Transmission patterns of C1-INH deficiency hereditary angioedema favors a wild-type male offspring

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Key Message : The transmission pattern of *SERPING1* mutation favors the transmission of wild-type alleles in males, especially when the father is the carrier. This could be because of a positive selection of wild-type male spermatids during spermatogenesis. These results will help clinicians provide better counselling to families for the risk of an affected child.

To the Editor,

Hereditary angioedema (HAE) is an uncommon genetic disorder, affecting approximately 1 in 50,000 people. Deficiency in the C1-INH (C1-inhibitor) 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, accounting for approximately 95% of cases. 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 (1,2). Although C1-INH-HAE inheritance follows an autosomal dominant pattern, a higher prevalence in females has often been observed in patients with HAE (3,4). 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 mutation transmission from either parent to their offspring.

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 C1-INH-HAE and a pathogenic variant in the *SERPING1*gene were analysed in detail. A detailed pedigree chart including all possible generations was prepared for all patients. Family members of the index patient, who were symptomatic, were either advised to visit the hospital or were contacted over phone to collect information about all affected relatives. 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 C1-INH-HAE. Results with p-value < 0.05 were considered statistically significant.

In total, 49% (mutant: 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 (mutant: 90/164 vs. wild type: 74/164; p=0.07), while it was inherited by 44.8% of the male offspring (mutant: 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 mutation was statistically significantly skewed, favouring wild-type allele to a male offspring (mutant: 43/102 (42.1%) vs. wild type: 59/102 (57.8%); p=0.02). There was no statistically significant difference during paternal transmission of mutation to a female offspring (mutant: 43/80 (53.7%) vs. wild type: 37/80 (46.2%); p=0.9) or a maternal transmission of mutation to either male (mutant: 56/119 (47%) vs. wild type: 63/119 (52.9%); p=0.3) or female offspring (mutant: 47/84 (55.9%) vs. wild type:37/84 (44%); p=0.1) (Table 1 and Figure 1).

C1-INH-HAE has an autosomal-dominant mode of inheritance (3). Therefore, the likelihood for each offspring to inherit the genetic defect should be ˜50% and should affect both males and females equally (5,6). In our observation from 42 families with genetically proven C1-INH-HAE, the total number of offspring who inherited the*SERPING1* gene mutation 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 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 not significant when father transmitted the mutation to a female offspring or a mother transmitted the mutation to either a male or female offspring. Overall, fewer males and more females inherited the mutation. These results are similar to previous observations of female predominance in HAE (3,4).

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) (5,6). In the present study, TRD was observed when father transmitted the mutation 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 reproductive system and may have an important physiological role (7,8). Rat testicular seminiferous epithelium has been shown to develop and stage-dependently express tissue kallikrein and the bradykinin receptor B2 (B2R) (9). Also, kallikrein activates sertoli cells' function and stimulates spermatocyte production and the incorporation of [3H] thymidine in rat testicular tissue (7). Clinical trials showed that systemic administration of kallikrein increases the number of spermatozoa and sperm motility (7). Bradykinin has been shown to stimulate rat pre-spermatogonia proliferation mediated by the B2R receptor (8). The KKS, together with the renin-angiotensin system is involved in the paracrine regulation of spermiogenesis at the testicular level (7). 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 mutation 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. recently reported that significantly fewer male offspring and more female offspring inherited the *SERPING1* mutation when father was transmitting the defect to their offspring. They suggested the probable selective selection of mutant female embryos and wild-type male embryos during embryogenesis (3). However, our observations suggest that TRD may possibly occur during spermatogenesis.

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 (6).

To conclude, our results suggest that the transmission pattern of *SERPING1* mutation favours the transmission of wild-type alleles in males, especially when the father is the carrier. This could be because of a positive selection of wild-type male spermatids during spermatogenesis. However, further research is needed to fully understand the mechanisms behind these observed patterns. These findings can provide the basis for carrying out studies to identify mechanisms for differential selection and survival of wild-type spermatids (Y) during spermatogenesis and help clinicians provide better counselling to families for the risk of an affected child.

Conflict of interest: None

Keywords: C1-INH-HAE, Inheritance, *SERPING 1* , Autosomal dominant, KKS, TRD

Abbreviation:

C1-INH	C1-inhibitor
HAE	Hereditary angioedema
KKS	kallikrein–kinin system
TRD	transmission ratio distortion

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Figure legends:

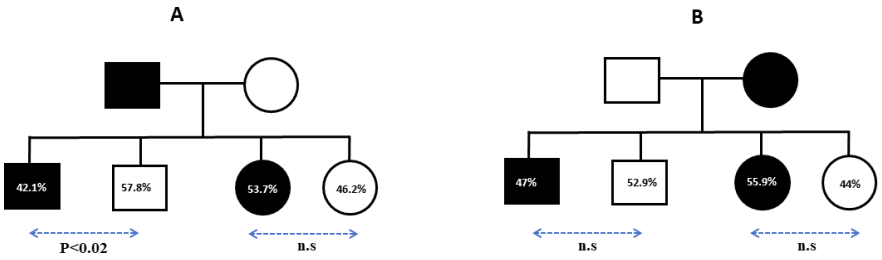
Figure 1 : Paternal (A) and maternal (B) transmission of the*SERPING1* mutation to the offspring. Solid circles represent female carriers and solid squares represent male carriers. White circles represent wild type female and white squares represent wild type male

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

Table legends:

Table 1: Inheritance pattern of HAE-C1-INH with SERPING1 mutation.



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`Table 1.docx` available at https://authorea.com/users/650695/articles/659069-transmission-patterns-of-c1-inh-deficiency-hereditary-angioedema-favors-a-wild-type-male-offspring