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Recurrent pregnancy loss in consanguineous couple with MVK gene variant identification by exome sequencing

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Abstract

Hyperimmunoglobin-D syndrome is a rare hereditary auto inflammatory disorder caused by mutation in Mevalonate Kinase (MVK) gene. The clinical presentation includes dysmorphology, progressive cerebellar ataxia also characterized by fetal hydrops, hydrocele and intrauterine growth restriction. Diagnosis is based on presence of symptoms with reduction in enzyme activity or by detecting mutations in MVK gene. We present a rare case of couple with recurrent pregnancy loss having clinical presentations of Mevalonic Aciduria. Whole exome sequencing of the couple detected novel variant in MVK gene c.71A>G (p.His24Arg) causing Hyper-IgD syndrome and Mevalonic Aciduria associated with recurrent pregnancy loss.

Keywords: Syndrome; Symptoms; Pregnancy.

Introduction

Recurrent Pregnancy Loss (RPL) is a frequently occurring human infertility related disease affecting 1 out of 100 pregnant women before the 20th week of gestation [1]. Major causes of RPL are parental and embryo genetic abnormalities, hormonal and metabolic disorders, autoimmune issues [2]. Mutations in MVK gene, mevalonate kinase, the key enzyme in non-sterol isoprenoid biosynthesis pathway. Two phenotypes of mevalonate kinase deficiency are known based on the level of enzymatic deficiency, mevalonic aciduria and hyperimmunoglobulinemia-D syndrome [3].

Hyperimmunoglobin-D syndrome and Mevalonic Aciduria is a rare autosomal recessive autoinflammatory disorder characterised by dysmorphology, psychomotor retardation, progressive cerebellar ataxia, and recurrent febrile crises, usually manifesting in early infancy, accompanied by hepatosplenomegaly, lymphadenopathy, arthralgia and skin rash [4]. Some severe cases of mevalonic aciduria are also characterized by hydrops fetalis, foetal ascites, hydrocele, hepatosplenomegaly, intrauterine growth restriction and polyhydramnios [5].

Case Study

A couple with consanguineous marriage was presented with a bad obstetrics history. They had experienced five recurrent miscarriages; all of them before 8th month of gestation. Clinical findings during the conception were indicative of conditions like polyhydramnios, fetal ascites, recurrent infections, fetal hydrops, bilateral hypo plastic lungs with fetal hepatomegaly and fetal tachycardia. The karyotyping analysis of the couple were not suggestive of any significant findings in association with pregnancy loss; showing a normal 46XY karyotype for male and female as 46XX.

There were no findings with other tests, the medical practitioner recommended for exome sequencing to check for unknown cause of recurrent pregnancy loss. The test revealed that both of them were heterozygous carrier for a mutation in the MVK gene which is known to cause Mevalonate kinase deficiency (Mevalonic aciduria). MVK (NM_000431.4) gene transcript in exon 2 with variant nomenclature c.71A>Gp. His24Arg was detected post exome analysis. The novel variant detected in this case has not been reported before as pathogenic in association with mevalonic aciduria conditions, hence this variant is classified as uncertain significance. Because there is a significant correlation between these conditions and the clinical findings observed during recurrent pregnancy loss in this test report, it is suspected that this gene is responsible for the conditions observed in the developing foetus that leads to pregnancy loss.

Discussion

In this report we describe a couple with heterozygous variant in MVK gene which is indicative of mevalonic aciduria. This is an autosomal recessive condition and as the couple is a carrier for the same variant in the MVK gene, there is a high probability that their baby would be affected by this condition. Autoinflammatory syndromes always pose diagnostic and therapeutic challenges to treating clinicians [6]. There are 65 mutations in MVK gene most commonly occurring ones are responsible for 70% of cases and Heterozygous mutations of the MVK gene is majorly responsible for Hyperimmunoglobin-D syndrome [7,8]. Genetic analysis using Next Generation Sequencing are helpful for differential diagnosis when the causes are unknown [9]. The variant identified was reported uncertain significance as there was no previous record of pathogenic significance submitted or published. The use of Next Generation Sequencing in diagnosis recurrent pregnancy loss helps in correlate clinically and genetically the root cause for the condition. However, the clinical manifestations correlated with that of Hyper-IgD syndrome and Mevalonic Aciduria. Hence, in this case a whole exome analysis has helped the couple to make an informed discussion about their future conception.

Declarations

We wish to confirm that there are no known conflicts of interest associated with this publication.

We confirm that the manuscript has been read and approved by all named authors. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

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