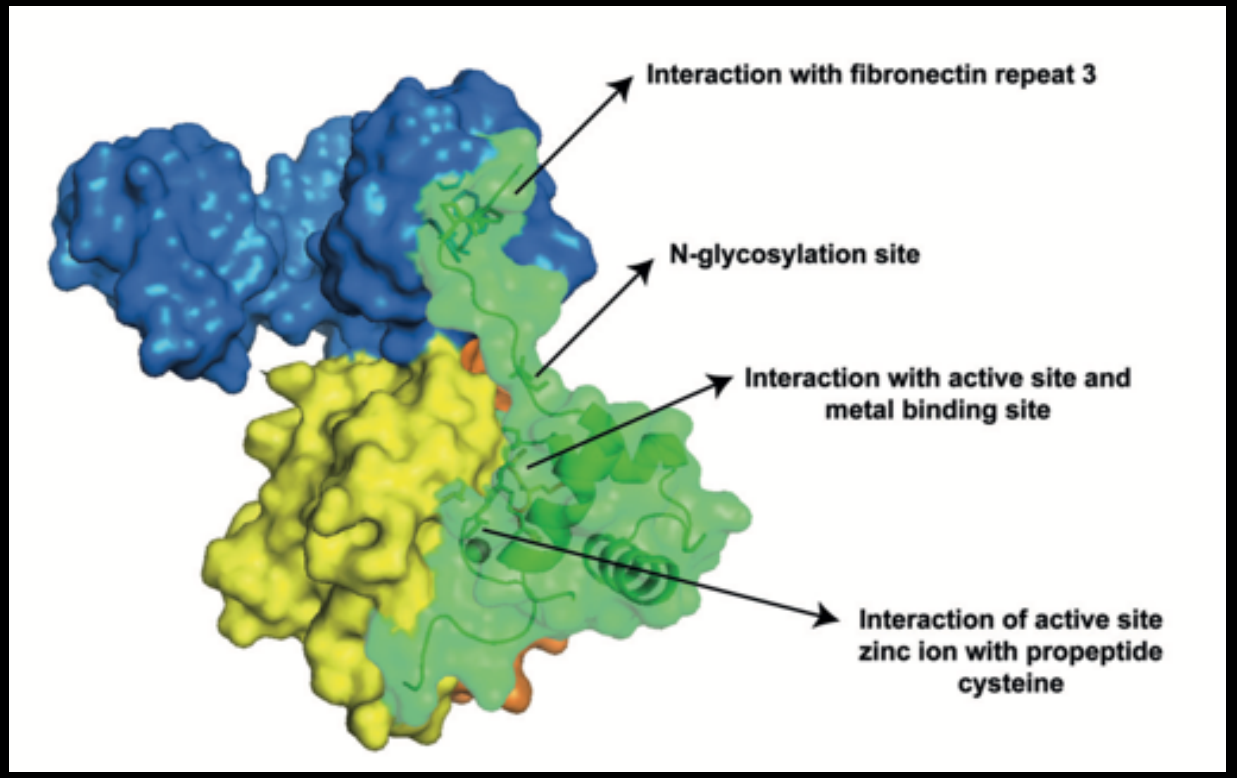
Genetic Association near *MMP9* with Choroidal Neovascularization in AMD



MMP-9 proprotein. Elkins et al. Acta Crystallogr D Biol Crystallogr 2002

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Elliott Sohn, MD
Associate Professor
Director of Retina Fellowships

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Oxford Biomedica

-PI for wet AMD gene therapy clinical trial (GEM/Retinostat)

Dutch Ophthalmic

-Faculty for JumpStart Retina (surgery course for incoming fellows)

Summary

- There is conflicting evidence whether mutation near *MMP9* is associated with exudative AMD
- 1712 subjects with AMD (672 dry, 1040 wet)
- 3 SNPs and a repetitive, polymorphic STRP in *MMP9* locus are associated with development of exudative AMD
- This the first study to independently confirm and expand an association between *MMP9* and wet AMD

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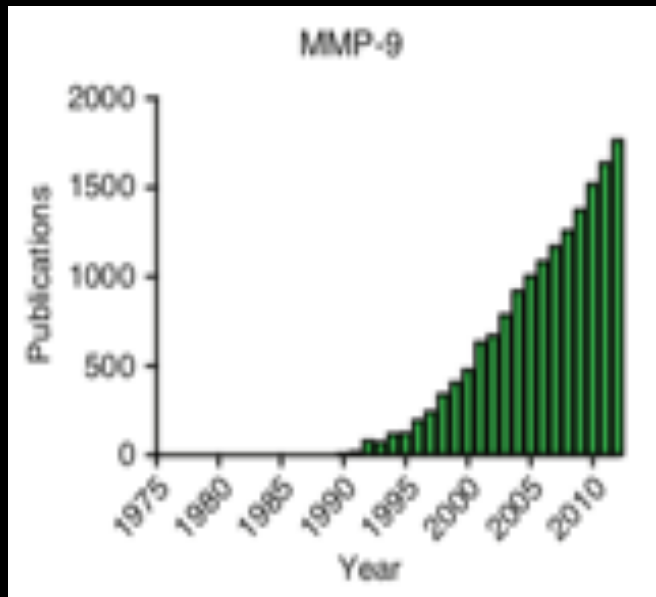
What is matrix metalloproteinase-9 (MMP-9)?

- Aka 92 kDa type IV collagenase or gelatinase B
- Zinc family of MMPs associated with extracellular matrix degradation
- Substrates include: elastin and collagen IV (Bruchs membrane)
- Implicated in numerous diseases: cancer, periodontal, atherosclerosis, emphysema, rheumatoid & osteo-arthritis, pemphigoid, more…



VanDooren et al 2013

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MMP-9, Bruchs, and choroidal neovascularization

- MMP-9 found in Bruchs membrane and choroid (choroidal macrophages)

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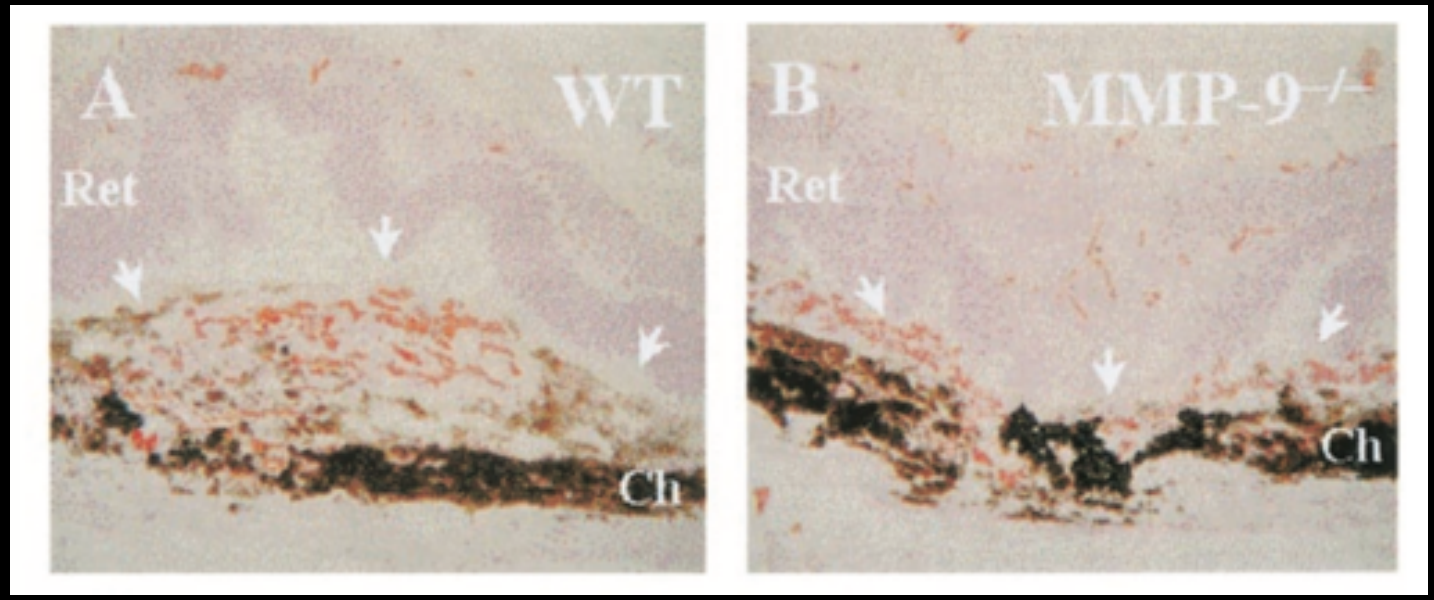
MMP-9, Bruchs, and choroidal neovascularization

- MMP-9 found in Bruchs membrane and choroid (choroidal macrophages)
- Elevated plasma MMP-9 in humans with AMD and CNV
- Absence of MMP-9 (knockout mice) prevents development of CNV



Lambert et al
FASEB 2003

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MMP-9 genetics and exudative AMD

- Fritsche et al (IAMDGC, Nature Genetics 2015) reported first genetic signal specific to wet AMD near *MMP-9* (SNP rs142450006, TTTTC/T)

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MMP9 Gene Polymorphism is not Associated with Polypoidal Choroidal Vasculopathy and Neovascular Age-related Macular Degeneration in a Chinese Han Population

Renpan Zeng, Xiongze Zhang, Kunfang Wu, Yu Su & Feng Wen

Ophthalmic Genetics 2014

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Study question:
Is genetic mutation near MMP-9 associated with exudative AMD in an independent cohort?

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Is genetic mutation near MMP-9 associated with exudative AMD in an independent cohort?

Replication is essential from a GWAS study to establish true genetic association;

especially when contrary findings were published in an independent study

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Selection of proxy SNPs in *MMP-9*

- Identified a set of SNPs in *MMP-9* locus associated with exudative AMD in the IAMDGC dataset
  - rs4810482, rs17576, rs17577
  - These SNPs are in linkage disequilibrium (D'>0.9) with each other as well as the rs142450006 SNP (i.e. they are NOT independent of one another)

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Confirmation that the 3 SNPs from the IAMDGC dataset are associated with exudative AMD (re-analysis)

	Re-analysis of IAMDGC cohort					
	Control vs Non-exudative		Control vs Exudative		Non-exudative vs Exudative	
Marker	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
rs4810482 (C)	1.01 (0.96-1.15)	0.82	0.88 (0.84-0.92)	5.8×10^{-9}	0.87 (0.83-0.91)	1.3×10^{-7}
rs17576 (G)	1.02 (0.97-1.07)	0.44	0.88 (0.84-0.92)	3.5×10^{-9}	0.86 (0.81-0.90)	3.8×10^{-9}
rs17577 (A)	0.97 (0.91-1.04)	0.44	0.82 (0.77-0.88)	7.2×10^{-10}	0.83 (0.77-0.89)	1.7×10^{-7}

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3 SNPs from the IAMDGC dataset do not increase risk for non-exudative AMD compared to controls (re-analysis)

	Re-analysis of IAMDGC cohort					
	Control vs Non-exudative		Control vs Exudative		Non-exudative vs Exudative	
Marker	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
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Phenotyping and genotyping of Iowa AMD Cohort

- 1712 patients with AMD seen at UIHC, categorized to non-exudative (n=672) and exudative (n=1040) AMD
- SNPs rs4810482, rs17576, rs17577 were genotyped using TaqMan

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3 *MMP-9* SNPs are associated with exudative AMD in the Iowa cohort

	Minor allele frequency			Non-exudative vs Exudative in Iowa cohort	
Marker	gnomAD	Non-exudative	Exudative	OR (95% CI)	P-value **Bonferroni corrected <0.017**
rs4810482 (C)	0.383	0.381	0.337	0.82 (0.71-0.95)	0.010
rs17576 (G)	0.356	0.375	0.341	0.86 (0.75-0.99)	0.046
rs17577 (A)	0.148	0.153	0.128	0.80 (0.67-0.99)	0.041

Originally reported *MMP-9* SNP is an STRP

- Rs142450006, reported as 4bp in/del, actually lies within a short tandem repeat polymorphism (STRP)
  - We discovered a tetranucleotide repeat sequence $(TTTC)_n$ at this locus

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  - We discovered a tetranucleotide repeat sequence $(TTTC)_n$ at this locus
- Developed a PCR-based assay to genotype AMD patients at this locus by determining the number of TTTC repeats
- → significant association between the most common allele of the STRP and exudative AMD (OR=0.78, 95% CI 0.64-0.95; p=0.016).

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Conclusions

- First independent confirmation of genetic association of *MMP-9* locus with exudative AMD
- Originally reported SNP by Fritsche and IAMDGC colleagues is an STRP
- MMP-9 may play a specific role in CNV formation
  - Only locus known to be associated only with CNV in AMD
- Future work will elucidate mutation of this locus, function of MMP-9 and reveal new biological pathways and therapeutic targets for AMD

The University of Iowa
Institute for Vision Research

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