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Short communication

Transmission patterns of C1-INH deficiency hereditary angioedema favors a wild-type male offspring: Our experience at Chandigarh, India

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ABSTRACT

Background: Deficiency of C1-inhibitor (C1-INH) protein, caused by pathogenic variants in the Serpin family G member 1 (*SERPING1*) gene, is the commonest pathophysiological abnormality (in ~95 % cases) in patients with hereditary angioedema (HAE). C1-INH protein provides negative control over kallikrein–kinin system (KKS). Although the inheritance of the HAE-C1-INH is autosomal dominant, female predominance has often been observed in patients with HAE.

Objective: To analyze the risk of transmission of *SERPING1* gene variant from father or mother to their offspring.

Methods: Pedigree charts of 42 families with a confirmed diagnosis of HAE-C1-INH and a pathogenic variant in the *SERPING1* gene were analysed. Patients with HAE who had had at least one child were included for analyses to assess the risk of transmission from the father or mother to their offspring.

Results: Overall, 49 % (189/385) of all offspring inherited the genetic defect. In the subgroup analyses, 54.8 % (90/164) female offspring and 44.8 % (99/221; $p < 0.02$) male offspring inherited the genetic defect. Inheritance of the genetic defect was significantly lower in male offspring. Fathers with *SERPING1* gene variant had a statistically significant skewed transmission of the wild type to the male offspring as compared to the variant (57.8 % wild type vs. 42.1 % variant; $p < 0.02$), whereas no statistically significant difference was found when a father transmitted the variant to a female offspring. Mothers with *SERPING1* gene variant had no statistically significant difference in variant transmission to male or female offsprings.

Conclusion: Results of the study suggest that the transmission pattern of *SERPING1* gene variant favours the transmission of wild-type alleles in males, especially when the father is the carrier; hence, overall, fewer males and more female offspring inherited the variant. This could be because of a selection of wild-type male sperms during spermatogenesis, as the KLK system has been reported to play a crucial role in the regulation of spermatogenesis. Although, a similar pattern was observed in the maternal transmission of the *SERPING1* gene variant; the difference was not statistically significant, likely because of a small sample size.

1. Introduction

Hereditary angioedema (HAE) is an uncommon genetic disorder, affecting approximately 1 in 50,000 people. Deficiency in the C1-inhibitor (C1-INH) protein, resulting from pathogenic variants in the Serpin family G member 1 (*SERPING1)* gene, represents the most frequent pathophysiological anomaly in hereditary angioedema (HAE) patients (Ponard et al., 2020; Lumry and Settipane 2020), accounting for approximately 80 % of HAE families (Leiden Open Variation Database (LOVD), 2023). The C1-INH protein negatively regulates the kallikrein-kinin system (KKS). Deficiency of C1-INH protein leads to uncontrolled release of bradykinin, causing recurrent episodes of subcutaneous and/or submucosal swellings and occasionally life-threatening laryngeal oedema (Ponard et al., 2020; Lumry and Settipane 2020). Although HAE-C1-INH inheritance follows an autosomal dominant pattern, a higher prevalence in females has often been observed in patients with

Abbreviations: C1-INH, C1-inhibitor; HAE, Hereditary angioedema; KKS, kallikrein–kinin system; TRD, transmission ratio distortion.

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HAE (Bork et al., 2022; Bouillet et al., 2008). There is a paucity of literature on transmission discordance between male and female offspring in patients with HAE. In the present study, we aimed to analyze the risk of *SERPING1* gene variant transmission from either parent to their offspring.

2. Material and methods

In this study, we analysed the clinic records of patients diagnosed to have HAE. Patients were enrolled from the Primary Immunodeficiency Clinic in the institute. Pedigree charts of 42 families with a confirmed diagnosis of HAE-C1-INH and a pathogenic variant in the *SERPING1* gene (supplementary Fig. 1) was analysed (Manuscript on comprehensive profile of these variants is in communication). A detailed pedigree chart including all possible generations was prepared for all patients. All first-degree relatives of the index case (both symptomatic and asymptomatic) were approached and were screened for HAE (3 asymptomatic family members who had a pathogenic variant in the *SERPING1* gene were also included). Patients with HAE who had had at least one child were included for analyses to assess the risk of transmission from the father or mother to their offspring. The genetic testing was carried out for all families with HAE using either Sanger sequencing for the *SERPING1* gene or targeted next-generation sequencing (for a panel of 12 genes including the *SERPING1* gene) or whole exome sequencing. Multiplex ligation-dependent probe amplification (MLPA) was also carried out in a few families. The statistical software SPSS (version 22.0) was used for the data analysis. The chi-square test was used to evaluate the observed distribution of offspring of parents with HAE-C1-INH. Results with p-value < 0.05 were considered statistically significant.

3. Results

In total, 49 % (variant: 189/385 vs. wild type:196/385; $p = 0.6$) of all offspring inherited the genetic defect. In the subgroup analyses, the genetic defect was inherited by 54.8 % of the female offspring (variant: 90/164 vs. wild type: 74/164; $p = 0.07$), while it was inherited by 44.8 % of the male offspring (variant: 99/221 vs. wild type: 122/221; $p = 0.02$). Inheritance of the genetic defect was significantly lower in male offspring. The paternal transmission of *SERPING1* gene variant was statistically significantly skewed, favouring wild-type allele to a male offspring (variant: 43/102 (42.1 %) vs. wild type: 59/102 (57.8 %); $p = 0.02$). There was no statistically significant difference during paternal transmission of variant to a female offspring (variant: 43/80 (53.7 %) vs. wild type: 37/80 (46.2 %); $p = 0.9$) or a maternal transmission of variant to either male (variant: 56/119 (47 %) vs. wild type: 63/119 (52.9 %); $p = 0.3$) or female offspring (variant: 47/84 (55.9 %) vs. wild type:37/84 (44 %); $p = 0.1$) (Table 1 and Fig. 1).

4. Discussion

HAE-C1-INH has an autosomal-dominant mode of inheritance (Bork et al., 2022). Therefore, the likelihood for each offspring to inherit the genetic defect should be ~50 % and should affect both males and females equally (Meyer et al., 2012; Huang et al., 2013). In our observation from 42 families with genetically proven HAE-C1-INH, the total number of offspring who inherited the *SERPING1* gene variant was found to be approximately 50 %. However, there was significant difference in the risk of transmission depending upon the gender of the transmitting parent and the gender of the offspring. In case of paternal inheritance, the transmission of pathogenic variant to the male offspring was significantly less. However, the difference was insignificant when the father transmitted the variant to a female offspring or a mother transmitted the variant to either a male or female offspring. Overall, fewer males and more females inherited the variant. These results are similar to previous observations of female predominance in HAE (Bork et al., 2022; Bouillet et al., 2008).

The skewed transmission of mutation is called the mendelian transmission ratio distortion (TRD). TRD can occur during biological processes such as gametogenesis (spermatogenesis or oogenesis-biased chromosome segregation during meiosis), fertilisation (probability of fertilisation varies among gametes), and embryogenesis (genotype-specific viability selection) (Meyer et al., 2012; Huang et al., 2013). In the present study, TRD was observed when father transmitted the variant to male offspring. This may suggest that TRD possibly occurred during spermatogenesis, favouring the selective development of wild-type spermatids bearing a Y chromosome.

Interestingly, all components of KKS have been identified in the male genital secretion and may have an important physiological role in the male reproductive system (Schill and Miska, 1992; Blaukat, 2003; Sato, 1980). Effects of kallikrein and bradykinin on pre-spermatogonial cell proliferation and sperm motility involved in the regulation of spermatogenesis and sperm function (Schill and Miska, 1992; Sato, 1980). Kallikrein activates sertoli cells' function and stimulates spermatocyte production (Schill and Miska, 1992; Sato, 1980). Clinical trials showed that systemic kallikrein administration increases spermatozoa and sperm motility (Schill and Miska, 1992; Sato, 1980). The KKS, together with the renin-angiotensin system, is involved in the paracrine regulation of spermiogenesis at the testicular level, supported by the identification of renin and angiotensinogens in seminal plasma (Schill and Miska, 1992). Altogether, the experimental and clinical data suggest an intrinsic role of KKS in regulating spermatogenesis and sperm metabolism. Considering the regulatory role of KKS in reproduction, the variant in the *SERPING1* gene might confer a reproductive advantage during spermatogenesis to wild-type male spermatids.

Ours is the second report on transmission discordance in patients with HAE-C1-INH. Bork et al. reported that significantly less male offsprings and more female offsprings inherited the HAE-C1-INH-linked *SERPING1* variant and HAE with normal C1-INH (HAEnCI)-linked *F12*,

Table 1
Inheritance pattern of HAE-C1-INH with *SERPING1* gene variant.

Total offspring			**Total male offspring**			**Total female offspring**		
variant	Wild type	p value	variant	Wild type	p value	variant	Wild type	p value
189 (49 %)	196 (50.9 %)	0.6	99 (44.8 %)	122 (55.2 %)	**0.02**	90 (54.8 %)	74 (45.1 %)	0.07

Paternal Inheritance						**Maternal Inheritance**					
Male offspring			Female offspring			Male offspring			Female offspring		
variant	Wild type	p value	variant	Wild type	p value	variant	Wild type	p value	variant	Wild type	p value
43 (42.1 %)	59 (57.8 %)	**0.02**	43 (53.7 %)	37 (46.2 %)	0.9	56 (47 %)	63 (52.9 %)	0.3	47 (55.9 %)	37 (44 %)	0.1

Chi-square test was used to assess the difference in risk of transmission of the affected variant. A p-value < 0.05 was considered significant.

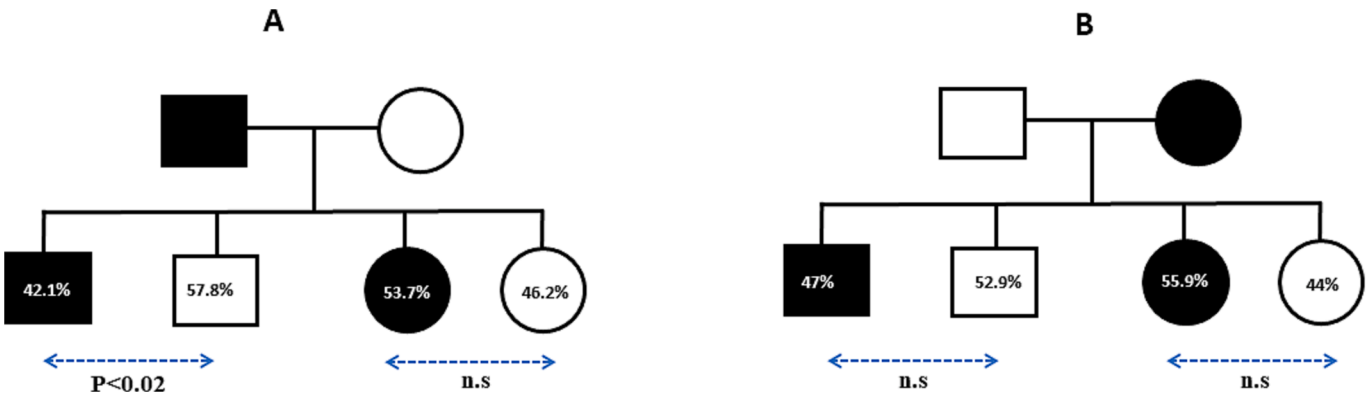

Fig. 1. Paternal (A) and maternal (B) transmission of the *SERPING1* variant to the offspring. Solid circles represent female carriers and solid squares represent male carriers. White circles represent wild type female and white squares represent wild type male. Chi-square test was used to assess the difference in risk of transmission of the affected variant. A p-value < 0.05 was considered significant. Abbreviation: n.s, not significant.

PLG (Plasminogen), *KNG1*(Kininogen 1), and *HS3ST6* (Heparan sulfate glucosamine 3-O-sulfotransferase 6) variants, independent of the sex of the transmitting parent. Because of these observations, authors concluded that pathogenic variants that cause HAE affect the embryogenesis rather than gametogenesis. However, in the present study, transmission discordance was found to be sex-dependent (i.e., father with the *SERPING1* gene variant preferably transmits the wild type allele to the male offspring), suggesting that TRD may possibly occur during spermatogenesis (Bork et al., 2022).

We observed similar TRD in maternal transmission of the *SERPING1* gene variant, although the difference was not significant. The observation in maternal transmission patterns could be attributed to the smaller sample size. Additionally, the differences could also be due to population-specific genetic backgrounds and varied physiological and hormonal influences impacting reproductive processes. The *SERPING1* gene and C1-INH protein may interact uniquely with reproductive biology pathways in different populations. However, validation of these results needs more studies in different populations.

Reports on TRD in humans are scarce, and the mechanism is still elusive. Further studies are required to identify the processes and understand the mechanism of TRD in humans. Apart from HAE, TRD is also reported in a few other autosomal dominant diseases such as long QT syndrome where in the maternal transmission of the long-QT syndrome mutations to daughters was significantly high, and in myotonic dystrophy and spinocerebellar ataxia type 3, where female carriers transmitted the deleterious alleles more often to their offspring (Huang et al., 2013).

To conclude, our results suggest that the transmission pattern of *SERPING1* gene variant favours the transmission of wild-type alleles in males, especially when the father is the carrier. We propose that this could be because of a positive selection of wild-type male spermatids during spermatogenesis. However, further research is needed to understand the mechanisms behind the observed transmission patterns. More data from different populations would be needed for validation of these results. Also, a larger cohort study is needed for a definitive conclusion on the observed TRD in maternal transmission of the *SERPING1* gene variant.

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CRediT authorship contribution statement

Sanghamitra Machhua: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Ankur Kumar Jindal:** . **Suprit Basu:** Writing – original draft, Formal analysis, Data curation. **Isheeta Jangra:** Writing – original draft, Investigation, Formal analysis. **Prabal Barman:** Writing – original draft, Formal analysis, Data curation. **Rahul Tyagi:** Writing – original draft, Investigation, Formal analysis, Data curation. **Archan Sil:** Writing – original draft, Funding acquisition, Formal analysis. **Reva Tyagi:** Writing – original draft, Formal analysis, Data curation. **Anit Kaur:** Writing – review & editing, Supervision, Investigation, Formal analysis, Data curation. **Sanchi Chawla:** Investigation, Formal analysis, Data curation. **Sendhil M. Kumaran:** Writing – review & editing, Supervision, Formal analysis, Data curation. **Sunil Dogra:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Manpreet Dhaliwal:** Writing – review & editing, Investigation, Formal analysis. **Saniya Sharma:** Writing – review & editing, Investigation, Formal analysis. **Amit Rawat:** Writing – review & editing, Supervision, Investigation, Formal analysis, Data curation. **Surjit Singh:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.imbio.2024.152790.

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