Original Article

Inheritance Pattern of Hereditary Angioedema Indicates Mutation-Dependent Selective Effects During Early Embryonic Development

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What is already known about this topic? Apart from indications by previously observed predominance of female carriers of *F12* mutations in a small number of families with hereditary angioedema (HAE) with a specific mutation in the *F12* gene, there was no knowledge that HAE-linked mutations could impact on embryonic development.

What does this article add to our knowledge? We found strong indications for a simultaneous selective advantage of female embryos and disadvantage of male embryos carrying the HAE mutation, with a likely additional loss of at least 20% of males in hereditary angioedema with normal C1-INH.

How does this study impact current management guidelines? The presented data will be valuable for genetic counseling of patients with various types of HAE.

BACKGROUND: Hereditary angioedema (HAE) may be caused by a genetic deficiency of functional C1 inhibitor (C1-INH) or linked with mutations in the *F12, PLG*, and other genes in combination with normal C1-INH (HAEnCI). Although the types of hereditary angioedema due to deficiency of functional C1 inhibitor and HAEnCI are autosomal dominant inherited, there is the impression that in the types of HAEnCI more females carry disease-linked mutations.

OBJECTIVE: The aim of this study was to analyze the passing on of the HAE-specific mutations to the next generations in families with various types of HAE.

METHODS: Methods comprised pedigree analysis, Sanger sequencing analysis, biochemical analysis of parameters of the kallikrein-kinin system, and statistical analysis of the results. We analyzed a total of 1494 offspring of individuals carrying an HAE-linked mutation.

RESULTS: In HAE, less male and more female offspring of mutation carriers than expected for autosomal dominant inheritance inherited the familial mutation. In addition, there were less male offspring than expected in HAEnCI. This was independent of paternal or maternal inheritance.

CONCLUSION: We conclude that there is a sex- and mutation-dependent selection during early embryogenesis, possible around the time of implantation, favoring male wild-type and female mutant embryos. It also appears that 20% to 25% of male embryos carrying the HAE mutation are lost specific in HAEnCI. These findings point out that there is a potentially important role of the kallikrein-kinin system during early embryonic development. © **2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:1029-37)**

Key words: *Angioedema; C1 inhibitor; Embryogenesis; Genetics; Factor XII; Hereditary angioedema; HS3OST6; Inheritance; Kininogen; Plasminogen*

Hereditary angioedema (HAE) is characterized by recurrent and self-limited episodes of localized edema in various organs. Clinical symptoms include skin swellings, abdominal pain attacks, tongue swellings, and potential life-threatening laryngeal attacks. Types of HAE include the classical HAE due to the deficiency of functional C1 inhibitor (HAE-C1-INH) and various new types of HAE without a C1-INH deficiency, that is, HAE with normal or subnormal activity of C1-INH (HAE with normal C1-INH, HAEnCI).[1]

HAE-C1-INH is linked with mutations in the *SERPING1* gene, which is encoding C1 inhibitor, a protease inhibitor that regulates activation of both the complement and contact systems.[2] Mutations result in low levels of functional C1-INH in plasma. During acute swelling attacks, the kallikrein-kinin system (KKS) is activated with the overproduction of the vasoactive

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Abbreviations used

AOS- Angioedema Outpatient Service
ANGPT1- Angiopoietin-1
C1-INH- C1 inhibitor
HAE- Hereditary angioedema
HAE-C1-INH- Hereditary angioedema due to deficiency of functional C1 inhibitor
HAE-FXII- Hereditary angioedema with a specific mutation in the F12 *gene*
HAEnCI- Hereditary angioedema with normal C1-INH
HS3OST6- Heparan sulfate glucosamine 3-O-sulfotransferase 6
KKS- Kallikrein-kinin system
KNG1- Kininogen 1
MYOF- Myoferlin
PLG- Plasminogen

peptide bradykinin.[1] HAE-C1-INH has been described to be inherited autosomal dominant[3,4] and in rare cases autosomal recessive.[5-7]

In families with HAEnCI, various mutations in so far 6 different genes were identified. They comprise (a) 4 different *F12* gene mutations resulting in protein changes of the proline-rich region in the coagulation factor XII (HAE-FXII),[8,9] (b) a mutation in the *PLG* gene encoding plasminogen (HAE-PLG),[10] (c) a mutation in the *ANGPT1* gene encoding angiopoietin-1 (HAE-ANGPT1),[11] (d) a mutation in the *KNG1* gene encoding kininogen 1 (HAE-KNG1) that changes the N-terminal cleavage site of bradykinin in high-molecular-weight kininogen and low-molecular-weight kininogen,[12] (e) a mutation in the *MYOF* gene encoding for myoferlin (HAE-Myoferlin),[13] and (f) a mutation recently identified in the *HS3ST6* gene encoding the heparan sulfate glucosamine 3-O-sulfotransferase 6 (HAE-HS3OST6).[14] There are further HAE families who present with HAEnCI but in whom the genetic cause of the disease is still unknown ("HAE-unknown").[12] For all 6 genes linked with HAEnCI, autosomal dominant inheritance has been described. Up to now 186 families with 452 patients with HAE-FXII and 34 families with 152 patients with HAE-PLG have been reported. For the *HS3OST6*, *MYOF*, and *ANGPT1* genes, 1 family for each has been identified so far.

A clinicogenetic analysis of families with HAE-FXII indicated a significant predominance of female carriers of *F12* mutations compared with male carriers.[15] The aim of the present study was to analyze the transmission of HAE-linked mutations based on pedigree analysis in families with various types of HAE.

METHODS

Probands

Probands of this study comprised patients with HAE-linked mutations in the *SERPING1*, *F12*, *PLG*, *KNG1*, and *HS3OST6* genes and their offspring. All probands came from Angioedema Outpatient Service (AOS) of the Department of Dermatology of the University Medical Center of Mainz, Germany. Mutational status was established by genetic testing. All data including family history were obtained when patients and relatives attended the AOS.

Patient materials and ethics

All subjects analyzed in this study gave written informed consent before participation. The local ethics committee approved the study.

Pedigree analysis

Pedigrees were routinely established when patients attended the AOS for the first time. The pedigrees were routinely checked and supplemented at all following visits. In case further family members attended the AOS, information about the pedigree was confirmed, added, or corrected. To quantify the transmission of the mutation from parents to offspring, we formed 1 or more "small virtual families" from each of the pedigrees. They consisted of mother, father, and offspring. Either the father or the mother carried the mutation. In the offspring, sex (m:f) and carrier status of the mutation (HAE-specific mutation:wild-type) were recorded. All mutation carriers who had 1 or more offspring were included in the analysis and, vice versa, mutation carriers without offspring were excluded. The analysis was performed independent of clinical manifestation of HAE and solely based on the presence of causative HAE mutations.

Sanger sequencing

All mutations have been either identified or verified (in case of prior identification by whole exome sequencing) by Sanger sequencing. Sanger sequencing of HAE-linked mutations in the *SERPING1*, *F12*, *PLG*, *KNG1*, and *HS3OST6* genes was performed as described elsewhere.[10,12,14,15]

Biochemical analysis of C1-INH

C1-INH activity in plasma was determined using the chromogenic substrate C_2H_5CO-Lys(ε-Cbo)-Gly-Arg-pNA (Technochrom C1-Inhibitor; Technoclone, Vienna, Austria). Plasma levels of C1-INH antigen and C4 antigen were assayed by radial immunodiffusion (NOR Partigen C1-INH and C4; Siemens Healthcare Diagnostics, Marburg, Germany).

Reference population

As reference population for the percentage of male/female births the total birth numbers in Germany from 1950 to 2020 have been used. Data are publicly available at the German Federal Office of Statistics (Statistisches Bundesamt; https://www-genesis.destatis.de/genesis//online?operation=table&code=12612-0001&bypass=true&levelindex=1&levelid=1626161594945#abreadcrumb).

Statistics

To determine statistical significance a proportion test was performed. Reference values were either the male/female birth rate based on the total births in Germany (between 1950 and 2020) or the expected inheritance of autosomal dominant mutations (50% likelihood for each offspring to inherit the mutation). Significant *P* values are displayed in the respective figures.

RESULTS

In this study, HAE-C1-INH, HAE-FXII, HAE-PLG, HAE-KNG1, and HAE-HS3OST6 were included. HAE-ANGPT1 and HAE-Myoferlin were excluded because the HAE patient series of our AOS did not contain those HAE types. Moreover, HAE-unknown was excluded because the genetic cause is unknown. A total of 256 families with HAE and known HAE-linked familial mutations were examined (Table I). The majority of families (201 of 256) were families with patients with HAE-C1-INH; the remaining families (55 of 256) were families with HAE with normal C1-INH (without C1-INH deficiency). Among them, there were 30 families with HAE-FXII, 23 with HAE-PLG, 1 with HAE-KNG1, and 1 with HAE-HS3OST6. The total number of parents carrying a known HAE mutation

TABLE I. Genetically defined types of hereditary angioedema and number of families and offspring of mutation carriers investigated in this study

HAE type	Gene	Genomic location	First description	Families (n)	Offspring of mutation carrier (n)
HAE-C1-INH	*SERPING1*	11q12.1	Stoppa-Lyonnet et al[3]	201	1102
HAEnCI-all	↓	↓	↓	55	392
HAE-FXII	*F12*	5q35.3	Dewald and Bork[8]	30	164
HAE-PLG	*PLG*	6q26	Bork et al[10]	23	211
HAE-KNG1	*KNG1*	3q27.3	Bork et al[12]	1	10
HAE-HS3OST6	*HS3ST6*	16p13.3	Bork et al[14]	1	7
Total				256	1494

HAE, Hereditary angioedema; *HAE-C1-INH*, hereditary angioedema due to deficiency of functional C1 inhibitor; *HAE-FXII*, hereditary angioedema with a specific mutation in the *F12* gene; *HAEnCI*, hereditary angioedema with normal C1-INH; *HS3OST6*, heparan sulfate-glucosamine 3-O-sulfotransferase 6; *KNG1*, kininogen 1; *PLG*, plasminogen.

TABLE II. Mutational status of investigated individuals based on sex and inheritance

	Paternal inheritance						Maternal inheritance					
	Male offspring			Female offspring			Male offspring			Female offspring		
HAE type	Total	Carrier	No carrier	Total	Carrier	no Carrier	Total	Carrier	No carrier	Total	Carrier	No carrier
HAE-C1-INH	277	126	151	263	150	113	282	134	148	280	147	133
HAEnCI-all	47	13	34	55	34	21	130	41	89	160	101	59
HAE-FXII	13	4	9	23	14	9	56	14	42	72	49	23
HAE-PLG	34	9	25	32	20	12	66	26	40	79	46	33
HAE-KNG1	0	0	0	0	0	0	4	1	3	6	3	3
HAE-HS3OST6	0	0	0	0	0	0	4	0	4	3	3	0

HAE-C1-INH, Hereditary angioedema due to deficiency of functional C1 inhibitor; *HAE-FXII*, hereditary angioedema with a specific mutation in the *F12* gene; *HAEnCI*, hereditary angioedema with normal C1-INH; *HS3OST6*, heparan sulfate-glucosamine 3-O-sulfotransferase 6; *KNG1*, kininogen 1; *PLG*, plasminogen.

TABLE III. Percentage of male and female offspring compared with expected values

	Expectation				Observation				
	Male offspring		Female offspring		Male offspring		Female offspring		
HAE type	n	%	n	%	n	%	n	%	*P*
HAE-C1-INH	566	51	536	49	559	51	543	49	.654
HAEnCI-all	201	51	191	49	177	45	215	55	.013
HAE-FXII	84	51	80	49	69	42	95	58	.017
HAE-PLG	108	51	103	49	100	47	111	53	.244
HAE-KNG1	5	51	5	49	4	40	6	60	.471
HAE-HS3OST6	4	51	3	49	4	57	3	43	.761

HAE-C1-INH, Hereditary angioedema due to deficiency of functional C1 inhibitor; *HAEnCI*, hereditary angioedema with normal C1-INH; *HAE-FXII*, hereditary angioedema with a specific mutation in the *F12* gene; *PLG*, plasminogen; *KNG1*, kininogen 1; *HS3OST6*, heparan sulfate-glucosamine 3-O-sulfotransferase 6.

was 993; they had a total number of 1494 offspring (Table I). These offspring were analyzed for their sex and inheritance of the familial HAE mutation. Furthermore, the sex of the parent carrying the HAE mutation was taken into account (Table II). For all data we summed up all HAEnCI families (HAEnCI-all) as well as looking at them for each gene (HAE-FXII, HAE-PLG, HAE-KNG1, and HAE-HS3OST6).

Sex of offspring in various types of HAE

Total birth numbers in Germany from 1950 to 2020 show a relative consistent percentage of 51.4% male births and 48.6% female births (standard deviation 0.1). These values were taken as expected value for the sex of the offspring within the HAE families investigated. For HAE-C1-INH, 51.3% male birth did not differ significantly from the expected distribution (Table III, Figure 1, *A*), but for HAEnCI-all with only 45.1% male births, there was a significant difference to the expected values ($P < .05$) (Table III, Figure 2, *A*).

Looking in detail at the individual genes mutated in HAEnCI the lower-than-expected male birth rate was repeated for all genes (Table III). In HAE-FXII, this was significant (42.1%; $P < .05$) and independent of the sex of the transmitting parent (Figure 3, *A*). In HAE-PLG, the trend was the same for total numbers (47.4%), but paternal inheritance was not following this trend (Figure 4, *A*). In HAE-KNG1 (40%) and HAE-HS3OST6 (57.1%), the number of offspring was too low to be informative (Table III).

Inheritance of HAE-linked mutations

The inheritance pattern of all investigated families was consistent with autosomal dominant inheritance. Therefore, the likelihood for each offspring to inherit the mutation should be 50%. For HAE-C1-INH, the total numbers showed values very

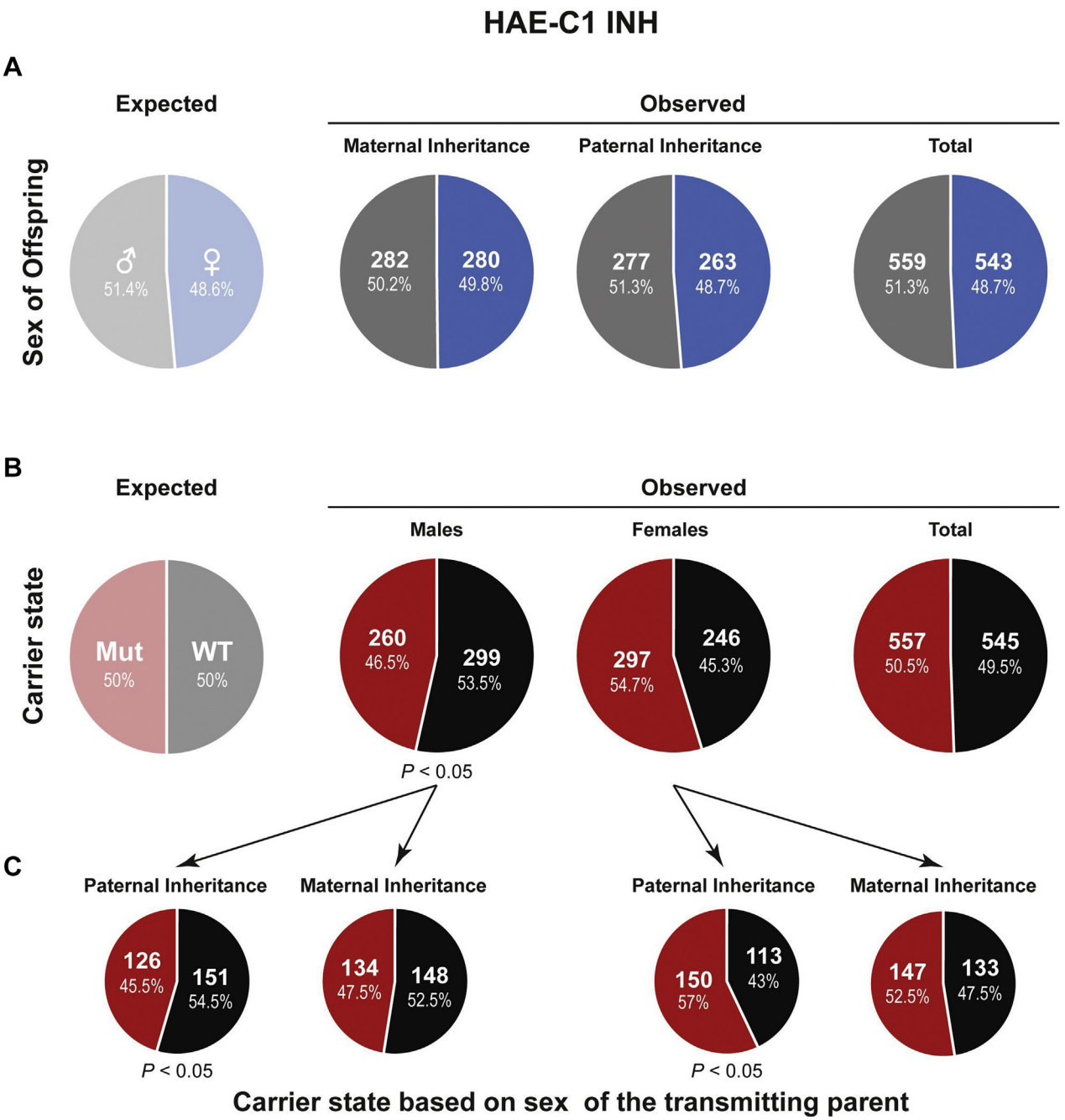

FIGURE 1. Inheritance of hereditary angioedema due to deficiency of functional C1 inhibitor (HAE-C1-INH)-linked *SERPING1* mutations: (**A**) numbers and percentage of male and female offspring of mutation carriers (total and based on the sex of the mutation-carrying parent), (**B**) transmission of the HAE-linked mutation (total and based on the sex of the offspring), and (**C**) transmission based on the sex of the mutation-carrying parent. *WT,* Wild-type.

close to the expectation: 50.5% of all offspring inherited the mutation. But looking at the distribution of mutation carriers regarding sex there were deviations from the expectation: 54.7% ($P < .07$) of all female offspring and only 46.5% ($P < .05$) of all male offspring inherited the HAE-linked *SERPING1* mutation (Table IV, Figure 1, *B*).

Taking all known HAEnCI mutations as a single group, the numbers for all offspring independent of their sex showed slightly less events where the mutation was passed on to the offspring than expected (48.2%). Looking at the inheritance depending on the sex of the offspring there were, similar to HAE-C1-INH, also deviations from the expected values. Although 62.8% ($P < .001$) of all female offspring inherited the HAE-linked mutation, this happened for only 30.5% ($P < .001$) of all male offspring (Table IV, Figure 2, *B*).

Taking the various individual genes mutated in HAEnCI as separate groups, similar patterns could be observed for all genes examined. *F12* mutations were passed on to a total of 49.4% of all

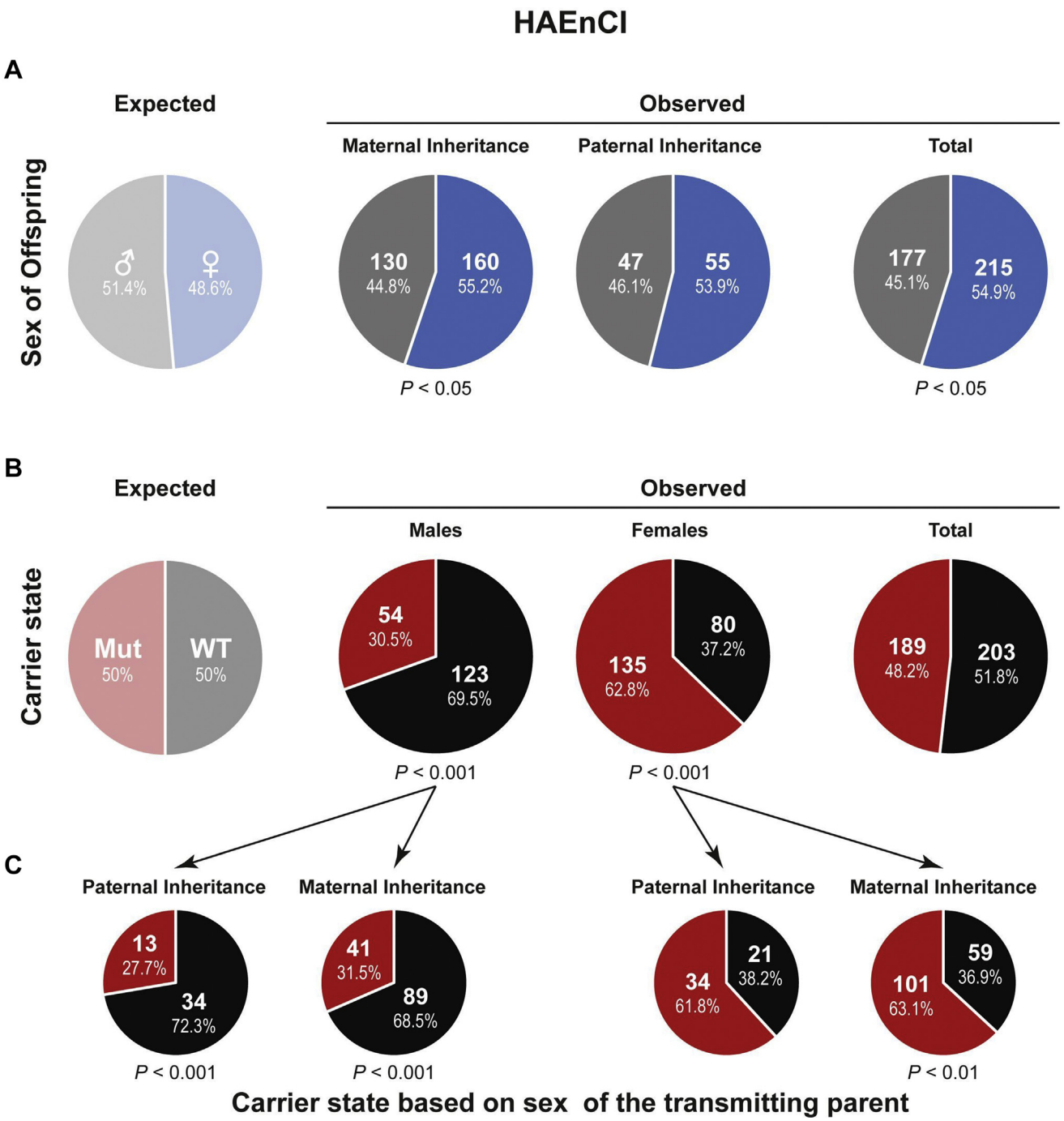

FIGURE 2. Inheritance of the hereditary angioedema with normal C1 inhibitor (HAEnCl)-linked mutations (*F12*, *PLG*, *KNG1*, and *HS3ST6*): (**A**) numbers and percentage of male and female offspring of mutation carriers (total and based on the sex of the mutation-carrying parent), (**B**) transmission of the HAE-linked mutations (total and based on the sex of the offspring), and (**C**) transmission based on the sex of the mutation-carrying parent. *WT*, Wild-type.

offspring, but there were substantial deviations when looking at transmission in males and females with 66.3% ($P < .01$) of the females and only 26.1% ($P < .001$) of the males inheriting the HAE-linked mutation (Table IV, Figure 3, *B*). For *PLG* mutations, a total of 47.9% of all offspring inherited the mutation, with transmission in 59.5% ($P < .05$) of the females and 35.0% ($P < .001$) of the males (Table IV, Figure 4, *B*). In HAE-KNG1 and HAE-HS3OST6, the number of offspring was too low for statistical analysis, but a similar trend could be observed. For the *KNG1* mutation, 1 of 4 males and 3 of 6 females inherited the mutation. The *HS3ST6* mutation was inherited by 3 females but none of the 4 males (Table IV).

The sex of the parent transmitting the HAE mutation did not have considerable influence on the percentage of offspring

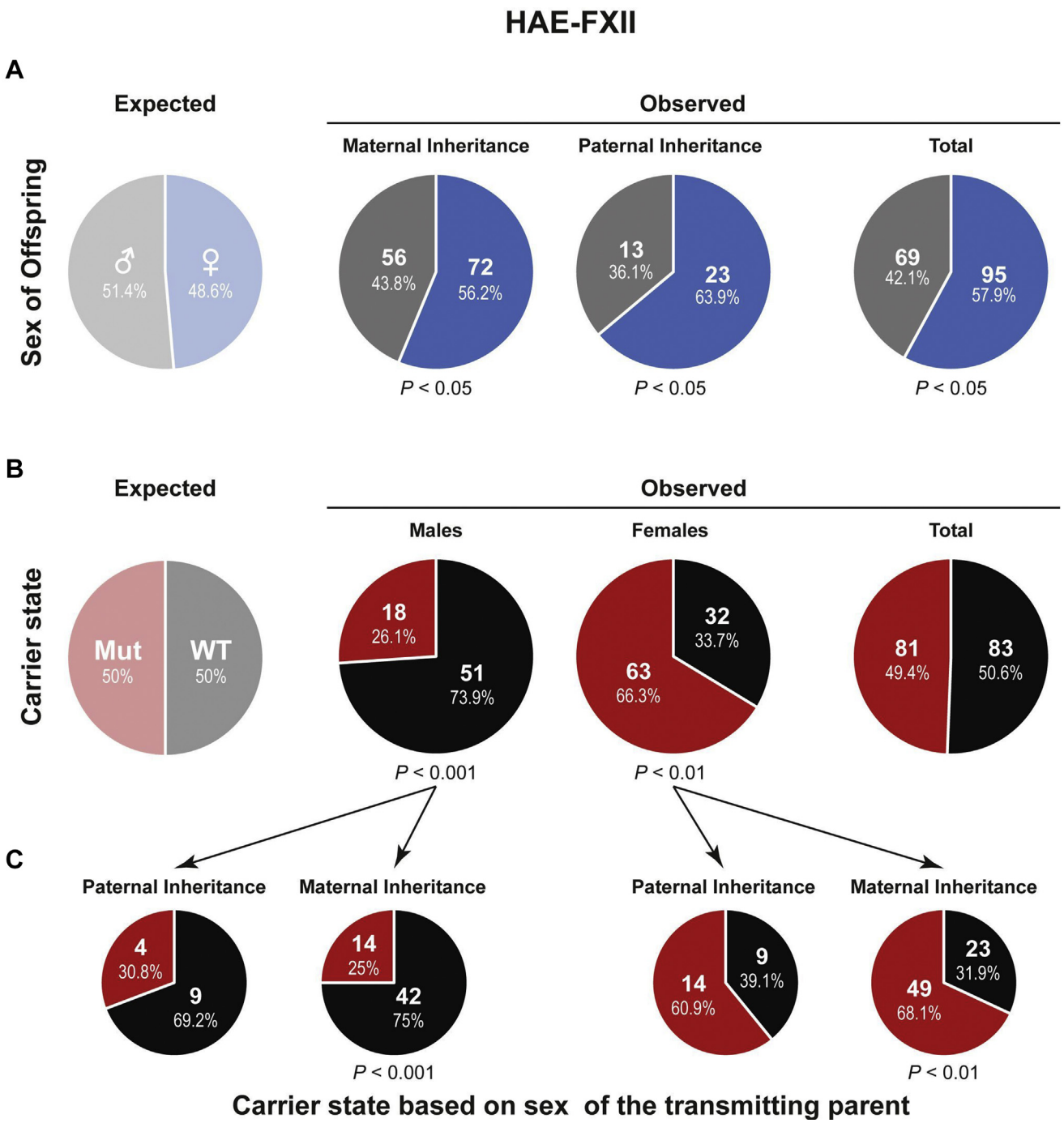

FIGURE 3. Inheritance of hereditary angioedema (HAE)-linked *F12* mutations in HAE with a specific mutation in the *F12* gene (HAE-FXII): (**A**) numbers and percentage of male and female offspring of mutation carriers (total and based on the sex of the mutation-carrying parent), (**B**) transmission of the HAE-FXII-linked mutation (total and based on the sex of the offspring), and (**C**) transmission based on the sex of the mutation-carrying parent. *WT,* Wild-type.

inheriting the mutation; the patterns were similar independent of maternal or paternal transmission (Figures 1, *C*, 2, *C*, 3, *C*, and 4, *C*).

Miscarriages

Patients did not report about an increased number of miscarriages, with 1 exception: 1 woman had HAE-HS3OST6 and 5 spontaneous abortions between the seventh week and sixth month of pregnancy.[14]

DISCUSSION

Here we report on the influence of HAE-linked mutations on embryologic development. Previous studies discussed the link

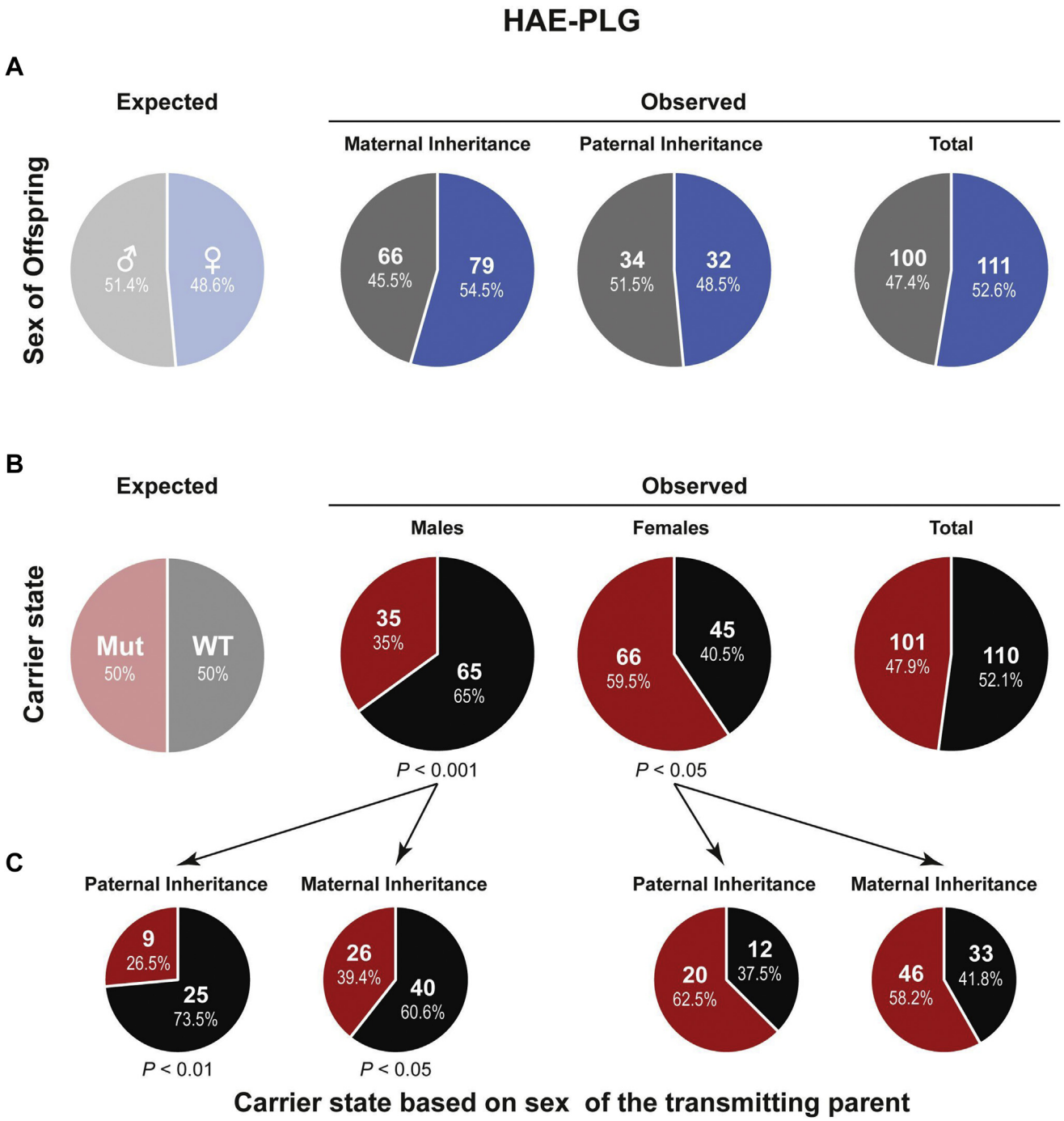

FIGURE 4. Inheritance of the hereditary angioedema (HAE)-linked mutation in HAE-PLG: (**A**) numbers and percentage of male and female offspring of mutation carriers (total and based on the sex of the mutation-carrying parent), (**B**) transmission of the HAE-linked mutation (total and based on the sex of the offspring), and (**C**) transmission based on the sex of the mutation-carrying parent. *PLG*, Plasminogen; *WT*, wild-type.

between bradykinin/KKS to nephron differentiation, neuronal differentiation, and placental development, but not the specific HAE genes.[16-18]

Clinically, HAE mutations do not cause angioedema in all individuals carrying the mutation. To exclude any effects due to incomplete penetrance or other effects such as age of onset of clinical symptoms, symptomatic versus asymptomatic individuals, or various trigger factors, we focused for this analysis solely on genetics. All families examined showed an autosomal dominant inheritance of the respective HAE-linked mutation; 1 mutated allele was sufficient to cause the disease. Possible cases of incomplete penetrance might make it complicated to draw conclusions in individual cases, but in this study, there were either additional family members confirming the autosomal dominant inheritance

TABLE IV. Percentage of mutation carriers based on sex compared with expected values

	Expectation				Observation					
	Male offspring		Female offspring		Male offspring			Female offspring		
HAE type	n	%	n	%	n	%	*P*	n	%	*P*
HAE-C1 INH	280	50	272	50	260	47	.01	297	55	.062
HAEnCI-all	89	50	108	50	54	31	1.4×10^{-8}	135	63	4.2×10^{-4}
HAE-FXII	35	50	48	50	18	26	1.3×10^{-5}	63	66	.002
HAE-PLG	50	50	56	50	35	35	5.2×10^{-4}	66	59	.045
HAE-KNG1	2	50	3	50	1	25	.145	3	50	.527
HAE-HS3OST6	2	50	2	50	0	0	.02	3	100	.046

HAE-C1-INH, Hereditary angioedema due to deficiency of functional C1 inhibitor; *HAEnCI*, hereditary angioedema with normal C1-INH; *HAE-FXII*, hereditary angioedema with a specific mutation in the *F12* gene; *PLG*, plasminogen; *KNG1*, kininogen 1; *HS3OST6*, heparan sulfate-glucosamine 3-O-sulfotransferase 6.

or the same mutation was identified in other families with a clear autosomal dominant inheritance pattern. Considering the gender of the offspring in general, HAE-C1-INH was within normal limits regarding the frequency of males and females born—it was very close to the values in the reference population. However, looking at the frequency of the transmission of the familial mutation, values deviated from the expected values. Although the total numbers (for all offspring) did come close to the 50% (which are expected for autosomal dominant inheritance), the situation looked different when differentiating between male and female offspring. Significantly less males and more females than expected (close to significance) inherited the mutation independently of the sex of the parent transmitting the mutation.

In HAEnCI, we found significantly less male offspring of mutation carriers than expected. The transmission of the mutation was affected, too. Similar to HAE-C1-INH, less males and significantly more females than expected inherited the mutation. This imbalance was more pronounced than in HAE-C1-INH and far stronger in males with less than a third of them inheriting the mutation. Considering that there were less male offspring and less transmissions of the HAE mutation to male offspring in HAEnCI, it appears likely that there is an additional factor influencing inheritance here. Although the selection favors mutant female and wild-type male embryos (or disfavors wild-type female and mutant male embryos), it appears that additionally approximately 20% to 25% of male embryos carrying the mutation do not develop in HAEnCI. These effects were similar for all genes investigated in HAEnCI. Again, this was independent of the sex of the parent transmitting the mutation. It is noteworthy that the same trend can be observed in the published pedigrees for the *MYOF* and *ANGPT1* mutations.[11,13]

As the sex of the parent transmitting the mutation did not result in different inheritance patterns, we concluded that the impact of the HAE mutations is not happening during gametogenesis, but rather during embryogenesis. This is raising a question of an increased number of miscarriages. In patients with HAE-C1-INH, the number of spontaneous abortions (miscarriages) was not increased,[19-23] and an increased number of spontaneous abortions has not been reported in HAEnCI, with 1 exception: a recently described woman with 5 spontaneous abortions and no birth of a healthy child.[14] Thus, it appears likely that the selection happens during early embryogenesis. This could have been unnoticed by the patients because it has been reported that generally approximately 10% to 20% of pregnancies in the European population remain unnoticed due to early miscarriages.[22] We cannot exclude a recall bias for miscarriages but believe that spontaneous abortions during a later point in time of pregnancy would have been noticed. Supportive of a selection during early embryogenesis is a research report concluding that the KKS is active during the decidualization of endometrial stroma cells, which is a prerequisite for the implantation of human embryos.[24] Furthermore, the presence of FXII protein in endometrial stroma cells could be confirmed after *in vitro* decidualization.[24] Additional hints of an important function of the KKS during early embryo development are that *SERPING1* has been found to be downregulated in endometrial samples of women with unexplained recurrent miscarriages,[25] and *KNG1* has been found to be expressed and upregulated during early pregnancy in the equine endometrium.[26]

Considering the differences observed between HAE-C1-INH and HAEnCI, and even the differences within HAEnCI, it cannot be excluded that the mutated proteins contribute via a KKS-independent function to the embryonal selection observed. For example, plasmin has been indirectly implicated in downstream functional effects of transforming growth factor β and fibroblast growth factor-2, which are both involved in embryogenesis.[27]

Why the sex of the embryo appears to be a factor here remains unclear, but it has been shown that the sex of mouse embryos can have an impact during decidualization when knocking down the forkhead box A2 protein.[28]

In conclusion, the present study strongly suggests that there is a selection in HAE during early embryogenesis that simultaneously favors female embryos and disfavors male embryos carrying an HAE mutation. Despite this being balanced out in total numbers, it appears that it leads to an additional loss of 20% to 25% of male embryos carrying the mutation in HAEnCI. This selection is likely to happen around the time of implantation. It will be of interest to investigate the role of the KKS and the role of the sex of the embryos during this phase of development.

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