Mini Review
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SERPING1 Gene Mutations Associated with Hereditary Angioedema

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Abstract

Hereditary Angioedema is an autosomal dominant disorder caused by deficiency of complement component-1 (C1) and esterase inhibitor (Cl-INH). This disorder leads to the overproduction of bradykinin, which in turn leads to increased vascular permeability and edema. There are three types of hereditary angioedema, such as type I, II and III which are distinguished by their underlying causes and protein levels of C1-inhibitor in the blood stream.The mutations observed in *SERPING1* gene results in functional impairment of C1-INH. This gene provides instructions for making C1-inhibitor protein. Advanced genomic techniques have been used in detecting the pathogenic variations which are responsible for this disorder. This review highlights the mutations observed in *SERPING1* gene that is associated with Hereditary angioedema.

Keywords: C1-inhibitor; Hereditary angioedema; Autosomal dominant; Mutation; Exons

Introduction

Hereditary angioedema (HAE) is caused by C1-inhibitor deficiency (C1-INH-HAE) and it is a rare autosomal dominant disorder characterized by clinical symptoms such as severe abdominal pain,nausea, vomiting, swelling of the limbs, face and the intestinal tract [1]. HAE is classified into three types of such as Type I, II and III, in which the most common is Type-I which represents upto 85% of HAE and the incidence of this disease is 1/50,000 live birth worldwide.In HAE, type I and II is clinically characterised by the excessive accumulation of fluids in body tissues thereby leading to episodes of swelling. Further, HAE-type III subjects are primarily women, older at first symptomsof onset, experience higher amount of laryngeal attacks and other cause of type III remains still unclear. [2]. Figure 1 illustrates the worldwide prevalence rate of selected rare diseases for the year 2017. Aggressive attacks might occur in the upper airways, and leads to death because of asphyxiation have been previously reported in neonates as young as 2 weeks old [3]. The abnormality in HAE patients is basically a mutation of the C1-inhibitor (C1-INH) gene, which further results in the decreased synthesis of functional C1-INH antigenic protein [4]. Till date more than 400 mutations in the *SERPING1* gene have been found to be associated with various types of hereditary angioedema. Likewise, mutations that cause HAE type-I leads to reduced levels of C1-inhibitor in the blood stream, while variations that cause type-II results in the over production of C1-inhibitor leading to abnormal functions [5].

SERPING1 Gene

The cytogenetic location of Serpin family G member-1 *(SERPING1) gene* is 11q 12.1 spanning 8 exons with protein comprising 500 amino acids [6]. Figure 2 explains the chromosomal location, exon structure, location of reported mutations at their corresponding genomic positions with their protein.The main function of this gene is to provide instructions for making C1-inhibitor protein, which is a form of serine protease inhibitor (Serpin). These serpins help to control the chemical reactions by blocking the activity of certain proteins. The C1-inhibitor is essential for controlling processes involved in maintaining blood vessels, including inflammation. These C1-inhibitors have the ability to block the activity of several proteins in the blood, such as plasma kallikrein and activated form of factor XII [7]. The nucleotide substitutions, small insertions, deletions, duplications and de novo mutations were identified in *SERPING1* gene in cases with C1-INH-HAE [8].

Mutations in *SEPRING1* Gene

A study published in the year 2016 from Jordan (Western Asia) comprising 14 participants showing the clinical symptoms with C1-INH-HAE revealed mutations in *SERPING1* gene

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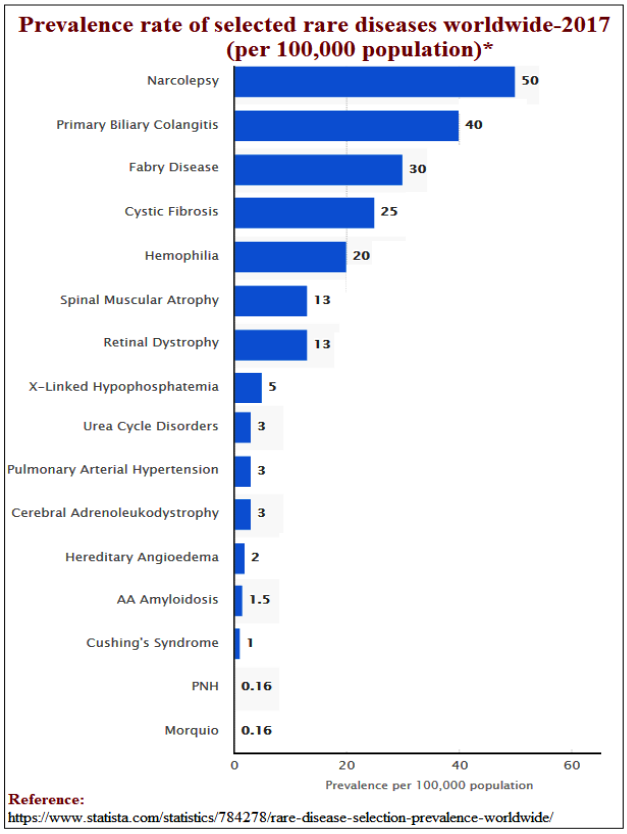

Figure 1: Worldwide prevalence rate of selected rare diseases for the year 2017.

such asc. 203C>T (p.Thr46Ile) located in N-terminal domain of C1-inhibitor protein and c.800C>T (p.Ala245Val) variants influencing the phenotype [9]. Similar study published in Brazil with clinically proven HAE (thirty) subjects in which 16 of them were from unrelated families documented mutations including small deletions(c.97_115del19; c.553delG; c.776_782del7; c.1075_1089del15 and c.1353_1354delGA), one nonsense mutation (c.1480C>T), two intronic alterations (c.51+1G>T; c.51+2T>C) and missense mutations (c.498C>A; c.550G>C; c.752T>C; c.889G>A; c.1376C>A; c.1396C>T; c.1431C>A) showing possibility to perform genetic analysis in that cohort [10]. The mutational spectrum of *SERPING1* gene in Serbian HAE patients (44 subjects from 27 families) were identified by multiplex ligation-dependent probe amplification and DNA sequencing approach. The analysis revealed 6 nonsense, 6 missense mutations, 2 deletions, 1 insertion, 2 deletions and two novel variants (c.300C>T and c.1184_1185insTA) highlighting the heterogeneity of mutations in that study population [8].

A recent study from Brazilians with clinical characteristics of FXII-HAE in 42 families documented 134 participants (77.6% females) harboured a pathogenic mutation in F12 region and T328K substitution was observed in 132 individuals and c.971_1018+24del72 deletion was identified in 2 patients [11]. A 24-year-old Korean woman with clinical symptoms of HAE type-2 has been screened for variants in the *SERPING1* gene revealed missense mutation in 8th exon, heterozygous (1396 C/T) mutation caused (Arginine-466-Cysteine) substitution in C1-INH, suggesting for genetic counselling in her family [12]. Further, a study from 19 HAE patients of Swiss origin investigated the mutational spectrum of candidate gene documented

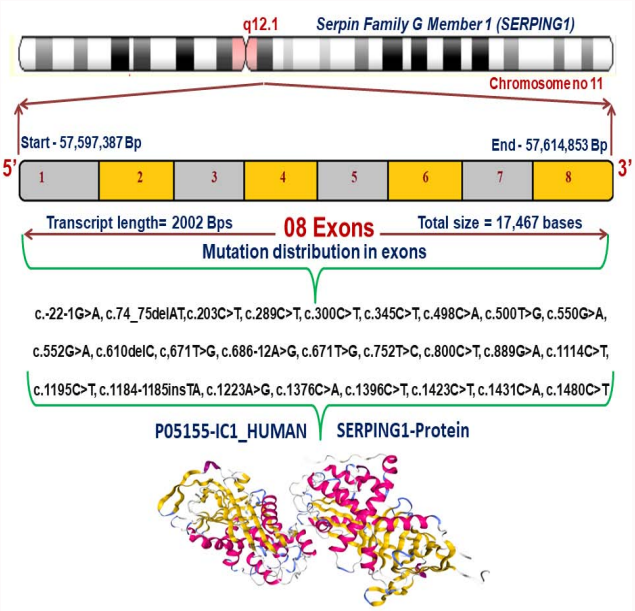

Figure 2: Exon structure of *SERPING1* gene with reported mutations.

3 novel mutations and recommended for newly designed genetic screening tests for HAE in other family members [13].

Conclusion

This review highlights the necessity to focus on *SERPING1* gene variations and their effect on the phenotype. HAE impact has been documented from different ethnic populations all over the world. It is essential to have knowledge on disease etiology; pathogenic mutations and advanced diagnostic methods available for genetic screening which in turn helps in reducing the mortality of hereditary angioedema.

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