EDITORIAL

Childhood-Onset Movement Disorders at the Forefront: From Genes to Precision Therapy

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Childhood-onset movement disorders have undergone a transformation. Once treated as rare and phenotypically imprecise conditions at the periphery of neurology, they now occupy a central position at the intersection of neurogenetics, neuromodulation, and precision therapeutics. The inaugural MDS-PAS Pediatric Movement Disorders Course (read more about this in *Moving Along*: https://www.movementdisorders.org/Moving-Along/Highlights-from-the-1st-MDS-PAS-Pediatric-Movement-Disorders-Conference.htm), held in Boston in June 2025, was both a measure of that progress and a catalyst for what is to come. More than 200 clinicians, scientists, and trainees from 22 countries attended—nearly half of them trainees—across a 3-day program that deliberately blended didactic lectures across eight scientific sessions with interactive video rounds, poster sessions, and unsolved-case discussions; post-meeting evaluations were exceptional, with the overwhelming majority of respondents reporting an intent to change their clinical practice. The energy in the room reflected a field that has, in a remarkably short span, moved from the margins toward the center of clinical neuroscience. This collection of linked reviews, drawn directly from the conference's scientific sessions, is intended both to capture that moment and to chart where the field is headed.

Three reviews anchor the collection and together they trace an arc from cause toward cure (Fig. 1). Bernardi and colleagues[1] map the genetic and phenotypic landscape of epilepsy–dyskinesia syndromes—the "Venn diagram" where the genetics of epilepsy and the genetics of movement disorders overlap. Muñoz Chesta and colleagues[2] offer a gap analysis of deep brain stimulation (DBS) in children, the neuromodulatory therapy that has become indispensable for the most severe hyperkinetic disorders. de Gusmão and Katanaev[3] survey the rapidly expanding universe of novel and emerging therapies from repurposed small molecules to in vivo gene editing. Read in sequence, the three reviews move from genes to mechanisms to phenotype, then to neuromodulation, and finally to precision therapy (Fig. 1)—the same trajectory along which the field itself is now traveling.

The starting point is genetic architecture. Bernardi and colleagues[1] synthesize more than 100 genes that converge on a shared set of molecular pathways—regulation of neuronal excitability, glutamatergic and GABAergic signaling, G-protein–coupled signaling, transcriptional regulation, synaptic vesicle cycling, autophagy, and transmembrane transport—to produce the overlapping phenotypes of epilepsy and movement disorder.[1,4] Their central observation is that the movement disorder, long overshadowed by seizures in published cohorts, is frequently the most disabling and persistent feature, often outlasting seizure control. They confront the twin challenges of genetic heterogeneity and phenotypic pleiotropy head-on: a single gene such as *ATP1A3* can produce several distinct phenotypes,[1,5] whereas status dystonicus can arise from variants across many different genes.[6,7] They also chart the temporal logic of these conditions—epilepsy commonly declares itself in the first year of life, whereas movement disorders emerge months to years later—and highlight the genotype–phenotype correlations now beginning to firm up, in which a variant's functional consequence can predict the dominant clinical picture.[7] Drawing on clustered data from the largest published cohorts, the authors translate this complexity into complementary categorical and phenomenology-based classifications, turning a bewildering catalog of genes into a navigable, bedside framework organized around the leading motor phenotype.[1] This is the conceptual foundation on which the

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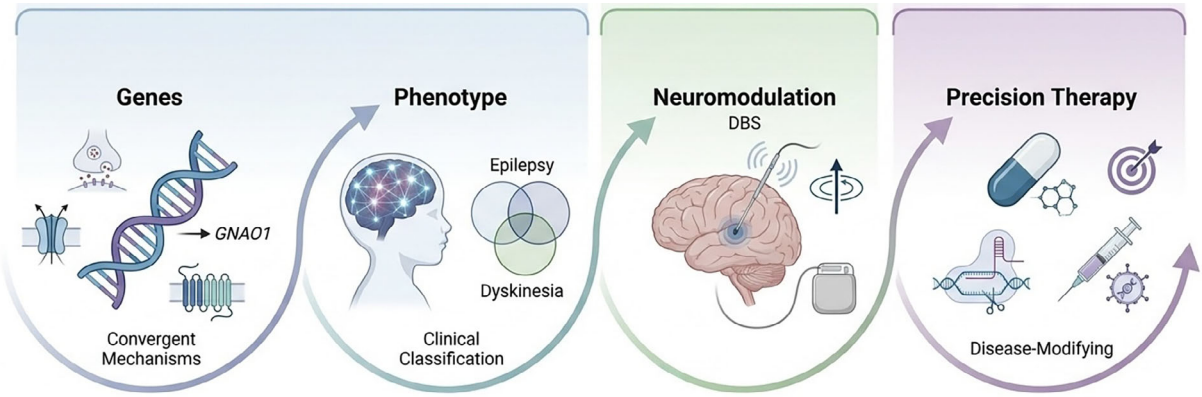

FIG. 1. From genes to precision therapy: the conceptual arc of childhood-onset movement disorders and the three linked reviews of this collection. The field is traced across four connected stages: (1) genes and convergent molecular mechanisms; (2) phenotype and clinical classification; (3) neuromodulation; and (4) disease-modifying precision therapy. The three reviews map onto this arc: Bernardi and colleagues span the genetic and phenotypic stages; Muñoz Chesta and colleagues address neuromodulation; and de Gusmão and Katanaev survey precision therapy. The same genes (e.g., *GNAO1*) and the shared emergency of status dystonicus recur across all three reviews, illustrating how a precise molecular diagnosis informs prognosis, surgical candidacy, and mechanism-based therapy alike. Abbreviation: DBS, deep brain stimulation. [Color figure can be viewed at wileyonlinelibrary.com]

rest of the collection rests: only by recognizing these disorders as a unified nosological spectrum can we phenotype them rigorously and match them to mechanism-specific therapies.

When pharmacology fails—as it frequently does in severe, monogenic hyperkinetic disorders—neuromodulation warrants serious consideration. Muñoz Chesta and colleagues remind us that 25 years of pediatric DBS experience does not simply extend the literature in adult patients.[2] Children present with a broader range of diagnoses, complex mixed-motor phenotypes, growing brains and bodies, and outcomes that adult-derived rating scales were never designed to capture. Etiology remains the most decisive determinant of benefit: isolated monogenic dystonias such as those caused by *TOR1A*, *SGCE*, and *KMT2B* variants respond robustly to pallidal stimulation, whereas acquired and structural dystonias respond more variably. Their gap analysis is admirably candid about what remains unproven: optimal targets and stimulation parameters in secondary dystonia, the emerging role of multitarget DBS for co-occurring intractable epilepsy and dystonia, novel targeting strategies such as awake bedside electrophysiological recording, the search for neurophysiological biomarkers from local field potentials, adaptive closed-loop stimulation, and, critically, the definition of a meaningful "response" in a child whose goals encompass function and participation rather than rating-scale points alone. They also detail novel tools such as *DBSMatchMaker* (https://dbsmatchmaker.com/), a tool that is aiding clinicians and facilitating research,[8,9] as well as the practical realities that distinguish pediatric surgery, including anesthesia regimens that preserve intraoperative physiology, age-dependent imaging sequences for direct targeting, and higher rates of hardware complication in growing children, and the long arc of care that follows, as DBS implanted in childhood is a lifelong therapy requiring coordinated transition to adult services. DBS has transformed the management of refractory status dystonicus,[6,10] reducing mortality from historical rates; yet the authors are clear that clinical practice has outpaced the evidence, and that disparities in global access remain stark.[2]

The third review captures a field in the midst of a therapeutic revolution. De Gusmão and Katanaev catalog advances from just the past 3 years, a period in which the majority of newly approved drugs in the United States have been for rare diseases.[3] They demonstrate how drug repurposing, guided by high-throughput mechanistic screening, identified zinc as a candidate for *GNAO1*-related disorder,[11] and how serendipity refined by mechanism brought caffeine and theophylline to *ADCY5*-related disease[12] and inhaled high-flow oxygen to *ATP1A3*-related paroxysmal events.[13] Novel small molecules have achieved regulatory approval (e.g., omaveloxolone for Friedreich ataxia and trofinetide for Rett syndrome), whereas ecopipam has advanced through late-phase trials for Tourette syndrome. Beyond small molecules, the authors trace the maturation of gene-directed therapy: gene replacement, now an approved reality for aromatic L-amino acid decarboxylase deficiency, with benefit sustained for years; in vivo base and prime editing, with striking proof-of-concept correction of *ATP1A3*-related disease in animal models[14]; and a growing portfolio of antisense oligonucleotides rationally tailored to gain-of-function, loss-of-function, and splicing mechanisms across conditions such as *KIF1A*-related disorder, Angelman syndrome, ataxia-telangiectasia, and *SCN2A*-related encephalopathy, several already in n-of-1 or early-phase human studies. This is precisely the disease-modifying horizon that the first review's molecular taxonomy is built to enable.

What makes these three reviews a true collection, rather than three parallel essays, is how tightly they interlock.[1-3] The same genes recur through every lens. *GNAO1* is at once a prototypical epilepsy–dyskinesia syndrome, a leading indication for DBS in status dystonicus, and the flagship example of high-throughput drug repurposing. *ATP1A3* defines the concept of genetic heterogeneity and phenotypic pleiotropy in the first review and motivates in vivo gene editing in the third. Status dystonicus threads through all three—a life-threatening emergency answered by neuromodulation in one review and informs precision pharmacology in another. The field is converging on a model in which a precise molecular diagnosis simultaneously informs prognosis, surgical candidacy, and eligibility for mechanism-based therapy—a model in which the boundary between symptomatic and disease-modifying treatment is beginning to blur.[15]

Equally striking is that all three reviews, arriving from different directions, converge on the same structural imperatives. Each calls for rigorous, harmonized phenotyping and for validated, child-specific outcome measures suited for ultra-rare and heterogeneous disorders—measures that capture function and quality of life, not impairment alone. Each emphasizes the need for natural-history data and collaborative infrastructure, international registries, multicenter consortia, and shared data and platforms, such as *DBSMatchMaker*,[8,9] to generate evidence that no single center could produce. And each confronts the ethical fault line: as orphan-drug pricing and access to DBS remain prohibitive across much of the world, the promise of precision medicine risks widening, rather than narrowing, global disparities in care. These are not incidental caveats appended to otherwise optimistic reviews. They are the defining challenges of the coming decade, and they will be met only through deliberate, coordinated, and international effort.

Behind every gene, target, and molecule in these reviews is a child and a family for whom these advances are not abstractions but the difference between a crisis controlled and a crisis endured. That is why the conference placed such deliberate emphasis on mentorship, interactivity, and broad inclusion, and why nearly half its participants were trainees: the challenges these reviews lay out are generational, and meeting them will require a workforce as global and diverse as the patients we serve. The regional variation in pediatric movement disorders practice, shaped by population-specific genetics and prevalences, variable access to diagnostics and specialists, and uneven proximity to cutting-edge science means that no single center holds the full picture. Building a truly international community is therefore not a matter of collegiality alone but a scientific necessity.

That effort is already underway. The MDS Pediatric Movement Disorders Special Interest Group, the now-global Pediatric Video Rounds running across both hemispheres, an emerging framework for pediatric movement disorder fellowships, and plans for a second MDS-PAS Pediatric Movement Disorders Conference in 2027 all reflect a community organizing itself to meet the moment. This collection is part of that same project. It is not a retrospective on a successful meeting but a statement of intent: that childhood-onset movement disorders, and by extension, the children and families who live with them, belong firmly at the forefront of our specialty, our society, and this journal. We are grateful to the editors, reviewers, authors, faculty, and trainees who made both the conference and these review articles possible, and we look forward, with optimism, to the science still to come. ■

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Supporting Data

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