Incomplete Penetrance and Variable Expression of Familial Autosomal Recessive C9 Deficiency

Olivia Humpel B.S., Henry Blunk D.O., Hashim Syed D.O., Robert Hostoffer D.O., LhD, MSMEd, FACOP, FAAP, FACOI, FCCP

Lake Erie College of Osteopathic Medicine, Bradenton, Florida; Allergy Immunology Fellowship, University Hospitals, Cleveland Medical Center, Cleveland, Ohio; University Hospitals Parma Medical Center, Internal Medicine; Allergy & Immunology Associates Inc, Mayfield Heights, Ohio

ABSTRACT

A 27-year-old female patient presented to the allergy and immunology clinic for a history of recurrent infections. She reported a current chronic upper respiratory tract infection, as well as past vaginal yeast infections, oral thrush, and pneumonia. Genetic testing revealed a heterozygous c.460C>T (p.Arg154) mutation on exon 4 of the C9 gene. Complement C9 level was normal. Further investigation of the patient's family history revealed that all female relatives were carriers, yet only the mother and older sister expressed low complement C9 levels. Despite autosomal recessive inheritance and variable expression of complement C9 levels, all three daughters reported recurrent oral and vaginal yeast infections.

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.

MATERIALS/METHODS

1. Genetic testing (Invitae)

Genetic testing involved sequence analysis and deletion/duplication testing of the 407 genes in the Ivitae Primary Immunodeficiency Panel and an additional 8 genes requested: C9, LIG4, LPIN2, STAT4, STX11, ATP6A6P1, CFH, RTEL1. Genomic DNA obtained from the submitted sample (saliva) was enriched for targeted regions using hybridization-based protocol and sequenced using Illumina technology Enrichment and analysis focused on the coding sequence of the indicated transcripts, 20bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions and other non-coding regions were not interrogated. This assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions, and deletion <15bp in length, and exon-level deletions and duplications.

RESULTS

Relative	*Arg154 Mutation*	*C9 Level*	*Infection history*
Mother	Yes	Low	None
Father	No	—	—
Older sister	Yes	Low	Oral and vaginal yeast Urinary tract
Non-identical twin sister	Yes	Normal	Oral and vaginal yeast Urinary tract
Patient	Yes	Normal	Oral and vaginal yeast Upper and lower respiratory tract

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

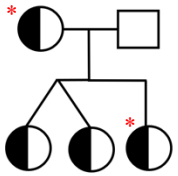

Figure 1: Arg154 autosomal recessive inheritance.
* Indicates expression of clinically low C9 levels.
Only the three heterozygous daughters have history of recurrent infection.

DISCUSSION

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 95 Stop) 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. All three children demonstrated increased susceptibility to infection, while only two 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.