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Exome Study in Clinical Diagnosis at a Tertiary Care Hospital in South India

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Abstract

Aim: To understand the genetic disease spectrum in a hospital setting using exome analysis by NGS technology.

Methods: We have applied clinical exome studies in our patient groups who presented for a year from 1st April 2017 to 31st March 2018. The data were from all patients from the hospital records irrespective of age and sex from any background who were either referred to or had a direct OPD walk in to the genetic clinic. Those patients who had a suspected family history of a genetic disease were included for testing. The test was applied only in cases if there was a definitive phenotypic evidence of the condition. The patients were included irrespective of a specialty of referral.

Results: Among a total of 171 families who sought clinical consultation, exome analysis were indicated in 33 patients. In that, 25 patients had a molecular positivity for the suspected condition and 8 members had been ruled out of the disease. Genetic counselling was given to all 171 patients and in many cases; an extended family screening and counselling were given. The genotype-based prognostication was added to the phenotype prognostication in these patients for the first-time adding value to the patient care not only in diagnosis but also in making management decisions incorporating the new knowledge.

Conclusion: This study is now our basic framework for genotype-based follow-up in our patient groups and an impetus to practice clinical genomic medicine at a hospital level. This is the first time we have incorporated diagnostic sequencing in South India at a hospital setting.

Keywords: Exome study; Molecular diagnosis

Introduction

As genetic testing has been the order of the day in clinical practice in many specialties, it is time we apply consolidated studies in the benefit of diagnosis and prognostication in families. Single gene studies are slowly replaced by clinical exome analysis in this domain. It is also that patients and doctors have slowly moved to precision medicine with evidence-based treatment methodologies. In that, the need for creating genotype evidence in terms of management is necessitating exome studies judiciously.

Method

We applied clinical exome study in partnership with labs that were instrumental in sampling, storage and analysing the data needed for the families and the referring physician. NGS technology was used and Sanger sequencing applied in selected cases. We used the illumina based sequencing technology in all the patients. The ACMG guidelines were used in characterizing and scoring the variants identified as pathogenic, likely pathogenic and uncertain significance. The sequencing data interpretation and references can be given if required and not included due to the volume.

Results

Among a total of 171 patients who were referred for a clinical consultation from 19 different specialties, a clinical exome was applied in 33 patients (20%). A molecular diagnostic variant was identified in 25 and ruled out in 8. A pathogenic variant is identified in 8 patients, likely pathogenic in 5 and uncertain (novel) significance in 12. All variants of uncertain significance are considered novel and deserves reporting as the population studied in this group are for the first time. The results were also used in arriving at a prenatal diagnosis in two families. All the patients are on a follow-up revised management plan from the benefit of genotype diagnostics.

Discussion

Hospital based genotype testing has been slowly growing in India but has been very patchy and optimal so far. Nevertheless, genomic medicine is actively practiced by specialists and physicians. There is a lot of interest to apply the tools of genomic medicine in clinical care of patients. To begin with we did not have a data set to understand the clinical spectrum of patients in the local population. There was clear lack of information such as lack of knowledge of age at presentation, inheritance type, and heterogeneity of disease groups involved in genetic disorder, subtype of diagnosis presenting, zygosity of affect etc. Even hospital-based literature was meagre and there were patchy case reports presented so far. There are few case reports on exome-based analysis in diagnosis in Indian patients exclusively from a hospital setting [1]. This is one of the early reports that have prospectively looked into the spectrum of cases that presented to a hospital with genetic complaints that were not previously specifically studied, in a South Indian hospital. Some of the direct benefits of testing included identifying the diagnostic variants, molecular diagnosis of a clinical

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Page 2 of 2

phenotype, extended carrier screening in asymptomatic siblings, prenatal carrier screening in recessive conditions, prenatal diagnosis in fetal medicine and prognosticating in clinical management. It was observed that the most common reason of referral was the need for a counselling followed by a need for a diagnosis [2]. Firstly, novelty of the variants identified needs to be further explored and may be significant because of the freshness of population groups studied. It can add or change the classification of variants of uncertain significance if followed up in future [3]. This is also because the test was applied only in cases with a definitive phenotypic evidence of the condition studied. In many cases, the genotypes identified were used to exclusively identify the subtype and complications that can be anticipated in the patient precisely. The pathogenicity of variants was effectively used to counsel the significance of the insult and explain the urgency of prognosis in families.

Conclusion

We gave a significant risk for variants that were pathogenic, mild to moderate risk in likely pathogenic and no risk in normal variants. In case a variant identified was of uncertain significance, the counselling was guarded and gave the benefit of doubt to the families. In that the need to study and analyse the variants novelty was stressed and closely followed for any unanticipated phenotype events. This is a new beginning for practitioners in South India and this report is now our basic framework register to start a new chapter in clinical genetics for genotype based diagnostics and follow-up care in our patient groups and an impetus to practice clinical genomic medicine at a hospital level in South India. Yet again this application of NGS in day to day practice has helped benefit the patients in a multitude of ways.

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