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 [23]. 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.