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Neuromegen: Achieving rapid diagnosis for neurodevelopmental disorders

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Diagnosis of neurodevelopmental diseases is significantly complicated by their variability of presentation. These disorders may present symptoms that could be erroneously attributed to a common disease, delaying diagnosis and ultimately contributing to reduced awareness. Technological advances in next generation sequencing (NGS) and target enrichment approaches have led to major changes in diagnostic workflows in this field. We discuss the milestones achieved with these developments, focusing on the results achieved for epileptic disorders. In a 4-year cohort study, a customized NGS-based panel (EPI-panel) was applied to the diagnostic workflow of over 215 infantile-onset epilepsy patients from Spain and Portugal. Simultaneous sequencing of 226 genes was performed using solution hybridization technology (Sure Select XT, Agilent) and subsequent sequencing using the MiSeq platform (Illumina). EPI-panel consists of (i) a custom panel design that is periodically updated with new disease-associated genes proposed in the literature; (ii) a variant-prioritization algorithm that takes into account specific population frequencies and mutation-susceptibility profiles for genes. We detected 98 variants in 50 different genes involved in neuronal excitability, neurodevelopment, synaptic transmission, metabolic pathways, and brain morphogenesis. An overall diagnostic yield of 40–50% was achieved. *De novo* mutations and CNVs constituted an important percentage of the genetic burden in the cases analyzed. The incorporation of the Neuromegen tools into the diagnostic protocol for these disorders shortens the time to diagnosis to 1–2 weeks, reduces the number of tests and treatments required, and can be used to orient genetic counseling.

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