

Representation of Women Among Individuals With Mild Variants in *ABCA4*-Associated Retinopathy

A Meta-Analysis

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[+ Supplemental content](#)

IMPORTANCE Previous studies indicated that female sex might be a modifier in Stargardt disease, which is an *ABCA4*-associated retinopathy.

OBJECTIVE To investigate whether women are overrepresented among individuals with *ABCA4*-associated retinopathy who are carrying at least 1 mild allele or carrying nonmild alleles.

DATA SOURCES Literature data, data from 2 European centers, and a new study. Data from a Radboudumc database and from the Rotterdam Eye Hospital were used for exploratory hypothesis testing.

STUDY SELECTION Studies investigating the sex ratio in individuals with *ABCA4*-AR and data from centers that collected *ABCA4* variant and sex data. The literature search was performed on February 1, 2023; data from the centers were from before 2023.

DATA EXTRACTION AND SYNTHESIS Random-effects meta-analyses were conducted to test whether the proportions of women among individuals with *ABCA4*-associated retinopathy with mild and nonmild variants differed from 0.5, including subgroup analyses for mild alleles. Sensitivity analyses were performed excluding data with possibly incomplete variant identification. χ^2 Tests were conducted to compare the proportions of women in adult-onset autosomal non-*ABCA4*-associated retinopathy and adult-onset *ABCA4*-associated retinopathy and to investigate if women with suspected *ABCA4*-associated retinopathy are more likely to obtain a genetic diagnosis. Data analyses were performed from March to October 2023.

MAIN OUTCOMES AND MEASURES Proportion of women per *ABCA4*-associated retinopathy group. The exploratory testing included sex ratio comparisons for individuals with *ABCA4*-associated retinopathy vs those with other autosomal retinopathies and for individuals with *ABCA4*-associated retinopathy who underwent genetic testing vs those who did not.

RESULTS Women were significantly overrepresented in the mild variant group (proportion, 0.59; 95% CI, 0.56-0.62; $P < .001$) but not in the nonmild variant group (proportion, 0.50; 95% CI, 0.46-0.54; $P = .89$). Sensitivity analyses confirmed these results. Subgroup analyses on mild variants showed differences in the proportions of women. Furthermore, in the Radboudumc database, the proportion of adult women among individuals with *ABCA4*-associated retinopathy ($652/1154 = 0.56$) was 0.10 (95% CI, 0.05-0.15) higher than among individuals with other retinopathies ($280/602 = 0.47$).

CONCLUSIONS AND RELEVANCE This meta-analysis supports the likelihood that sex is a modifier in developing *ABCA4*-associated retinopathy for individuals with a mild *ABCA4* allele. This finding may be relevant for prognosis predictions and recurrence risks for individuals with *ABCA4*-associated retinopathy. Future studies should further investigate whether the overrepresentation of women is caused by differences in the disease mechanism, by differences in health care-seeking behavior, or by health care discrimination between women and men with *ABCA4*-AR.

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The inherited retinal degeneration Stargardt disease (STGD1) is caused by biallelic pathogenic variants in *ABCA4*. Its clinical hallmarks are macular degeneration, fundus flecks, and peripapillary sparing of the retina.¹ The disease has a highly variable onset but typically starts in the second decade of life.² Individuals with early- or late-onset retinopathy may not show all clinical hallmarks, and therefore the entire disease spectrum is described as *ABCA4*-associated retinopathy (*ABCA4*-AR). *ABCA4*-AR is the most frequent heritable macular dystrophy.

ABCA4-AR is caused by the disrupted function of the *ABCA4* protein that normally reduces the number of cytotoxic molecules in photoreceptors and the retinal pigment epithelium. The combined severity of genetic variants, categorized as mild, moderately severe, and severe, relate to a more severe phenotype of *ABCA4*-AR, ranging from early-onset STGD1 and panretinal cone-rod dystrophy to intermediate and late-onset STGD1 (Figure 1A).^{3,4} Two mild variants usually do not cause *ABCA4*-AR.³

However, this *ABCA4* genotype-phenotype model does not predict the penetrance of disease. The mild variant c.5603A>T⁵ has an allele frequency indicating that in the general population, only about 5% of people carrying this variant with a severe pathogenic variant in trans can be affected. Siblings with c.5603A>T and a same second *ABCA4* variant have shown a difference of multiple decades in disease onset as well as discordance in disease penetrance, where men seem to be less (severely) affected.⁶ Follow-up studies also indicate reduced penetrance for other mild variants.^{4,7} Apart from reduced penetrance of variants that are present in biallelic individuals in whom disease is expected, the opposite has also been observed: individuals with an STGD1-like phenotype who have 2 mild variants.⁸⁻¹¹ These examples indicate that *ABCA4*-AR is possibly multifactorial: modifiers could impact the onset and severity of the disease.

Key Points

Question Are women overrepresented among different groups of *ABCA4*-associated retinopathy?

Findings In this meta-analysis including 6 cohorts and 3154 individuals, a significant overrepresentation of women was observed among individuals with *ABCA4*-associated retinopathy carrying a mild variant with reduced penetrance, but not among individuals with *ABCA4*-associated retinopathy without such a variant.

Meaning These findings indicate that among individuals with *ABCA4*-associated retinopathy carrying a mild *ABCA4* variant with reduced penetrance, sex is likely a modifying factor in developing *ABCA4*-associated retinopathy or in presenting to the clinic.

In 2020, Runhart et al⁷ found that the ratio of women to men with biallelic *ABCA4* variants who carry a noncomplex mild reduced penetrant (mild_rp) variant is higher compared with the ratio in patients carrying 2 nonmild variants, where the ratio equaled 1. Later, Lee et al¹² could not replicate these findings, reporting more women in both groups. Similar to the findings of Runhart et al,⁷ multiple studies examining more than 75 individuals with *ABCA4*-AR reported a higher number of women among individuals carrying *ABCA4* variants, while only 1 such study reported more men and 1 study reported approximately the same numbers of men and women.²

Overall, these studies might indicate that more women are affected by *ABCA4*-AR than men and that this difference is larger in the group of affected individuals with a mild_rp *ABCA4* variant. In the present study, meta-analyses were performed with published data^{7,12,13} and 3 novel datasets to further investigate whether women are overrepresented among individuals with *ABCA4*-AR who carry a known mild_rp variant as

Figure 1. Genotype-Phenotype Model

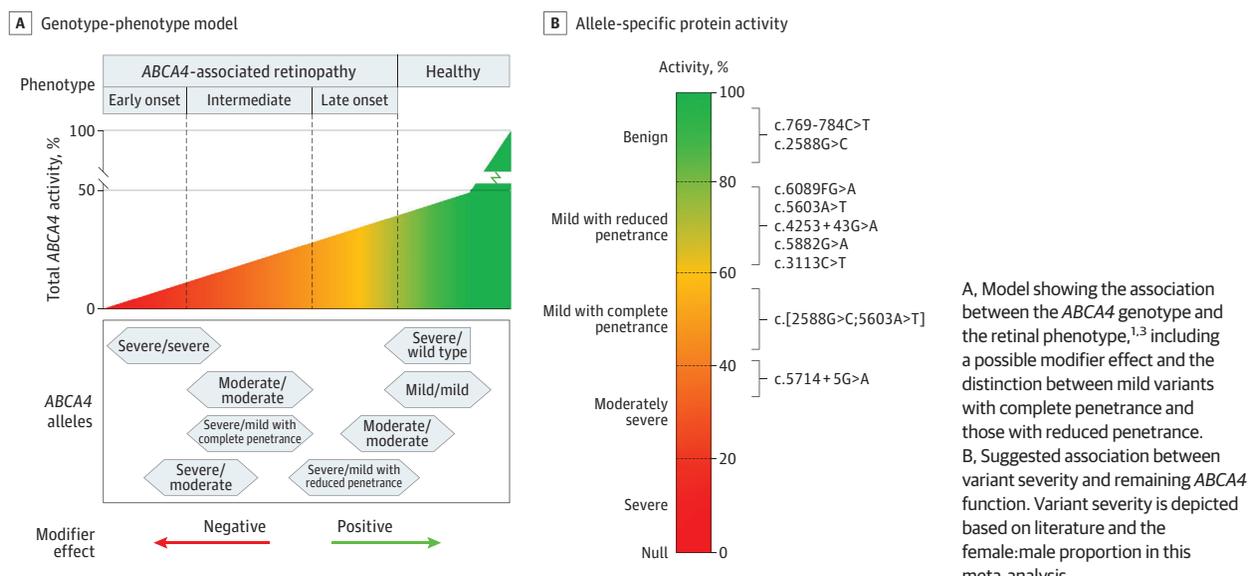


Table. Study Participants From Novel Sources

Allele	Lille University Hospital (scanning)		Lille University Hospital (exon sequencing)		Moorfields Eye Hospital London		Corradi et al, ¹³ (2023)	
	Women	Men	Women	Men	Women	Men	Women	Men
<i>ABCA4</i> mild_rp alleles								
c.2588G>C	7	9	6	5	39	33	NA	NA
c.3113C>T	3	NA	6	6	2	2	1	1
c.4253 + 43G>A	2	NA	10	2	5	2	8	3
c.5603A>T	4	NA	41	17	19	12	25	17
c.5714 + 5G>A	9	8	15	15	20	20	4	2
c.5882G>A	23	21	77	55	92	74	53	36
c.6089G>A	2	2	5	4	13	5	5	NA
c.2588G>C & c.5714 + 5G>A	NA	NA	NA	NA	1	NA	NA	NA
c.3113C>T & c.5714 + 5G>A	NA	NA	NA	NA	NA	1	NA	NA
c.5714 + 5G>A & c.5882G>A	NA	NA	1	NA	NA	NA	NA	NA
c.5714 + 5G>A (homozygous)	NA	NA	NA	NA	1	1	NA	NA
c.5882G>A (homozygous)	NA	1	1	NA	5	2	3	1
Total mild_rp	50	41	162	104	197	152	99	60
<i>ABCA4</i> nonmild alleles								
	88	65	189	190	199	252	57	55

Abbreviations: mild_rp, mild with reduced penetrance; NA, not applicable.

well as among individuals with *ABCA4*-AR who do not carry such a variant.

Methods

Objective

Based on the hypothesis that sex is a modifying factor that impacts all groups of *ABCA4*-AR with a bigger effect in the milder range of the spectrum (Figure 1A), it was investigated whether women are overrepresented in 2 groups of individuals with *ABCA4*-AR: (1) a mild_rp group, individuals with a mild_rp variant, and a (2) nonmild group, individuals without known mild_rp variants.

This meta-analysis followed Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines.¹⁴ Data collection, sequencing methods, variant categorization and statistical analyses are described in the eMethods in Supplement 1 and eTables 4-6 in Supplement 2. In short, variants were categorized as mild as described earlier,⁷ apart from the exclusion of c.769-784C>T, which based on underrepresentation among STGD1 individuals was reclassified as benign (F.P.M. Cremers, unpublished data, April 2023). Additional variants that were suspected to be mild were categorized as uncertain and excluded from the nonmild groups. The literature search was performed on February 1, 2023; data from the centers were from before 2023.

Statistical Analysis

Random-effects meta-analyses were subdivided into main, exploratory, and sensitivity analyses for mild_rp and nonmild groups. Exploratory subgroup analyses were performed for mild_rp variants. In all aforementioned analyses, proportions of women were compared with 0.5. *P* values for the 2 main objectives were considered statistically significant if smaller than .025.

Exploratory analyses were conducted on genetic datasets from Radboudumc and Rotterdam Eye Hospital to compare the proportions of women among adult-onset *ABCA4*-AR vs autosomal (non-*ABCA4*) retinopathies and among adult individuals with a differential diagnosis including STGD1 who were referred for genetic testing vs those not referred for genetic testing.

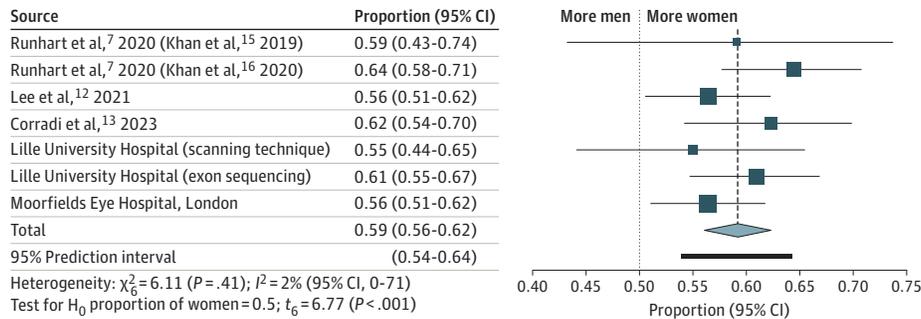
Sensitivity analyses were performed excluding data with possibly incomplete variant identification. χ^2 Tests were conducted to compare the proportions of women in adult-onset autosomal non-*ABCA4*-AR and adult-onset *ABCA4*-AR and to investigate if women with suspected *ABCA4*-AR are more likely to obtain a genetic diagnosis. All meta-analyses were conducted with the statistical software R version 4.1.3 (R Foundation) between March and October 2023, using the inverse variance method within the metaprop function from the meta package version 6.5-0.11-13.

Results

Novel *ABCA4* Variant Data

Data from 244 and 645 individuals with *ABCA4*-AR from scanning and exon-sequencing techniques, respectively, from Lille University Hospital were included in the study, as well as data from 800 individuals from Moorfields Eye Hospital London and 271 individuals described by Corradi et al.¹³ In total, these data included 18 individuals with 2 mild_rp noncomplex variants. Individuals with c.2588G>C without c.5603A>T were mainly reported in the scanning dataset from Lille University Hospital and the Moorfields Eye Hospital London dataset. These datasets likely reported only a few cases with c.5603A>T in cis because the latter variant was long considered benign because of its high frequency. An overview of the data are given in the Table.

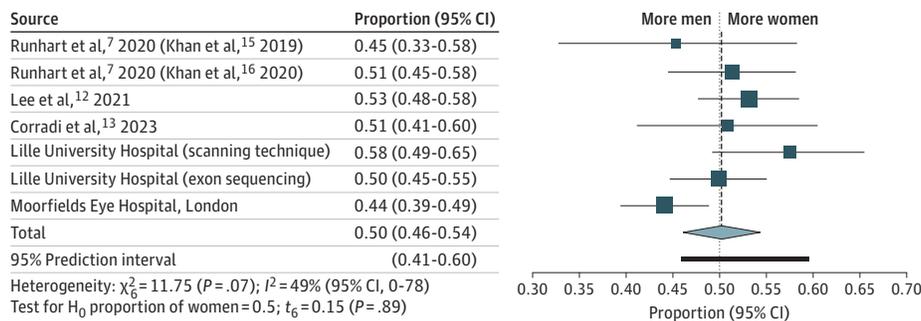
Figure 2. Forest Plot of Proportions of Women Among Individuals With Mild Variants With Reduced Penetrance



Box sizes are proportionate to the number of individuals per study. Data from Khan et al were derived from 2 studies^{15,16} that were taken up separately in this meta-analysis. Data from Lille University Hospital were divided based on the technique used to identify genetic variants. The dashed line indicates the total

proportion of women; diamond, combined estimate of the proportion of women with the 95% confidence interval; black bar, prediction interval of the estimated combined proportion; dotted line, proportion of 0.5, with which the data were compared.

Figure 3. Forest Plot of Proportions of Women Among Individuals With Nonmild Variants



Box sizes are proportionate with the number of individuals per study. Data from Khan et al were derived from 2 studies^{15,16} that were taken up separately in this meta-analysis. Data from Lille University Hospital were divided based on the technique used to identify genetic variants. The dashed line indicates the total

proportion of women; diamond, combined estimate of the proportion of women with the 95% confidence interval; black bar, prediction interval of the estimated combined proportion; dotted line, proportion of 0.5, with which the data were compared.

Proportion of Women in the MildRP and Nonmild Groups

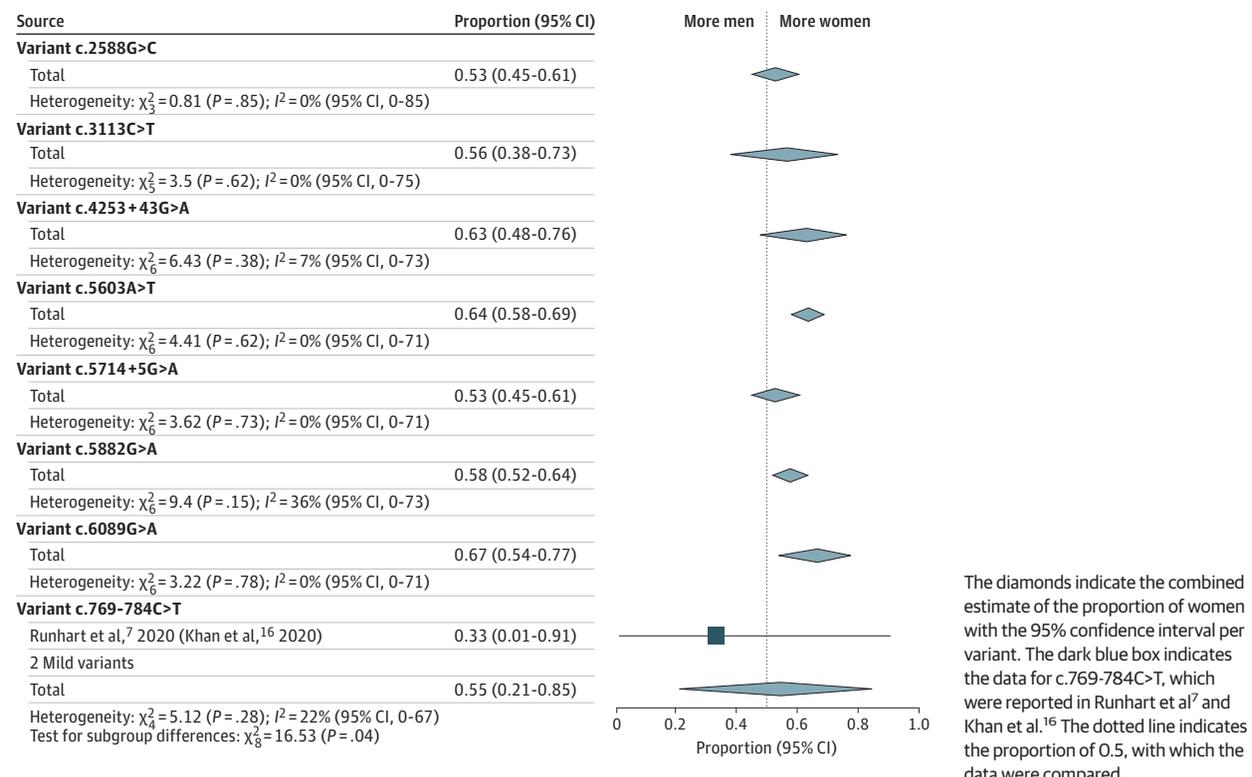
The random-effects meta-analysis on the proportion of women in the mild_rp group shows that the proportion of women in this category is significantly higher than 0.5 (mean proportion, 0.59; 95% CI, 0.56-0.62; 95% prediction interval, 0.54-0.64; $P < .001$) (Figure 2^{15,16} and eTable 2 in Supplement 1), while the proportion of women in the nonmild group was estimated to be 0.50 (95% CI, 0.46-0.54; 95% prediction interval, 0.41-0.60; $P = .89$) (Figure 3^{15,16} and eTable 3 in Supplement 1). The sensitivity analyses show similar results (mean proportion for mild_rp, 0.61; 95% CI, 0.56-0.65; prediction interval, 0.53-0.67; mean proportion for nonmild, 0.51; 95% CI, 0.48-0.54; prediction interval, 0.46-0.56) (eFigures 1 and 2 in Supplement 1), indicating that the main findings are robust. Study differences in proportions of women may be caused by cultural and/or genetic differences.

The exploratory subgroup analyses on the specific mild_rp variants show differences between mild_rp variants (main analysis, Figure 4 and eFigure 3; sensitivity analysis, eFigure 4 in Supplement 1). In the main analysis, variant c.6089G>A had the highest overall proportion of women (0.67; 95% CI,

0.54-0.77). Also c.5603A>T had a high proportion of women (0.64; 95% CI, 0.58-0.69). The variants c.2588G>C and c.5714 + 5G>A showed the lowest overall proportions of women (both 0.53 with 95% CI, 0.45-0.61). Only variants c.5603A>T, c.5882G>A and c.6089G>A excluded the proportion of 0.5 from their 95% confidence intervals.

Genetic Diagnoses in Adult Women and Men With ABCA4-AR and Autosomal Non-ABCA4-AR

Individuals with ABCA4-AR caused by mild_rp variants often experience a later onset of the disease than individuals without mild_rp variants. Therefore, the overrepresentation of women in the mild_rp group might be due to a difference in obtaining a diagnosis as a result of differences in health care-seeking behavior between adult men and women. If this is true, an overrepresentation of women is also expected among adult individuals with other retinopathies. The exploratory hypothesis that the sex ratio in obtaining a genetic diagnosis in adults is different for individuals with ABCA4-AR than for individuals with non-ABCA4-AR was investigated by consulting a genetic inherited retinal disease (IRD) database of the

Figure 4. Summarized Forest Plot of Proportions of Women Among Individuals With Specific Mild Variants With Reduced Penetrance in the Main Analysis

Radboudumc for the number of women and men who are genetically diagnosed with an autosomal form of retinopathy and who had genetic material sent in for testing after their 18th birthdays. The proportion of women (652/1154 = 0.56) among individuals with *ABCA4*-AR, (mean [SD] age, 44.6 [17.0] years) was 0.10 higher (95% CI, 0.05-0.15) than the proportion of women (280/602 = 0.47) among individuals with a retinopathy caused by variants in another autosomal gene (mean [SD] age, 44.3 [14.8] years).

Genetic Diagnoses in Adult Women and Men With a Clinical STGD1 Diagnosis

The exploratory hypothesis that adult women are more likely than men to obtain a genetic diagnosis after having received a clinical diagnosis was tested. The proportion of women in Dutch patients from the Rotterdam Eye Hospital who were given a differential diagnosis including STGD1 at 18 years or older who were sent for genetic testing was compared with the proportion of women in patients who were not sent for genetic testing. The numbers of women and men among adult individuals who did not obtain a genetic diagnosis were 21 and 27, respectively, while among individuals who did obtain a genetic diagnosis, there were 74 women and 58 men. Although 78% of women (for whom testing status was known) had genetic testing vs 68% of men, the proportions of women between the genetically tested (0.56) and not genetically tested (0.44) groups was not different (difference, -0.12; 95% CI, -0.28 to 0.04).

Discussion

In 2020, a sex imbalance between patients with *ABCA4*-AR from multiple countries with mild_rp variants vs those without mild variants was reported.⁷ A later study from the United States could not significantly replicate this imbalance.¹² In this meta-analysis, data from both studies as well as new data from 3 European centers were analyzed to investigate if women are overrepresented among patients with mild_rp variants as well as among patients without known mild variants. The proportion of women was significantly higher than 0.5 among individuals with a mild_rp *ABCA4* variant. This effect was not observed among individuals without a known mild_rp variant.

Previous studies showed no significant difference in the age at onset or best-corrected visual acuity between women and men with the mild variants c.5603A>T or c.5882G>A, respectively. Lee et al¹² suggested that a sex imbalance may therefore not be caused by a difference in the biological disease mechanism between women and men and instead may be explained by a difference in health care-seeking behavior between women and men. Interestingly, when the sex data from adult individuals with an autosomal retinopathy other than *ABCA4*-AR, from an IRD database from Radboudumc, were compared with those with an *ABCA4*-AR, the proportion of women was higher in the group of individuals with *ABCA4*-AR. This suggests that the identified overrepresentation is specific for *ABCA4*-AR and might not be based on sex-specific

health care-seeking behavior, although there might be a discrepancy between seeking health care and obtaining a diagnosis. Sex may therefore be a modifying factor specifically for individuals with mild_rp variants.

Mild Variants

Subgroup analyses show that particularly c.5882G>A, c.5603A>T, and c.6089G>A show a high proportion of women (0.58, 0.64, and 0.67, respectively), of which the confidence intervals do not include 0.5. It may be expected that these proportions would be negatively associated with the estimated reduced penetrance of the variants. However, this does not clearly seem to be the case (eTable 1 in Supplement 1). Nevertheless, the mild_rp variants were placed in the genotype-phenotype model based on the overall proportion of women per variant, where a higher proportion of women is assumed to relate to a smaller negative effect on ABCA4 function (Figure 1B).

The individual mild_rp variants likely result in a spectrum of residual ABCA4 activity and thereby their pathogenic effects. We propose a quantitative model based on remaining ABCA4 activity. This may be true for splice variants resulting in variable proportions of differentially spliced messenger RNA transcripts, but missense variants might exert different spatiotemporal effects in photoreceptor cells and the retinal pigment epithelium (RPE). The variant c.5882G>A has been associated with a specific phenotype, possibly indicating a specific variant effect.¹⁷

Contradictory Findings on Causes of the Observed Sex Imbalance

Retrospective data from Runhart et al⁷ and Lee et al¹² indicate that women with mild_rp variants do not have an earlier onset or a worse visual acuity than men with mild_rp variants. However, in general, women with STGD1 do show an earlier age at onset than men.¹⁸ Furthermore, a Radboudumc genetic IRD database shows a difference between the proportions of women among individuals with ABCA4-AR and among individuals with autosomal retinopathies not associated with ABCA4, suggesting an ABCA4-specific effect.

Biological Sex Differences Possibly Impacting the ABCA4-AR Disease Mechanism

Diseases that are not directly related to sex-specific characteristics can still show differences in prevalence and expression between women and men.¹⁹⁻²¹ Moreover, sex differences in the retina have been observed in humans.²²⁻²⁴ Therefore, possible sex differences should be considered and investigated carefully.

No biological mechanism involved in ABCA4-AR is currently known to be associated with sex. One factor that might be investigated more closely is the effect of high-density lipoprotein (HDL) cholesterol levels, which are higher in women and have been suggested as possible risk factors in age-related macular degeneration.²⁵ These have been localized in the RPE, ganglion cells, and rod photoreceptor cells, suggesting a retina-specific processing and maturation of HDL cholesterol.²⁶ Recently, the lipid profile of the RPE and the

retina in general has been associated with STGD1,^{27,28} further suggesting a possible link between HDL cholesterol and STGD1. Furthermore, mitochondrial function, for which sex differences have been shown and which has been suggested to play a role in diseases that involve the RPE such as STGD1, could be investigated more.^{29,30} Finally, especially among teenagers with STGD1, more girls than boys are observed, which could indicate an association between hormones and disease onset.¹⁸

Behavioral Sex Differences Possibly Impacting Health Care-Seeking Behavior

Lee et al¹² suggest that a possible sex imbalance in STGD1 is likely caused by differences in health care-seeking behavior. Multiple studies indeed report that women are more likely to seek health care.³¹⁻³⁴ However, these studies do not control or barely control for sex-specific health care needs, which have been reported to likely exist³² and may be caused by increased health care needs during and years after fertility treatment and pregnancy,^{35,36} health care related to the menstrual cycle, perimenopause or menopause, and contraception.³⁷⁻⁴⁸ Interestingly, the difference in seeking health care between men and women is absent after the postmenopausal age of 65 years.³³

Apart from sex-specific health care needs, it has also become apparent that women historically have been receiving health care that has been designed for men,⁴⁹⁻⁵² is less effective for women, or may have adverse effects for women,⁵³ which could increase health care need. Moreover, studies show that women are often discriminated against in receiving the right health care, likely increasing the number of necessary visits.^{52,54,55}

Overall, a sex difference in health care-seeking behavior could still exist after correction for the possible increased health care needs of women. Several publications suggest that men may view health care seeking as “less masculine” and avoid health care.⁵⁶⁻⁵⁸ Furthermore, there might also be a sex difference specifically in seeking a genetic diagnosis.

Alternatively, a difference in health care-seeking behavior could be caused by confounding factors associated with sex or gender. Studies show that people with more academic education more often visit a specialist, get a genetic diagnosis, or test for genetic predisposition related to cancer.^{31,59} Therefore, the sex imbalance might partially be explained by factors such as education.

Possible Discrimination Impacting Medical Treatment

The latter study further reports that the type of education does not seem to be associated with an individual's obtaining genetic counseling.⁵⁹ They mention that physicians may refer individuals with certain educational backgrounds more than others, meaning that individuals may be discriminated based on their education.

Because women are reported to have less access to health care and seek less health care in middle- and low-income countries compared with high-income countries,⁶⁰⁻⁶⁴ it should be noted that this meta-analysis contains data from high-income countries. Therefore, if the identified overrepresentation of women in the group with mild_rp variants is caused

by, rather than just associated with, a difference in behavior or treatment, this effect might be specific to high-income countries. More specifically, it might be related to health care access, and possibly related to income, for participating individuals in research studies.

Limitations

With the expectation of modifiers influencing the disease outcome of individuals with *ABCA4*-AR, it was hypothesized that occasionally *ABCA4*-AR is caused by 2 mild_rp variants and, therefore, individuals with 2 mild_rp variants were included in the mild_rp groups. If sex is a modifier, the proportion of women in the group with 2 mild_rp variants might be even higher than among individuals with 1 mild_rp variant. The subgroup analysis results for individuals with 2 mild_rp variants (proportion, 0.55; 95% CI, 0.21-0.85) does not support this theory. However, the subgroup is small (24 patients) and could contain individuals who do not have *ABCA4*-AR as well as individuals in which additional *ABCA4* variants were missed, potentially creating a bias in the group.

Furthermore, the inclusion of c.2588G>C and c.5714 + 5G>A in the mild_rp category may be incorrect. Variant c.2588G>C commonly co-occurs with c.5603A>T. When not in cis with c.5603A>T, it most likely is benign (Z. Corradi, F.P.M. Cremers, unpublished data, 2023). Additionally, c.5714 + 5G>A has been indicated not to be a mild variant⁶⁵ and may reside

at the boundary of the intervals for mild and moderately severe variants (Figure 1B). However, the overall proportion of women in the group of mild_rp variants would be even higher if these variants were not included in this meta-analysis.

Finally, we assume that all individuals in this study are cis-gender and that they are male or female. However, studies indicate that this is not the case for up to 2% of individuals.^{66,67} This could have affected the results, although such an effect would be limited.

Conclusions

This study shows that among individuals with an *ABCA4*-AR diagnosis who are recruited mainly from centers in the United States and western Europe, women are overrepresented in the group of individuals who have a mild_rp allele. Future studies should further investigate whether the overrepresentation of women is caused by differences in the disease mechanism, by differences in health care-seeking behavior, or by health care discrimination between women and men with *ABCA4*-AR. A sex difference in the disease mechanism would mean that women are at an approximately 1.4-fold increased risk of developing *ABCA4*-AR compared with men when they carry a mild_rp variant. This effect could be incorporated in earlier described risk estimates used for genetic counselling.⁶⁸

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