who do not show clear patterns of additional comorbidity.[17,22,23] Inversely, many patients with ASD present with clear comorbidity, though no single genetic etiology has yet been identified.[24] From this logically follows that phenotypic comorbidity and genetic etiology are best considered independently, as has been proposed previously,[25] strongly suggesting that the 2 components may require not one, but 2 axes (Figure 1B).

Challenges of the concept in research

As discussed at the start, comorbidity in the context of syndromic autism is generally understood to extend far beyond ID. However, how confident can we be in distinguishing between ASD with and ASD without comorbidity of physical and/or morphological features in our current databases? The current operationalization relies on whether such additional physical features or conditions are reported. Whether that reliably reflects the actual presence or absence of comorbidity is dependent on both breadth and depth of the phenotyping efforts underlying these databases or case reports. In particular for large cohorts, the comprehensive phenotyping effort required to reliably capture such comorbidity is a tall order. However, even for smaller studies the issue can easily become muddled as illustrated by the following example. A recent report proposed deletions of 8p21·3 as a rare cause of nonsyndromic ASD.[26] The rationale for the label nonsyndromic here is based on the absence of physical anomalies or dysmorphic features. This is, indeed, the case in the 3 individuals heterozygous for this variant identified by the authors. However, for at least 2 previously reported individuals with the same variant, also cited by the authors, this may not be the case. One was identified in cohort of individuals with developmental delay/ID, ASD, and multiple congenital anomalies.[27] Another individual with an 8p21·3 deletion was in the original paper described to have dysmorphic facial features, macrocephaly, a high palate and broad uvula, cubitus valgus, and scattered gray hair at age 15.[28] Establishing comorbidity beyond ASD in (putative) pathogenic variants is a daunting challenge, particularly for rare variants, and a moving target at best. Further complicating the picture, these physical phenotypes follow the same pattern of variable penetrance as observed for ASD, something illustrated by these recent findings related to a recurrent pathogenic variant in *SHANK3*, which included dysmorphic, medical, or other organ anomalies in 28%, 22% and 11%, respectively, of numerous unrelated individuals heterozygous for this variant.[29]

Furthermore, though the term syndromic autism is meant to classify individuals, its use has spilled over to annotate genes (as in "syndromic and nonsyndromic genes for ASD"[30]), specifying whether such genes associated with ASD are also associated with comorbid features. Such "syndromic" genes are often linked to medical genetic conditions carrying different names (eg, *PTEN* and Hamartoma Tumor Syndrome,[31] or *SHANK3* and Phelan-McDermid Syndrome[32]). Note that the notion of nonsyndromic ASD genes is logically incompatible with the definition of syndromic ASD regarding the presence of a clear genetic etiology. It is worth observing that time can unduly influence whether a gene associated with ASD ends up being considered as syndromic or nonsyndromic. Indeed, as has been observed previously,[18] several genes initially defined as "nonsyndromic" have subsequently been linked to additional phenotypes, simply because through additional research, additional phenotypes were being reported in association with a gene, including phenotypes not directly related to the brain. This should come as no surprise as more than two thirds of human genes are found to be expressed in the brain.[33] The expectation is that most genes are

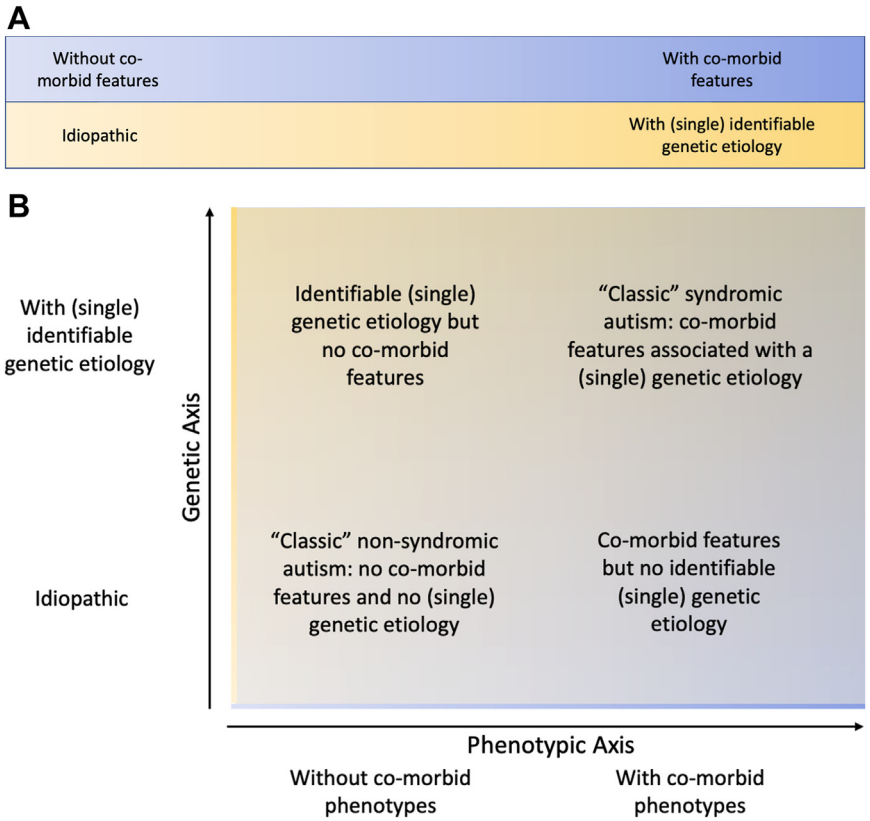

Figure 1 A. Phenotypic and genetic component of the concept "Syndromic Autism" are erroneously assumed to lie along one and the same axis. B. In reality, phenotypic and genetic components of the concept "Syndromic Autism" are likely along two different axes.

pleiotropic, that is, are associated to more than one biological function (and phenotype).[34,35] Consequently, many genetic variants related to ASD currently considered as nonsyndromic may be associated with additional physical phenotypes as more families are studied over time.

Table 1 provides an overview of a subset of genes selected from the evaluation of autism gene link evidence (EAGLE) framework. EAGLE evaluates evidence regarding the relevance of a gene with respect to ASD specifically, rather than potentially with a broad range of neurodevelopmental phenotypes,[63] and is publicly available through the SFARI Gene website.[64] We first removed genes annotated as syndromic by SFARI gene, as well as those associated with syndromes according to their clinical genome resource curation,[65] and then selected among the remaining genes those with EAGLE scores of 12 or higher, indicative of a definitive relation with ASD. This resulted in a subset of 13 genes. For each presumably nonsyndromic gene in this list, we examined additional phenotypes reported in the (recent) literature. As can be observed, epilepsy, hypotonia, and other NDD phenotypes are the exception rather than the rule in individuals with these variants. However, more to the point of the nonsyndromic annotation of these 13 genes is the report of dysmorphic features in 7, microcephaly or macrocephaly in 9, and conditions affecting organ systems other than the brain in 8 genes (including abnormalities involving gastro-intestine, endocrine system, heart, palate, eyes, kidney function, and overall growth).

Even when restricting the question of comorbidity to the presence or absence of ID, there is no consensus; the current view ranges from the confirmation that there is no such thing as genes specific to autism,[66] to the possibility that genes can be parsed into those associated with increased risk to mostly ASD, both ASD and ID, or mostly ID.[67,68] Given that most of the ASD associations reported to date are derived from cohorts where core phenotype (ASD) and comorbid phenotypes (eg, ID) are not clearly separated, the experiments required to answer this question has not yet been fully explored. Given all of the above, we question whether the distinction between syndromic ASD and nonsyndromic ASD, whether applied to individuals or to genes, is helpful for our research objectives. We compared an intersection set of 139 genes curated as ASD-related by 3 publicly available databases (AutDB,[69] AutismKB 2.0,[70] and SFARI Gene[71]), all accessed in November/December 2022 and found that only 36 (26%) were annotated as syndromic by all 3 databases, whereas 62 genes (45%) were uniquely annotated as syndromic by 1 but not the other 2 databases (see Figure 2).

Potential negative clinical consequences of the concept

The concept of syndromic autism erroneously suggests to some that its behavioral presentation can be differentiated from autism. The fundamental error in this reasoning is that

Table 1 An overview of additional phenotypes reported for 13 genes linked to ASD despite being considered as non-syndromic genes

Gene	EAGLE Curation (score) SFARI Curation	ClinGen Curation	Seizures / Hypotonia / Broad Range of NDDs[a]	Other Phenotypes Related to the Brain	Phenotypes in Other Organ Systems[b]	Ref
NRXN1	Definitive (143·75) SFARI: 1	Definitive: Complex NDD	+ / + / +	NR	Facial dysmorphic features	36,37
SCN2A	Definitive (109·3) SFARI 1	Definitive: Complex NDD	+ / + / NR[c]	Microcephaly, late-onset ataxia, cortical visual impairment, spasticity	Gastro-intestinal disturbances	38-40
GRIN2B	Definitive (29·65) SFARI 1	Definitive: Complex NDD	+ / + / +	Microcephaly, dystonic/dyskinetic movement disorder, regression, cortical visual impairment	Facial dysmorphic features	40-42
SHANK2	LoF: Definitive (18·55)	Definitive: Complex NDD	+ / + / +	Microcephaly and macrocephaly, dyspraxia ataxia	Facial dysmorphic features, clinodactyly	43-46
CUL3	Definitive (18·40) SFARI 1	Definitive: Complex NDD	+ / NR / +	Regression	Facial dysmorphic features, growth impairment / short stature, submucosal palatoschisis and bifid uvula, familial hyperkalemic hypertension, atrial septal defect and pulmonary valve stenosis. Reported in children with congenital cardiac defects.	47-50
GIGYF1	Definitive (17·25) SFARI 1	NC[d]	+ / + / +	Macrocephaly	Type 2 Diabetes, high glucose levels, low LDL levels	40,51,52
RFX3	Definitive (15·95) SFARI 1	NC	+ / + / +	Macrocephaly, regression	Facial dysmorphic features, overgrowth, hearing loss, hypogonadism, strabismus	53,54
ASH1L	Definitive (14·15) SFARI 1	Developmental disorder of mental health (dosage sensitivity)	+ / NR / +	Macrocephaly, regression	Facial dysmorphic features and multiple congenital abnormalities including heart defects and skeletal abnormalities. Reported in children with congenital cardiac defects.	40,50,55
KMT5B	Definitive (14·05) SFARI 1	Definitive: Complex NDD	+ / + / +	Macrocephaly	Facial dysmorphic features, overgrowth, morphological features fingers / toes	56
DSCAM	Definitive (13·50) SFARI 1	NC	+ / NR / +	Microcephaly	Growth retardation, short stature[e]	57
DYNC1H1	Definitive (13·45) SFARI 1	NC	+ / + / +	Hereditary motor neuropathy, spasticity, dystonia, gait abnormalities	Dysmorphic features, cataract, spinal muscular atrophy, congenital foot malformations, musculoskeletal abnormalities	58,59
GRIA2	Definitive (12·00) SFARI 1	NC	+ / + / +	Microcephaly, regression, dystonia, ataxia, irregular breathing pattern	NR	60
NLGN4X	Definitive (12·00) SFARI 1	Definitive: Complex X-linked NDD	+ / NR / +	NR	Strabismus	61,62

ASD, autism spectrum disorder; *EAGLE*, evaluation of autism gene link evidence; *LDL*, low-density lipoprotein; *NDDs*, neurodevelopmental disorders; *Ref*, references.

[a]NDDs: Neurodevelopmental disorders, including intellectual disability, ADHD, and various behavioral abnormalities (eg, pica, self-injurious behaviors, or aggression).

[b]For all phenotypes a high degree of variable penetrance is observed – in some instances, the number of observations is small given the rarity of the gene variant.

[c]NR: none reported.

[d]NC: Gene not (yet) curated.

[e]Very little information reported to date; findings here are observed in a child with a homozygous variant of DSCAM.

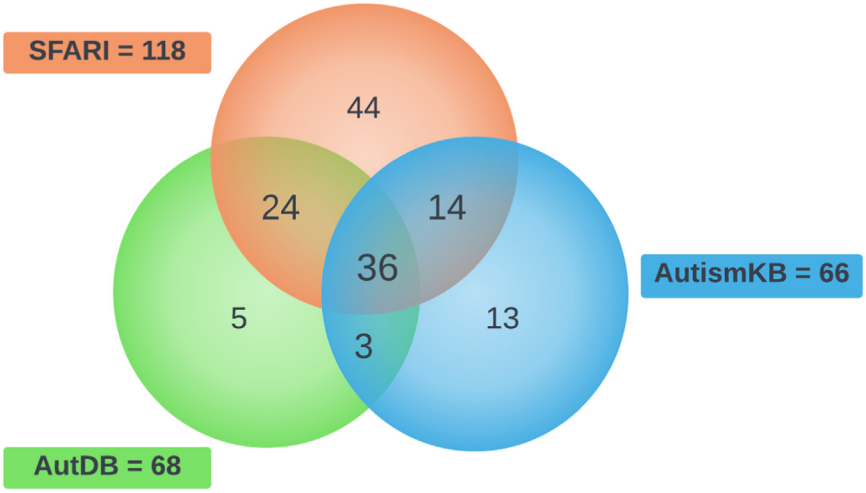

Figure 2 There are 437 genes for which each of the following three databases provide autism association curation data: AutDB,[69] AutismKB 2.0,[70] and SFARI Gene.[71] Of these 437 genes putatively linked to ASD, 139 genes are annotated as syndromic by at least one database. Of these, only 36 (26%) are listed as such consistently across the three databases, with 62 genes (45%) annotated as syndromic in only one of the three databases, illustrating the lack of a coherent view on what constitutes a syndromic ASD gene. ASD, autism spectrum disorder.

ASD, similar to virtually all psychiatric diagnoses in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases, is based exclusively on a phenomenological description of symptoms. Whether or not the abnormal behaviors exist in the context of a genetic disorder is not relevant in this context. The consequence of this approach is that ASD in individuals with a genetic disorder may be diagnosed as "behavior characteristic for this syndrome" rather than as ASD in its own right, thereby neglecting the potential clinical impact of a formal diagnosis of ASD.[72] In doing so, a false dichotomy emerges between ASD symptoms commonly seen in individuals with genetic disorder A and the "real" ASD phenotype in those without a clear etiology. From a clinical perspective, an important downstream effect is that patients with ASD in the context of a specific genetic disorder may fail to get access to the support and service that is required for the ASD.[73] In addition, the use of syndromic autism in clinical practice is readily perceived as indicative of clinical severity, which is inaccurate.

Proposed strategy going forward

If the main objective is to make meaningful distinctions within the population of individuals with ASD

Although neuropsychiatric and physical comorbidity, as well as an identifiable genetic etiology, are valuable specifications to the ASD diagnosis, circa 2023, their combined use in the concept "syndromic" is neither logically correct nor helpful. We suggest that the right way forward should build on the existing phenomenological basis as the foundation of the diagnosis, which subsequently can be enriched along both axes, that is, (1) whether comorbid symptoms are present,[25] and (2) whether a major causative genetic variant has been identified.[2] In the latter scenario, this recommendation aligns with the DSM-5,[74] which stipulates the use of a specifier "associated with a genetic condition," in such instances.[75]

The clinical implementation of this approach would not replace but augment our current DSM or International Classification of Diseases-based nosology. For the subset of individuals in whom a pathogenic variant is thought to be causative of or contribute to the ASD phenotype, this information can be added, as has been proposed previously.[75,76] Note that this approach should not be confused with the essentialist model, as it does not consider the gene (variant) as the defining feature of ASD nor presuppose an exclusive one-to-one relationship between gene (variant) and phenotype.[77]

Adding information regarding comorbidity such as ID, distinctive morphological features, and/or (congenital) physical conditions to the ASD diagnosis may have direct clinical utility as it indicates the *a priori* likelihood of identifying a pathogenic variant.[25,78,79] With the increased uptake of genetic testing in clinical practice, such integrated diagnostic practice can also be expected to contribute to the identification of rare genetic disorders, as well as to a more comprehensive understanding of the range of associated phenotypes. Recognizing rare, highly penetrant variants and their impact is an important step toward precision medicine strategies,[80-82] which can include individualized screening for comorbid conditions, genetic counseling,[2] and possibly guidance for development or implementation of targeted therapeutic interventions.[83]

If the main objective is to distinguish genes or genetic variants with potential relevance to ASD

From the genotype perspective, genes and genetic variants can be annotated for their association with ASD.[63] Rather than *a priori* distinguishing syndromic from nonsyndromic ASD genes, a better strategy would be to annotate each gene

for its relationship with additional comorbidities such as ID, morphological features, and physical conditions. This approach would be in line with the clinical synopses available for many pathogenic variants in OMIM online catalog.[84] Importantly, the evaluation of evidence for association with ASD should be distinguished from evidence for association with the broader umbrella construct neurodevelopmental disorder,[65] because neurodevelopmental disorder includes other phenotypes such as ID and attention deficit hyperactivity disorder.[63]

Challenges and new directions

We acknowledge that the proposed strategy is not without challenges. Although for some pathogenic variants, the associated risk for ASD is substantial and well established, for others the effect size of phenotypic impact is modest. What if a pathogenic variant with 5%, or even 50%, risk of ASD is identified in an individual with ASD? Can such variant be assumed to be causative regarding the ASD phenotype? What if phenotypic impact is likely conveyed by the combined action of 2,[85] or more rare pathogenic variants,[86] a scenario that may occur in approximately 5% of individuals with ASD, based on recent findings?[87] Although various systematic approaches exist that aid in the evaluation of pathogenicity of variants,[88-90] virtually all pathogenic variants display incomplete penetrance with regard to phenotypic expression, including ASD. Therefore, instead of using definitive terms such as "causative" or "caused by" to describe the effect of pathogenic variants, formulations such as "contributory" or "related to [variant x]" are more accurate reflections of their role in individual patients.[75]

Rare and common genetic variants are often considered as 2 distinct classes, though variants in reality exist on an allele frequency spectrum ranging from exceedingly rare to highly common. Nonetheless, driven by differences in both technical and statistical requirements, individual genetic studies typically report on either common or rare variant findings in ASD. Although the genetic component of the concept syndromic autism refers to rare genetic variants, the field is starting to elucidate the potential role of individual common variants in ASD.[91] In addition, the cumulative effect of thousands of common risk variants is being catalogued, which can be summarized in a polygenic risk score (PRS). The current PRS for ASD can explain approximately 2.5% of variance in ASD liability in the population.[91] This effect size of PRS is expected to grow as a function of increasing cohort sizes of the underlying GWAS studies, similar to the trend that is observed for schizophrenia.[92,93]

However, both common and rare variants coexist in a continuum in individual patients, and their combined phenotypic impact is increasingly scrutinized.[94-96] Here, one possible angle is to examine to what extent common variants, summarized as PRS, can modulate the phenotypic expression (eg, of ASD) in individuals with a rare pathogenic variant, thereby explaining some of the variable penetrance observed in most rare genetic disorders.[97,98] Incorporating new types of genetic variation such as tandem repeat expansions[99] in PRS calculations may also increase power. These types of integrated analyses, though they are increasingly complex, may also create novel opportunities for clinical translation; applied in individuals heterozygous for rare high impact variants, the PRS can be used to improve individual risk prediction with positive predictive values nearing the range of clinical utility.[100] Such approaches are increasingly emerging and may hold promise for the ambition of precision medicine; maintaining a distinction between syndromic or nonsyndromic ASD will likely not be contributory to these efforts.

Conclusions

We propose that the term syndromic ASD may no longer be useful. In addition to the risk of conflating 2 fundamentally different denotations—the symptom presentation characteristic for ASD ("autistic syndrome") versus the presence of comorbid features and/or a presumed genetic etiology ("syndromic autism")—our main argument holds that the underlying assumption of the concept syndromic ASD, that is, that comorbidity and genetic etiology necessarily concur, is wrong. We submit that this is not merely an academic discussion because continued usage of this terminology may have negative impacts on both clinic and research. We conclude by reiterating the importance of documenting comorbidity, as well as any contributory genetic variation in relation to ASD. However, we submit that only by considering these components in their own right, we will be able to access the full potential value of both strands of information and maximize their scientific and clinical impact on our understanding of ASD.

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Conflict of Interest

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