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Analysis of hemopexin plasma levels in patients with age-related macular degeneration

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Purpose: A protein quantitative trait locus (pQTL) analysis recently revealed a strong association between hemopexin (HPX) levels and genetic variants at the complement factor H (*CFH*) locus. In this study, we aimed to determine HPX plasma levels in patients with age-related macular degeneration (AMD) and to compare them with those in controls. We also investigated whether genetic variants at the *CFH* locus are associated with HPX plasma levels.
Methods: HPX levels were quantified in 200 advanced AMD cases and 200 controls using an enzyme-linked immunosorbent assay and compared between the two groups. Furthermore, HPX levels were analyzed per genotype group of three HPX-associated variants (rs61818956, rs10494745, and rs10801582) and four AMD-associated variants (rs794362 [proxy for rs187328863], rs570618, rs10922109, and rs61818924 [proxy for rs61818925]) at the *CFH* locus.
Results: HPX levels were similar in the control group compared with the AMD group. The three variants at the *CFH* locus, which were previously associated with the HPX levels, showed no association with the HPX levels in our data set. No significant differences in HPX levels were detected between the different genotype groups of AMD-associated variants at the *CFH* locus.
Conclusions: In this study, HPX levels were not associated with AMD or AMD-associated variants at the *CFH* locus. The finding of a previous pQTL study that variants at the *CFH* locus were associated with HPX levels was also not confirmed in this study.

Age-related macular degeneration (AMD) is a multifactorial eye disease and a common cause of vision loss in the elderly population [1, 2]. A substantial fraction of genetic heritability has been identified in large genome-wide association studies (GWAS) for AMD [3]. Among the strongest association signals are genetic variants at the complement factor H (*CFH*) locus, which encompasses the *CFH* gene and complement factor H-related genes (*CFHR1*, *CFHR2*, *CFHR3*, *CFHR4*, and *CFHR5*). Several AMD GWAS variants at the *CFH* locus have been associated with altered factor H (FH) or FH-related (FHR) protein levels in plasma. For example, the genotype of rs6677604, an intronic variant in *CFH*, was associated with plasma FH and FHR1 levels [4]. Furthermore, four AMD-associated variants at the *CFH* locus (rs10922109, rs570619, rs187328863, and rs61818925) have been shown to be associated with FHR4 levels in the blood [5]. These alterations in FH and FHR protein levels are thought to contribute to AMD pathogenesis [4, 5].

Three other variants at the *CFH* locus were found to be strongly associated in trans with hemopexin (HPX) levels in a large protein quantitative trait locus (pQTL) analysis [6]. HPX binds heme in the blood with high affinity and transports it to the liver. This prevents the accumulation of reactive oxygen species [7]. The three HPX-associated variants are located in exon 10 of *CFHR4* (rs10494745; leading to a glycin-to-glutamic acid amino acid substitution), intergenic between *CFHR2* and *CFHR5* (rs10801582) and intronic in *CFHR4* (rs61818956). Remarkably, these three variants together explain 61% of the variance in HPX levels [6]. Lower *CFHR4* expression levels were also associated with lower HPX protein levels. Furthermore, rs10494745 is an expression quantitative trait locus for the RNA expression levels of *CFHR4* in the liver [6, 8]. This suggests co-regulation between FHR4 and HPX.

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Table 1. AMD cases and controls used for HPX measurements.

	AMD cases (nvAMD: n=177 and GA: n=23, total: n=200)	Controls (n=200)
Mean age (years)	76.3	74.9
Gender distribution		
Male	97 (48.5%)	96 (48.0%)
Female	103 (51.5%)	104 (52.0%%)
Mean BMI (kg/m^2)	26.5	26.4
Number of smokers		
Current	25 (12.5%)	6 (3.0%)
Never	61 (30.5%)	90 (45.0%)
Past	84 (42.0%)	103 (51.5%)
Not known	30 (15.0%)	1 (0.5%)
rs61818956		
CC	103 (51.5%)	129 (64.5%)
CT	78 (39.0%)	60 (30.0%)
TT	19 (9.5%)	11 (5.5%)
rs10494745		
GG	155 (77.5%)	177 (88.5%)
GA	42 (21.0%)	21 (10.5%)
AA	3 (1.5%)	2 (1.0%)
rs10801582		
GG	150 (75.0%)	131 (65.5%)
GA	47 (23.5%)	60 (30.0%)
AA	3 (1.5%)	9 (4.5%)
rs794362		
AA	176 (88.0%)	189 (94.5%)
AG	24 (12.0%)	11 (5.5%)
GG	0 (0%)	0 (0%)
rs570618		
TT	70 (35.0%)	17 (8.5%)
TG	95 (47.5%)	98 (49.0%)
GG	35 (17.5%)	85 (42.5%)
rs10922109		
CC	130 (65.0%)	50 (25.0%)
CA	58 (29.0%)	107 (53.5%)
AA	12 (6.0%)	43 (21.5%)
rs61818924		
TT	15 (7.5%)	23 (11.5%)
TA	83 (41.5%)	94 (47.0%)
AA	102 (51.0%)	83 (41.5%)

For the variants, the number of subjects per genotype group are given.

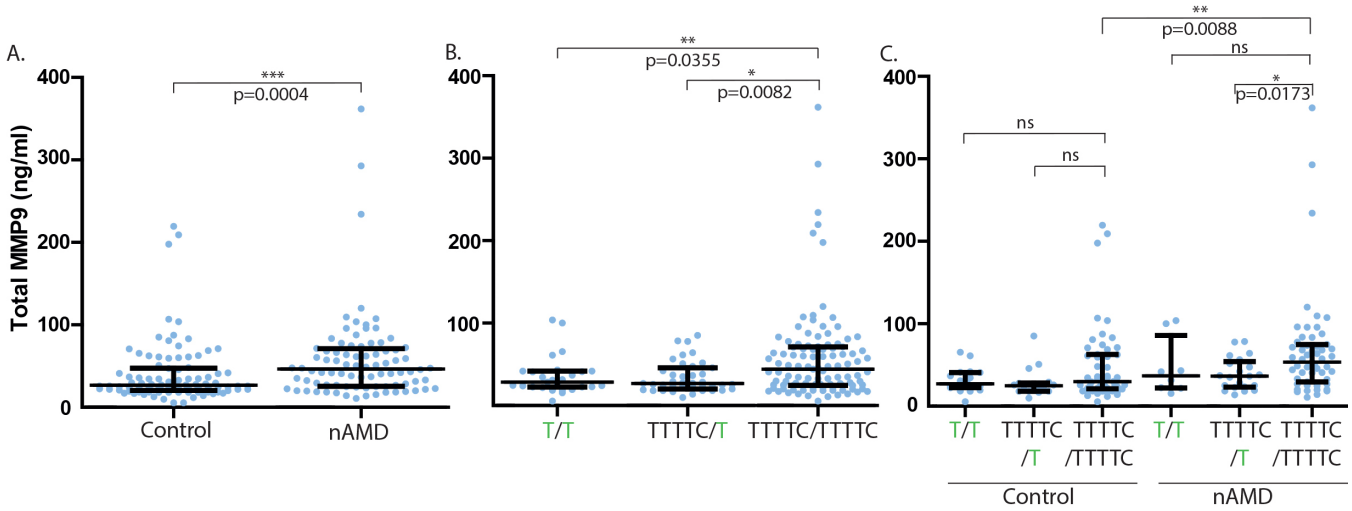

Figure 1. Hemopexin (HPX) levels plotted against sex, smoking, age, and body mass index (BMI). A and B: Bars represent median values, and whiskers represent interquartile ranges. C and D: HPX levels were log-transformed to perform linear regression. Sex, smoking, and BMI were significantly associated with HPX levels (see Table 2).

Table 2. Results of association analysis between HPX levels and gender, smoking, age and BMI.

Various	p-value	Median HPX levels per group / R^2 of the regression
Gender	0.001	
Male		797.2 µg/ml (25% percentile: 727.9, 75% percentile: 876.0)
Female		858.3 µg/ml (25% percentile: 777.2, 75% percentile: 933.7)
Smoking	0.012	
Current		774.9 µg/ml (25% percentile: 672.3, 75% percentile: 910.3)
Past		827.9 µg/ml (25% percentile: 751.5, 75% percentile: 910.3)
Never		837.6 µg/ml (25% percentile: 755.9, 75% percentile: 930.4)
Age	0.098	R^2 = 0.0030; Beta = 0.056
BMI	0.003	R^2 = 0.022; Beta = 0.150

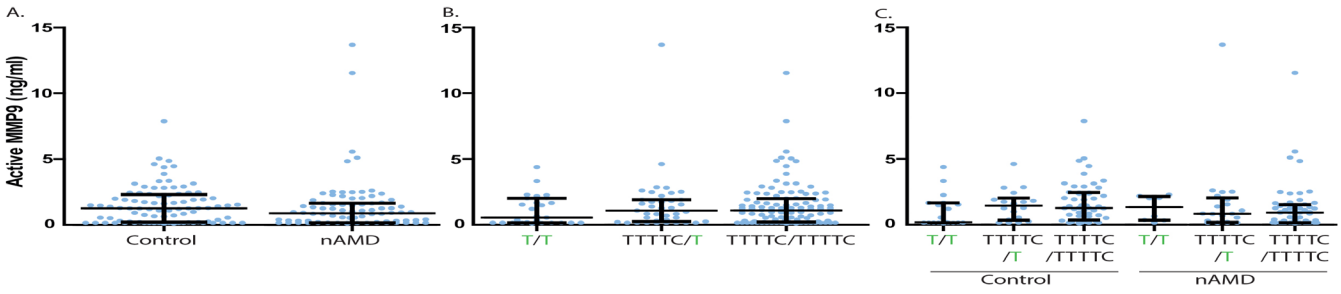

Figure 2. Hemopexin (HPX) levels of the controls compared with those of the patients with age-related macular degeneration. Bars represent median values, and whiskers represent interquartile ranges.

Table 3. For each of our analyses, we describe the sample sizes, minimally detectable differences with 80% power and the results of the linear regression analyses (ratio of medians, 95% confidence interval and p-value).

AMD status	AMD	Number of samples per group	Minimally detectable difference (in µg/ml)	Ratio of medians	95% confidence interval	p-value of association
		200	**35**	**1.015**	**0.983-1.048**	**0.137**
	Control	200				
rs61818956	CC	232	37.5	1.009	0.975-1.043	0.22
	CT	138				
rs10494745	GG	332	48.07	1.015	0.942-1.030	0.328
	GA	63				
rs10801582	GG	281	39.71	1.01	0.955-1.025	0.415
	GA	107				
rs794362	AA	365	61.9	0.993	0.941-1.049	0.397
	AG	35				
rs570618	TG	193	40.6	0.995	0.955-1.038	0.027
	GG	120				
rs10922109	CC	180	37.7	0.995	0.962-1.029	0.08
	CA	165				
rs61818924	TA	177	36.8	0.99	0.937-1.047	0.27
	AA	185				

Since one of the genotype groups is small for most of the variants evaluated (Table 1), we calculated power and ratio of medians based on the two largest genotype groups.

HPX belongs to acute-phase proteins, whose expressions are upregulated in response to inflammation [7]. HPX may also be involved in the regulation of the complement system via the regulation of free heme levels. Heme can bind with complement component 3 (C3) and thereby activate the alternative pathway of the complement system [9, 10]. In a mouse model with sickle cell disease, heme triggered complement activation, but this effect was attenuated by the addition of HPX [11]. By scavenging heme, HPX could function as a complement inhibitor. On the other hand, FHR proteins are thought to hinder complement inhibition. They compete with FH for binding to C3b, a fragment formed after cleavage

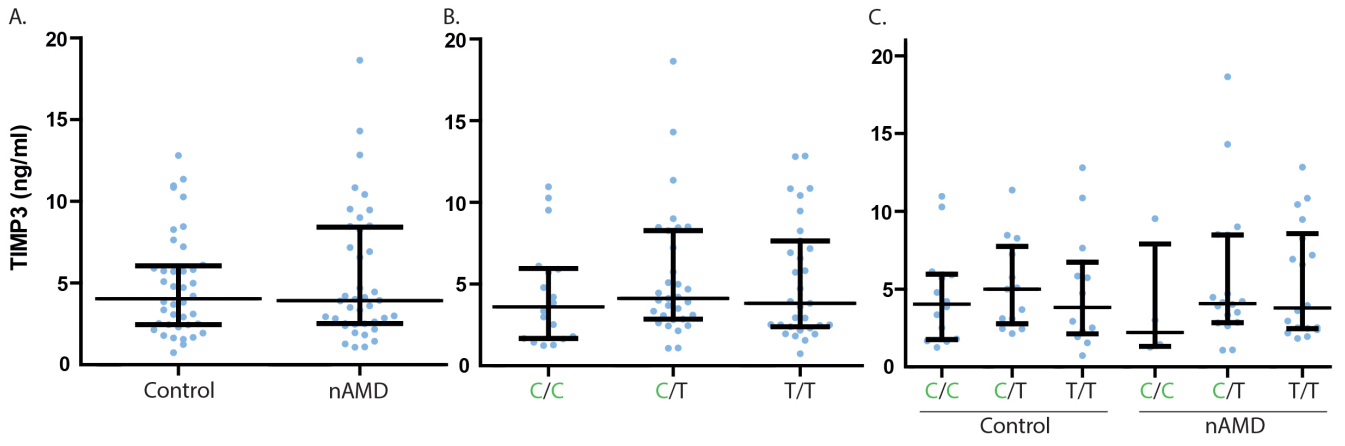

Figure 3. Hemopexin (HPX) levels in the genotype groups of variants previously found to be associated with HPX levels [6]. Three HPX-associated variants were analyzed: rs61818956 (A), rs10494745 (B), and rs10801582 (C). Bars represent median values, and whiskers represent interquartile ranges.

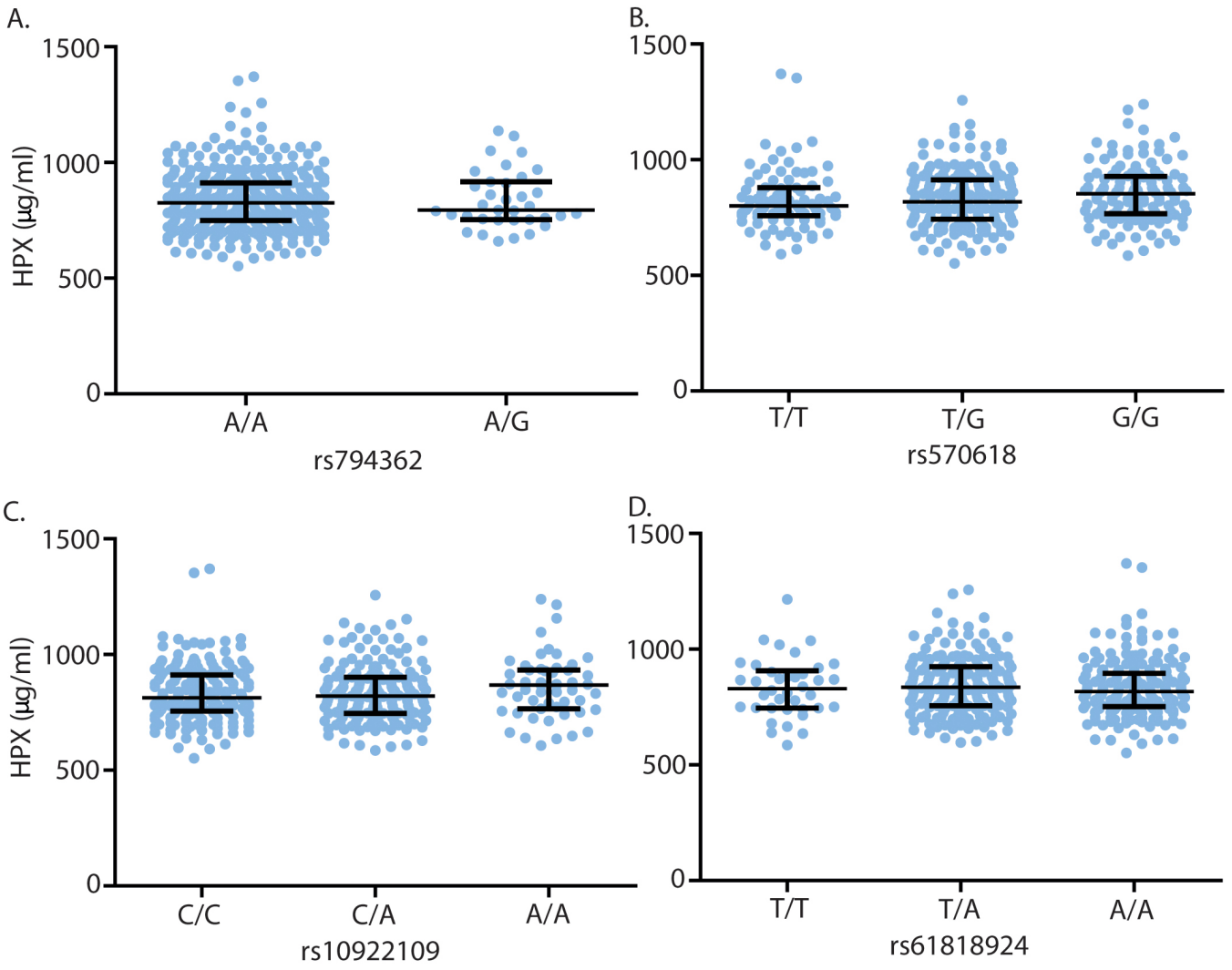

Figure 4. Hemopexin (HPX) levels in the genotype groups of variants in the *CFH* locus found to be associated with age-related macular degeneration (AMD) [3]. Four AMD-associated variants were analyzed: rs794362 (A), a proxy for rs187328863; rs570618 (B); rs10922109 (C); and rs61818924 (D), a proxy for rs61818925. Bars represent median values, and whiskers represent interquartile ranges.

of C3, which triggers further activation of the complement system. While FH induces cleavage of C3b, thereby inhibiting complement activation, FHR proteins only bind to C3b without triggering its degradation [5, 12]. Taken together, this suggests that HPX is functionally linked to the complement system, and the association between HPX levels and variants at the *CFH* locus might be relevant to the context of AMD pathogenesis.

In this study, we aimed to investigate HPX levels in plasma samples from patients with AMD in comparison with those in plasma samples from controls. Furthermore, we determined the genotypes of the HPX- [6] and AMD-associated variants [3] at the *CFH* locus in all subjects and investigated whether they were associated with plasma HPX levels.

METHODS

Study population: For this study, 200 controls and 200 patients with advanced AMD (including 177 with neovascular AMD and 23 with geographic atrophy) who were identified from the European Genetic Database (EUGENDA) were selected. EUGENDA is a multicenter database for the clinical and molecular analyses of samples from patients with AMD that were collected at the Radboud University Medical Center, Nijmegen, The Netherlands, and at the University Hospital of Cologne, Cologne, Germany. The study was conducted

in accordance with the tenets of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act. Approval was obtained from the local ethics committee of both university hospitals, and written informed consent was acquired from all participants. All individuals included in the study agreed to plasma measurements and genotyping. The patients' AMD and control statuses were assigned using multimodal image grading according to the standard protocol of the Cologne Image Reading Center by certified graders [13]. Each AMD sample was age-matched (+/− 2 years) to a control sample.

For all samples, genotype information was available in our EUGENDA database. We did not select samples based on genotypes to prevent potential bias in the data. However, we retrieved the genotypes of the HPX-associated variants (rs61818956, rs10494745, and rs10801582) and AMD-associated variants at the *CFH* locus [3] after selecting the samples. As the minor alleles of four of the eight AMD-associated variants at the *CFH* locus were rare in our study population, we only included the following four common variants in the analysis of the association between genotypes and HPX levels: rs794362 (proxy for rs187328863), rs570618, rs10922109, and rs61818924 (proxy for rs61818925).

Genotyping: Blood was drawn into EDTA tubes, which were subsequently centrifuged, and the cell pellets were used for DNA isolation within 72 h or otherwise stored at −80 C. Genomic DNA was extracted using Chemagen chemistry on a Hamilton robot. A custom-designed Human Cor eExome array (Illumina Inc., San Diego, CA) was used to genotype the samples within the International AMD Genomics Consortium. All details regarding the design of the array, annotation, imputation, and quality control of the genotype data have been described previously [3].

HPX quantification: Plasma was obtained using a standard centrifugation protocol, and within 1 h after blood withdrawal, the samples were stored at −80 ºC. Enzyme-linked immunosorbent assays (ELISAs) were outsourced to Tebubio Europe (Le Perray en Yvelines, France). The Raybiotech Human Hemopexin ELISA kit (Ref. ELH-HPX, lot 1,113,202,126; Tebubio Europe) was used to quantify HPX levels. All samples were analyzed in duplicate. The two replicates deviated less than 10% from each other.

Power calculation: We performed a power calculation for each analysis. As one of the homozygous genotype groups was small for most of the variants evaluated, we calculated power based on the two largest genotype groups. Using the number of subjects in each group and the standard deviation of our measurements, we calculated minimally detectable differences with 80% power in our study.

Statistical analysis: The data analysis was performed using SPSS for Windows version 22 (SPSS IBM, New York). Two-tailed Mann-Whitney *U* tests were used to determine possible associations between HPX levels and sex or smoking. Linear regression was used (after log transformation of the data) to test for possible associations between HPX levels and age or body mass index (BMI). As gender, BMI, and smoking were found to be associated with HPX levels ($p < 0.05$), we corrected for these factors when comparing the HPX levels in the AMD group with those in the control group and between the different genotype groups by using a multivariate analysis after log transformation of the data. When comparing the AMD cases with the controls, the effect was considered significant if the p value was <0.05. When comparing HPX levels between the different genotype groups, we corrected for multiple testing; therefore, $p < 0.00625$ is needed for significance.

RESULTS AND DISCUSSION

To investigate whether AMD status is associated with HPX levels, HPX levels were quantified in plasma samples from 200 patients with advanced AMD and 200 controls (Table 1). First, we analyzed whether HPX levels were associated with age, sex, BMI, and smoking behavior. We found associations between the HPX levels and sex ($p = 0.001$), BMI ($p = 0.003$), and smoking ($p = 0.012$; Figure 1; Table 2). Next, we determined whether the HPX levels differed between the AMD and control groups in a multivariate analysis correcting for sex, BMI, and smoking, and found no significant differences between the groups (Figure 2; Table 3). Our power analysis revealed that the minimally detectable difference with 80% power was 35.0 µg/ml (Table 3). We detected a difference of 1.5% between the median of the AMD group and that of the control group, which corresponds to a difference in HPX level of 12.36 µg/ml. This study suggests that the HPX levels showed no differences > 35.0 µg/ml between the AMD and control groups.

We then tested whether we could confirm the associations of rs61818956, rs10494745, and rs10801582 with the HPX levels identified in the pQTL study by Suhre et al. 2016 [6]. This was not the case, as we did not observe significant differences in HPX levels between any of the genotype groups (Figure 3, Table 3). We calculated the minimally detectable differences with 80% power based on the two largest genotype groups, as the number of subjects with the variant on both alleles was limited in our study (Table 1). We cannot compare these minimally detectable differences (Table 3) with the differences found by Suhre et al. [6], as they measured HPX levels in arbitrary units. They used a

larger cohort (1000 subjects in the discovery cohort and 338 in the replication cohort) and found clear effects (rs10494745: Beta = −1.025, p = 1.804×10^{-52}, rs10801582: Beta = −0.737, p = 1.104×10^{-49}, rs61818956: p = 1.13×10^{-74}; found after imputation). The magnitude of the differences between the genotype groups remains to be determined in absolute values. Our study suggests that the differences in HPX level between the homozygous reference and the heterozygous genotype groups were not >37.5, 48.07, and 39.71 µg/ml for rs61818956, rs10494745, and rs10801582, respectively (Table 3).

Finally, we determined the genotypes of the AMD-associated variants at the *CFH* locus identified by Fritsche et al. [3]. For four common variants (rs794362, rs570618, rs10922109, and rs61818924), we assessed whether the genotypes of these variants were associated with the HPX levels. We did not detect a significant association between any of these variants and the HPX levels (Figure 4, Table 3).

The HPX-associated variant rs10494745 also regulates *CFHR4* expression in the liver. *CFHR4* expression is associated with HPX protein levels, which suggests that HPX and FHR4 expression levels might be partly regulated by the same variants. As FHR4 levels are also thought to be important in the development of AMD, we hypothesized that AMD-associated variants at the *CFH* locus might also regulate HPX expression levels. However, we did not detect any significant associations between the AMD-associated variants and the HPX levels. In accordance with this observation, we determined whether the HPX-associated variants were in linkage disequilibrium with any of the AMD-associated variants, but this was not the case. As only the associations between HPX levels and variants in the *CFH* locus and between HPX and FHR4 levels are known, it would be interesting to analyze causation in future analyses using, for example, Mendelian randomization to obtain deeper insight into the mechanism. Furthermore, on the basis of this study, we cannot exclude the possibility that HPX protein levels might be differently regulated locally in patients with AMD compared with controls, which might not be reflected in the blood. Considering that HPX travels between the blood and the liver, and that the liver produces several AMD-related proteins, it might be interesting to investigate HPX protein levels in the liver and compare these with those in AMD status and genotypes.

In conclusion, HPX levels were not associated with AMD or AMD-associated variants at the *CFH* locus. The finding of the previous pQTL study that described the associations of variants at the *CFH* locus with HPX levels was also not confirmed in this study.

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