A Variant of the HTRA1 Gene Increases Susceptibility to Age-Related Macular Degeneration
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the AMD phenotype: CFH influences the drusen that characterize dry AMD, whereas HTRA1 influences CNV, the hallmark of the wet disease type. These two processes can be combined, which leads to the composite phenotypes that are seen in some cases of AMD.

References and Notes

19. Materials and methods are available online as supporting material on Science Online.
26. We express our greatest appreciation to the patients, the control subjects, and their families for participating in this study; and we thank S. Chiang and B. Zhang for technical and logistic assistance. Supported in part by the Lin Por Yen Eye Foundation (D.L., C.P.), the David Woods Kemper Memorial Foundation (C.B.), Macular Vision Research Foundation (C.B., J.H.), the Ellison Medical Foundation (J.H.), an institutional award from the Howard Hughes Medical Institute to the Yale School of Medicine (I.H.), and grants from the Claude D. Pepper Older Americans Independence Center at Yale University School of Medicine (I.H.), the NIH (M.S., C.B., J.H.), and the Verto Institute (J.H.). HTRA1 sequencing data are available online at http://www.yale.edu/dataDownload.html.

SUPPORTING ONLINE MATERIAL
www.sciencemag.org/cgi/content/full/314/5807/1049/DC1
Materials and Methods
Figs. S1 to S5
Tables S1 to S8
References and Notes
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A Variant of the HTRA1 Gene Increases Susceptibility to Age-Related Macular Degeneration

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Age-related macular degeneration (AMD) is the most common cause of irreversible vision loss in the developed world and has a strong genetic predisposition. A locus at human chromosome 10q26 affects the risk of AMD, but the precise gene(s) have not been identified. We genotyped 581 AMD cases and 309 normal controls in a Caucasian cohort in Utah. We demonstrate that a single-nucleotide polymorphism, rs11200638, in the promoter region of HTRA1 affects the risk of AMD, but the precise gene(s) have not been identified. We genotyped an additional 139 AMD patients for these two variants. The results for both SNPs increased in significance (rs10490924, P = 1.2 × 10−9; rs11200638, P = 1.6 × 10−11), with variant rs11200638 remaining the best single variant explaining the association [ORhet = 1.90 (1.40, 2.58); ORhet = 7.51 (3.75, 15.04)]. We next considered association analyses based on genotypes at both rs11200638 and the CFH rs1061170 (Y402H) variant at chromosome 1q31. In a global two-locus analysis enumerating all nine two-locus genotype combinations, the association with AMD was significant (x2 = 56.56, 8 df; P = 2.2 × 10−9). Table 1 shows the risk estimates for each two-locus genotype combination compared with the baseline of no risk genotypes (TT at CFHY402H and GG at

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The association of rs11200638 to AMD was significant when analyzed conditional on the presence of the CFH C risk allele (P = 5.9 × 10^{-5}). In particular, this conditional analysis indicates an allele-dosage effect such that homozygotes for the A risk allele of rs11200638 are at an increased risk [OR_{het} = 7.29 (3.18, 16.74)] over that of heterozygotes [OR_{risk} = 1.83 (1.25, 2.68)] in all AMD cases, even when compared with a baseline that includes individuals who carry the risk genotypes at CFH. With an allele-dosage model, the estimated population attributable risk (PAR) for rs11200638 is 49.3%. Consistent with an additive effect, the estimated PAR from a joint model with CFH and 309 controls (see also table S1A). The resulting OR_{het} is 1.83, and the 95.0% confidence interval is (1.25, 2.68), which indicates a significant association with AMD.

The HTRA1 gene encodes a member of the serine protease family of serine proteases expressed in the mouse retina (17). HTRA1 appears to regulate the degradation of extracellular matrix proteoglycans. This activity is thought to facilitate access of other degradative matrix enzymes, such as collagenases and matrix metalloproteinases, to their substrates (18). Conceivably, overexpression of HTRA1 may alter the integrity of Bruch’s membrane, favoring the invasion of choroid capillaries through the extracellular matrix, as occurs in wet AMD. HTRA1 also binds and inhibits transforming growth factor-β (TGF-β), an important regulator of extracellular matrix deposition and angiogenesis (17). DeWan et al. (19) report that the same HTRA1 SNP is associated with a wet AMD phenotype in a Chinese population. Together, these findings support a key role for HTRA1 in AMD susceptibility and identify a potential new pathway for AMD pathogenesis.

**References and Notes**

20. We thank the participating AMD patients and their families. We thank G. Brinton, J. Carver, A. Grandaal, M. Teske, A. Jorgensen, E. Brinton, and R. MacArthur for assistance in obtaining blood samples; W. Baehr, R. Marc, and N. Perrimon for critical reading of the manuscript; D. Lim and E. Smith for editorial assistance; and the Utah Lions Eye Bank and P. Shohale for assistance in obtaining eye donor tissues. We acknowledge the following grant support to K.Z.: NIH (R01EY14428, R01EY14448, P30EY01400, and GCRC M01-R000064), Foundation Fighting Blindness, Ruth and Milton Steinbach Fund, Ronald McDonald House Charities, Macular Vision Research Foundation, Research to Prevent Blindness, Val and Edith Green Foundation, and the Simmons Foundation; to H.S.: Ruth and Milton Steinbach Fund; to Z.Y.: Knights Templar Eye Research Foundation; to N.C.: K07 (NRC C98364); to J.H.: NIH (RO1EY15777), Elliott Medical Foundation, Macular Vision Research Foundation, an institutional award from Howard Hughes Medical Institute to Yale School of Medicine, and grants from the Claude D. Pepper Older Americans Independence Center at Yale University School of Medicine, and the Vetro Institute; to V.S.: Mayo Clinic and Foundation.

**Supporting Online Material**

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Materials and Methods

Figs. S1 and S2

Tables S1 and S2

References

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