High efficiency and clinical relevance of exome sequencing in the daily practice of neurogenetics

Quentin Thomas, Antonio Vitobello, Frédéric Tran Mau-Them, Yannis Duffourd, Agnès Fromont, Maurice Giroud, Benoit Daubail, Agnès Jacquin Jacquin-Piques, Marie Hervieu-Begue, Thibault Moreau, et al.

Conclusions

The current study highlights the genetic features of the MHC region associated with the risk of PD across ethnicities, enhancing our understanding of the immunologic pathophysiology of PD.

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Background and aims

Exome Sequencing's (ES) relevance as a diagnostic tool in a real-life practice with heterogeneous cohort of patients presenting for neurogenetic evaluation is still debated and has yet to be assessed. Here, we report a prospective study using clinical ES (cES) as a first-tier test or after a non-contributive diagnostic odyssey in various progressive neurological disorders, regardless of age at onset, familial history or clinical spectrum, assessing the efficiency and relevance of cES in the daily practice of Neurology and Genetic Departments.

Methods

Sixty-seven probands with various progressive neurological disorders (cerebellar ataxias, neuromuscular disorders, spastic paraplegias, movement disorders and individuals with complex phenotypes labeled “other”) were recruited over a 4-year period regardless of their age, gender, familial history and clinical framework. Individuals could have had prior genetic tests as long as it was not cES. cES was performed in a proband-only (60/67) or trio (7/67) strategy depending on available samples and was analyzed with an in-house pipeline including software for CNV and mitochondrial-DNA variant detection.

Results

In 29/67 individuals, cES identified clearly pathogenic variants leading to a 43% positive yield. When performed as a first-tier test, cES identified pathogenic variants for 53% of individuals (10/19). Difficult cases were solved including double diagnoses within a kindred or identification of a neurodegeneration with brain iron accumulation in a patient with encephalopathy of suspected mitochondrial origin.

Conclusions

This study shows that cES is a powerful tool for the daily practice of neurogenetics offering an efficient (43%) and appropriate approach for clinically and genetically complex and heterogeneous disorders.

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Diagnostic yield of clinical exome testing in neurology patients of from tertiary care centre

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Background and aims

Since last few years genetic testing has become easily available. In developing countries where cost may forbid testing, evaluating clinical exome sequencing(CES) might be financially more feasible than whole exome sequencing (WES) for heterogenous mendelian disorders. However there are few studies to assess diagnostic yield of CES. Our study looked at diagnostic yield of clinical exome panel for phenotypic subgroup of neurological disorder with a presumed genetic aetiology.

Methods

Retrospective analysis of all patients who were subjected to CES between 2016 and 2019 at neurology department of KEM hospital was done. It was done in patients in whom clinical picture was highly suggestive of genetic aetiology. CES data was generated at standard genetic laboratory

Results

Exome data from 95 adult and child neurological patients were analysed. Likely or definite causative variants were found in 52 individuals, achieving an overall diagnostic rate of 55%. Molecular diagnosis could be established in 34/47 (72%) patients with neuromuscular disease, 6/24 (25%) with epileptic disorders, 6/14 (43%) with movement disorders and 6/10 (60%) with suspected intellectul disability and delay. In 20(21%) patients the management changed in terms of specific drugs and diet.

Conclusions

Diagnostic CES identified underlying genetic defect definitively or likely in 55% of neurological patients. Highest diagnostic yield was achieved in neuromuscular group (72%). Diagnostic yield was high because of stringent selection of patients. Confirmation of diagnosis by genetics paves way for genetic counselling, avoids invasive diagnostic tests and decreases economic burden to family.

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Spectrum of IEM in children who presented as neurodevlopmental delay in Children’s Hospital, Multan

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Background and aims

Objective: To determine the frequency, presentation and outcome of various inborn errors of metabolism who presented as neurodevelopmental delay in Children’s Hospital, Multan.