Representation of Women Among Individuals with Mild Variants in *ABCA4*-associated Retinopathy: A Meta-analysis

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Word count: 2922

Revision date: 18 January 2024

Key points

Question

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

Findings

In this meta-analysis of six cohorts including 3,154 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^{rp} *ABCA4* variant, sex is likely a modifying factor in developing *ABCA4*-associated retinopathy or in presenting to the clinic.

Abstract

Importance

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

Objective

To investigate if women are overrepresented among individuals with *ABCA4*-associated retinopathy: (i) carrying at least one mild allele, and (ii) carrying non-mild alleles.

Data Sources

Literature data, data from two 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.

Data Extraction and Synthesis

Random-effects meta-analyses were conducted to test if the proportions of women among individuals with *ABCA4*-associated retinopathy with (i) mild and (ii) non-mild variants differed from 0.5, including subgroup analyses for mild alleles. Sensitivity analyses were performed excluding data with possibly incomplete variant identification. Chi-square 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.

Main Outcomes and Measures

Proportion of women per *ABCA4*-associated retinopathy group. Exploratory: Sex ratio comparisons for individuals with *ABCA4*-AR versus those with other autosomal retinopathies and for individuals with *ABCA4*-associated retinopathy who underwent genetic testing versus those who did not.

Results

Women were significantly overrepresented in the mild variant group (proportion: 0.59, 95% confidence interval [0.56; 0.61], $P < .001$); but not in the non-mild variant group (proportion: 0.50, 95% confidence interval [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 *ABCA4*-associated retinopathy individuals (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 will be relevant for prognosis predictions and recurrence risks of individuals with *ABCA4*-associated retinopathy.

Introduction

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>T,[5] has an allele frequency which indicates that in the general population only ~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 two mild variants.[8-11] These examples indicate that *ABCA4*-AR is possibly multifactorial: modifiers could impact the onset and severity of the disease.

In 2020, Runhart *et al*. found that the ratio of women to men with biallelic *ABCA4* variants who carry a non-complex mild reduced penetrant (mild^{rp}) variant is higher compared to the ratio in patients carrying two non-mild variants, where the ratio equaled one.[7] Later, Lee *et al*. could not replicate these

findings, reporting more women in both groups. Similar to the findings of Runhart *et al*. multiple studies examining >75 individuals with *ABCA4*-AR report a higher number of women among individuals carrying *ABCA4* variants, while only one such study reports more men and one study reports 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, which include published data[7,12,13] and three novel datasets, in order to further investigate if women are overrepresented among individuals with *ABCA4*-AR who carry a known mild^{rp} variant as 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 if women are overrepresented in two groups of individuals with *ABCA4*-AR; (i) mild^{rp} group: individuals with a mild^{rp} variant; (ii) non-mild group: individuals without known mild^{rp} variants.

For this meta-analysis MOOSE guidelines were followed.[14] Data collection, sequencing methods, variant categorization and statistical analyses are described in the eMethods. Variant categorization 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 re-classified as benign (FPM Cremers, unpublished data). Additional variants that were suspected to be mild were categorized as 'uncertain' and excluded from the 'non-mild' groups. Statistics in brief: random effects meta-analyses were subdivided into main and, exploratory, sensitivity analyses for mild^{rp} and non-mild groups. Exploratory subgroup analyses were performed for mild^{rp} variants. In all aforementioned analyses, proportions of women were compared to 0.5. P-values for the two main objectives were considered statistically significant if smaller than 0.025. Exploratory analyses were conducted on genetic datasets from Radboudumc and Rotterdam Eye Hospital to compare the proportions of women among adult onset *ABCA4*-AR versus autosomal (non-*ABCA4*) retinopathies and among adult individuals with a differential diagnosis including STGD1 that were referred for genetic testing versus those not referred for genetic testing.

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 persons from Moorfields Eye Hospital London and 271 individuals described by Corradi *et al*.[13] In total, these data included 18 individuals with two mild^{rp} non-complex 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 due to its high frequency. An overview of the data is given in Table 1.

Proportion of women in the mild^{rp} and non-mild 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 (average proportion 0.59, 95% confidence interval [0.56; 0.62], 95% prediction interval [0.54; 0.64], $P < .001$; Figure 2, eTable 2), while the proportion of women in the non-mild group was estimated to be 0.50 (95% confidence interval [0.46; 54], 95% prediction interval [0.41; 0.60], $P = .89$; Figure 3, eTable 3). The sensitivity analyses show similar results (average proportion for mild^{rp}: 0.61, confidence interval [0.56; 0.65], prediction interval [0.53;0.67]; average proportion for non-mild: 0.51, confidence interval [0.48; 0.54], prediction interval [0.46;0.56]; eFigures 1-2) 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, although these are not significant (main analysis ($P = .04$; Figure 4, eFigure 3; sensitivity analysis ($P = .70$; eFigure 4)). In the main analysis, variant c.6089G>A has the highest overall proportion

of women (0.67 with 95% confidence interval [0.54; 0.77]). Also c.5603A>T has a high proportion of women (0.64 with 95% confidence interval [0.58; 0.69]). The variants c.2588G>C and c.5714+5G>A show the lowest overall proportions of women (both 0.53 with 95% confidence interval [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 healthcare-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*-associated retinopathy was investigated by consulting a genetic IRD database of the 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 an *ABCA4*-AR , (average age 44.6, SD: 17.0 years) was 0.10 higher than the proportion of women (280/602=0.47) among individuals with a retinopathy caused by variants in another autosomal gene (average age 44.3, SD: 14.8 years) (95% CI [0.05;0.15])).

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 that were given a differential diagnosis including STGD1 at the age of 18 years or older who were sent in for genetic testing was compared to the proportion of women in patients who were not sent in for genetic testing. The number of women and men among adult individuals that did not obtain a genetic diagnosis were 21 and 27, respectively, while among individuals that 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 versus 68% of men, the proportions of women between the genetically tested (0.56) and not genetically tested (0.44) groups was not significantly different (difference -0.12, 95% CI [-0.28; 0.04]).

Discussion

In 2020, a sex imbalance between *ABCA4*-AR patients from multiple countries with mild^{rp} variants versus those without mild variants was reported[7]. A later study from the USA could not significantly replicate this imbalance.[12] In this meta-analysis, data from both studies as well as new data from three 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 of onset or best corrected visual acuity between women and men with the mild variants c.5603A>T or c.5882G>A, respectively. Lee *et al*. 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 healthcare-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 to 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 healthcare-seeking behaviour, although there might be a discrepancy between healthcare-seeking 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), of which the confidence intervals do not include 0.5. It may be expected that these proportions would correlate negatively with the estimated reduced penetrance of the variants. However, this does not clearly seem to be the case (eTable 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 mRNA 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.[15]

Contradictory findings on causes of the observed sex imbalance

Retrospective data from Runhart and Lee indicate that women with mild^{rp} variants do not have an earlier onset or a worse visual acuity than men with mild^{rp} variants.[7,12] However, in general women with STGD1 do show an earlier age of onset than men.[16] 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 to *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.[17-19] Moreover, sex differences in the retina have been observed in humans.[20-22] Therefore, possible sex differences should be considered and investigated carefully.

No biological mechanism involved in *ABCA4*-AR is currently known to be associated to sex. One factor that might be investigated more closely is the effect of high-density lipoproteins (HDL) cholesterol

levels, which are higher in women and have been suggested as possible risk factors in age-related macular degeneration.[23] These have been localized in the RPE, ganglion cells and rod photoreceptor cells, suggesting a retina-specific processing and maturation of HDL cholesterol.[24] Recently, the lipid profile of the RPE and the retina in general has been associated with STGD1,[25,26] 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.[27,28] Finally, especially among teenagers with STGD1, more girls than boys are observed, which could indicate a relationship between hormones and disease onset.[16]

Behavioral sex differences possibly impacting healthcare-seeking behavior

Lee *et al*. suggest that a possible sex imbalance in STGD1 is likely caused by differences in healthcare-seeking behaviour.[12] Multiple studies indeed report that women are more likely to seek healthcare.[29-32] However, these studies do not or barely control for sex-specific healthcare needs, which have been reported to likely exist[30] and may be caused by increased healthcare needs during and years after fertility treatment and pregnancy,[33,34] healthcare related to the menstrual cycle, (peri)menopause and contraception.[35-46] Interestingly, the difference in seeking healthcare between men and women is absent after the post-menopausal age of 65[31].

Apart from sex-specific healthcare needs, it has also become apparent that women historically have been receiving healthcare that has been designed for men,[47-50] is less effective for women or may have adverse side effects for women,[51] which could increase healthcare need. Moreover, studies show that women are often discriminated against in receiving the right healthcare, likely increasing the number of necessary visits.[50,52,53]

Overall, a sex difference in healthcare-seeking behavior could still exist after correction for the possible increased healthcare needs of women. Several publications suggest that men may view healthcare

seeking as “less masculine” and avoid healthcare.[54-56] Furthermore, there might also be a sex difference specifically in seeking a genetic diagnosis.

Alternatively, a difference in healthcare seeking behavior could be caused by confounding factors that correlate 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.[29,57] The sex imbalance might therefore, 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.[57] They mention that physicians may refer individuals with certain educational backgrounds more than others, meaning that individuals may be discriminated based on their education.

Since women are reported to have less access to healthcare and seek less healthcare in middle- and low-income countries compared to high-income countries,[58-62] 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 high-income country specific. More specifically, it might be related to healthcare access, possibly related to income, of 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 two mild^{rp} variants and, therefore, individuals with two mild^{rp} variants were included in the mild^{rp} groups. If sex is a modifier, the proportion of women in the group with two mild^{rp} variants might be even higher than among

individuals with one mild^{rp} variant. The subgroup analysis results for individuals with two mild^{rp} variants (proportion 0.55, confidence interval [0.21; 0.85]), does not support this theory. However, the subgroup is small (24 patients) and could contain individuals that do not have *ABCA4*-AR as well as individuals in which additional *ABCA4* variants have been 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). Additionally, c.5714+5G>A has been indicated not to be a mild variant[63] . 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 cisgender and that they are male or female. However, studies indicate that this is not the case for up to 2% of individuals.[64,65] This could have affected the results, although such an effect would be limited.

Conclusions and implications

This study shows that among individuals with an *ABCA4*-AR diagnosis who are recruited mainly from centers in the USA and western Europe, women are overrepresented in the group of individuals that have a mild^{rp} allele. Future studies should further investigate whether the overrepresentation of women is caused by differences in the disease mechanism, in healthcare-seeking behavior or by healthcare 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 to men when they carry a mild^{rp} variant. This effect could be incorporated in earlier described risk estimates used for genetic counselling.[66]

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Conflict of Interest Disclosures

The authors declare no competing interests.

Funding

Studies of Ms Cornelis, Dr. Cremers and Dr. Roosing were funded by the Foundation Fighting Blindness USA, grants BR-GE-0120-0775-LUMC, BR-GE-1018-0738-RAD, PPA-0517-0717-RAD, and by Novartis.

The work of Dr. Roosing was funded by the Foundation Fighting Blindness USA, grant CD-GE-0621-0809-RAD, and PPA-0622-0841-UCL.

The studies of Dr. Hitti-Malin and Dr. Cremers were supported by the HRCI HRB Joint Funding Scheme (2020-007), the Stichting Oogfonds Nederland (UZ 2020-17), Pro Retina Deutschland, Stichting tot Verbetering van het Lot der Blinden, Stichting voor Ooglijders and the Stichting Blindenhulp.

Ms Corradi and Dr. Cremers were supported by European Union's Horizon 2020 research and innovation programme Marie Sklodowska-Curie Innovative Training Networks (ITN) StarT (grant No. 813490).

Dr. Dhaenens was supported by 'Groupement de Coopération Sanitaire Interrégional G4 qui réunit les Centres Hospitaliers Universitaires Amiens, Caen, Lille et Rouen (GCS G4)' and by the Fondation Stargardt France.

Dr. Oldak and Dr. Szaflik from the *ABCA4*-study group were supported by the National Science Center (Poland) grant number N N402 591640 (5916/B/P01/2011/40) (to M.O.).

Data Sharing Statement

The specific combinations of biallelic *ABCA4* variants per patient from the new datasets are available from the corresponding author on request.

Acknowledgements

We thank Charlie Bos for their advice on using inclusive language. The funders had no role in any of the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Prof. Dr. Frans P.M. Cremers had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure 1. Genotype-phenotype model. A. Model showing the relationship between the *ABCA4* genotype and the retinal phenotype[1,3] including a possible modifier effect and the distinction between mild^{cp} and mild^{rp}. B. Suggested relationship between variant severity and remaining ABCA4 function. Variant severity is depicted based on literature and the female:male proportion in this meta-analysis.

Figure 2. Forest plot of proportions of women among individuals with mild^{rp} variants. The x-axis displays the proportion of women. Dark blue boxes indicate the proportion of women per study. The box sizes are proportionate with the number of individuals per study. Horizontal lines indicate the 95% confidence interval per study. The dotted line indicates the total proportion of women. The light blue diamond indicates the combined estimate of the proportion of women with the 95% confidence interval. The red line indicates the prediction interval of the estimated combined proportion.. Data from Runhart *et al*. 2020 were derived from two studies 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 vertical reference line indicates the proportion of 0.5, that the data were compared to.

Figure 3. Forest plot of proportions of women among individuals with non-mild variants. The x-axis displays the proportion of women. Dark blue boxes indicate the proportion of women per study. The box sizes are proportionate with the number of individuals per study. Horizontal lines indicate the 95% confidence interval per study. The dotted line indicates the total proportion of women. The light blue diamond indicates the combined estimate of the proportion of women with the 95% confidence interval. The red line indicates the prediction interval of the estimated combined proportion. Data from Runhart *et al*. 2020 were derived from two studies 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 vertical reference line indicates the proportion of 0.5, that the data were compared to.

Figure 4. Summarized forest plot of proportions of women among individuals with specific mild^{rp} variants in the main analysis. The x-axis displays the proportion of women. The light blue diamonds indicate the combined estimate of the proportion of women with the 95% confidence interval per variant. The dark blue box indicates the data for c.769-784C>T, which were reported in (Runhart *et al.* 2020) only. The vertical reference line indicates the proportion of 0.5, that the data were compared to.

562 **Table 1 Study participants from novel sources**

	Lille University Hospital (Scanning)		**Lille University Hospital (Exon sequencing)**		**Moorfields Eye Hospital London**		**Corradi *et al.* (2023)**	
***ABCA4* mild^{rp} allele**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**
c.2588G>C	7	9	6	5	39	33	-	-
c.3113C>T	3	-	6	6	2	2	1	1
c.4253+43G>A	2	-	10	2	5	2	8	3
c.5603A>T	4	-	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	-
c.2588G>C & c.5714+5G>A	-	-	-	-	1	-	-	-
c.3113C>T & c.5714+5G>A	-	-	-	-	-	1	-	-
c.5714+5G>A & c.5882G>A	-	-	1	-	-	-	-	-
c.5714+5G>A (homozygous)	-	-	-	-	1	1	-	-
c.5882G>A (homozygous)	-	1	1	-	5	2	3	1
Total mild^{rp}	50	41	162	104	197	152	99	60
***ABCA4* non-mild alleles**	88	65	189	190	199	252	57	55

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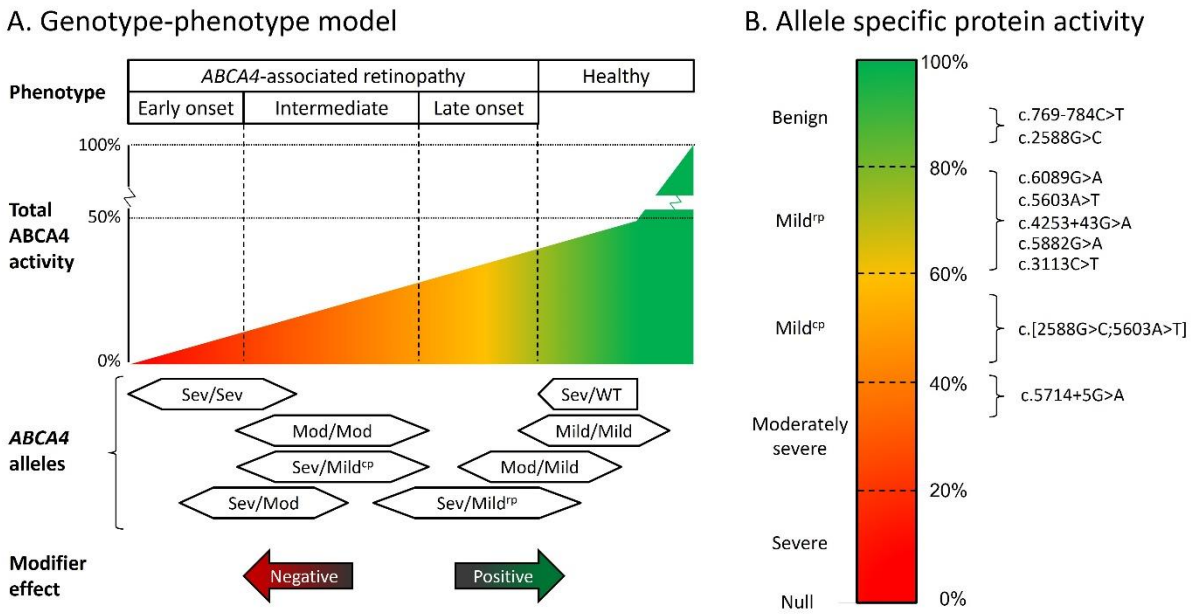

A. Genotype-phenotype model
Phenotype
ABCA4-associated retinopathy
Healthy
Early onset
Intermediate
Late onset
100%
50%
0%
Total ABCA4 activity
ABCA4 alleles
Sev/Sev
Mod/Mod
Sev/Mild^cp
Sev/Mod
Sev/WT
Mild/Mild
Mod/Mild
Sev/Mild^rp
Modifier effect
Negative
Positive
B. Allele specific protein activity
100%
80%
60%
40%
20%
0%
Benign
Mild^rp
Mild^cp
Moderately severe
Severe
Null
c.769-784C>T
c.2588G>C
c.6089G>A
c.5603A>T
c.4253+43G>A
c.5882G>A
c.3113C>T
c.[2588G>C;5603A>T]
c.5714+5G>A

Figure 1

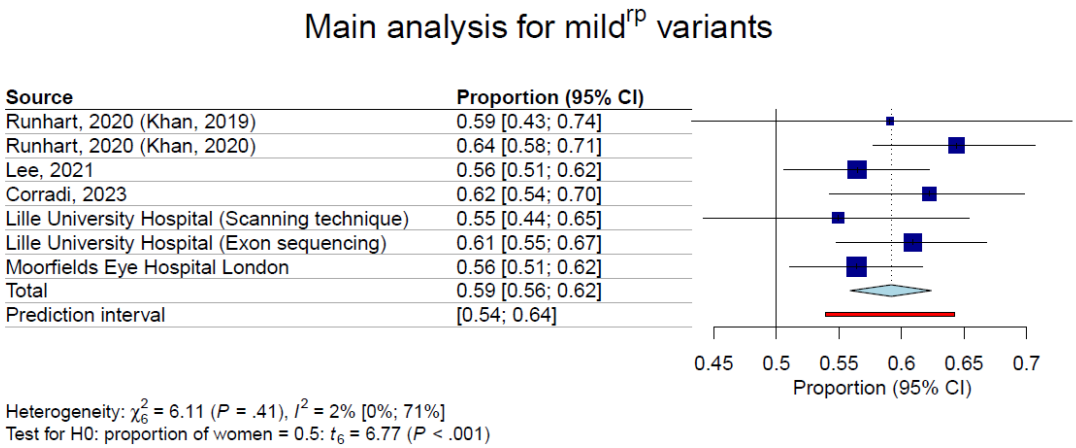
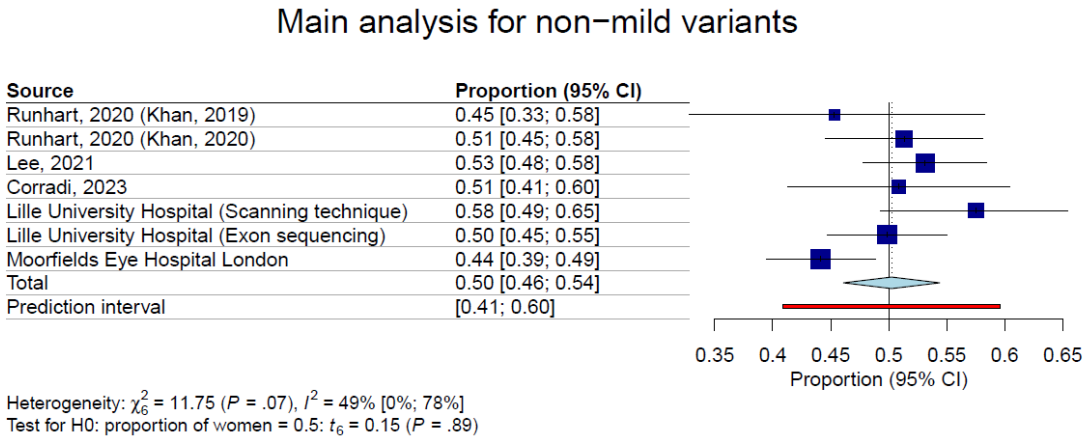

Main analysis for mild^rp variants
Source
Proportion (95% CI)
Runhart, 2020 (Khan, 2019)
0.59 [0.43; 0.74]
Runhart, 2020 (Khan, 2020)
0.64 [0.58; 0.71]
Lee, 2021
0.56 [0.51; 0.62]
Corradi, 2023
0.62 [0.54; 0.70]
Lille University Hospital (Scanning technique)
0.55 [0.44; 0.65]
Lille University Hospital (Exon sequencing)
0.61 [0.55; 0.67]
Moorfields Eye Hospital London
0.56 [0.51; 0.62]
Total
0.59 [0.56; 0.62]
Prediction interval
[0.54; 0.64]
0.45
0.5
0.55
0.6
0.65
0.7
Proportion (95% CI)
Heterogeneity: χ^2_6 = 6.11 (P = .41), I^2 = 2% [0%; 71%]
Test for H0: proportion of women = 0.5: t_6 = 6.77 (P < .001)

Figure 2



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574 **Figure 3**

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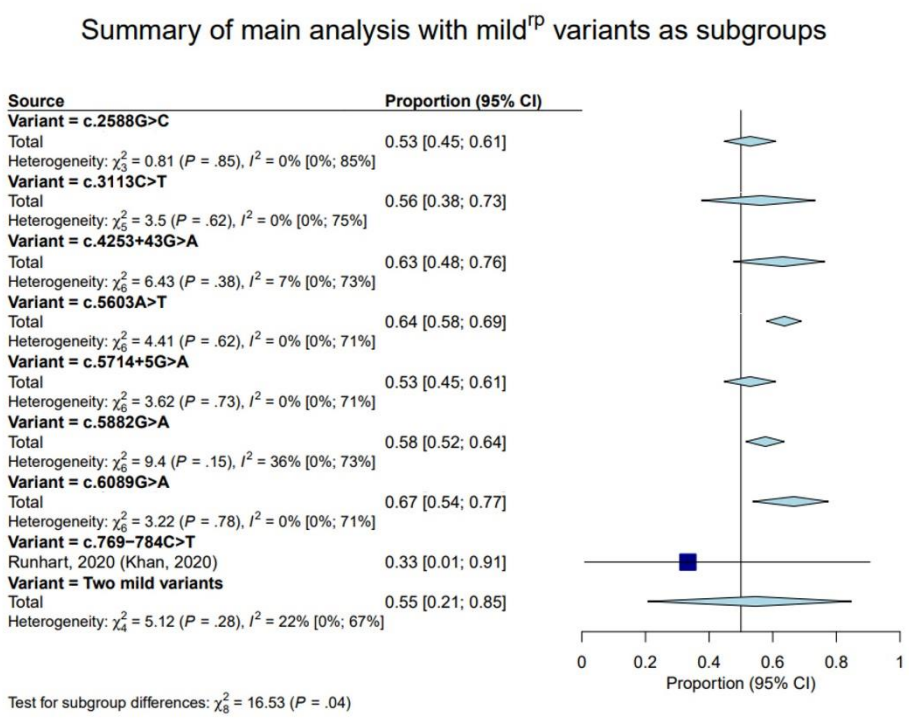

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579 **Figure 4**