A potential therapeutic target in age-related macular degeneration

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Evaluation of: Yang Z, Camp NJ, Sun H et al.: A variant of the HTRA1 gene increases susceptibility to age-related macular degeneration. Science 314(5801), 992–993 (2006) [1]. Age-related macular degeneration is a common cause of visual loss in the elderly, yet the genetic basis for this disease is poorly understood. Linkage studies show a major susceptibility locus at chromosome 10q26 and a single nucleotide polymorphism in a putative gene at this locus, LOC387715, is associated with age-related macular degeneration. We evaluate a recent study in which an alternative candidate gene, HtrA serine peptidase 1 (HTRA1), has been identified at the 10q26 locus. This gene possesses a variant in linkage disequilibrium with the previously reported LOC387715 polymorphism. The HTRA1 protein has several properties that make it an attractive candidate in the pathogenesis of age-related macular degeneration; it promotes angiogenesis via insulin-like growth factor-mediated and transforming growth factor-β-mediated pathways, and facilitates extracellular degeneration as seen in geographic atrophy and drusen formation. However, there is conflicting evidence of HTRA1 expression, which serves to highlight the need for further verification studies before HTRA1 can be considered as a potential new target in age-related macular degeneration therapy.

Age-related macular degeneration (AMD) is the most common form of irreversible vision loss in the developed world [1] with 30–50 million people affected and conservative estimates of 14 million people blind or severely visually impaired as a result [2]. Relatively little is known of the underlying genetic basis [3] and this may, in part, be due to the complex etiology of the disease itself. Age-related maculopathy exists in two main forms: atrophic (dry) or neovascular (wet). Approximately 85–90% of AMD is atrophic [4], and, while this only accounts for 10% overall AMD-related vision loss, there are no effective treatments currently available [2]. The neovascular form accounts for 90% of AMD-related vision loss and, while there have been considerable advances in therapeutic options for this group, not all individuals fit the strict treatment criteria [5]. Many of the more conventional treatments reduce the speed of vision loss rather than prevent it or improve overall vision [6].

Research into the underlying processes involved in AMD has become increasingly important, particularly as the elderly population grows. Cigarette smoking and a positive family history of AMD are well-documented risk factors [7]. The key to cracking the genetic basis for AMD is linkage analysis of large families. To date, almost all chromosomes in the human genome have been implicated in such studies [8], underlining the complexity of AMD. The most consistently replicated loci are chromosomes 1q25–31 and 10q26 [9–13]. A common coding variant (Y402H; rs1061170) of complement factor H (CFH), located on chromosome 1q31, has recently been identified as a major risk factor for AMD [14–16]. Similarly, association studies focusing on the 10q26 locus have revealed another coding variant (A69S; rs10490924) in a putative gene, LOC387715, with strong association to AMD [10,17,18]. Disappointingly, studies have failed to demonstrate how this putative gene may be implicated in AMD. Recent studies by Yang and colleagues in Utah [1] and DeWan and colleagues in China [4] help to explain this. They have identified a more attractive candidate gene in the 10q26 region and brought the association of LOC387715 into question. Using a case–control association analysis, Yang and colleagues found evidence of linkage disequilibrium between the established risk variant (rs10490924) and a promoter variant of the HTRA1 gene (rs11200638) [1]. We evaluate this study and discuss the significance of this finding.

Methods & results
Yang and colleagues used a case–control study, comparing 15 single nucleotide polymorphisms (SNPs) centered around the known rs10490924
risk locus [1]. All participants underwent a standard examination protocol and visual acuity assessment, including slit-lamp biomicroscopy and stereoscopic fundus photography. In total, 442 AMD cases (265 wet AMD and 177 soft confluent drusen) and 309 age- and ethnicity-matched controls from a Caucasian population were genotyped for each SNP.

The results showed an association at the rs10490924 locus comparable with previous studies (T allele in 39.7% cases vs 24.7% controls; \( p = 8.1 \times 10^{-8} \)), but another SNP, rs11200638, showed even stronger correlation (A allele in 40.3% cases vs 25.2% controls; \( p = 1 \times 10^{-9} \)). This association was also superior to combining both loci in a haplotype (TA haplotype; \( p = 2.2 \times 10^{-7} \)). The significance for both loci increased with the addition of a further 139 AMD cases (581 total: 392 wet and 189 soft drusen), but with rs11200638 remaining the stronger of the two (\( p = 1.6 \times 10^{-11} \) vs rs10490924; \( p = 1.2 \times 10^{-8} \)).

The study also included a two-locus analysis combining the rs11200638 genotype with the CFH rs1061170 (Y402H) genotype. Association with AMD was significant in all nine genotype combinations, with the double-risk genotype-drusen) and 309 age- and ethnicity-matched controls from a Caucasian population undergoing ocular tissues leads to abnormalities, including smaller lens and retinas, abnormal neural retinal arrangements, aggregations and detachments [23]. HTRA1 encodes a heat shock serine protease, activated by cellular stress,
expression of which increases with age [4,29]. It has considerable homology to heat shock serine peptidases in prokaryotes, which digest misfolded proteins, protecting bacteria from damage at high temperatures [25,26]. Eukaryotic HTRA1 has a proposed N-terminus insulin-like growth factor (IGF)-binding domain [26,27], suggesting a proteolytic role in releasing IGF from IGF-binding proteins. The HTRA1 protein has also been implicated as an inhibitor of transforming growth factor (TGF)-β-mediated signaling [23,24] and, unusually for a protease, tumor suppression [25,27]. The HTRA1 protein is also involved in the breakdown of extracellular matrix components in arthritic disease [19,28], a function which particularly suits the hypothesized role in the degenerative processes seen in AMD.

Discussion & conclusion
This is an interesting study that requires further verification by other trials. Linkage analyses have produced many susceptibility loci, where potential genes have shown association to AMD but not been successfully replicated. For example, the lipid transporter apolipoprotein E (APOE) has shown significant association with AMD in some studies, but refuted by others [12]. There are published data that conflict with the findings here. Several authors have assessed other HTRA1 variants without finding consistent associations with AMD or strong linkage disequilibrium with those SNPs that have [10,18], such as coding variant Cys384Gly (rs1803403), noted by Jakobsdottir and colleagues as more frequent in families with maculopathy than controls (11.8 vs 3.0%; p = 0.00009, significance lost in replicate data) [10]. Jakobsdottir and colleagues also observed lower HTRA1 expression in AMD cases compared with controls [10] in direct contrast to the study evaluated here. Yang and colleagues might be criticised for mixing all cases of AMD together and not conducting a subgroup analysis by type of AMD, thereby making a comparison with the study of wet AMD by Dewan and colleagues more difficult. It may also transpire that a clinical history of arthritis is relevant, in that HTRA1 has been implicated in this condition [19].

There is still strong evidence to support HTRA1 as an AMD susceptibility gene. The association seen by Yang and colleagues in a Caucasian population has been replicated in wet AMD in an Asian population [4]. Given that the consistently replicated Y402H CFH variant is rare in Asian populations [29], this transethnic trend adds strength to the HTRA1 hypothesis. The proposed interaction of HTRA1 with growth factors may also be important. HTRA1 may increase the amount of circulating IGF by cleavage from IGF-binding proteins. An increase in IGF will result in an increase in vascular endothelial growth factor, itself a marker for AMD susceptibility [30,31] and a therapeutic target for exudative AMD treatment [2]. Inhibition of TGF-β, a potent anti-angiogenic molecule, adds further support to HTRA1’s role in neovascular AMD [29]. Similarly, inhibition of TGF-mediated homeostatic functions observed in osteoarthritis [19,23,28] may have some implications in the atrophic events observed in early and dry AMD.

Interestingly, there does appear to be some conflicting, even paradoxical roles for HTRA1. Perhaps the contradiction extends from the protein’s dual temperature-dependent role as chaperone and protease in prokaryotes. Primarily, the function of a serine protease as a tumor suppressor is in itself seemingly paradoxical. In ovarian cancer, HTRA1 is down-regulated by deletions in the 10q26 region known as loss of heterozygosity (LOH). However, with considerable homology to the apoptosis-inducing HTRA2, HTRA1 can also induce cell death on re-expression [32], can improve the effectiveness of anticancer drugs cisplatin and paclitaxel and can even be upregulated by other chemotherapy agents [33]. The hypothesis to explain this paradox is that just as temperature changes influence HTRA activity in bacteria, alterations from normal cellular activity to abnormal cause a switch in HTRA1 from secreted, homeostatic functions to intracellular accumulation, leading to cell death [32,33], a process prevented by LOH events.

In the context of maculopathy, HTRA1 appears to act in dual roles. As a promoter of angiogenesis via IGF and TGF pathways, it has a potential function in wet AMD, whereas the strong expression in drusen [1], disruption of extracellular matrix homeostasis and protease activity supports a role in early and dry AMD. Interestingly, the CFH risk variant (Y402H) has been similarly implicated in both forms of AMD [22,34]. Perhaps it is the interaction with environmental factors, such as smoking [21] or antioxidant intake [2], that influence the transition from one form of AMD to another. As more is discovered regarding the pathophysiology of AMD, it appears that events driving atrophic and neovascular maculopathy could be linked, inviting the possibility of developing new therapies that target both the early and late stages of the disease process.
Bibliography


