Ethnicity-Related DMD Genotype Landscapes in European and Non-European Countries

**Objective** Genetic diagnosis and mutation identification are now compulsory for Duchenne (DMD) and Becker muscular dystrophies (BMD), which are due to dysferlin (DMD) gene mutations, either for disease prevention or personalized therapies. To evaluate the ethnic-related genetic assortments of DMD mutations, which may impact on DMD genetic diagnosis pipelines, we studied 328 patients with DMD and BMD from non-European countries.

**Methods** We performed a full DMD mutation detection in 328 patients from 10 Eastern European countries (Poland, Hungary, Lithuania, Romania, Serbia, Croatia, Bosnia, Bulgaria, Ukraine, and Russia) and 2 non-European countries (Cyprus and Algeria). We used both conventional methods (multiplex ligation-dependent probe amplification [MLPA] followed by gene-specific sequencing) and whole-exome sequencing (WES) as a pivotal study ran in 28 patients where DMD mutations were already identified by standard techniques. WES output was also interrogated for DMD gene modifiers.

**Results** We identified DMD gene mutations in 222 male patients. We identified a remarkable allele heterogeneity among different populations with a mutation landscape often country specific. We also showed that WES is effective for picking up all DMD deletions and small mutations and its adoption could allow a detection rate close to 90% of all occurring mutations. Gene modifiers haplotypes were identified with some ethnic-specific configurations.

**Conclusions** Our data provide unreported mutation landscapes in different countries, suggesting that ethnicity may orient genetic diagnosis flowchart, which can be adjusted depending on the mutation type frequency, with impact in drug eligibility.

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**EIF2AK2-Related Neurodevelopmental Disorder With Leukoencephalopathy, Developmental Delay, and Episodic Neurologic Regression Mimics Pelizaeus-Merzbacher Disease**

**Objective** To demonstrate that de novo missense single nucleotide variants (SNVs) in EIF2AK2 cause a neurodevelopmental disorder with leukoencephalopathy resembling Pelizaeus-Merzbacher disease (PMD).

**Methods** A retrospective chart review was performed of 2 unrelated males evaluated at a single institution with de novo EIF2AK2 SNVs identified by clinical exome sequencing (ES). Clinical and radiographic data were reviewed and summarized.

**Results** Both individuals presented in the first year of life with concern for seizures and developmental delay. Common clinical findings included horizontal and/or pendular nystagmus during infancy, axial hypotonia, appendicular hypertonia, spasticity, and episodic neurologic regression with febrile viral illnesses. MRI of the brain demonstrated severely delayed myelination in infancy. A hypomyelinating pattern was confirmed on serial imaging at age 4 years for proband 1. In proband 2, repeat imaging at age 13 months confirmed persistent delayed myelination. These clinical and radiographic features led to a strong suspicion of PMD. However, neither PLP1 copy number variants nor pathogenic SNVs were detected by chromosomal microarray and trio ES, respectively. Reanalysis of trio ES identified heterozygous de novo EIF2AK2 missense variant c.290C>T (p.Ser97Phe) in proband 1 and c.326C>T (p.Ala109Val) in proband 2.

**Conclusions** The autosomal dominant EIF2AK2-related leukoencephalopathy, developmental delay, and episodic neurologic regression syndrome should be considered in the differential diagnosis for PMD and other hypomyelinating leukodystrophies (HLDs). A characteristic history of developmental regression with febrile illnesses may help distinguish it from other HLDs.

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