Revisiting Factor H in Age-Related Macular Degeneration

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References

Background

- **AMD** is the leading cause of blindness in UK
- Significant heritable component (5-10x↑risk if parent/sibling affected)
- Complement proteins found in **drusen**
- Complement gene variants affecting the **alternative pathway** (e.g. complement factor H, **CFH**) ↑risk of AMD development/progression

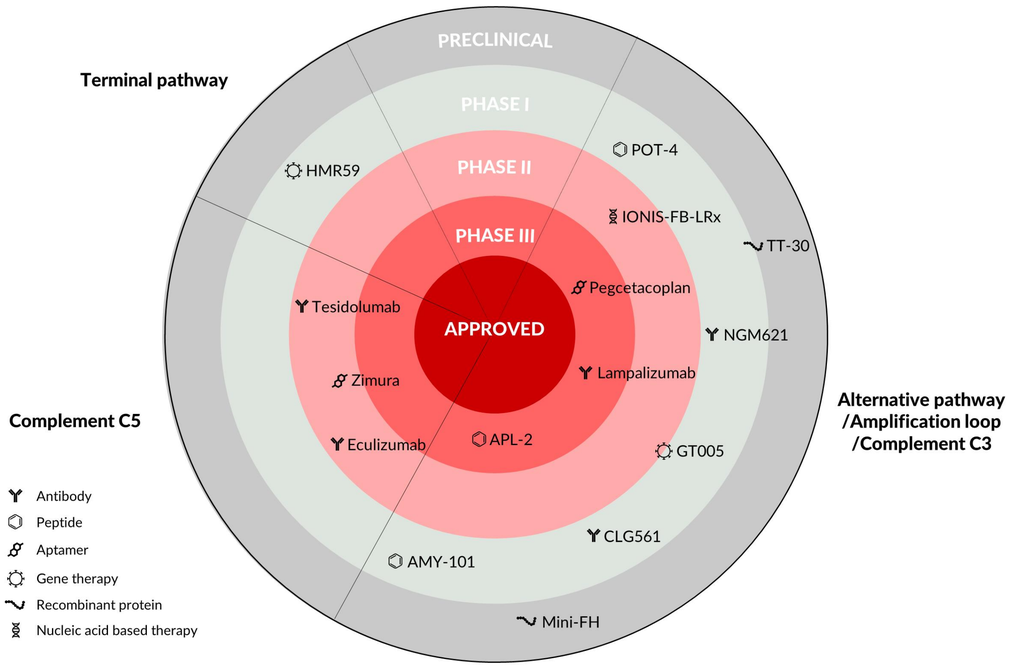
Complement

- 3x highly-regulated immune cascades: **classical, lectin, alternative**
- **C3b** creation by C3 convertases is key, a potent opsonin
- Culminate in membrane attack complex (**MAC**) aka terminal pathway
- The alternative pathway has an inbuilt **amplification loop**
- Roles in **host defence, immune clearance, angiogenesis, tissue remodelling, autophagy**
- Regulators (eg CFH, CFI) prevent damage to host tissues
- **CFH** is spliced into **FH** (key alternative pathway regulator) and **FHL-1** (key regulator in the Bruch's membrane and retina)

CFH variants → complement overactivity

- Most common: **Y402H** (rs1061170) OR 2.3 (↓inflammatory clearanc
- Most affect the **N-terminal**: I62V OR 2.4 (↑complement activity)
- Some affect the **C-terminal**: R1210C OR 20.3 (partial FH deficiency)
- Some **intronic** variants: rs1410996 OR 1.5 (?mechanism)

Complement inhibitors are an emerging treatment for AMD



Therapy considerations

• Target

- Supply of complement regulators may have enduring benefits compared to blockade of activators (↓injections)
- Targeting upstream components (e.g. C3) may ↑efficacy

• Route

- Bruch's membrane impermeable to many systemic complement proteins, **local inhibition** (e.g. intravitreal or subretinal: transvitreal/suprachoroidal) may overcome this

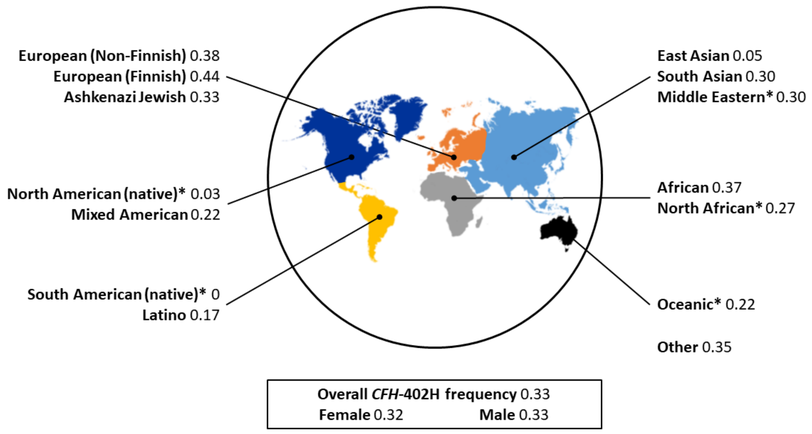
• Adverse effects

- **New-onset exudative AMD** observed in several studies (rates ~10% compared to fellow eye rates ~3%) - unclear mechanism, ?inhibition of anti-angiogenic macrophages

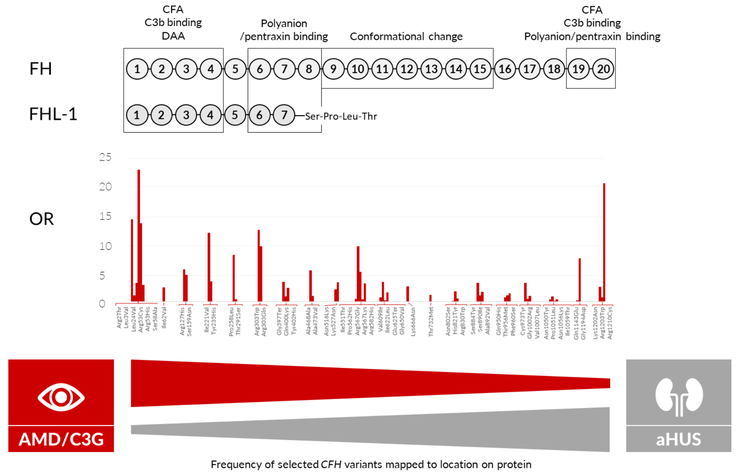
• Genetics

- CFH variants affect response to anti-VEGF therapy, pharmacogenetic interaction with anti-oxidants unclear
- Routine genetic screening not currently recommended but still important research tool
- Lampalizumab (anti-Factor D) ↓↓GA lesion growth in CFI variant carriers in Phase 2 (but no association in Phase 3)

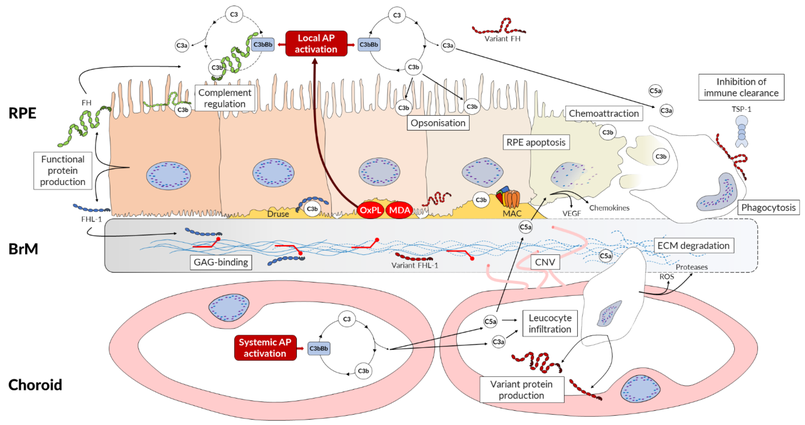
Y402H is the most common genetic risk factor for AMD



CFH variants predispose to AMD and renal disorders



AMD is a disease of general complement dysregulation



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Literature search

Cochrane, DARE, Medline, Embase, PubMed, WoS, Scopus, Google Scholar, OpenGrey, & Trip databases searched over the period 19/08/2019 - 31/05/2020. 2 500 unique abstracts were screened, of which 254 articles were included in our qualitative synthesis.

Disclosures

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