Incomplete Penetrance and Variable Expression of Familial Autosomal Recessive C9 Deficiency

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ABSTRACT

Complement-deficient individuals have increased susceptibility to certain bacteria. Deficiencies in late complement components and properdin are associated with recurrent Neisseria meningitides and Neisseria gonorrhoeae infection. The C5b to C9 terminal complement complex induces lysis of gram-negative bacteria of the Neisseria genus. As a cause of C9 deficiency, one study of a Swiss family found two different point mutations, both generating truncated proteins (exon 2 c.166C>T and exon 4 c.464C>T). Analyses of Japanese C9 deficiency have shown that a C-to-T transition leading to TGA stop codon for Arg95 in exon 4 of the C9 gene (Arg 95Stop) is most common.

Incomplete penetrance describes the binary phenomenon in which a genotype may or may not cause the expected clinical phenotype. The female relatives share a pathogenic variant in the C9 gene associated with autosomal recessive deficiency. Given their carrier status, it is not expected that this mutation would be sufficient to cause the clinical manifestations of C9 deficiency, revealing incomplete penetrance. All three children demonstrated increased susceptibility to infection, while only two actually expressed low C9 levels. This novel mutation displays variable expression given the range of clinical symptoms among related individuals.

We report a novel autosomal recessive Arg 154 premature stop mutation (c.460C>T) on exon 4 of the C9 gene that displays incomplete penetrance and variable expression in a family.

MATERIALS/METHODS

The membrane attack complex (MAC) perforin-like protein complement component 9 (C9) is the major component of the pore-forming multiprotein complex that targets intracellular pathogens. Deficiencies in late complement components (C5-C9) are associated with recurrent Neisseria infection. Other studies describe point mutations in exon 2 and exon 4 generating truncated proteins as a cause of C9 deficiency.

The female relatives share a pathogenic variant in the C9 gene associated with autosomal recessive deficiency. Given their carrier status, it is not expected that this mutation would be sufficient to cause the clinical manifestations of C9 deficiency, revealing incomplete penetrance. All three children demonstrated increased susceptibility to infection, while only two actually expressed low C9 levels. This novel mutation displays variable expression given the range of clinical symptoms among related individuals.

We report a novel autosomal recessive Arg 154 premature stop mutation (c.460C>T) on exon 4 of the C9 gene that displays incomplete penetrance and variable expression in a family.

INTRODUCTION

The membrane attack complex (MAC) perforin-like protein complement component 9 (C9) is the major component of the pore-forming multiprotein complex that targets pathogens. The MAC involves complement components C5b, C6, C7, C8, and C9. After components C5b to 8 bind the outer cell membrane, C9 molecules form a cylinder that inserts into the target cell and induces the lysis of intracellular pathogens. Most known defects responsible for C9 deficiency involve total lack of functional protein. As one of the most frequent genetic disorders in Japan, late complement component deficiencies (C5-C9) are clinically associated with neisserial infections. In these studies, Arg 95 stop mutations were found in most patients with the complete C9 deficiency. We report the first case of incomplete penetrance and variable expression of a novel autosomal recessive Arg 154 premature stop mutation on exon 4 of the C9 gene.

RESULTS

<table>
<thead>
<tr>
<th>Relative</th>
<th>Arg154 Mutation</th>
<th>C9 Level</th>
<th>Infection history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>Yes</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>Father</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older sister</td>
<td>Yes</td>
<td>Low</td>
<td>Oral and vaginal yeast</td>
</tr>
<tr>
<td>Non-identical twin</td>
<td>Yes</td>
<td>Normal</td>
<td>Oral and vaginal yeast</td>
</tr>
<tr>
<td>Patient</td>
<td>Yes</td>
<td>Normal</td>
<td>Oral and vaginal yeast</td>
</tr>
</tbody>
</table>

Table 1: Female carriers of Arg154 mutation in C9 gene, with variable expression of C9 levels and infection history.

DISCUSSION

Incomplete penetrance describes the binary phenomenon in which a genotype may or may not cause the expected clinical phenotype. The female relatives share a pathogenic variant in the C9 gene associated with autosomal recessive deficiency. Given their carrier status, it is not expected that this mutation would be sufficient to cause the clinical manifestations of C9 deficiency. All three children demonstrated increased susceptibility to infection, while only two actually expressed low C9 levels. Their mother also had low C9 levels, although she did not report a history of recurrent infections. This novel mutation also displays variable expressivity, in which the same variant causes a wide range of clinical symptoms (infections and serum C9 levels) among related individuals.

The C9 complement protein plays an important role in the lysis of pathogens as the terminal component of the membrane attack complex. As a result, late complement component deficiencies have been associated with gram-negative neisserial infection. Previous studies have demonstrated point mutations in the C9 gene that result in a truncated protein, complete C9 deficiency, and increased susceptibility to infection. We report a novel autosomal recessive Arg 154 premature stop mutation (c.460C>T) on exon 4 of the C9 gene that displays incomplete penetrance and variable expression in a family.

CONCLUSION

• We report a novel autosomal recessive Arg 154 premature stop mutation (c.460C>T) on exon 4 of the C9 gene that displays incomplete penetrance and variable expression in a family.
• We recommend treating C9 deficiency based on clinical presentation instead of an overreliance on laboratory results.
• Further investigation must determine how the structure and function of the C9 protein are affected by this mutation in a heterozygous patient.

Figure 1: Arg154 autosomal recessive inheritance.
* Indicates expression of clinically low C9 levels.
Only the three heterozygous daughters have history of recurrent infection.