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The genetics of hereditary angioedema

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ABSTRACT-Hematopoietic Angioedema has been studied extensively since the first description of the condition in 1888, and has evolved significantly since then. This has been driven of intensive research, laboratory advances, increased clinical observation, and a enhanced comprehension of the connection betwee n genetic and pathogenic factors.[1] Although the condition was initially thought to be a monogenic one, the clinical manifestation of HAE has been hypothesis to be affected by a variety of conditions or co-factors, and there is a growing body of evidence to suggest that multiple genes may be involved in the development of the disorder. Symptoms are recurrent area including Skin . The severity and occurrence of these symptoms can vary between individuals and may vary within the same family over time.[2]
There are two main types of Haematopoietic anemia {HAE}HAE caused by C1-inhibitory (C1-IH) inadequate (HAE) and HAE caused by normal C1-IH (HAE).

Types of HAE
Type I Haematitis is the most typical type of Haematitis is responsible about 90% of all Haematitis-related events.[3]
Type II Haematitis on the other hand, is the other 10% caused by either normal or higher than usual levels .Genetic basisThe description of HAE due to nC1-InH-HAE has led to a new subfield of research focused on the the genetic foundation of HAE in respect to receptor and enzyme play a role in Fibrinolysis (and the contact system).Genetics gene alteration is the cause HAE in 25-30% and HAE in 70-75%[4]
C1-INH-HAE's genetic composition

Changes in the gene SERPING1

This gene, also known as SERPING1, is a a serine inhibitor that is part of the family of serpins. It works by blocking certain proteins in the complement system, which is responsible for the production of bradykinin. It's encoded by the C1-inhibititor gene (GeneBank X54486) and serping1 gene The gene has eight exons and serv-en introns, with seven of them being protein-coding.[5]

What is Serpings?
It gives directions for producing the protein alpha-1 antitrypsin, a kind of inhibitor of serine proteases (serpin).

SERPING1 has a lot of Alu repeating in the introns, so it's really prone to changes and instability. It's thought that around 25% of people with C1-inH-HAE10 have a de novo mutation, and this is linked the Alu sequences. There are a few other things that could be causing this, like a CpG in and a duplicated (6). Plus, there are two other CpG changes in the reactive site - Arg444Cys vs. Arg444Leu - that could be caused by different mechanisms.[6]
Type II hemolytic anemia (HAE) is caused by a point mutation an inactive center loop, resulting in being inactive.
70 percent of HAE patients possess a mutation in the Arg444 results in the dysfunction of C1-InH14. [7]

Type I HAE mutations are very diverse and dispersed across entire .Up to 30 percent of are due to re-arrangements (less commonly, partial duplications and partial deletions).
Common mutations in Type I HAE are msense (34%), frameshift alteration and small indel (31%), splice-site (10), nonsens (1%) mutations.[8]

C1-inH-HAE is a dominant autosomal inherited disorder . The majority of patient are heterozygotes17, a few of homozygotes18- 2 a few mosaic reported23,24. In homozygous individuals, plasma levels of C1-inH are 6-30% above 50% as anticipated anticipating. This appears to be due not only to a synthesis flaw, but moreover to increased catabolism with patients with type I haematopoietic encephalopathy overexpression, or transinactivation of c1-inH translation of the wild type by mutated protein[9].

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It has noted that HAE severity ratings are inversely related to C1-inH activity at baseline (but not to other complement components). This is in contrast to the findings of a number of other research projects that have fallen short to demonstrate a correlation. Numerous studies have been conducted to investigate the relationship between mutations in the serping1 gene and clinical phenotype, however, the outcomes have been inconsistent the majority of been able to find any definitive evidence of a relationship.[10] The most extensive study to date, which was conducted in 2013, involved 255 patients and 116 unrelated family from four. The study revealed that misiense mutation had a lower risk of disease onset and were associated with a significantly lower likelihood of HAE attacks prior to 10 years of age, which has been associated with a severe disease course prior to this age.[11] HoweverThe study did not measure other measures of severity, such as Laryngeal or Abdominal Attacks or Frequency of Episodes. Another, smaller study revealed a strong relationship between the Clinical Severity Score and Laryngeal Facial Angioedema however, it did not find any connection to the beginning of the disease. In our view, due to the lack of standardised criteria for classification of HAE severity, it has been challenging to elucidate correlation between clinical symptoms and serping mutations phenotypic changes.[12] However, the high variation in clinical expression among patients with and without the same mutation and even within the the same patient throughout time suggested to us that serphing1 Mutations might not be enough to explain the variation in expressiveness in a clinical setting.[13]

It has been suggested that certain polymorphisms associated with pathogenic mutations on the SerpING1 gene may be indicative of a serious phenotype in the C1-InH-HAE gene, however, a correlation has not yet been observed for the P.V 480M polymorphism, which is a polymorphism of the P.1438 G>A, and the polymorphism of the p.4926 gene, which is a variant of the p.1438 T>C polymorphism, and has been reported to have contradictory results. Furthermore, it has been observed that the distribution of SerpING1 alterations varies between different countries and Caucasian populations, indicating that other elements, including modifications in the epigenetics of the gene or environmental factors such as radiation, hormones, and food habits, may, in some cases, contribute to the alteration of the Serping1 gene and/or its expression. Further research is necessary to support this hypothesis, however, larger populations are required.[14]

SerpING1 mutations have not been identified in more than 10% Many families exhibiting the classic clinical symptoms of HAE and reduced C4/C1-inH concentrations and activity, leading to the supposition that the disease may in some cases be caused by changes to the untranslated/intronic areas, which may alter serpING1 expression, or other mechanisms that lead to elevated consumption of post-translational C1-inH36.[15]

Other alterations

The primary enzyme in charge of breakdown is ACE.of bradykinins. This enzyme's failure to degrade properly has been linked to to a possible role in clinical expression of haematopoietic hepatic hepatosis (HAE). The polymorphism I/D in theACE gene41 is responsible for 47% of the enzyme levels. However, there is no evidence for a relationship link this mutation and clinical HAE symptoms. There is no evidence for an association between HAE manifestations and the polymorphisms investigated so far in some cell receptors, including the two well-known receptors (68C/T, 71C/T, and 71C/T) in the BDKR1 gene. There is also a polymorphism in another gene, 669c/G, 1098g/C, which mediates vascular permeability (BDKR2 gene polymorphism[16]

Genes related to nC1-INH-HAE

Individuals suffering from this condition have no C1-INH deficiency or activity and no changes in SERPING1. The pathophysiology of this condition is unknown, although contact pathway dysregulation has become increasingly recognized**.**[17]

Mutations in the F12 gene

The F12 gene has a mutation that accounts for approximately 25% of the patients with NCAH. 75% of the patients that have familial nCAH have no genetic basis.The mutations that have been identified so far are at exon and at intron. The most common mutation, found in most patients, is the threonine to lysine substitution.The threonine to arginine substitution (P.Thr 309Arg; also known as the leader protein substitution) has been identified in two families in this same codon.[18]There are also reports of 18-bp duplications and 72-bp deletions is this area abundant in proline.To this day, we do not fully understand the role of these genetic alterations

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in the pathogenesis of nC 1-inH-haE. An initial hypothesis was that the P.Thr 309Lys mutation may be associated with an increase in FXII enzyme activity53, however, this was not supported in a follow-up study54, and is currently considered to be unsubstantiated.P.Thr307Lys (P.Thr 309K) and P.Thr307Arg (P.Th307R) have been characterized in in vitro and in vivo mouse models and have been shown to result in O-linking loss of amino acid residue glycases.[19] This loss increases susceptibility. autoactivation of FXII, resulting in overexploitation of kallikreain-kinin formation by the FXII-zymogen pathway55.These mutations also cause FXII to be accelerated in response to plasmin activation by the contact system, a naturally occurring activator of FXII. This activation is not fully regulated by the C1-inH regulation, which may explain why HAE is seen in patients who have normal levels and activity of C1-InH[20].It has also been suggested that plasmin activation system variations may be associated with disease expression and/or activity, while more research is required.2**1**

The F12 gene mutation is predominantly heterozygous, however, the penetrance of this variant is very low, particularly among males (more than 90% of males with this mutation are not symptomatic, compared to 40% of women)58. There is one report of two Brazilian patients with this mutation, both from unrelated families, who were homozygous for the P. Thr 309Lys mutation.[22]

F12 mutations do not appear to be associated with clinical expression in homozygous C1-inH deficiency patients, as demonstrated by the finding that two of the individuals so far mentioned had severe phenotypes. However, further research is warranted to determine whether genotypes may be connected to the expression of serious illness.[23]

Other genetic alterations

The presence of polymorphisms in alleles of the ACE gene, which alter the levels or activity of enzymes involved in the degradation of bradykinin, has also been identified in the gene. In a first study, the polymorphisms XNPEP2 gene, respectively, the I allele and the A allele, were identified in three symptomatic individuals from a household that the gene. This suggested potential effect phenotypes, however, this hypothesis has not been in a more current research, which did not demonstrate any relationship between disease expression or severity.[24]

Recent research has added a fresh area of research to the existing one, which identified in a family containing . This family has been associated with a decrease in the ability of the Angiotensin-4-Trisphosphonate (ATP) gene variant, AngPT1, to bind to the natural receptor, TIE2, which is encoded by the angiotensin-3 receptor (ATP receptor). This variant is encoded by the AngPT1 gene, AngPT1(p. A119S).[25]

CONCLUSIONS

The initial assumption that HAE is a monogenic disease was losing weight. As we have gained a better understanding of how HAE works, we have begun to look for modifications to the genetic in other parts of the body's contact system and in related systems.[26] One of the biggest challenges is the lack of a standardized way to measure. For example, recent studies have shown that missense mutations (such as those in In Caucasian individuals, the 46C/T polymorphism in F12, gene43, and SerPING1, gene36, have all been linked to a later onset (and hence a lower severity) of disease.[27] These findings are promising, but should not be taken lightly as they do not explain why patients with the same mutation show such high variability in clinical presentation over time or even within the same patient[28]. Epigenetics and environmental factors are increasingly being explored as a possible explanation for this fluctuation. Regarding the instance of finding for modifications to the genetic critical as there is no biological markers and there are no clear clinical or lab diagnostic criteria[29].

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