

Progressive Myoclonus Epilepsies

Diagnostic Yield With Next-Generation Sequencing in Previously Unsolved Cases

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Abstract

Background and Objectives

To assess the current diagnostic yield of genetic testing for the progressive myoclonus epilepsies (PMEs) of an Italian series described in 2014 where Unverricht-Lundborg and Lafora diseases accounted for ~50% of the cohort.

Methods

Of 47/165 unrelated patients with PME of indeterminate genetic origin, 38 underwent new molecular evaluations. Various next-generation sequencing (NGS) techniques were applied including gene panel analysis ($n = 7$) and/or whole-exome sequencing (WES) (WES singleton $n = 29$, WES trio $n = 7$, and WES sibling $n = 4$). In 1 family, homozygosity mapping was followed by targeted NGS. Clinically, the patients were grouped in 4 phenotypic categories: “Unverricht-Lundborg disease-like PME,” “late-onset PME,” “PME plus developmental delay,” and “PME plus dementia.”

Results

Sixteen of 38 (42%) unrelated patients reached a positive diagnosis, increasing the overall proportion of solved families in the total series from 72% to 82%. Likely pathogenic variants were identified in *NEU1* (2 families), *CERS1* (1 family), and in 13 nonfamilial patients in *KCNK1* (3), *DHDDS* (3), *SACS*, *CACNA2D2*, *STUB1*, *AFG3L2*, *CLN6*, *NAXE*, and *CHD2*. Across the different phenotypic categories, the diagnostic rate was similar, and the same gene could be found in different phenotypic categories.

Discussion

The application of NGS technology to unsolved patients with PME has revealed a collection of very rare genetic causes. Pathogenic variants were detected in both established PME genes and

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Glossary

NGS = next-generation sequencing; **PME** = progressive myoclonus epilepsy; **ULD** = Unverricht-Lundborg disease; **WES** = whole-exome sequencing.

in genes not previously associated with PME, but with progressive ataxia or with developmental encephalopathies. With a diagnostic yield >80%, PME is one of the best genetically defined epilepsy syndromes.

Progressive myoclonus epilepsies (PMEs) are caused by heterogeneous genetic disorders and present with cortical myoclonus, generalized tonic-clonic seizures, and variable ataxia or cognitive impairment. In a multicenter Italian collaborative study, we reported the etiologies in a cohort of 204 PME patients from 165 unrelated families studied by classical pathologic, biochemical, and targeted genetic testing.¹ The cohort included “classical” PMEs, such as Unverricht-Lundborg (progressive myoclonic epilepsy type 1 [EPM1], 33%) and Lafora body (EPM2, 20%) diseases, and other PMEs resulting from more rare genetic diseases (19%). In 47 unrelated patients (28%), the etiology remained unidentified (Figure 1).

Since 2014, novel genetic causes and pathogenetic mechanisms for PME have been identified. These include pathogenic variants in *CERS1*,² involved in ceramide metabolism, *KCNK1*,³ with a dominant-negative effect on the voltage-gated K_v3 channel,⁴ and the *NUS1*, *DHDDS*, and *ALG10* genes, involved in dolichol-dependent protein glycosylation.⁵

We reanalyze the unsolved cases in the 2014 series¹ to assess the impact of newer diagnostic procedures, especially next-generation sequencing (NGS). Most of the newly solved cases have been reported elsewhere^{2–6}; we herein provide an overall perspective of the current diagnostic yield in PME.

Methods

We studied 38 unsolved unrelated PME patients who did not reach a positive causal diagnosis in our previously reported PME series; DNA was no longer available from the remaining 9 patients (Figure 2). We obtained informed consent from all patients (or their guardians), in line with local institutional review board requirements for genetic analyses. Seven unrelated patients were initially investigated using a NGS panel containing 240 genes known to cause epilepsies or PME. Subsequently, 29 unrelated patients including 3 unsolved by the panel had singleton whole-exome sequencing (WES).³ A trio-design WES approach was performed in 7 patients, including 2 unsolved by NGS panel and 5 unsolved by singleton WES. In 4 families with 2 or 3 affected siblings, WES was performed on all patients.⁵ In 1 family with 4 affected siblings, homozygosity mapping was followed by targeted NGS.²

All patients presented with cortical myoclonus and a progressive course, consistent with PME. The clinical presentation of each patient was reviewed by Istituto Neurologico Besta clinicians (L.C. and S.F.) and researchers at the University of Melbourne (K.L.O. and S.F.B.). Taking into account the clinical classification applied by Courage et al.,⁵ patients were categorized as (1) “Unverricht-Lundborg disease-like (ULD-like) PME” in case of late childhood/

Figure 1 Classification of 165 Families With PME From 2014 to 2021

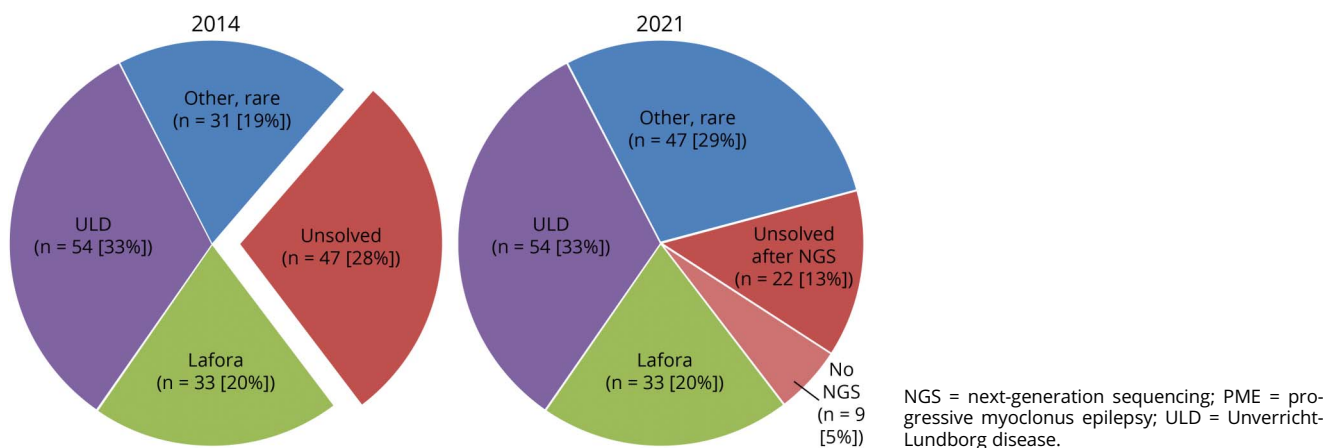
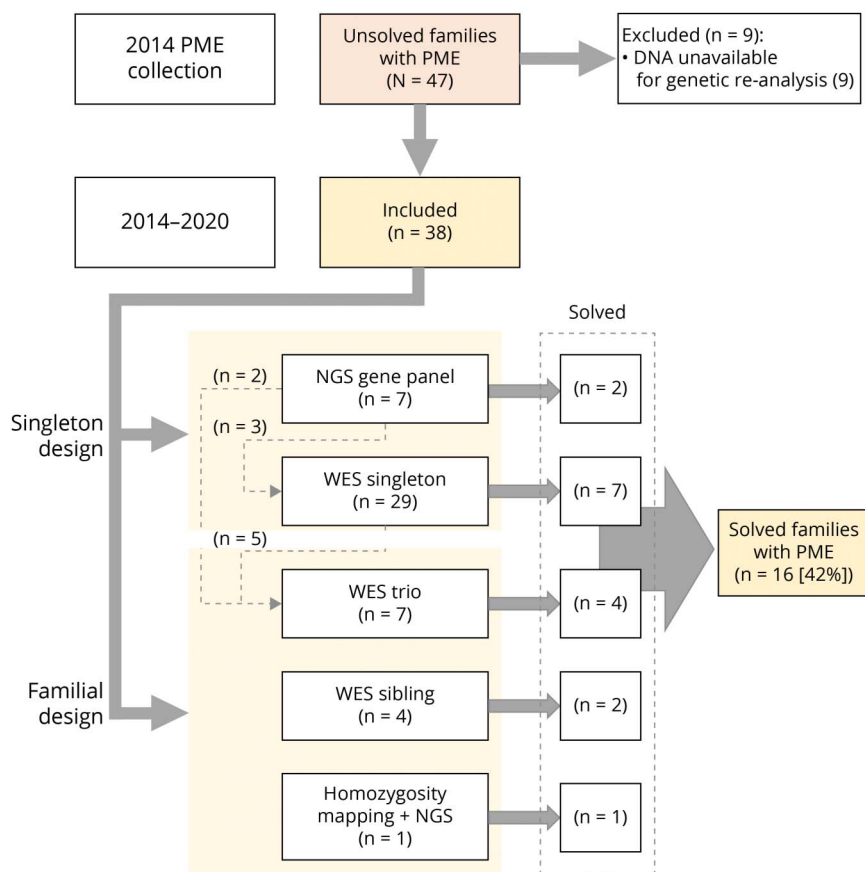


Figure 2 Diagram Flow of the Genetic Investigations Performed Between 2014 and 2020



NGS = next-generation sequencing; PME = progressive myoclonus epilepsy; WES = whole-exome sequencing.

adolescent onset of cortical myoclonus and minimal cognitive impairment similar to EPM1, (2) “late-onset PME” in case of clinical presentation similar to EPM1, but onset after 20 years of age, (3) “PME plus developmental delay” when progressive cortical myoclonus appeared after other symptoms suggesting a developmental encephalopathy (early psychomotor delay, ataxia or seizures), and (4) “PME plus dementia” when patients showed a severe and progressive cognitive impairment as part of the phenotype.

Data Availability

Anonymized data can be made available to qualified investigators upon request to the corresponding author.

Results

We found genetic causes in 16 of the 38 unrelated patients (42%). As shown in Figure 2, 2 patients were solved by NGS panel, 7 by WES singleton, 4 by WES trio, 2 by WES sibling, and 1 by homozygosity mapping.^{2–6} Table 1 reports the newly identified genetic variants.

Among “ULD-like” (16 cases), 3 had pathogenic variants in *KCNK1* and 3 in *CHD2*, *DHDDS*, or *AFG3L2*. The genetic defect remained undetermined in the remaining 10. Among

“late-PME” (6 patients), the WES of siblings revealed different *NEU1* pathogenic variants in 2 families, mutation of *DHDDS* in 1 patient, and mutation of *CLN6* in 1 other. In 2, the genetic cause remained unidentified.

In “PME plus developmental delay,” we included 11 patients. Homozygosity mapping revealed a pathogenic missense variant in *CERS1* (EPM8; #616230) in 4 siblings, belonging to an Algerian family.² Four sporadic cases had pathogenic variants in *NAXE*, *DHDDS*, *SACS*, and *CACNA2D2*. In the remaining 6 patients, the genetic cause remained unidentified.

Among the 5 patients with “PME plus dementia,” 1 had a pathogenic variant in *STUB1*.

In the 2014 article,¹ a cluster analysis based on clinical features associated with PME allowed grouping the 38 unsolved patients evenly into Cluster 1 (n = 20) and Cluster 2 (n = 18). Cluster 1 accounted for all patients now classified as “PME plus developmental delay” with a smaller subset of “ULD-like” and “PME plus dementia” patients. Cluster 2 was predominantly made up of “ULD-like” patients, all “late-onset PME” patients, and 1 patient classified as “PME plus dementia” (eFigure 1, links.lww.com/NXG/A490). Diagnostic

Table 1 Pathogenic Variants Detected in 16/38 Unsolved PME Families Since 2014

Gene	N	Variant(s)	Inheritance	Study	Citation	Phenotype
<i>KCNC1</i>	1	c.959 G > A; p.Arg320His (Het)	de novo	WES singleton	Muona et al., 2015 ³	"ULD-like" (Cluster 1)
<i>KCNC1</i>	1	c.959 G > A; p.Arg320His (Het)	de novo	WES singleton	Muona et al., 2015 ³	"ULD-like" (Cluster 1)
<i>KCNC1</i>	1	c.959 G > A; p.Arg320His (Het)	de novo	NGS panel	Oliver et al., 2017 ⁴	"ULD-like" (Cluster 2)
<i>AFG3L2</i>	1	c.1875 G > A; p.Met625Ile (Hom)	AR	WES singleton	Muona et al., 2015 ³	"ULD-like" (Cluster 2)
<i>DHDDS</i>	1	c.614 G > A; p.Arg205Gln (Het)	—	WES singleton	Courage et al., 2021 ⁵	"ULD-like" (Cluster 2)
<i>CHD2</i>	1	c.1541_1567del; p.(514_523del) (Het)	—	WES singleton	—	"ULD-like" (Cluster 1)
<i>NEU1</i>	3 sib	c.200 G > T; p.Ser67Ile (Hom)	AR	WES sibling (quartet)	Canafoglia et al., 2014 ⁶	"Late PME" (Cluster 2)
<i>NEU1</i>	2 sib	c.679 G > A; p.Gly227Arg; c.913C > T; p.Arg305Cys (Comp Het)	AR	WES sibling (pair)	Canafoglia et al., 2014 ⁶	"Late PME" (Cluster 2)
<i>CLN6</i>	1	c.814C > G; p. Leu272Val; c.721A > G; p.Met241Val (Comp Het)	AR	NGS panel	Berkovic et al., 2019 ⁸	"Late PME" (Cluster 2)
<i>DHDDS</i>	1	c.283 G > A; p.Asp95Asn (Het)	—	WES singleton	Courage et al., 2021 ⁵	"Late PME" (Cluster 2)
<i>CERS1</i>	4 sib	c.549C > G; p.His183Gln (Hom)	AR	Homozygosity mapping + NGS	Vanni et al., 2014 ²	"PME + DD" (Cluster 1)
<i>NAXE</i>	1	c.128C > A; p.Ser43Ter (Hom)	AR	WES trio	Courage et al., 2021 ⁵	"PME + DD" (Cluster 1)
<i>DHDDS</i>	1	c.632 G > A; p.Arg211Gln (Het)	de novo	WES trio	Courage et al., 2021 ⁵	"PME + DD" (Cluster 1)
<i>SACS</i>	1	c.8393C > A; p.Pro2798Gln c.2996T > C; p.Ile999Thr (Comp Het)	AR	WES singleton	Muona et al., 2015 ³	"PME + DD" (Cluster 1)
<i>CACNA2D2</i>	1	c.1260 G > A; p.Thr420 = c.1112A > G; p.Tyr371Cys (Comp Het)	AR	WES trio	Courage et al., 2021 ⁵	"PME + DD" (Cluster 1)
<i>STUB1</i>	1	c.169C > T; p; Pro57Ser (Hom)	AR	WES trio	Courage et al., 2021 ⁵	"PME + Dementia" (Cluster 1)

Abbreviations: Comp Het = compound heterozygote; Het = heterozygous; Hom = homozygous; Late PME = late-onset PME; NGS = next-generation sequencing; PME + DD = PME plus developmental delay; ULD-like = Unverricht-Lundborg disease-like.

success was achieved in 9/20 Cluster 1 cases and 7/18 for Cluster 2.

Overall, concerning the 165 PME unrelated patients reported in 2014, the genetically identified causes increased from 72% to 82%. Figure 1 compares the diagnostic yield and breakdown for the entire Italian series from 2014 to 2021 and (eTable 1, [links.lww.com/NXG/A490](https://www.lww.com/NXG/A490)) lists all genes with pathogenic variants.

Discussion

This reanalysis with next-generation sequencing resulted in a positive diagnosis in 42% of PME unrelated patients who were unsolved at the time of our previous study.¹ One clinically relevant observation relates to the atypical presentation of known PME disorders, which can hinder the diagnosis, as

occurred with the diagnosis of sialidosis (#256550) in 2 families. Patients presented as "late-onset PME" and escaped diagnosis because of nonindicative biochemical findings and an unapparent cherry-red spot.⁶

Since 2014, NGS facilitated the discovery of many pathogenic variants in genes not previously identified as a causative for PME.⁵ Some, such as *KCNC1*,^{3,4} can be considered "specific" PME genes, giving rise in a typical age-range to a classical picture of worsening cortical myoclonus. Other findings, however, suggest that in some patients, in whom the syndromic picture is still that of a PME, the disorder results as a "variant" phenotype of genetic disorders typically presenting with other symptoms. In fact, until the studies published by Muona et al.,³ and Courage et al.,⁵ *AFG3L2* (#614487), *SACS* (#270550), and *STUB1* (#615768) were known to be associated with autosomal recessive ataxia and *CACNA2D2* (#618501) with ataxia or epileptic encephalopathy. The spectrum

of *NAXE* is phenotypically broad, giving rise to lethal neuro-metabolic disorder with acute-onset ataxia or epilepsy and movement disorders, occasionally including myoclonus.⁷ *CHD2* is a well-established epileptic encephalopathy gene and was only recently associated with PME.⁵

The “new” genetic diagnoses were similarly distributed between “Cluster 1 and 2” that we identified in our original 2014 report,¹ and the same occurred for the 4 phenotypic categories applied in this study. Moreover, mutations of the same gene, for instance *DHDDS*, may result either in “PME plus developmental delay,” “ULD-like PME,” or “late-onset PME” phenotypes. Conversely, we did not observe different phenotype categories within families.

Previous retrospective series from referral centers have reported high diagnostic yields in PME,⁸⁻¹⁰ but these studies likely suffer from referral and recall biases. Although the Italian series is not strictly epidemiologic, it was multicenter and had a prospective component, so it approximates the real-world representation of PME in a Caucasian population without major founder effects.

A methodological limit of this study resides on heterogeneous diagnostic procedures preceding WES. Our observation may indicate that, following an early screening of the most classical causes of PME (e.g., EPM1, resulting from *CSTB* dodecamer repeat expansion), and in the absence of typical signs revealing well-known disorders causing PME (e.g., cherry-red spot in sialidoses), WES represents the most suitable diagnostic procedure for achieving the causal diagnosis in the unsolved patients. When possible, affected family members and unaffected parents should be sequenced to maximize diagnostic yield and the chances for novel discovery.

The extensive re-evaluation by means of WES in our unclassified cases suggests that in PME it is possible to achieve a high genetic diagnostic yield (>80%), thus making PMEs 1 of the most genetically well-defined groups of all epilepsies.

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