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Long overdue: including adults with brain disorders in precision health initiatives

Brenda M. Finucane[1], **Scott M. Myers**[1], **Christa Lese Martin**[1], **David H. Ledbetter**[1]

[1]Autism & Developmental Medicine Institute, Geisinger

Abstract

Developmental brain disorders (DBD), including autism spectrum disorder, intellectual disability, and schizophrenia, are clinically-defined and etiologically-heterogeneous conditions with a wide range of outcomes. Rare pathogenic copy number and single nucleotide genomic variants are among the most common known etiologies, with diagnostic yields approaching 50% for some DBD cohorts. Incorporating genetic testing into the care of adult patients with DBD, paired with targeted genetic counseling and family cascade testing, may increase self-advocacy and decrease stigma. In the long-term, breakthroughs in the understanding of DBD pathophysiology will hinge on the identification, engagement, and study of individuals with rare genetic DBD etiologies, consistent with successful precision medicine approaches to the treatment of cancer and cardiovascular disease.

Keywords

developmental; psychiatric; brain disorders; Autism; intellectual disability; global developmental delay; epilepsy; cerebral palsy; schizophrenia; diagnostic genetic testing; genomic screening; precision medicine; population health

Introduction

Developmental brain disorders (DBD), including autism spectrum disorder (ASD), schizophrenia, and intellectual disability, are relatively common, clinically-defined, and etiologically-heterogeneous conditions with a wide range of severity and outcomes [1,2]. Rare copy number (CNVs) and single nucleotide variants (SNVs) that result in loss of gene function are among the most common known etiologies, with numerous reports over several decades linking specific genetic diagnoses to DBD clinical phenotypes [3,4]. Hundreds of distinct genetic etiologies are now known, collectively representing a significant and growing subset of pediatric and adult-onset DBD.

Corresponding author: Brenda Finucane, M.S., L.G.C., Genetic Counselor and Professor, Geisinger, Autism & Developmental Medicine Institute, 120 Hamm Drive, Suite 2A, Lewisburg, Pennsylvania USA.

Evidence suggests that hundreds of different rare genetic disorders converge into a more circumscribed number of shared neurobiological pathways, ultimately leading to an interconnected matrix of brain disorders [1,4]. Many genes and CNVs implicated in the etiology of DBD demonstrate wide phenotypic variability and can manifest as clinically-distinct presentations. Thus, the expression of the same pathogenic variant may take the form of ASD in one person, epilepsy in another, and bipolar disorder in another, even within the same family. Unlike the individually-small effect sizes of common variants that additively contribute to polygenic risk, rare loss-of-function variants have large, primary impacts on neuronal pathways and can be considered causative of brain dysfunction. These large effects are modulated in part by background genomic variation, now being quantified as polygenic risk scores, which may then be further modified by environmental exposures and stochastic developmental variation [1,5]. Given these many secondary influences on primary brain dysfunction, the high degree of variable expressivity of DBD presentations for a single genetic disorder is not surprising.

Consensus recommendations from expert groups and professional societies have been in place for over a decade for clinical genetic testing in children with DBD. These now include exome sequencing (ES) as a first tier-diagnostic test for the evaluation of ASD and developmental delay / intellectual disability [6]. Similar guidelines for adults have been slow to emerge, even as thousands of children with DBD inexorably cross over the threshold into adulthood every year.

Most major insurers in the United States offer coverage for fragile X testing and chromosomal microarray analysis, although many healthcare plans have not yet codified specific policies for next-generation sequencing technologies, such as ES [7]. Those with explicit coverage for DBD-related genetic testing often restrict claims to children. However, at least one health insurer has recently recognized the potential benefits of genetic testing for adults with DBD, lifting the artificial age limit on covering ES for developmental disorders while adding neuropsychiatric disorders, such as schizophrenia, as covered indications [8]. Developmental pediatricians and child neurologists have increasingly become aware of the recommendations for clinical genetic testing, but the same has not been true for adult healthcare providers. Most adults with DBD are not offered diagnostic testing and often live with multiple symptom-based clinical diagnoses without ever knowing the underlying genetic etiologies that may provide unifying explanations for these disparate findings. Here, we describe the rationale for diagnostic genetic testing, along with advances in population DNA screening that may accelerate both the incidental and intentional identification of DBD-related etiologies.

The case for diagnostic genetic testing in adults

Although individually rare, it is well-established that genetic etiologies collectively account for a significant proportion of childhood DBD (Table 1). A specific genetic cause can be determined in a quarter of individuals with ASD and half of those with ID using a combination of clinically-available chromosomal microarray analysis and ES [6,9–15]. Many rare genetic causes of epilepsy involve biological pathways with particular relevance for pharmacological treatment [10]. Pathogenic variants also account for a significant

proportion of cerebral palsy, a disorder once considered almost exclusively due to hypoxic and ischemic perinatal events [11,12]. There are far fewer published surveys of diagnostic testing for conditions such as schizophrenia and bipolar disorder, where the research focus has historically been on identifying common variants through genome-wide association studies rather than on rare variants. Numerous CNVs have been reported in schizophrenia [13–15], including well-described conditions such as the 22q11.2 deletion syndrome [16]. The diagnostic yield of genetic testing in other adult DBD is less clear, but studies using new technologies, including genome sequencing, are ongoing (17,18 – also in this issue of the Journal).

The rationale for pursuing diagnostic genetic testing in pediatric populations is well-accepted, including the establishment of an etiological genetic diagnosis that can direct medical care, as well as the potential healthcare cost savings related to a reduction in the "diagnostic odyssey" [19–21]. Comparatively fewer studies have assessed the clinical utility of genetic testing in adults with DBD. The 22q11.2 deletion syndrome [16], with its complex and variable medical phenotypes and 25% risk for schizophrenia, is often cited to illustrate the value of genetic diagnosis for anticipatory medical guidance through the lifespan. Several other known genetic DBD etiologies include actionable adult-onset manifestations, such as a lifetime cancer risk for individuals with pathogenic *PTEN* variants [22], maturity onset diabetes of the young (MODY5) in those with 17q12 microdeletions [23], and renal failure in adults with tuberous sclerosis complex [24]. However, as in pediatric DBD populations, one cannot argue for widespread diagnostic genetic testing solely on the basis of clinical utility, as many genetic etiologies of DBD are non-syndromic with primary effects on cognition and behavior.

Absent medical actionability, there is growing recognition of the broader benefits to patients of learning a genetic cause for their existing symptoms [25,26]. Although genetically-targeted treatments are not yet available for most rare DBD etiologies, genetic diagnosis may open the door to promising clinical trials and expert resources. Knowledge of genomic variants can also inform reproductive decision-making for adults with DBD, and for their relatives who can pursue targeted cascade testing [26,27]. A less tangible benefit, but one with particular relevance to DBD, relates to the psychological utility of understanding the etiology of one's developmental and psychiatric history. There is often value to "knowing for the sake of knowing" a genetic diagnosis by correcting misconceptions about DBD causes, reducing stigma, and fostering links with etiology-specific support and advocacy groups [25–30]. In our experience disclosing DBD-related genetic test results as part of Geisinger's MyCode Community Health Initiative, many adults expressed profound relief to finally have a medical explanation for their disabilities [Martin et al., submitted]. As one participant remarked, "It's one thing to know that psychiatric problems run in families, but it's another thing to see my actual lab report."

When one considers the known high rates of behavioral, cognitive, and medical comorbidities among adults with DBD, there has been a striking lack of attention given to diagnostic genetic testing and research in this population as compared to pediatrics [30,31]. The pervasive absence of etiological inquiry for adults with complex DBD contrasts with most other areas of specialty medicine, where the differential work-up of presenting

symptoms is an essential part of clinical practice. In the United States, insurance coverage for “behavioral health” is separated out from “physical medicine,” further punctuating an artificial dichotomy between DBD and other types of medical illness. Accurate diagnostic genetic testing is now widely available for DBD, yet adult healthcare providers have been largely absent in developing guidelines for standards of care that would drive insurance reimbursement. One exception is the International Society of Psychiatric Genetics whose recent guidelines, while conservative, acknowledge the importance of diagnostic testing to rule out rare genetic etiologies [32]. A handful of genomic initiatives, such as those led by Geisinger and the Simons Foundation, are prioritizing the return of DBD-related WES results to research participants (Martin et al., submitted) [33]. Although these promising efforts are moving forward, widespread adoption remains slow and may soon be overtaken by the large volume of genetic DBD etiologies revealed as a by-product of population-based genomic screening.

DBD at the intersection of precision medicine and population health

Advances in the understanding of DBD causation have occurred within the broader context of transformational change in population health, led by genomic medicine [19,34–36]. The cost of genetic testing has dramatically declined over the past decade, allowing health systems and insurers to consider the long-term value of population-based exome and genome sequencing for preventive medicine. At the same time, large commercial genetics laboratories offer billing and shipping services, facilitating sample collection and increasing patient access. In addition, the widespread adoption of electronic health record (EHR) systems has improved the consistency, long-term storage, and portability of patient information [37]. When linked with genomic data from voluntary patient biobanks, EHR findings fuel translational research aimed at achieving precision medicine for human disease.

In oncology and cardiology, successful examples of genomics-enabled research strategies have already emerged. The discovery of widely-prescribed statin drugs was made possible by research initially focused on a rare genetic form of hypercholesterolemia which revealed an underlying pathway with ‘druggable’ biochemical targets [38]. Likewise, the study of specific genetic etiologies of cancer has transformed the practice of oncology over the past decade, dramatically improving outcomes for all cancer patients [39]. Although the brain’s specific circuitry and influence on behavior are far from fully characterized, research on rare genetic etiologies of DBD will pave the way for an improved overall understanding of brain disorders, with and without known genetic causes.

In current clinical practice and research studies, pathogenic DBD-related variants are readily detectable as incidental findings of genomic sequencing, yet guidance is lacking about the circumstances under which such results should be disclosed, if at all, to patients. The American College of Medical Genetics and Genomics (ACMG) has identified a list of 59 medically-actionable genes that should be reviewed in the context of any genome-wide clinical genetic testing, with disease-causing variants returned to patients as secondary findings [40]. These primarily include genes that confer significant risks for cancer and cardiovascular disease, all with associated medical recommendations that have the potential

for early detection and improved health outcomes [40,41]. Two of the results recommended for disclosure, *PTEN* disorders and tuberous sclerosis complex, happen to include neurodevelopmental and psychiatric phenotypes, although their inclusion on the ACMG list relates to their medically actionable non-DBD health risks [22,24]. At least 2% of all clinical genome-wide test results include an ACMG-recommended returnable secondary finding [42–44]. By comparison, DBD-related CNVs alone have been reported in 1% of samples from large unselected population studies, including surveys of the U.K. Biobank [45], deCODE [46], and the population biobank of Estonia [47]. Geisinger's MyCode® Community Health Initiative, which pairs EHR information with genomic data from its biorepository, currently has ES results from >145,000 research participants, primarily comprised of unselected adults presenting for primary and specialty healthcare [48]. Consistent with other studies, approximately 1% of individuals in MyCode harbors a pathogenic DBD-related CNV (Martin et al., submitted). The prevalence of SNVs is still being determined, but pathogenic DBD SNVs are expected to be more common than CNVs. Despite their clinical relevance and significant personal utility, DBD-related incidental findings are not yet recommended for return, although their estimated prevalence in unselected populations rivals the detection rate of all the ACMG medically-actionable variants combined.

While population health initiatives await the full integration of genomic findings into translational medicine, there are discussions within the genomics community about expanding the scope of returnable secondary findings. This dialogue includes consideration of clinically relevant results which, while not strictly "medically actionable", have significant personal utility for individuals and families [30]. Given their prevalence and the potential benefits of disclosure, rare DBD-related etiologies should be at the forefront of this discussion. As is currently the practice for all secondary findings, the return of CNVs and other DBD-related results should be optional. This is consistent with public perceptions of genomic test disclosure, which value patient autonomy while prioritizing disease severity, regardless of medical actionability (49). The practice of returning such results is not entirely new, as medical geneticists and genetic counselors have decades of experience revealing unexpected genetic diagnoses secondarily identified through parental testing of children with known DBD etiologies [50]. As with the original ACMG list, additional research and pilot studies will be needed to develop thoughtful disclosure protocols and methods for monitoring patient response [47,51]. Particular attention should be focused on the potential for genetic stigmatization, given the past history of research abuses related to vulnerable DBD populations [52]. Developmental and psychiatric disorders are already among the most highly stigmatizing of all human conditions, not only in western cultures but throughout the world. Based on our experience so far, we anticipate that 'medicalizing' DBD by revealing underlying genetic etiologies may paradoxically decrease shame and stigma among individuals with brain disorders.

Conclusion

A growing number of distinct, genetic disorders can now be identified as causative of DBD, allowing healthcare providers to move beyond vague discussions of multifactorial risk to more targeted, medical explanations for brain dysfunction. Combined diagnostic yields of

widely-available genetic tests are approaching 50% for some DBD clinical cohorts, reflecting the important collective impact of rare etiologies. Knowing an underlying genetic cause can inform prognosis and medical care, particularly in pediatric populations. In adults, medicalizing DBD through diagnosis of genetic etiologies, paired with targeted genetic counseling and family cascade testing, may decrease stigma, increase self-advocacy, and lead to closer engagement of these patients with healthcare providers. Incorporating genetic testing into the care of adult DBD patients could ultimately translate into more cost-effective utilization of healthcare resources and improved compliance with treatment recommendations. In the long-term, breakthroughs in the understanding of DBD pathophysiology will hinge on the identification, engagement, and study of individuals with rare genetic DBD etiologies, consistent with successful precision medicine approaches to the treatment of cancer and cardiovascular disease [53]. As next generation sequencing moves out of the genetics clinic and into mainstream medicine, there is strong interest in harnessing its predictive and diagnostic power toward the realization of effective treatments for DBD.

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Table 1.

Diagnostic Yields of Genetic Testing for Developmental Brain Disorders (DBD)

DBD	Chromosomal Microarray*	Exome Sequencing*	Selected Relevant Publications	Comments
ID / Global Developmental Delay	15%	35%	Srivastava et al., 2019[6] Waggoner et al., 2018[9]	Numerous published studies; strong evidence for combined diagnostic yield approaching 50%
ASD	10%	15%	Srivastava et al., 2019[6] Waggoner et al., 2018[9]	Numerous published studies; strong evidence for combined diagnostic yield approaching 25%**
Epilepsy	8%	45% (23% for targeted epilepsy panels)	Sánchez-Fernández et al., 2019[10]	Wide range of diagnostic yields across study cohorts, depending on epilepsy phenotype and other factors**
Cerebral Palsy	10-31%	14-65%	Matthews et al., 2019[11] Corbett et al., 2018[12]	Relatively small studies with a mix of cohorts selected by motor phenotypes and comorbidities**
Schizophrenia	3-7%	<1% (single study[13])	Balakrishna and Curtis, 2020[13] Singh et al., 2018[14] Lowther et al., 2017[15]	Does not include several published ES studies aimed at gene discovery. The single ES study noted here examined only genes reported for neuropsychiatric phenotypes, possibly excluding other relevant DBD genes**

*averaged across multiple published studies investigating diagnostic yield for each DBD

**The comorbid presence and severity of ID affects yield across all other disorders