

Association of a Variant in VWA3A with Response to Anti-Vascular Endothelial Growth Factor Treatment in Neovascular AMD

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PURPOSE. Anti-vascular endothelial growth factor (VEGF) therapy for neovascular AMD (nvAMD) obtains a variable outcome. We performed a genome-wide association study for anti-VEGF treatment response in nvAMD to identify variants potentially underlying such a variable outcome.

METHODS. Israeli patients with nvAMD who underwent anti-VEGF treatment ($n = 187$) were genotyped on a whole exome chip containing approximately 500,000 variants. Genotyping was correlated with delta visual acuity (deltaVA) between baseline and after three injections of anti-VEGF. Top principal components, age, and baseline VA were included in the analysis. Two lead associated variants were genotyped in an independent validation set of patients with nvAMD ($n = 108$).

RESULTS. Linear regression analysis on 5,353,842 variants revealed five exonic variants with an association P value of less than 6×10^{-5} . The top variant in the gene VWA3A ($P = 1.77 \times 10^{-6}$) was tested in the validation cohort. The minor allele of the VWA3A variant was associated with worse response to treatment ($P = 0.02$). The average deltaVA of discovery plus validation was -0.214 logMAR (\approx a gain of 10.7 Early Treatment Diabetic Retinopathy Study letters) for homozygote for the major allele, 0.172 logMAR for heterozygotes (\approx a loss of 8.6 Early Treatment Diabetic Retinopathy Study letters), and 0.21 logMAR for homozygote for the minor allele (\approx a loss of 10.5 Early Treatment Diabetic Retinopathy Study letters). Minor allele carriers had a higher frequency of macular hemorrhage at baseline.

CONCLUSIONS. An VWA3A gene variant was associated with worse response to anti-VEGF treatment in Israeli patients with nvAMD. The VWA3A protein is a precursor of the multimeric von Willebrand factor which is involved in blood coagulation, a system previously associated with nvAMD.

Keywords: age-related macular degeneration, pharmacogenetics, anti-vascular endothelial growth factor, neovascularization, genetics

Neovascular AMD (nvAMD) shows a variable response to anti-vascular endothelial growth factor (VEGF)-based therapies. Overall, between 8% and 16% of patients show partial or no response to these therapies.¹ Identifying factors associated with treatment-outcome is important to understand causes of poor response to therapy, select the most appropriate therapy for the individual patient, and develop novel, more effective treatments for nvAMD. Such information would be extremely useful for both the patients and clinicians, as well as researchers.

Several factors, including age and baseline visual acuity (VA), may partially underlie treatment outcomes in nvAMD.^{2,3} Yet, these factors do not account for the majority of the variability in treatment response. Another potential source of personalized response to therapy is variation in genetic background. Several studies have evaluated candidate genetic variants for association with treatment outcome in AMD, yet none of the potential variations showed consistent association.⁴⁻¹³ An unbiased genetic approach may be required to identify genetic

variants for treatment outcome. Few such genome-wide association studies have been performed. The current studies have found an association with an NRP1 gene variant and worse outcome using unbiased analysis of exome data,⁵ although another study that performed a pooled sample genome-wide association study found an association with OR52B4.⁴ In addition, a worldwide genome study was performed by us and other cohorts, and found an association with the a common variant in the CCR3 gene worldwide, but not in the Jerusalem population studied ($P = 0.935$).¹⁴

Potentially, such genetic factors are population specific. Worldwide studies indicate the need to focus on one parameter with regards to response, as well as the challenge of harmonization between datasets, whereas single population and group datasets usually do not have the power to replicate. More specifically, populations that are close knit would allow for greater harmonization and greater specificity when looking for genetic factors that influence treatment outcome.¹⁵ Therefore, we set out to investigate the Israeli population with regards to treatment outcome for nvAMD, in correlation to their whole genome.

METHODS

Treatment-naïve patients with atrophic AMD and patients with nvAMD and age-matched controls ($n = 659$; female/male, 294/365; average age \pm SEM, 75.4 ± 0.33 years; range, 60–97 years) were recruited from the retina clinic of the Department of Ophthalmology at the Hadassah-Hebrew University Medical Center (further described as the full cohort). Of the full cohort, the discovery cohort for pharmacogenetic analysis of anti-VEGF treatment only included patients with nvAMD who were treatment naive and fit specific criteria ($n = 187$; female/male, 114/73; average age \pm SEM, 77.8 ± 0.6 years). This group of patients will be referred to as the discovery group. Criteria for inclusion included age greater than 60 years, diagnosis of AMD according to the Age-Related Eye Disease Study¹⁶ criteria, and diagnosis of choroidal neovascularization according to fluorescein angiogram (FA) and optical coherence tomography (OCT). Eyes with other potential choroidal neovascularization causes such as myopia, trauma, or uveitis were excluded. An additional set of patients with nvAMD undergoing anti-VEGF therapy fitting the same criteria as the first set and from the same population were recruited for validation ($n = 108$; female/male, 66/42; average age \pm SEM: 79.6 ± 0.76 years; range, 60–96). Patients underwent anti-VEGF therapy using either bevacizumab ($n = 293$) or ranibizumab ($n = 1$) with a loading dosage of three monthly injections followed by treatment according to a treat-and-extend algorithm. Demographics, medical and ophthalmic history, and findings from ophthalmic examinations were collected. OCT and FA images at baseline from the patients with nvAMD were reviewed. VA was collected in Early Treatment Diabetic Retinopathy Study (ETDRS) letters and was transformed into logMAR values for analysis. Age and baseline VA were included in the analysis, because these factors were previously associated with anti-VEGF treatment outcome. The study was approved by the local Ethics Committee on Research Involving Human Subjects, and adhered to the tenets of the Declaration of Helsinki. All participants signed an informed consent form.

The discovery cohort was genotyped on the same chip, either via the International AMD Gene Consortium at the Center for Inherited Disease Research (USA) or via the

Genomics Core Facility (Technion, Israel). The custom chip has been detailed previously (International AMD Genomics Consortium), and contains approximately 250,000 tagging markers for imputation and approximately 250,000 custom markers for AMD.¹⁷ We expected imputation accuracy to be suboptimal when using 1000 Genomes data alone as a reference panel, because our patients have primarily Jewish or Middle-Eastern ancestries, which are not represented in 1000 Genomes. Thus, simultaneous imputation with two reference panels was performed on the full cohort via standardized protocols using both the 1000 Genomes data¹⁸ (GRCh37) and an Ashkenazi Jewish reference panel provided by the Ashkenazi Genome Consortium¹⁹ via standard protocol. Although not all patients were Ashkenazi (57%), there is correlation between Ashkenazi and Sephardic/Israeli Arab ancestries,²⁰ such that imputation using our method is expected to be relatively accurate even for the non-Ashkenazi patients. Other analyses were performed using standard bioinformatic analysis tools, including PLINK²¹ (<https://www.cog-genomics.org/plink2>), GCTA (<http://cns.genomics.com/software/gcta/#Overview>),²² EPACTS (<https://genome.sph.umich.edu/wiki/EPACTS>), R/Bioconductor (<https://cran.r-project.org/>), ShapeIt (<http://www.shapeit.fr/>)²³, and VCFtools (<http://vcftools.sourceforge.net/>).

The chip was initially imputed to 37,126,112 variants. Then, quality control was performed according to standard protocols on both variants and on patients.²⁴ Variants with imputation quality score (R^2) less than 0.6 and a minor allele frequency (MAF) of less than 0.01, along with the pseudoautosomal region of Chr X were excluded from analysis. Variants that showed deviation from Hardy-Weinberg equilibrium were excluded. The gender of patients was verified using sex chromosome analysis. Relationships between patients were determined using identity-by-descent analysis, and all related patients with a PIHAT of greater than 0.3 were excluded. A principal components analysis (PCA) was performed via PLINK and GCTA to account for population stratification, and informative PCA eigenvalues were used as covariates in the analysis to account for this issue. PCA plots were created to visualize the informative PCA eigenvalues (Fig. 1A). There were eventually 5,353,842 variants that were used for the analysis, including most likely genotype for the imputed single nucleotide polymorphisms (SNPs), and the lambda value once calculated was 1.072, indicating no population stratification during analysis. All position values for SNPs are given in GRCh 37.

We used the change in VA (Δ VA) as an outcome, measured in units of logMAR. The Δ VA was defined as the baseline VA before treatment, subtracted from the VA 1 month after three injections of anti-VEGF for the 3-month time period. Genome-wide variant association for Δ VA was performed, and included informative PCA eigenvalues (PC1, PC2), the baseline VA, and the age at first injection as covariates. All common variants were tested using the quantitative linear regression model (q.lm) via EPACTS, using both imputed and non-imputed variants. The results were visualized using R to develop both Manhattan, and Q-Q plots generated with qqman (<https://cran.r-project.org/web/packages/qqman/index.html>). Q-Q plots were visualized and checked for errors (Fig. 1B). Final results were visualized using R to develop both Manhattan and Q-Q plots generated with qqman. The suggestive threshold for further investigation and significance was set at less than 6×10^{-5} .

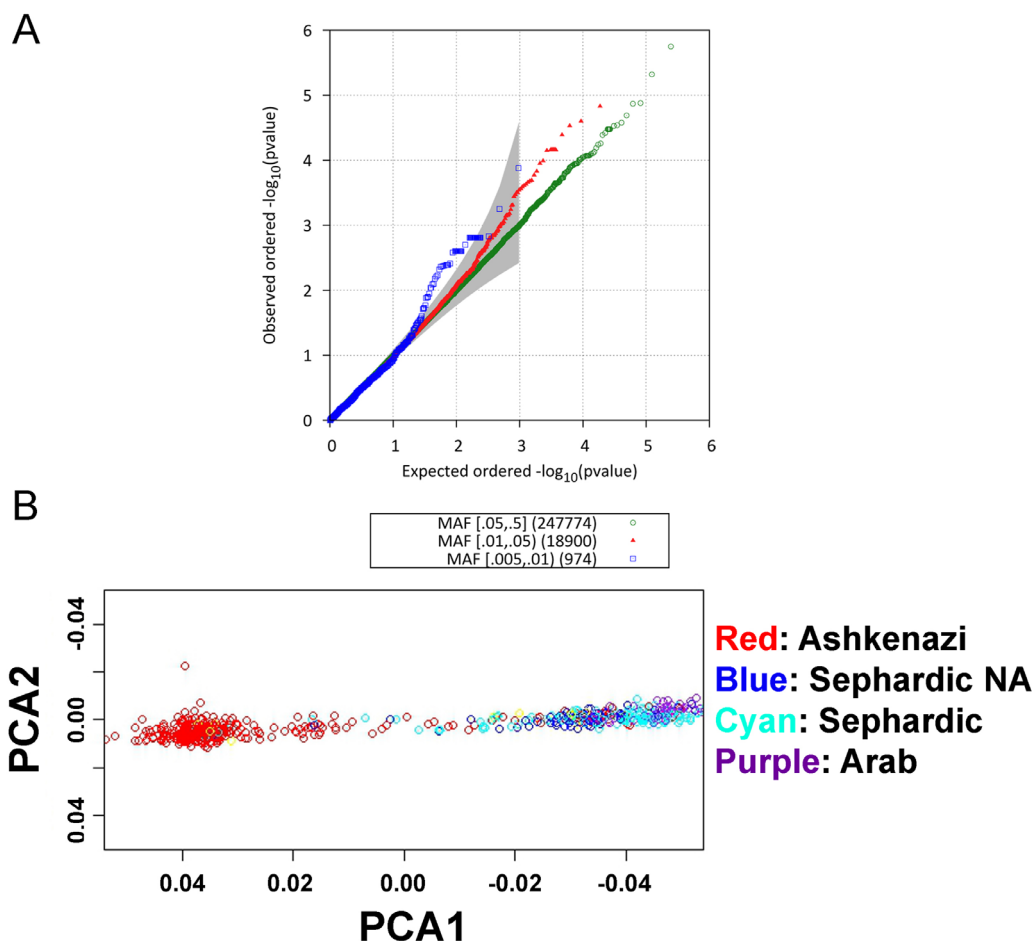


FIGURE 1. PCA plot and Q–Q plot of the discovery set. Quality control (QC) was performed on the discovery set of patients with nvAMD ($n = 187$), and PCA plots (*left*) and Q–Q plots (*right*) were generated to evaluate to exclude biased population stratification. PCA plots show a separation from the Ashkenazic, Sephardic, Sephardic North African (NA), and Arab populations. Minor allele frequencies (MAF) over 0.05 were included.

The lead variants were selected for genotyping in a new validation set of 108 patients from the same population (same percentages of cohort population subtypes were affirmed) and same retinal clinic that did not undergo whole genome genotyping and were not investigated previously. These patients corresponded with the same criteria for the patients with nvAMD as listed elsewhere in this article. Genotyping of lead variants was performed using KASP primers (LGC Group, Middlesex, UK). Association analysis of the validation set of patients was performed in the same manner as the discovery cohort, except for the inclusion of PCA covariates (because those samples did not have genome-wide data). Statistical significance threshold for the validation set was set at less than 0.05.

Other clinical parameters (OCT central subfield at baseline and at 3 months [Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany], demographics, sex) were evaluated on all patients with nvAMD in the cohort for association with top genetic variants that were found to be associated with anti-VEGF treatment in this study using EPACTS and R. Demographics and clinical information for the discovery and replication cohorts can be found in [Table 1](#).

Protein modeling analysis was performed using Pfam (<http://pfam.xfam.org/>)²⁵ and Phyre2 (<http://www.sbg.bio.ic.ac.uk/phyre2/html/page.cgi?id=index>),²⁶ along with the

NCBI data on the leading associated variant, according to standard protocols.

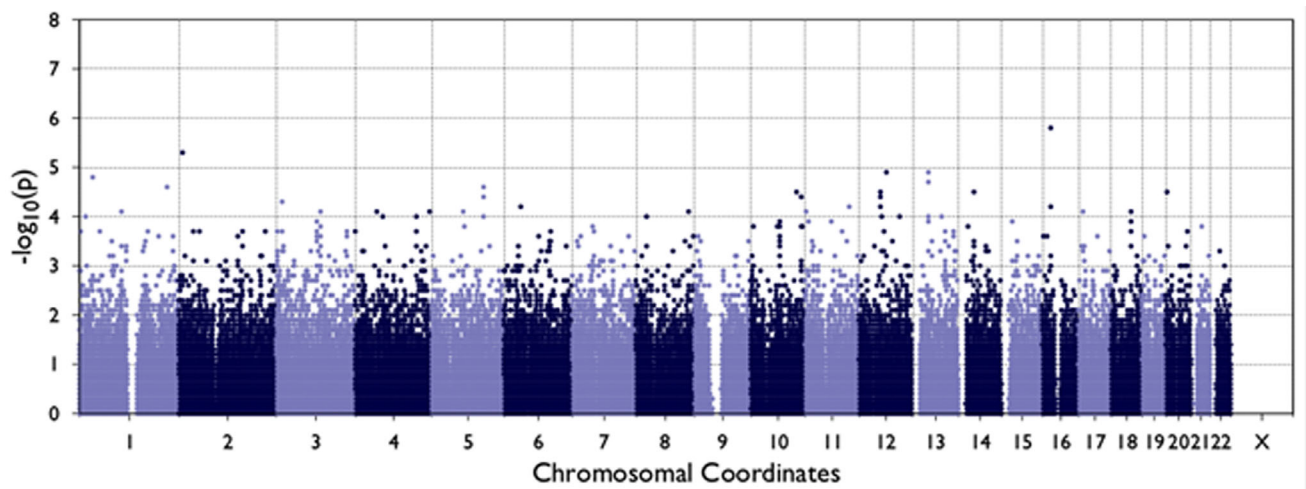
RESULTS

After linear regression testing, at a nominal threshold of a P value of less than 6×10^{-5} , 19 variants were significant for association with treatment outcome, and 5 of those variants were exonic variants (top directly genotyped variants shown in Supplementary Table S1). We chose to focus on directly genotyped, nonimputed exonic variants as these would have the greatest impact on protein binding and activity. Of those nonimputed exonic variants, the highest-ranking P values for the three lead variants were on Chr 16:22137603 (according to reference genome GrCh37, rs55732851), in the gene VWA3A ($P = 1.77 \times 10^{-6}$; Beta, 0.48 ± 0.09), Chr 1:35227162 (rs9426009), in the gene GJB4 ($P = 1.47 \times 10^{-5}$; Beta, 1.31 ± 0.29), and in Chr 12:55355033 (rs997173), in the gene TESPA1 ($P = 3.24 \times 10^{-5}$; Beta, 0.34 ± 0.08). The minor allele frequencies of these SNPs were checked against the reported allele frequencies from the exome chip data from the Ashkenazi Genome Consortium to validate that these SNPs were not significant owing to frequency or significance in the Ashkenazi population, or population stratification, but rather only connected to response to treatment and

TABLE 1. Demographics and Clinical Parameters Evaluated in the Analysis of the Discovery and Replication Cohorts, Including Ethnicity and Genotype of the VWA3A SNP

| | <i>N</i> | Age, Mean ± SEM | M/F | Delta VA, Mean ± SEM | Macular Hemorrhage (Y/N) | DeltaCSF, Mean ± SEM | Genotype GG/GA/AA |
|----------------|----------|-----------------|-------|----------------------|--------------------------|----------------------|-------------------|
| Discovery | | | | | | | |
| Ashkenazi | 113 | 79.2 ± 0.79 | 44/69 | −0.08 ± 0.07 | 38/75 | −98.7 ± 19.7 | 84/27/2 |
| None Ashkenazi | 74 | 75.93 ± 0.89 | 30/44 | −0.24 ± 0.08 | 31/43 | −152 ± 32.6 | 69/4/1 |
| Replication | | | | | | | |
| Ashkenazi | 56 | 80.41 ± 1.49 | 22/34 | −0.06 ± 0.08 | 21/35 | −75.96 ± 19.04 | 40/7/9 |
| None Ashkenazi | 52 | 78.08 ± 1.04 | 21/31 | −0.12 ± 0.06 | 15/37 | −54.9 ± 56.6 | 38/4/10 |

CSF, change in central subfield OCT measures; VA, change in visual acuity at 3 months.

**FIGURE 2.** Manhattan plot of the discovery set. Manhattan plots representing on the *y* axis the $-\log_{10} P$ value of the whole genome association analysis on variants shown on the *x* axis, related to response to treatment (classified as deltaVA) after 3 months of anti-VEGF injections were created. The minimal threshold for significance was set at 6×10^{-5} .

not to the population at hand, and that the MAF remained above 0.05 in the general populations. Linkage to other SNPs was also evaluated using SNAP proxy (<http://archive.broadinstitute.org/mpg/snap/ldsearch.php>) and only variants within the same gene were found to be in linkage ($R^2 > 0.6$), therefore, only the highest ranking variant per gene was chosen for analysis (Fig. 2).

Of these three top variants in the discovery set, two variants were chosen for replication owing to the genes having a known function and owing to known association with the coagulation system and AMD. These two variants were tested in the replication set of 108 patients with nvAMD who fit the original criteria but had not been used for the original analysis: the SNP in VWA3A and the SNP in TESPA1. The same association analysis was applied to the replication cohort, and the SNP in TESPA1 was not found to be associated with response to treatment ($P = 0.53$). However, the SNP in VWA3A was found to be associated with response to treatment in the replication set as well (epacts q.lm testing and Student's *t*-test on replication set: $P = 0.02$ per genotype, $P = 0.03$ per allele). The average deltaVA for the replication set was -0.17 logMAR for those homozygote for the major allele, 0.05 logMAR for those heterozygote, and 0.121 logMAR for those homozygote for the minor allele. The discovery replication sets' genotype for VWA3A were each tested separately via epacts q.lm testing for association with deltaVA, including all covariates, but without the primary components PC1

and PC2 to evaluate if population stratification had an effect on the results, and the P value remained constant (discovery set: $P = 1.328 \times 10^{-6}$; replication set, $P = 0.02$). In the general Ashkenazi population, this SNP (rs55732851, G>A) is found with a MAF of 0.09, and in the European population, the MAF is 0.075.

After these separate testings, the results of the discovery and the replication set ($n = 295$ patients with nvAMD) were then combined for the VWA3A SNP, leading to epacts q.lm testing of discovery plus replication genotype with all covariates (q.lm Linear Wald test $P = 2.2 \times 10^{-5}$; Student's *t*-test, genotype $P = 0.0001$ and allele $P = 0.0002$). Combining the testing via Student's *t*-test increased the significance, from 0.01 in the discovery cohort, and 0.02 in the replication cohort, to 0.0001 genotype value in the combined discovery plus replication. Randomizing both patient VA (random phenotype) and randomizing patient genotype were not significant ($P > 0.05$). The combined data of discovery plus replication showed an average deltaVA for the homozygotes of the major allele of VWA3A was -0.214 logMAR, as compared with heterozygote deltaVA of 0.172 logMAR, and homozygote to the minor allele was 0.21 logMAR, indicating a worse response for individuals carrying the minor allele. This indicated a gain of 10.7 ETDRS letters (conversion performed via standard tables²) for those homozygote of the major allele, a loss of 8.5 ETDRS letters for those heterozygote, and a loss of 10.5 ETDRS letters

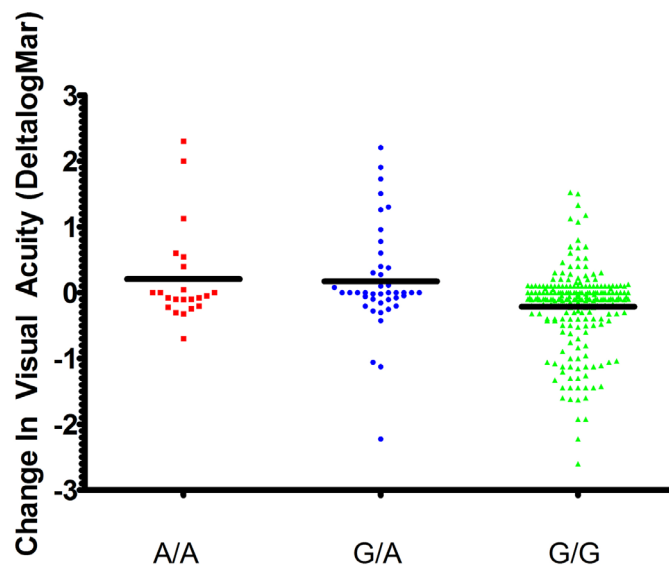


FIGURE 3. VWA3A allele results: discovery and replication sets combined. Change in VA (deltaVA) was graphed in a beehive scatter plot to demonstrate the allelic effect of the SNP in VWA3A. Patients with one or more allele had a consistently worse response after three months of anti-VEGF injections. X, genotype; Y, deltaVA in logMAR units (final minus baseline VA). Negative values indicate greater improvement in VA.

TABLE 2. Genotype of the Discovery, Replication, and Discovery Plus Replication Sets for the Variant Found in VWA3A, Along With Average deltaVA, Sex, and Average Age per Genotype

| Genotype | No. of Patients | Average DeltaVA | Sex F/M | Average Age |
|--------------------------------|-----------------|-----------------|---------|-------------|
| Discovery and replication sets | | | | |
| G/G | 231 | -0.213694098 | 141/90 | 78.32 |
| G/A | 42 | 0.172276384 | 27/15 | 78.34 |
| A/A | 22 | 0.205510462 | 12/10 | 78.4 |
| Total | 295 | | | |
| Discovery set | | | | |
| G/G | 153 | -0.237761133 | 94/59 | 77.87 |
| G/A | 31 | 0.216610113 | 18/13 | 77.85 |
| A/A | 3 | 0.741220232 | 2/1 | 78.23 |
| Total | 187 | | | |
| Replication set | | | | |
| G/G | 78 | -0.166485684 | 47/31 | 79.1 |
| G/A | 11 | 0.047335874 | 9/2 | 79.6 |
| A/A | 19 | 0.120924709 | 10/9 | 79.43 |
| Total | 108 | | | |

for those homozygote for the minor allele (Fig. 3; Table 2). The minor allele of the SNP was also associated with worse response to treatment in the Ashkenazi subgroup of the same cohort ($n = 169$ of 295 patients with nvAMD, $P = 0.0001$ according to genotype and $P = 9.2 \times 10^{-5}$ according to allele).

All 52 variants that were previously associated with the risk for having AMD were checked in this study to see if there was a connection to treatment response, but none was found to be associated with treatment even at the 0.05 significance threshold.

Clinical and demographic parameters were evaluated against association with the VWA3A lead SNP. No association was found between gender, ethnicity, age, hypertension, diabetes, or baseline VA, or with central subfield or change in central subfield at 3 months OCT data tested ($P > 0.05$). A

weak association was found between macular hemorrhage at baseline and the presence of the minor allele in VWA3A ($\chi^2 P = 0.05$; $n = 293$ patients; $n = 76/230$ homozygote for the major allele who had hemorrhage vs. $n = 29/63$ with the minor allele who had hemorrhage). The average deltaVA between those with hemorrhage and without was not significant when not accounting for genotype (-0.07 ± 0.07 for those with hemorrhage vs. -0.16 ± 0.04 for those without, Student's t -test $P = 0.28$). An example of the A/G heterozygote for the minor allele OCT and FA versus a G/G homozygote major allele OCT and FA can be seen in Figure 4. The baseline VA of both the discovery and replication set homozygotes for the major allele (GG) did not differ (Student's t -test, 0.38). No variable differed significantly between ethnic groups.

The SNP in VWA3A is exonic and directly genotyped (dbSNP ID: rs55732851; cDNA and HUGO protein nomenclature, NM 173615:4:c1637G>A, NP 775886.3:p.Cys546Tyr, c.546C>Y); therefore, the protein change (missense) was modeled using Phyre2. No significant change in the beta helix that this portion of the protein encodes for was found despite the missense change. The maximum combined annotation dependent deletion score (<https://cadd.gs.washington.edu/snv>) was 1.57 for this variant, with SIFT and PolyPhen scores of tolerated and benign, despite combined annotation dependent deletion classifying this variant as a regulatory or nonsynonymous feature. According to Mutation Tester (<http://www.mutationtaster.org/>), the change does not abrogate a splice site, but protein features might be affected.

DISCUSSION

In this study of 295 patients with nvAMD (187 discovery set, 108 replication set) we have identified a novel candidate SNP in the gene VWA3A, which is associated with response, at a lower P value of 2.2×10^{-5} after two independent discovery and replication sets, to anti-VEGF treatment in the Israeli population. Most of the population studied here is Ashkenazi

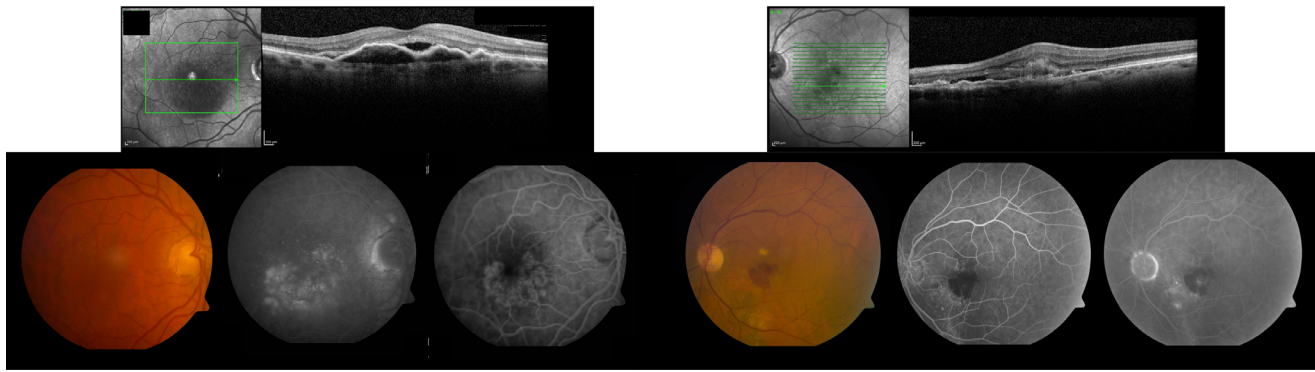


FIGURE 4. Examples of clinical findings in homozygotes for the major allele and heterozygote of VWA3A major and minor alleles. The left side of the figure are (top): OCT (bottom left) color fundus photograph; (bottom right) early stage FA; and (bottom middle) late stage FA, from a patient in this study with a G/G genotype for the SNP in VWA3A, who showed no signs of hemorrhage. In contrast, are the right side of the figure, which are on (top): OCT (bottom left) color fundus photograph; (bottom middle) early stage FA; and (bottom right) late stage FA, from a patient in this study with an G/A genotype for the SNP in VWA3A, who shows signs of hemorrhage. Pictures have been edited with black only to remove patient information.

Jewish, and this SNP is not associated with AMD in the Ashkenazi population in general, and is also not specific to the Ashkenazi population.¹⁹ However, the minor allele of this SNP was still associated with worse response to treatment in both the Ashkenazi population, and the general Israeli population in our cohort. In clinical trials and practice, a change of 5 or more ETDRS letters on the visual score (one ETDRS line) is considered to be the clinically actionable end point. Therefore, our results which demonstrate a difference in the deltaVA between homozygotes for the major allele and carriers of the minor allele, which are greater than 15 ETDRS letters would be highly clinically relevant.

This is the first genome-wide association study in response to treatment to have been performed in the Israeli population to date, and one of few studies of this sort worldwide.^{4,5} This SNP has not been found to be associated with treatment response previously. It is possible that this candidate variant is important for treatment outcome in other populations or that it is specific to the Israeli population. Such associations may be population specific, because previous studies found the gene OR52B⁴ and the gene NRP1⁵ to be associated with response to treatment, whereas in our study they were not ($P > 0.05$ for both genes).

VWA3A is one of the components and precursors of the von Willebrand factor, involved in blood clotting, platelet plug formation, hemostasis, and thrombosis. The von Willebrand factor is a multimeric glycoprotein usually found in blood plasma. Mutations in the von Willebrand factor gene cause clotting disorders, but here we are focusing on the precursors of the 3A domain.^{27,28} Coagulation genes have been thought to play a role in response to photodynamic therapy in the past.²⁹ Only one pathogenic mutation in a case study has been reported in a similar protein, VWA3B, which, as homozygous, causes cerebellar ataxia.³⁰

The 3A domain is involved specifically in collagen binding, and this domain plays a key role in platelet adhesion in damaged blood vessels. Binding to collagen (specifically types I and III) via the 3A domain, which comes from the connective tissue of the vessel wall, allows the platelet plug to start formation. The 3A domain is one of the most well studied domains of the von Willebrand factor multifamily and the structures determined, allowing for the Phyre2 results that we presented here.^{27,28,31,32} According to

our bioinformatics protein modeling, this variant does not change VWA3A enough to cause an obvious structural defect in the precursor protein, yet it is still unknown exactly what sort of effect on hemostasis such a missense variant would have, because minor structural variant changes can have an effect on hemostasis.³³⁻³⁵ We found a potential connection between presence of the minor allele in this variant and macular hemorrhage at baseline. This finding may indicate perturbed ocular blood coagulation for carriers of the variant.

Caveats of the current study include its relatively small sample size. In general, the accepted threshold for association studies is 5×10^{-8} in the European population; however, when investigating exonic variants, a lower threshold of 1×10^{-6} can be used.³⁶ Here, a P value of approximately 1×10^{-6} was detected for the VWA3A SNP in the discovery set, above our threshold set at 6×10^{-5} . Owing to this, we investigated and used two-step testing to validate these lower P value results. Via an independent replication dataset from the same population and center that was not used for the original association study, an association of this SNP and outcome was confirmed, with a P value of 0.02 in the replication set, and then joint testing for a P value of 2.2×10^{-5} including all covariates. This lower P value may indicate this SNP as a candidate gene for larger sample sizes or other populations. The different magnitude of the effect size between the discovery and replication sets may be due to lower sample sizes in this cohort. Yet, in each of the cohorts, the deltaVA showed clinically meaningful differences between the genotype groups. Another potential caveat is that OCT data did not find a difference at baseline between the genotypes of the VWA3A SNP. Conceivably, this variant is not connected with leakage and retinal thickening, but rather connected with ocular hemorrhage. The hemorrhage itself would potentially affect the VA, but retinal thickness would not be associated with this effect.

This novel candidate variant may be of special interest to worldwide Jewish and Middle Eastern populations who suffer from AMD, as well as in association with response to treatment in other population isolates that have not yet been evaluated. This study further shows the importance of investigating genetics and pharmacogenetics in specific populations, owing to their unique genetic makeup. Further studies

on larger sample sizes should be performed to ascertain if this SNP is associated with response in other populations or other large-scale studies. Recognizing that there are unique genetic factors involved in response to treatment would help in determining the best treatment options for patients and designing improved therapies for poor responders of the current available treatment options.

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