Whole Exome Sequencing (WES) Use in Clinical Pediatric Neurology

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Abstract

Whole exome sequencing (WES) is a relatively new technology that is becoming clinically available to patients without substantial barriers of cost. This technology allows clinicians to sequence the entire protein coding regions of DNA, providing substantially greater detail than previous genetic sequencing methods. We briefly explain the methodology used in this technology. Currently, there are a large number of Variants of Unknown Significance (VUS) due to the rare nature of variants that occur in neurodevelopmental disorders and the small amount of genetic samples that have been collected. As WES becomes more accessible and utilized it is predicted that the threshold for variant significance will begin to be met. This clinical genetic information is not only necessary for diagnosis of a disorder, but also informs treatment.

Introduction

Whole Exome Sequencing (WES) is the most advanced and widely accessible clinical genetic evaluation tool currently available. Previously, chromosomal analysis, Polymerase Chain Reaction (PCR), chromosomal microarrays, and Sanger sequencing were the frontline in genetic testing for cases that presented with phenotypes that were not easily discernible by means of other top notch diagnostic practices. Now, with Next-Generation Sequencing (NGS), clinicians are able to run massive quantities of DNA for sequencing and are able to identify single genes or specific regions for variants. Additionally, NGS captures a much broader spectrum of DNA variations than previous methods. Essentially all genetic alterations can be detected with NGS with the exception of regions with high repeat expansions, for example those that lead to Fragile X syndrome as well as Huntington’s disease, due to the difficulty of reconstructing the multiple identical small reads. This capability allows for unbiased genetic investigation of the entire exome, and thus entirely novel and unexpected variants can be discovered and used to unravel the many unexplained conditions seen in pediatrics.

In a cohort of 78 pediatric patients all presenting with an unexplained neurodevelopmental disorder, 41% came back with pathogenic or likely pathogenic variants, and another 41% were reported to have at least one Variant of Unknown Significance (VUS), likely benign variant, and/or benign variant. Only 18% of the cohort had WES reports with no variant detected. These results indicate that the use of WES improves detection of disease causing variants, and in all 41% with a presumptive diagnosis, their symptom management was impacted. In some cases, WES results may not impact the patient’s treatment plan directly, but also inform family members about their risk of having another child with this should they choose to procreate.

Methods

We performed a thorough review of the relevant literature regarding whole exome sequencing in clinical pediatric neurology. We do not perform WES in-house...
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and send all clinical samples to industrial laboratories. The methodology with which these labs perform WES is beyond the scope of this article, however, if this information is of interest it can be found by contacting those clinical laboratories which provide WES as a service.

Discussion

Due to the limited number of genetic samples that have been collected, and the relatively rare nature of the variants that occur in neurodevelopmental disorders, there are a large number of variants of unknown significance. In order for a variant to be determined ‘pathogenic’ or ‘likely pathogenic,’ or on the opposite side of the spectrum ‘benign’ or ‘likely benign,’ laboratories must support that in 90% of cases the variant either yields a disease state or does not result in a condition respectively. Thus, with very small sample populations and the relative rarity of the variants involved in pediatric neurological cases, it is difficult for the 90% threshold to be met to assign these variants as pathogenic or benign. As whole exome sequencing becomes in increasingly popular, this threshold will begin to be met for more genetic variations, leading to less variants of unknown significance and more significant determinations.

Pediatric neurological disorders tend to have overlapping phenotypes and are not easily treated. The commonly accepted therapeutic approaches to most pediatric neurological conditions are physical, behavioral, and interventional therapies which report variable success along with the use of pharmaceutical agents which are often prescribed on a ‘trial and error’ basis. The continued use of WES in cases of pediatric neurological disorders will provide significant evidence for the genetic variations involved in these disorders and will allow for more personalized medicine.

The fields of pharmacogenomics and precision medicine are innovative approaches to medicine which use genetic information to make informed decisions about treatment methods as well as illuminate risk factors for disease. As more information regarding the genetics underlying pediatric neurological disorders is discovered, this data can be used to inform physicians of more effective treatments in these disorders. For example, when a pathogenic genetic variant is identified in a patient, prior knowledge of effective pharmaceuticals for patients with this genetic variant would allow a physician to make an educated prediction of which drug would likely provide the most benefit to their patient. While it is not a perfect method, this information points clinicians in the right direction, and as more data is collected, the accuracy of pharmacogenomics and precision medicine will only improve.

Conclusion

Identifying pathogenic mutations in neurological disorders which present with a highly variable spectrum of symptoms can dramatically alter the course of treatment and prevent misdiagnosis. In the case of epileptic encephalopathies which are often initially indistinguishable, discovery of a pathogenic may affect the course of treatment. Baumer et al. found that in a case with “SCN2A-Related Early-Onset Epileptic Encephalopathy” their patient responded well to treatment with phenobarbital. Often, sodium channel blocker AEDs are a first line treatment option for infantile epilepsies as they have been shown to be highly effective in seizure abolition and remission. However, in the case of channelopathies caused by genetic variants, the efficacy may be altered. Since sodium and potassium channels regulate action potential firing, depending on the type of mutation, blocking sodium channels may not control or may even worsen seizures.

Additionally, those with pathogenic mutations that result in lifelong epilepsies may be ideal candidates for implantation of a Vagus Nerve Stimulator (VNS) device, especially in those patients who do not respond well to AEDs or have failed several therapeutic combinations. In a study of 100 pediatric patients receiving VNS devices, the patients had tried an average of 8.4 total AED therapies before implant, and were on between 0 and 5 drugs at time of implant. Following device implant, 45% of patients achieved greater than 50% seizure reduction and 18% were seizure free at six month follow up. This study indicated that those with medically refractory epilepsies, with or without gene mutations, may benefit from treatment with a VNS device when AED therapy alone has been unsuccessful. In a study of 21 patients with SCN1A gene mutations who received VNS implantation, 9 of 12 implanted at one institution had a greater than 50% reduction in seizures, with 4 of the 12 reporting improvement in cognitive or speech development. Of the 8 patients not implanted at the primary institution, 7 reported subjective benefit, with 4 reporting seizure free at six month follow up.
In a case of early infantile intractable epilepsy seen in our clinic with an identified duplication of the whole SCN2A and SCN3A genes, immediate seizure reduction was seen with VNS implantation after failure of several AEDs. This patient was the first to have this variant identified in a female, and was the youngest to undergo VNS implantation according to the medical literature. Many studies have been published to show the successful rate of positive identification of pathogenic mutations in epilepsy patients. Helbig et al. showed that patients with epilepsy were 1.5 times more likely to receive positive results, and WES was particularly useful in patients with severe, early onset epilepsies. Regardless of age of onset or whether whole exome sequencing is used as a first measure or after a long diagnostic journey, it has been shown to be effective in diagnosing a wide variety of neurological conditions as well as being time- and cost-saving to patients suspected of having a neurogenetic condition.

References