within this region was significantly associated with AMD in this study (table 2).

rs11200638, a SNP located upstream of rs2672587, has been reported to be strongly associated with AMD.[13,15,17] rs11200638 is located 512 bp upstream of the transcription initiation point within the putative AP2 binding sites. *In vitro* and *in vivo* data from two laboratories have reported that this polymorphism leads to a transcriptional up-regulation of *HTRA1* and sequentially triggers the onset of AMD.[13] Chan et al detected an up-regulation of *HTRA1* in the macular lesions of AMD using immunohistochemical analysis.[25] Grau et al demonstrated that the amyloid precursor protein (APP), a precursor of amyloid beta (Aß) which is a major hallmark of Alzheimer's disease (AD), is one of the native substrates of HTRA1.[26] Aß has been shown to exist in substructures of drusen in the retinas of AMD patients but not in the drusen from controls.[27] Several studies have shown that localized chronic inflammation triggered by complement activation in AD and AMD can be attributed to Aß.[1] It has also been suggested that the accumulation Aß affects the balance of VEGF and pigment epithelium-derived factor (PEDF) in the RPE, which may lead to the CNV in eyes with AMD. [28] Furthermore, anti-Aß antibody has been proven to be effective asfor immunotherapies of AMD.[29] Although a rs11200638-dependent up-regulation of

HTRA1 has been negated by others,[12] it is still unclear whether *LOC387715* or/and *HTRA1* is a genetic risk(s) for AMD on 10q26.

Unfortunately, rs11200638 was absent from the Affymetrix Human Mapping 500K Array Set. Thus, we have genotyped rs11200638 separately by sequencing analysis (data not shown). rs11200638 was included in block two together with rs10490924, and separately from rs2672587 (data not shown), i.e., the most strongly associating haplotype block includes gene regions for both *LOC387715* and *HTRA1*.

The remaining seven SNPs in Table 2 appear to be non-significant (fFig. 2), although additional case-control analysis may be neccessary. Amongst them, rs2714212 is located in intron 3 of the low density lipoprotein-related protein 1B (*LRP1B*) gene on chromosome 2 (data not shown). LRP1B is a member of the low-density lipoprotein receptor family.[30] Together with its closely related receptor LRP1, LRP1B has been suggested to be involved in Aß production in AD.[30] rs3763022 is located in the 3'-UTR region of *SH3TC2* gene on chromosome 5 (data not shown). A mutation in the *SH3TC2* gene mutation ishas been known tothat lead to inherited motor and sensory neuropathies (HMSN), also called Charcot-Marie-Tooth disease (CMT). rs10510110 is located together with *PLEKHA1*, a gene existing approximately 20 Kbp upstreams of *LOC387715*,[11] on block 1 of 10q26 locus (Ffig. 3). No gene or RNA have been registered on databases

within the corresponding haplotype blocks on 6q14, 19q13, 13q21, and 15q12 in which rs2874794, rs12462443, rs9599819 and rs1295534 are located (data not shown). However, there is a possibility of the existence of unknown mechanisms related to these regions. These loci may be critical for the development of AMD in combination with *LOC387715* (rs10490924) and/or *HTRA1* (rs11200638), and other behavioral, nutritional, and environmental factors. Further investigations are required of the individual regions to determine the molecular mechanisms related to the pathogenesis of AMD.

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Supplemental material

Supplemental Table 1

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Figure legends

Figure 1. Genome-wide association study for wet -type AMD susceptibility loci.

The analyseis compared 100 stage 5b AMD cases with 200 population-based controls (stage three analysis). The x-axis represents genomic locations, and the y-axis shows $-\log_{10}$ (genotypic *P*-value). All of the SNPs on autosomal chromosomes with genotypic *P* values < 0.01 are plotted.

Figure 2. Determination of statistical significant SNPs.

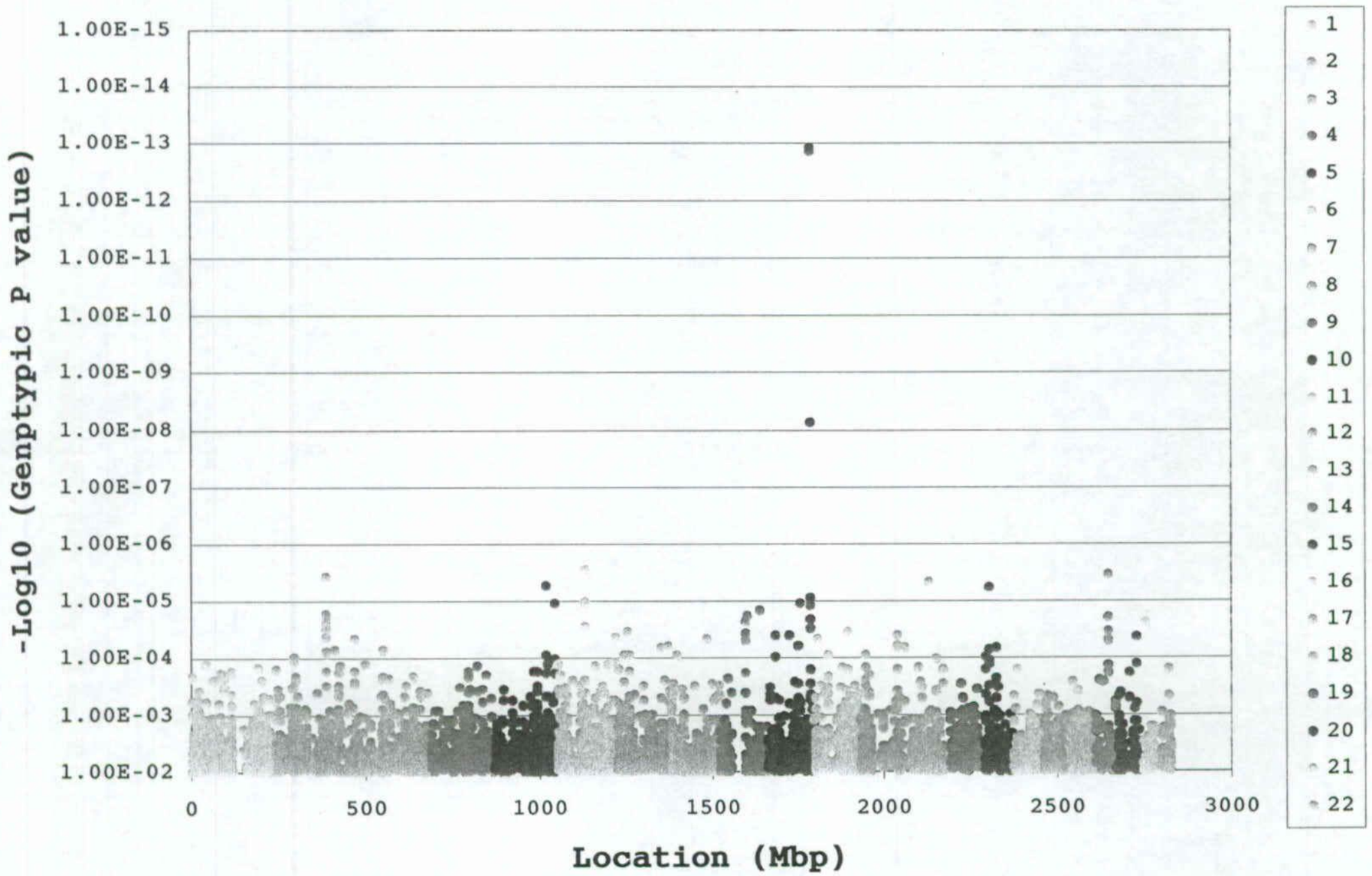
The Benjamini-Hochberg method to correct for multiple testing was used to identify SNPs significantly associated with AMD. A false discovery rate of 0.05 was used to determine statistical significance.

Figure 3. Haplotype block structure of the AMD-associated regions.

Squares shaded pink or red indicate significant linkage disequilibrium between SNP pairs (bright red indicates pairwise $D' = 1$), white squares indicate no evidence of significant linkage disequilibrium, and blue squares indicate pairwise $D' = 1$ without statistical significance. Locations of the regions on each chromosome are shown in scales above.

Genes within the views are shown by arrows. SNPs with a genotypic *P*- value < 10^{-6} in stage three analysis are indicated by open arrowheads. Haplotype block including these SNPs are surrounded with bold lines.

(A.) Haplotype block patterns on chromosome 10. rs10490924 and rs3750848 waere included in block two within the *LOC387715* gene region. rs2672587 is located between block two and three. rs10510110 is located on block one together with the *PLEKHA1* gene.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1.00E-08
1.00E-07
1.00E-06
1.00E-05
1.00E-04
1.00E-03
1.00E-02
0
500
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1500
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Location (Mbp)
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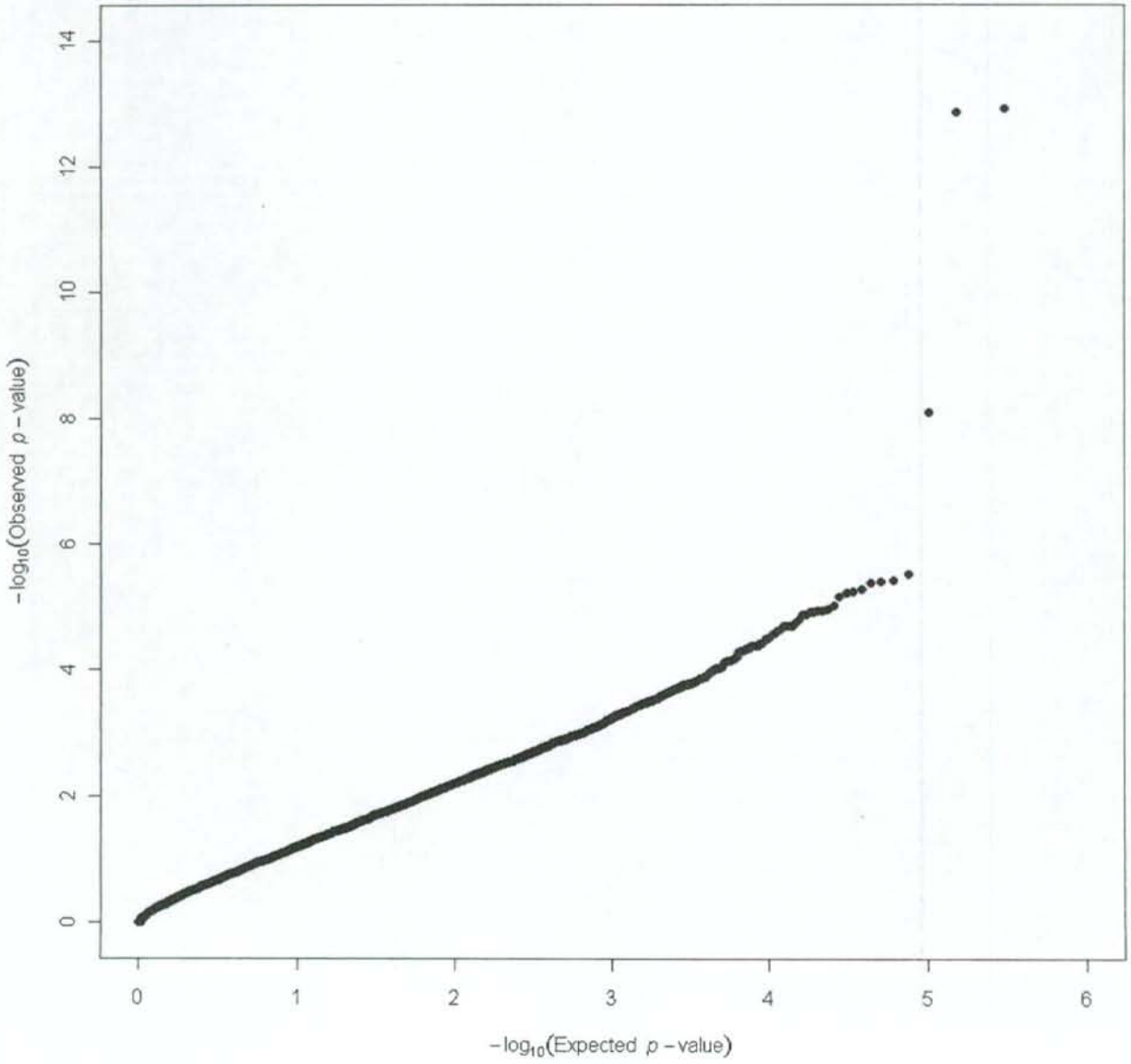
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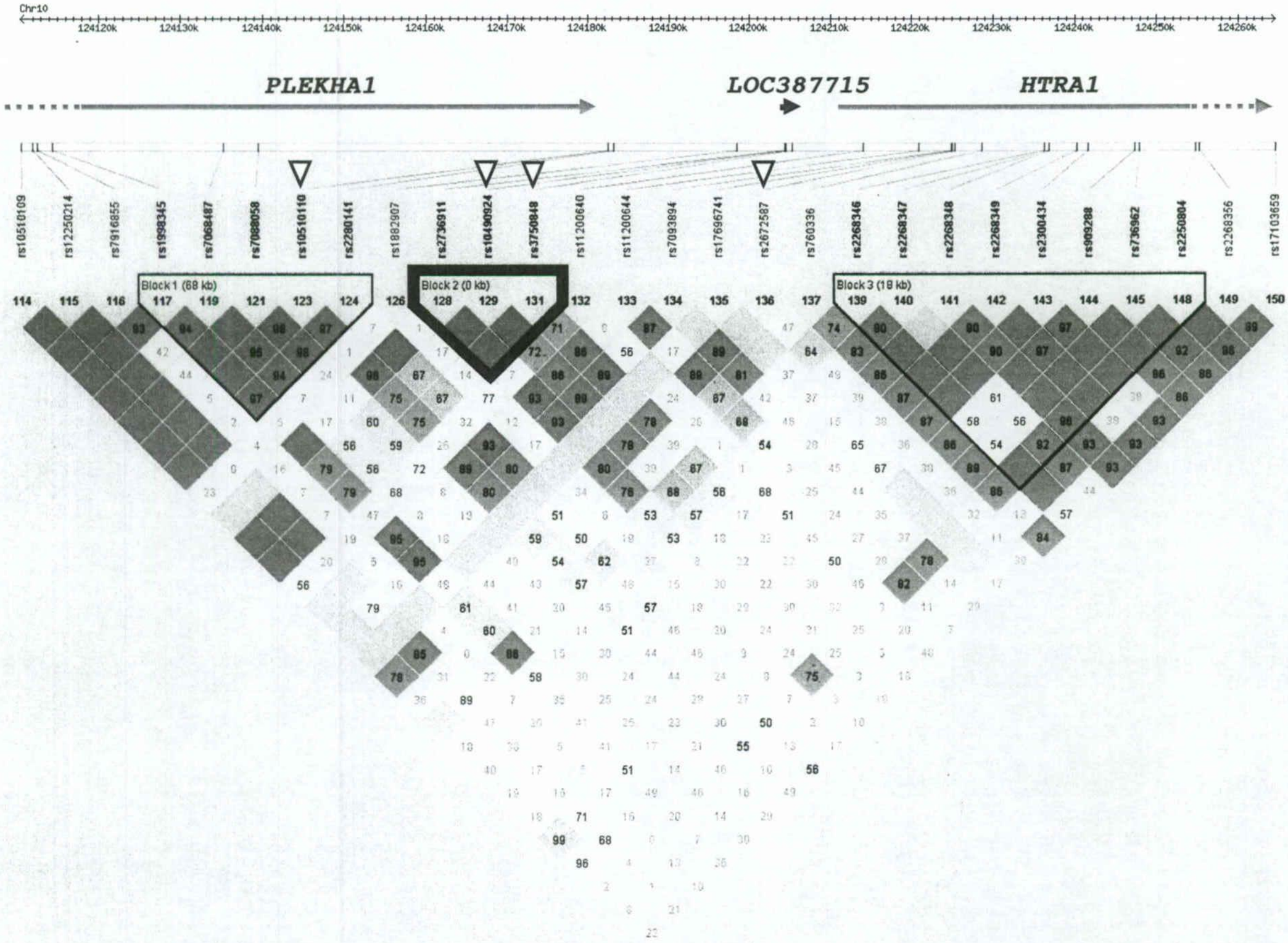
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rs909288
rs736962
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rs2268356
rs17103659
Block 1 (68 kb)
Block 2 (0 kb)
Block 3 (18 kb)

Table 1. Characteristics of AMD cases and control subjects in this study

Characteristic (AMD)					
Sex -no. (%)					
Male	73 (73.00)				
Female	27 (27.00)				
Mean age at recruitment- yr (SE)					
Total	74.56 (0.88)				
Male	73.64 (0.99)				
Female	77.04 (1.83)				
Age distribution - no. (%)					
	50s	60s	70s	80s	90s
Total	7 (7.00)	24 (24.00)	34 (34.00)	34 (34.00)	1 (1.00)
Male	6 (8.22)	17 (23.29)	29 (39.72)	20 (27.40)	1 (1.37)
Female	1 (3.70)	7 (25.93)	5 (18.52)	14 (51.85)	0 (0.00)

Characteristic (Control)						
Sex - no. (%)						
Male	91 (45.5)					
Female	109 (54.5)					
Mean age at recruitment - yr (SE)						
Total	71.00 (0.75)					
Male	71.00 (1.09)					
Female	71.00 (1.03)					
Age distribution - no. (%)						
	30s	40s	50s	60s	70s	80s
Total	3 (1.5))	4 (2.00))	18 (9.00)	43 (21.50)	96 (48.00)	36 (18.00)
Male	0 (0.00)	2 (2.20)	9 (9.89)	19 (20.88)	45 (49.45)	16 (17.58)
Female	3 (2.75)	2 (1.83)	9 (8.26)	24 (22.02)	51 (46.79)	20 (18.35)

Table 2. Summary of ten SNPs analyzed in this study

SNP	Nearest gene	Location		P value OR (95%CI)
rs10490924	*LOC387715*	10q26	Allele	9.70×10^{-15} 4.00 (2.79-5.74)
			Genotype	2.41×10^{-13}
			Heterozygote	6.11×10^{-6} 3.61 (2.02-6.46)
			Homozygote	1.19×10^{-13} 8.29 (4.62-14.89)
rs3750848	*LOC387715*	10q26	Allele	1.65×10^{-14} 3.97 (2.77-5.69)
			Genotype	3.39×10^{-13}

			Heterozygote	1.38×10^{-13}
				3.57 (1.99-6.39)
			Homozygote	6.48×10^{-6}
				8.24 (4.59-14.80)
rs2672587	*HTRA1*	10q26	Allele	1.67×10^{-10}
				3.14 (2.20-4.48)
			Genotype	8.02×10^{-9}
			Heterozygote	1.08×10^{-5}
				3.73 (2.01-6.92)
			Homozygote	2.91×10^{-8}
				4.63 (2.68-7.98)
rs2874794	*SH3BGRL2*	6q14	Allele	5.56×10^{-6}
				2.23 (1.58-3.17)
			Genotype	6.46×10^{-6}

			Heterozygote	3.05×10^{-6}
				2.21 (1.22-3.99)
			Homozygote	0.0087
				3.93 (2.22-6.96)
rs12462443	*ZNF507*	19q13	Allele	0.00016
				1.96 (1.39-2.76)
			Genotype	1.53×10^{-5}
			Heterozygote	3.70×10^{-6}
				3.94 (2.12-7.30)
			Homozygote	0.15
				1.60 (0.87-2.95)
rs2714212	*LRP1B*	2q22	Allele	0.0084
				1.87 (1.17-2.99)
			Genotype	4.04×10^{-6}