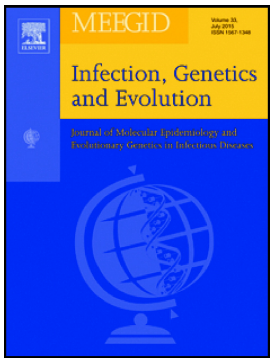

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Disease profiles in the Indigenous Australian population are suggestive of a common complement control haplotype

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Abstract. Aboriginal and Torres Strait Islander People (respectfully referred to as Indigenous Australians herein) are disparately burdened by many infectious and chronic diseases relative to Australians with European genetic ancestry. Some of these diseases are described in other populations to be influenced by the inherited profile of complement genes. These include complement factor B, H, I and complement factor H-related (*CFHR*) genes that can contribute to a polygenic complotype. Here the focus is on the combined deletion of *CFHR1* and *3* to form a common haplotype (*CFHR3-1Δ*). The prevalence of *CFHR3-1Δ* is high in people with Nigerian and African American genetic ancestry and correlates to a higher frequency and severity of systemic lupus erythematosus (SLE) but a lower prevalence of age-related macular degeneration (AMD) and IgA-nephropathy (IgAN). This pattern of disease is similarly observed among Indigenous Australian communities. Additionally, the *CFHR3-1Δ* complotype is also associated with increased susceptibility to infection with pathogens, such as *Neisseria meningitidis* and *Streptococcus pyogenes*, which also have high incidences in Indigenous Australian communities. The prevalence of these diseases, while likely influenced by social, political, environmental and biological factors, including variants in other components of the complement system, may also be suggestive of the *CFHR3-1Δ* haplotype in Indigenous Australians. These data highlight a need to define the Indigenous Australian complotypes, which may lead to the discovery of new risk factors for common diseases and progress towards precision medicines for treating complement-associated diseases in Indigenous and non-Indigenous populations. Herein, the disease profiles suggestive of a common complement *CFHR3-1Δ* control haplotype are examined.

1. Introduction. Complement is a humoral system of proteins with greater than 50 soluble and membrane-bound members, which are fundamental in protecting the host from invading pathogens (1, 2). Activating the complement cascade generates protein components with multiple functions, including marking non-self surfaces for opsonisation and phagocytosis, releasing potent chemokines and cytokines, and ultimately resulting in pathogen or controlled host-cell death (3). Misdirected complement activation can cause severe disease in the host and is therefore heavily regulated. Although the complement system is ancient, with the first complement analogues evolving 700 million years ago in sea urchins, some human complement regulatory genes have only been acquired in higher-order primates as recently as 19 million years ago (4, 5). These more evolutionarily recent complement components, such as the complement factor H-related genes (*CFHR*), have diverse haplotypes worldwide that cluster by ethnicity, resulting in populations with distinct complement phenotypes (6, 7). For example, European populations have a different haplotype of complement regulatory components when compared to Sub-Saharan African populations, proposedly driven by selective pressures of autochthonous infectious diseases (8, 9). The combination of conserved and evolutionarily newer and more variable complement proteins forms a 'complotype', the combination of genetic variants within complement genes.

As each complotype interacts with infectious and autoimmune diseases differently, commonalities in diseases attributed to responses to infection and complementopathy can suggest similar complotypes. The Aboriginal and Torres Strait Islander population of Australia (respectfully referred to as Indigenous Australians hereafter) are the oldest living culture globally and have endured substantial health inequity as a consequence of colonisation, dispossession, and political oppression, including high rates of infectious diseases in the last few centuries (10). Herein, data is considered on the occurrence in Indigenous Australians of autoimmune diseases and altered susceptibility to infections that are known to be associated with genetic variation in a number of complement genes, including the relatively common and recently acquired concomitant deletion of *CFHR1* and *CFHR3* (*CFHR3-1Δ*). The disease profile suggests that Indigenous Australians may carry the *CFHR3-1Δ* haplotype alone or as a polygenic risk factor and supports future studies that may impact our understanding of the *CFHR3-1Δ* haplotype in relation to health outcomes.

2. *CFHR3-1Δ*: A common haplotype that influences autoimmune and infectious diseases. Complement factor H (FH) is a major negative controller of the alternative pathway of the complement system, and the FH family is comprised of FH like-1 and complement FH-related (FHR) proteins(5, 11, 12). *CFHR3* and *CFHR1* are situated in tandem on chromosome 1, downstream of *CFH*

(5). Flanking the 5' end of *CFHR3* and the 3' end of *CFHR1* are 29 kb duplicated regions of the chromosome. The genotype *CFHR3-1Δ* is an 86.4 kb deletion caused by the excision of these genes by nonallelic homologous recombination at the 29kb duplicated regions (Figure 1). Notably, *CFHR3-1Δ* is the most common structural variant generated by genomic rearrangements in the *CFH/CFHR* locus but other variants and genomic rearrangements also occur and can influence plasma FH levels and contribute to disease outcomes (13, 14). Characterisation of complotypes has revealed copy number variants of the *CFHR* family grouped by genetic ancestry in a multiethnic study by Holmes *et al* (6). The authors reported lower frequencies of *CFHR3-1Δ* in Caucasian populations (<20% in all studied groups) and much higher frequencies in populations of African descent, such as Nigerian (53%) and African American (42%) groups (6). The highest rates of *CFHR3-1Δ* in Sub-Saharan African ethnicities appear to follow human migration patterns out of Africa and be carried forward into Indian populations, such as Western Indians (Gujarati), with a frequency of 38.3% (15). There is genetic evidence of an association between the migration of early Indian and Australian populations prior to European colonisation. (15, 16). Hence, genetic elements in early Indian populations have the potential to carry forward into Indigenous Australian populations, including the *CFHR3-1Δ* haplotype (6, 15, 16, 17, 18). Interestingly, *CFHR3-1Δ* is protective of some diseases but also associated with an increased risk of others. For instance, elevated FHR1 and FHR3 but not FH is seen in age-related macular degeneration (AMD), whereby variants in the *CFH/CFHR* gene locus are considered the main susceptibility factor for disease (19, 20). *CFHR3-1Δ* protects against the development of AMD and also IgA nephropathy (IgAN) (6, 21, 22, 23, 24, 25, 26). Conversely, *CFHR3-1Δ* increases the risk of developing rarer autoimmune disorders such as systemic lupus erythematosus (SLE) (6, 26, 27) and atypical haemolytic uraemic syndrome (a-HUS) (28, 29, 30). The *CFHR3-1Δ* genotype can also occur in a more complex complotype, with case reports describing *CFHR3-1Δ* and *CFI* mutations associated with *Streptococcus pneumoniae* (*S. pneumoniae*)-associated thrombotic microangiopathy (31), *CFHR3-1Δ* and a C3 variant associated with complement-mediated kidney disease (32) multiple genetic changes in *CFH/CFHR1* associated with disease, as reviewed for a-HUS (14) and with other complement variants such as those that occur in *CFI* and *CFHR1* also contributing to AMD (33, 34, 35). Additionally, due to positive selective pressures, a population's prevalence of the *CFHR3-1Δ* haplotype is geographically associated with endemic infectious diseases that interact with FHR proteins (6). For example, the *CFHR3-1Δ* haplotype decreases the risk of diseases such as malaria and leprosy, which drive the haplotype selection in Sub-Saharan Africans, who have the highest rates of *CFHR3-1Δ* in the world concomitant with a high burden of malaria and other infectious diseases (36, 37, 38). The frequency of *CFHR3-1Δ* in the Indigenous Australian population has not yet been studied and an Indigenous-led approach to

undertake a scientific study of this kind is needed with trust, accountability and equity as a foundation. The goal of this review is to provide this scientific rationale (39).

3. Evidence for higher frequencies of *CFHR3-1Δ* among Indigenous Australians based on non-infectious disease prevalence: low rates of IgAN and AMD but high rates of SLE. Due to numerous socioeconomic, political, and environmental pressures, Indigenous Australians are disproportionately burdened by various infectious and chronic diseases compared to non-Indigenous Australians with European ancestry (10). Indigenous Australians are known to have lower rates of IgAN and AMD and higher rates of SLE: a typical disease pattern of the *CFHR3-1Δ* haplotype. The polygenic nature of these diseases are notable, and there are well-described co-associations of *CFHR3-1Δ* with other *CFH/CFHR* gene cluster variants that are also likely to influence disease susceptibility. On a population level, however, the combined susceptibility profile to IgAN, AMD and SLE suggests at least *CFHR3-1Δ*.

Chronic kidney disease is a major cause of morbidity and mortality for Indigenous Australians, with end-stage kidney failure (ESKF) prevalence approximately 6-fold higher and occurring 30 years younger in the Indigenous Australian population (40, 41). However, analysis of renal biopsies suggests that IgAN is less prevalent among Indigenous Australians with ESKF (between 12.7-19.1% Indigenous Australians versus 24.4% for non-Indigenous Australians, p = 0.001), despite a predisposition to other kidney diseases (Table 1) (42). Similarly, while AMD is a leading cause of blindness and vision impairment among non-Indigenous Australians, contributing to 10.3% of all vision loss cases, AMD among Indigenous Australian people is uncommon (43, 44). Since increasing age is a significant risk factor for developing AMD, the shorter life expectancy of Indigenous Australians may contribute, at least in part, to these observations (45). In the National Indigenous Eye Health Survey, vision loss because of advanced AMD was infrequently reported (prevalence of 0.95% in Indigenous Australians vs 10.3% in non-Indigenous Australians). In the Central Australia Ocular Health Study, there were no reported cases of vision loss from AMD (study size >1300) (43, 44). More recently, the Australian National Eye Health Survey found rates among non-Indigenous Australians for intermediate and late AMD to be 10.5% and 0.96%, respectively. By comparison, the prevalence of intermediate AMD was 5.7%, and for late AMD, only three cases (0.17%) were found among Indigenous Australians compared to 33 cases among non-Indigenous Australians (Table 1) (46). Hence, AMD-related vision loss and clinical findings of AMD are less common amongst Indigenous Australians.

In contrast, although protection from IgAN and AMD are known benefits of the *CFHR3-1Δ* haplotype, the *CFHR3-1Δ* haplotype increases the risk of SLE (23, 27, 47). Indigenous Australians are disproportionately affected by SLE (27, 48, 49, 50, 51, 52, 53), with a prevalence approximately four-fold higher than in Caucasians from the same geographical area in Central Australia (1 per 1360 versus 5170, Table 1) (52). The disparity of SLE prevalence observed in Central Australian Indigenous communities was also observed in other communities from the Northern Territory (48). In a study of 24,900 people, Indigenous Australians had 1 case of SLE per 1900 people, approximately twice the prevalence of SLE when compared to the reported national average of 1 per 4000. Additionally, two separate studies conducted in far North Queensland communities described rates of SLE in two distinct Indigenous Australian communities to be four-fold higher than in Australians of European descent from the same community and region (Table 1) (49, 50). Furthermore, the rates of SLE-associated mortality were estimated as 3-fold higher in Indigenous Australians compared to non-Indigenous Australians, although this increased SLE-associated mortality may be confounded by limited access to treatment and services. Nevertheless, these mortality rates mirror the comparative mortality rates of SLE patients of African descent (54). Compounding evidence from multiple communities thus demonstrates that SLE is more prevalent and potentially more aggressive in Indigenous Australian people, regardless of region, and maps to the observation of other ethnic groups carrying high prevalence of the *CFHR3-1Δ* phenotype.

4. The predicted impact of *CFHR3-1Δ* on infectious diseases relevant to Indigenous Australian Communities. The primary function of complement is to defend against invading pathogens. The potential impact of specific complotypes, such as *CFHR3-1Δ*, on infectious diseases in Indigenous Australians needs to be considered. The Australian Institute of Health and Welfare report on the overall burden of chronic and infectious diseases among Indigenous Australians highlights alarming infectious disease disparities. In particular, the increased burden of disease associated with two important pathogens, *Neisseria meningitidis* and *Streptococcus pyogenes,* was outlined. While social and environmental factors certainly contribute to the prevalence of these bacterial infections, these two organisms are also well described to employ mechanisms for evading complement alternative pathway (AP)-mediated cell killing and thus are advantaged in infecting individuals with a reduced suite of complement proteins (55, 56).

N. meningitidis is the causal agent of several clinically important diseases, including meningococcal meningitis, with Indigenous Australians having four times higher rates than non-Indigenous Australians (2.77 vs 0.72 per 100 000 cases) (57, 58). The interactions between *N. meningitidis* and

complement are well characterised, where the lectin binding pathway and AP activity are vital for the clearance of this bacteria (59, 60). To protect the bacteria from complement and subvert the host defences, *N. meningitidis* binds the host complement AP regulatory protein, FH through its own bacterially derived FH binding protein (FHbp). This recruits FH to the bacterial cell surface, whose normal function is to protect surfaces from AP-driven complement attack, which negates AP-driven complement activation and cell killing. In support of the importance of this role of *N. meningitidis* immune evasion through binding FH is the genome-wide association study linking CFH variants with meningococcal disease susceptibility (61, 62). Additionally, FHR-3 also binds FHbp (Figure 2) and competitively inhibits FHbp binding to FH (63, 64). Consequently, when both FH and FHR-3 are present, there is less FH-FHbp bound to the *N. meningitidis* cell surface and more complement-mediated bacterial cell killing. Conversely, a reduction or loss of FHR-3, for instance, as a part of the *CFHR3-1Δ* haplotype, is predicted to result in increased FH-FHbp bound to the surface of *N. meningitidis*, which will assist in the evasion of complement mediated bacterial cell killing (Figure 2). Similar competition of FHR1 with FH binding to malondialdehyde modified self surfaces is the proposed rationale for the protective effect of *CFHR3-1Δ* against AMD, where reduced FHR1 is predicted to increase FH binding to surfaces and protect against complement-mediated damage (65). Evidence, however, suggests the depiction in Figure 2 for *N. menigitidis* interactions with FH, is simplistic. Although *CFHR3-1Δ* is prevalent in populations where *N. meningitidis* disease is high, studies have failed to find an association of the *CFHR3-1Δ* haplotype with *N. meningitidis* risk (66) or only observed links of *CFHR3-1Δ* with *N. meningitidis* risk in the context of other variants in the *CFH/CFHR* cluster (67). For instance, a *CFHR3* SNP was linked to a decrease in circulating FH and protection against meningococcal disease, which mechanistically was due to the SNP negatively regulating FH expression at the promoter level. Thus the balance of FH and FHR3 may contribute to the overall susceptibility to *N. meningitidis* disease (63, 67, 68). Further, variations in *N. meningitidis* FHbp expression, driven by strain variation in the promoter region, are associated with invasive meningococcal disease risk (69, 70, 71). Therefore, a deficit in FHR-3, as seen in the *CFHR3-1Δ* haplotype, would be expected to result in greater susceptibility to *N. meningitidis* infection and has a likely complex interplay with host FH levels and *N. meningitidis* expression of FHbp to impact disease.

Streptococcus pyogenes is another pathogen that disproportionately burdens the Indigenous Australian community and the complement AP plays a critical role in regulating *S. pyogenes* infection (72, 73, 74). Like *N. meningitidis*, *S. pyogenes* avoid complement-mediated destruction through the bacterial M protein and probably other FH binding properties, which bind FH and prevent AP activation on the bacterial surface (75). The interaction between the M protein of *S. pyogenes* and

FHR-3 has yet to be described, but based on >85% sequence homology to regions of FH that bind the M protein (short consensus repeats [SCR] 6 and 7 (75), an interaction of *S. pyogenes* M protein with FHR-3 is likely. Furthermore, genetically conferred protection from *S. pyogenes* due to a common complement FH haplotype has been described by Haapasalo et al. (2008), where the CFH Y402H allotype has reduced binding to the surface of *S.pyogenes* resulting in improved complement-mediated destruction of the bacteria (76). Interestingly, *CFHR3-1Δ* is in linkage disequilibrium with CFH and occurs with Y402 more frequently than the Hardy-Weinberg equilibrium would estimate (77). The Y402H variant is also notable for increasing the risk of AMD. Thus, the CFH 402H/CFHR3-1^{+} genotype is associated with a reduced risk of *S. pyogenes* and an increased risk of AMD, but the CFH Y402/*CFHR3-1Δ* genotype is associated with an increased risk of *S. pyogenes* infection and reduced AMD. It is not clear, however if the AMD and *S. pyogenes* risk is associated with independent actions of *CFHR3-1Δ* or a linked FH variant, again highlighting the potential contribution of multiple variants in the *CFH/CFHR* locus. The predicted risk of the Y402/*CFHR3-1Δ* genotype mirrors the phenotype of the studied Indigenous Australian populations – increased risk of *S. pyogenes* infection and reduced risk of AMD. These associations further highlight that the vulnerability of Indigenous Australians to *S. pyogenes* infections may not only be driven by sociоeconomic and health inequities but also influenced by the *CFHR3-1Δ* haplotype.

While acute *S. pyogenes* infections are problematic, significant health outcomes are impacted by post-infectious sequelae, whereby antibodies produced against the *S. pyogenes* M-protein can cross-react with host tissues (78). These immune responses can cause progressive tissue damage, particularly in the heart and kidneys, leading to rheumatic heart disease (RHD) and acute post-streptococcal glomerulonephritis (PSGN). There is a high diversity of *S.pyogenes emm* types associated with skin and throat infections in Northern Australia and Indigenous communities where RHD rates are high (79), and thus M-protein variants also contribute to the likelihood of RHD. PSGN causes acute kidney damage that typically resolves within two weeks but dramatically reduces life expectancy among Indigenous Australians (72, 78). For PSGN, the disproportionate burden is clear; in a 2018 study, 94% of the 323 cases were in Indigenous Australians (80). Similarly, comparative rates of PSGN in Central Australia revealed a 13.4-fold higher rate (228.7 vs 17 per 100,000) of PSGN in Indigenous Australians compared to non-Indigenous Australians (72). These data together resemble trends in the Nigerian population, where PSGN is the leading cause of child morbidity linked to renal disease (81). Significantly, PSGN correlates to chronic renal disease later in life, especially when patients have comorbidities such as diabetes and obesity (82). Similarly, RHD is also a significant post-streptococcal sequela that disproportionately affects Indigenous Australians. In 2013, a survey of Australians in the Northern Territory revealed that the Indigenous Australian

population accounted for 97.6% of RHD cases, despite accounting for only 30% of the surveyed population (83, 84). In a national registry of newly diagnosed individuals with RHD between 2013 and 2017, 83% (1041 of 1254) were Indigenous Australians (85, 86). Thus, RHD is clearly a significant and disproportionate problem among Indigenous Australian communities, with rates amongst the highest in the world and comparable to those in Sub-Saharan Africa, with the highest prevalence of at least one *CFHR3-1Δ* allele (50%) worldwide (87, 88). Although there may not be a direct relationship between *CFHR3-1Δ* and RHD or PGSN, and *S. pyogenes* strain differences are also a contributing factor, the *CFHR3-1Δ* complotype in predisposing to repeat *S. pyogenes* infection may significantly influence the development of these very important diseases.

5. Summary and the benefit of defining *CFHR3-1Δ* in Indigenous Australians. In summary, the data presented here of observations from clinical data and national health surveillance programs on disease susceptibility profiles in Indigenous Australians support disparate patterns of specific complement-associated, immune-mediated and infectious diseases. Although social and health equity issues are clear contributors to both infectious and non-infectious diseases in the Indigenous Australian population, the increased prevalence and morbidity of SLE, *N. meningitidis* and *S. pyogenes* infections, and the decreased prevalence of AMD and IgAN may partly be explained by an increased prevalence of the *CFHR3-1Δ* genotype in Indigenous Australian communities. This strongly justifies directly testing the hypothesis that Indigenous Australians bear the *CFHR3-1Δ* complotype and should be undertaken with full consideration of the *CFH/CFHR* gene cluster to define *CFHR3-1Δ* associations and those diseases potentially also associated with multiple complement gene variants (89). Genomic research in the Indigenous Australian population requires sincere ethical consideration, with establishment of a strong and honest relationship between the researchers and community, and the investigations should be Indigenous-led. Prior studies and existing databases focused on Indigenous Australian genetic research have paved the way for future research that is collaborative and respectful (85, 87, 88, 90). Retrospective improvements for engagement, involvement, translation, and governance of Indigenous Australian genetic research have also been published (91). We note that the definition of the Indigenous Australian complotype should foremost benefit and be governed by the communities involved. Such knowledge may assist in developing personalised medicine approaches to target complement factors and improve health outcomes for Indigenous Australians and other populations suffering from complement-mediated disease.

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Figure Legends

Figure 1. Mechanism for formation of *CFHR3-1Δ*. Recombination and excision of *CFHR1* and *CFHR3* results in the *CFHR3-1Δ* haplotype: *CFH*, *CFHR3*, *-1* and *-4*, on chromosome 1q31.3 are flanked by identical 29 kb sequences (red boxes). Homologous sequences across these 29 kb repeat sequences can undergo (1) recombination, followed by (2) excision of *CFHR1* and *-3* genes, leaving (3) the *CFHR3-1Δ* haplotype, lacking *CFHR1* and *-3* genes. FHR = factor H related.

Figure 2. Mechanism by which FHR-3 contributes to counteracting *Neisseria meningitidis* immune evasion and facilitates bacterial cell killing via the complement system. A. FHR-3 competes with FH for binding to the bacterial FHbp on the bacterial cell surface, allowing complement to deposit, form the MAC and lyse and kill the bacteria. **B.** Without FHR-3, FH is increased, and *N. meningitidis* binds complement FH via the bacterial FHbp, which subsequently protects the bacteria from surface complement activation, MAC formation and cell lysis, leading to bacterial survival. FHR = Factor H related, FHbp = Factor H Binding Protein, MAC = Membrane attack complex.

Table 1: The prevalence of systemic lupus erythematosus (SLE), age-related macular degeneration (AMD) and IgA nephropathy (IgAN) in Indigenous and non-Indigenous Australians with expected odds ratios.

Disease	Indigenous Australian Prevalence (%)	Non- Indigenous Australian Prevalence (%)	Odds Ratio For Indigenous vs non-Indigenous	Expected Odds Ratio for *CFHR3-1Δ*$^{-/-}$ †	Age Matched	Location Matched	Reference
SLE	0.05	0.02*	2.5	1.5	No	Yes	(48)
	0.07	0.02	3.5		No	Yes	(52)
	0.09	0.05	1.8		No	Yes	(90)
	0.09	0.02*	4.5		No	No	(90)
Intermediate AMD	5.7	10.5	0.54	0.31	Yes	Yes	(46)
Advanced AMD	0.17	0.96	0.18				
Vision impairing AMD	0.95	10.3	0.092		Yes	Yes	(91)
IgAN**	19.10	24.40	0.78	0.35 - 0.56	No	Yes	(40)
RHD	0.67	0.0109	61.1	NA	Yes	Yes	(85)

AMD = age-related macular degeneration; RHD = rheumatic heart disease; SLE - systemic lupus erythematosus

*Estimated national average at the time of study

**Frequency in biopsied nephritic patient kidneys

† Determined as $\frac{Disease\ Prevalance(CFHR3{-}1^{-/-})}{Disease\ Prevalance(CFHR3{-}1^{+/+})}$

References

1. Melis JP, Strumane K, Ruuls SR, Beurskens FJ, Schuurman J, Parren PW. Complement in therapy and disease: Regulating the complement system with antibody-based therapeutics. Molecular immunology. 2015;67(2 Pt A):117-30.
2. Ricklin D, Hajishengallis G, Yang K, Lambris JD. Complement: a key system for immune surveillance and homeostasis. Nat Immunol. 2010;11(9):785-97.
3. Muller-Eberhard HJ. The membrane attack complex of complement. Annual review of immunology. 1986;4:503-28.
4. Al-Sharif WZ, Sunyer JO, Lambris JD, Smith LC. Sea urchin coelomocytes specifically express a homologue of the complement component C3. J Immunol. 1998;160(6):2983-97.
5. Male DA, Ormsby RJ, Ranganathan S, Giannakis E, Gordon DL. Complement factor H: sequence analysis of 221 kb of human genomic DNA containing the entire fH, fHR-1 and fHR-3 genes. Molecular immunology. 2000;37(1-2):41-52.
6. Holmes LV, Strain L, Staniforth SJ, Moore I, Marchbank K, Kavanagh D, et al. Determining the population frequency of the CFHR3/CFHR1 deletion at 1q32. PLoS One. 2013;8(4):e60352.
7. Sunyer JO, Zarkadis IK, Lambris JD. Complement diversity: a mechanism for generating immune diversity? Immunol Today. 1998;19(11):519-23.
8. Ermini L, Wilson IJ, Goodship TH, Sheerin NS. Complement polymorphisms: geographical distribution and relevance to disease. Immunobiology. 2012;217(2):265-71.
9. Ireland J, Carlton VE, Falkowski M, Moorhead M, Tran K, Useche F, et al. Large-scale characterization of public database SNPs causing non-synonymous changes in three ethnic groups. Hum Genet. 2006;119(1-2):75-83.
10. Gracey M, King M. Indigenous health part 1: determinants and disease patterns. Lancet. 2009;374(9683):65-75.
11. Lucientes-Continente L, Marquez-Tirado B, Goicoechea de Jorge E. The Factor H protein family: The switchers of the complement alternative pathway. Immunological reviews. 2023;313(1):25-45.
12. Skerka C, Chen Q, Fremeaux-Bacchi V, Roumenina LT. Complement factor H related proteins (CFHRs). Molecular immunology. 2013;56(3):170-80.
13. Piras R, Breno M, Valoti E, Alberti M, Iatropoulos P, Mele C, et al. CFH and CFHR Copy Number Variations in C3 Glomerulopathy and Immune Complex-Mediated Membranoproliferative Glomerulonephritis. Front Genet. 2021;12:670727.
14. Valoti E, Alberti M, Iatropoulos P, Piras R, Mele C, Breno M, et al. Rare Functional Variants in Complement Genes and Anti-FH Autoantibodies-Associated aHUS. Frontiers in immunology. 2019;10:853.
15. Pugach I, Delfin F, Gunnarsdottir E, Kayser M, Stoneking M. Genome-wide data substantiate Holocene gene flow from India to Australia. Proc Natl Acad Sci U S A. 2013;110(5):1803-8.
16. Malaspinas AS, Westaway MC, Muller C, Sousa VC, Lao O, Alves I, et al. A genomic history of Aboriginal Australia. Nature. 2016;538(7624):207-14.
17. Metspalu M, Kivisild T, Metspalu E, Parik J, Hudjashov G, Kaldma K, et al. Most of the extant mtDNA boundaries in south and southwest Asia were likely shaped during the initial settlement of Eurasia by anatomically modern humans. BMC Genet. 2004;5:26.
18. Tobler R, Rohrlach A, Soubrier J, Bover P, Llamas B, Tuke J, et al. Aboriginal mitogenomes reveal 50,000 years of regionalism in Australia. Nature. 2017;544(7649):180-4.
19. Lores-Motta L, van Beek AE, Willems E, Zandstra J, van Mierlo G, Einhaus A, et al. Common haplotypes at the CFH locus and low-frequency variants in CFHR2 and CFHR5 associate with systemic FHR concentrations and age-related macular degeneration. Am J Hum Genet. 2021;108(8):1367-84.
20. McHarg S, Clark SJ, Day AJ, Bishop PN. Age-related macular degeneration and the role of the complement system. Molecular immunology. 2015;67(1):43-50.

21. Cantsilieris S, White SJ, Richardson AJ, Guymer RH, Baird PN. Comprehensive analysis of Copy Number Variation of genes at chromosome 1 and 10 loci associated with late age related macular degeneration. PLoS One. 2012;7(4):e35255.
22. Dhillon B, Wright AF, Tufail A, Pappworth I, Hayward C, Moore I, et al. Complement factor h autoantibodies and age-related macular degeneration. Investigative ophthalmology & visual science. 2010;51(11):5858-63.
23. Jullien P, Laurent B, Claisse G, Masson I, Dinic M, Thibaudin D, et al. Deletion Variants of CFHR1 and CFHR3 Associate with Mesangial Immune Deposits but Not with Progression of IgA Nephropathy. J Am Soc Nephrol. 2018;29(2):661-9.
24. Xie J, Kiryluk K, Li Y, Mladkova N, Zhu L, Hou P, et al. Fine Mapping Implicates a Deletion of CFHR1 and CFHR3 in Protection from IgA Nephropathy in Han Chinese. J Am Soc Nephrol. 2016;27(10):3187-94.
25. Zhu L, Zhai YL, Wang FM, Hou P, Lv JC, Xu DM, et al. Variants in Complement Factor H and Complement Factor H-Related Protein Genes, CFHR3 and CFHR1, Affect Complement Activation in IgA Nephropathy. J Am Soc Nephrol. 2015;26(5):1195-204.
26. Soraru J, Isbel N, Wong G, Coates PT, Mantha M, Abraham A, et al. Baseline characteristics of patients with atypical haemolytic uraemic syndrome (aHUS): The Australian cohort in a global aHUS registry. Nephrology (Carlton). 2020;25(9):683-90.
27. Zhao J, Wu H, Khosravi M, Cui H, Qian X, Kelly JA, et al. Association of genetic variants in complement factor H and factor H-related genes with systemic lupus erythematosus susceptibility. PLoS Genet. 2011;7(5):e1002079.
28. Park J, Yhim HY, Kang KP, Bae TW, Cho YG. Copy number variation analysis using next-generation sequencing identifies the CFHR3/CFHR1 deletion in atypical hemolytic uremic syndrome: a case report. Hematology. 2022;27(1):603-8.
29. Wilson PC, Love-Gregory L, Corliss M, McNulty S, Heusel JW, Gaut JP. Beyond Panel-Based Testing: Exome Analysis Increases Sensitivity for Diagnosis of Genetic Kidney Disease. Kidney360. 2020;1(8):772-80.
30. Zipfel PF, Wiech T, Stea ED, Skerka C. CFHR Gene Variations Provide Insights in the Pathogenesis of the Kidney Diseases Atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy. J Am Soc Nephrol. 2020;31(2):241-56.
31. Matsumoto Y, Ikezumi Y, Kondoh T, Yokoi K, Nakajima Y, Kumagai N, et al. An Infant Case of Streptococcus Pneumoniae-Associated Thrombotic Microangiopathy with Heterozygous CFI Mutation and CFHR3-CFHR1 Deletion. Tohoku J Exp Med. 2022;258(3):183-93.
32. Jandal A, Zhong W, Gopal D, Horner V, Frater-Rubsam L, Djamali A, et al. What lies in-between: C3 glomerulopathy with non-hemolytic renal microangiopathy and an ultra-rare C3 variant. Am J Med Sci. 2023;365(3):286-93.
33. de Breuk A, Lechanteur YTE, Heesterbeek TJ, Fauser S, Klaver CCW, Hoyng CB, et al. Genetic Risk in Families with Age-Related Macular Degeneration. Ophthalmol Sci. 2021;1(4):100087.
34. den Hollander AI, Mullins RF, Orozco LD, Voigt AP, Chen HH, Strunz T, et al. Systems genomics in age-related macular degeneration. Exp Eye Res. 2022;225:109248.
35. Hageman GS, Hancox LS, Taiber AJ, Gehrs KM, Anderson DH, Johnson LV, et al. Extended haplotypes in the complement factor H (CFH) and CFH-related (CFHR) family of genes protect against age-related macular degeneration: Characterization, ethnic distribution and evolutionary implications. Ann Med. 2006;38(8):592-604.
36. Rosa TF, Flammersfeld A, Ngwa CJ, Kiesow M, Fischer R, Zipfel PF, et al. The Plasmodium falciparum blood stages acquire factor H family proteins to evade destruction by human complement. Cell Microbiol. 2016;18(4):573-90.
37. Silver KL, Higgins SJ, McDonald CR, Kain KC. Complement driven innate immune response to malaria: fuelling severe malarial diseases. Cell Microbiol. 2010;12(8):1036-45.
38. Zhang DF, Wang D, Li YY, Yao YG. Mapping genetic variants in the CFH gene for association with leprosy in Han Chinese. Genes and immunity. 2014;15(7):506-10.

39. Hudson M, Garrison NA, Sterling R, Caron NR, Fox K, Yracheta J, et al. Rights, interests and expectations: Indigenous perspectives on unrestricted access to genomic data. Nat Rev Genet. 2020;21(6):377-84.
40. Hoy WE, Mott SA, Mc Donald SP. An expanded nationwide view of chronic kidney disease in Aboriginal Australians. Nephrology (Carlton). 2016;21(11):916-22.
41. Hoy WE, Mott SA, McDonald SP. An update on chronic kidney disease in Aboriginal Australians. Clinical nephrology. 2020;93(1):124-8.
42. Hoy WE, Samuel T, Mott SA, Kincaid-Smith PS, Fogo AB, Dowling JP, et al. Renal biopsy findings among Indigenous Australians: a nationwide review. Kidney Int. 2012;82(12):1321-31.
43. Landers J, Henderson T, Craig J. The prevalence and causes of visual impairment in indigenous Australians within central Australia: the Central Australian Ocular Health Study. Br J Ophthalmol. 2010;94(9):1140-4.
44. Taylor HR, Xie J, Fox S, Dunn RA, Arnold AL, Keeffe JE. The prevalence and causes of vision loss in Indigenous Australians: the National Indigenous Eye Health Survey. Med J Aust. 2010;192(6):312-8.
45. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. Lancet. 2018;392(10153):1147-59.
46. Keel S, Xie J, Foreman J, van Wijngaarden P, Taylor HR, Dirani M. Prevalence of Age-Related Macular Degeneration in Australia: The Australian National Eye Health Survey. JAMA Ophthalmol. 2017;135(11):1242-9.
47. Hughes AE, Orr N, Esfandiary H, Diaz-Torres M, Goodship T, Chakravarthy U. A common CFH haplotype, with deletion of CFHR1 and CFHR3, is associated with lower risk of age-related macular degeneration. Nat Genet. 2006;38(10):1173-7.
48. Anstey NM, Bastian I, Dunckley H, Currie BJ. Systemic lupus erythematosus in Australian aborigines: high prevalence, morbidity and mortality. Aust N Z J Med. 1993;23(6):646-51.
49. Grennan DM, Bossingham D. Systemic lupus erythematosus (SLE): different prevalences in different populations of Australian aboriginals. Aust N Z J Med. 1995;25(2):182-3.
50. Nigam A, Baer R, Green S, Neuen BL, Vile A, Mantha M. Lupus nephritis in Indigenous Australians: a single-centre study. Intern Med J. 2020;50(7):830-7.
51. Ong C, Nicholls K, Becker G. Ethnicity and lupus nephritis: an Australian single centre study. Intern Med J. 2011;41(3):270-8.
52. Segasothy M, Phillips PA. Systemic lupus erythematosus in Aborigines and Caucasians in central Australia: a comparative study. Lupus. 2001;10(6):439-44.
53. Vincent FB, Bourke P, Morand EF, Mackay F, Bossingham D. Focus on systemic lupus erythematosus in indigenous Australians: towards a better understanding of autoimmune diseases. Intern Med J. 2013;43(3):227-34.
54. Contreras G, Lenz O, Pardo V, Borja E, Cely C, Iqbal K, et al. Outcomes in African Americans and Hispanics with lupus nephritis. Kidney Int. 2006;69(10):1846-51.
55. Hovingh ES, van den Broek B, Jongerius I. Hijacking Complement Regulatory Proteins for Bacterial Immune Evasion. Front Microbiol. 2016;7:2004.
56. Jozsi M. Factor H Family Proteins in Complement Evasion of Microorganisms. Frontiers in immunology. 2017;8:571.
57. Archer BN, Chiu CK, Jayasinghe SH, Richmond PC, McVernon J, Lahra MM, et al. Epidemiology of invasive meningococcal B disease in Australia, 1999-2015: priority populations for vaccination. Med J Aust. 2017;207(9):382-7.
58. Welfare AIoHa. Australian Burden of Disease Study: Impact and causes of illness and death in Australia 2011. . In: Welfare AIoHa, editor. Canberra2016.
59. Granoff DM, Welsch JA, Ram S. Binding of complement factor H (fH) to Neisseria meningitidis is specific for human fH and inhibits complement activation by rat and rabbit sera. Infect Immun. 2009;77(2):764-9.

60. Jarva H, Ram S, Vogel U, Blom AM, Meri S. Binding of the complement inhibitor C4bp to serogroup B Neisseria meningitidis. J Immunol. 2005;174(10):6299-307.
61. Davila S, Wright VJ, Khor CC, Sim KS, Binder A, Breunis WB, et al. Genome-wide association study identifies variants in the CFH region associated with host susceptibility to meningococcal disease. Nat Genet. 2010;42(9):772-6.
62. Martinon-Torres F, Png E, Khor CC, Davila S, Wright VJ, Sim KS, et al. Natural resistance to Meningococcal Disease related to CFH loci: Meta-analysis of genome-wide association studies. Sci Rep. 2016;6:35842.
63. Caesar JJ, Lavender H, Ward PN, Exley RM, Eaton J, Chittock E, et al. Competition between antagonistic complement factors for a single protein on N. meningitidis rules disease susceptibility. eLife. 2014;3.
64. Schneider MC, Prosser BE, Caesar JJ, Kugelberg E, Li S, Zhang Q, et al. Neisseria meningitidis recruits factor H using protein mimicry of host carbohydrates. Nature. 2009;458(7240):890-3.
65. Alic L, Papac-Milicevic N, Czamara D, Rudnick RB, Ozsvar-Kozma M, Hartmann A, et al. A genome-wide association study identifies key modulators of complement factor H binding to malondialdehyde-epitopes. Proc Natl Acad Sci U S A. 2020;117(18):9942-51.
66. Bradley DT, Bourke TW, Fairley DJ, Borrow R, Shields MD, Zipfel PF, et al. Susceptibility to invasive meningococcal disease: polymorphism of complement system genes and Neisseria meningitidis factor H binding protein. PLoS One. 2015;10(3):e0120757.
67. Kumar V, Pouw RB, Autio MI, Sagmeister MG, Phua ZY, Borghini L, et al. Variation in CFHR3 determines susceptibility to meningococcal disease by controlling factor H concentrations. Am J Hum Genet. 2022;109(9):1680-91.
68. Hodeib S, Herberg JA, Levin M, Sancho-Shimizu V. Human genetics of meningococcal infections. Hum Genet. 2020;139(6-7):961-80.
69. Earle SG, Lobanovska M, Lavender H, Tang C, Exley RM, Ramos-Sevillano E, et al. Genome-wide association studies reveal the role of polymorphisms affecting factor H binding protein expression in host invasion by Neisseria meningitidis. PLoS Pathog. 2021;17(10):e1009992.
70. Spinsanti M, Brignoli T, Bodini M, Fontana LE, De Chiara M, Biolchi A, et al. Deconvolution of intergenic polymorphisms determining high expression of Factor H binding protein in meningococcus and their association with invasive disease. PLoS Pathog. 2021;17(3):e1009461.
71. Yee WX, Barnes G, Lavender H, Tang CM. Meningococcal factor H-binding protein: implications for disease susceptibility, virulence, and vaccines. Trends Microbiol. 2023.
72. Dowler J, Wilson A. Acute post-streptococcal glomerulonephritis in Central Australia. Aust J Rural Health. 2020;28(1):74-80.
73. Mika A, Reynolds SL, Pickering D, McMillan D, Sriprakash KS, Kemp DJ, et al. Complement inhibitors from scabies mites promote streptococcal growth--a novel mechanism in infected epidermis? PLoS Negl Trop Dis. 2012;6(7):e1563.
74. van der Maten E, de Bont CM, de Groot R, de Jonge MI, Langereis JD, van der Flier M. Alternative pathway regulation by factor H modulates Streptococcus pneumoniae induced proinflammatory cytokine responses by decreasing C5a receptor crosstalk. Cytokine. 2016;88:281-6.
75. Sharma AK, Pangburn MK. Localization by site-directed mutagenesis of the site in human complement factor H that binds to Streptococcus pyogenes M protein. Infect Immun. 1997;65(2):484-7.
76. Haapasalo K, Jarva H, Siljander T, Tewodros W, Vuopio-Varkila J, Jokiranta TS. Complement factor H allotype 402H is associated with increased C3b opsonization and phagocytosis of Streptococcus pyogenes. Mol Microbiol. 2008;70(3):583-94.
77. Raychaudhuri S, Ripke S, Li M, Neale BM, Fagerness J, Reynolds R, et al. Associations of CFHR1-CFHR3 deletion and a CFH SNP to age-related macular degeneration are not independent. Nat Genet. 2010;42(7):553-5; author reply 5-6.
78. Katzenellenbogen JM, Ralph AP, Wyber R, Carapetis JR. Rheumatic heart disease: infectious disease origin, chronic care approach. BMC Health Serv Res. 2017;17(1):793.

79. Holt DaG, P. Staphylococcus aureus and Streptococcus pyogenes in the north: distinctively different. Microbiology Australia. 2022(43):104-7.
80. Chaturvedi S, Boyd R, Krause V. Acute Post-Streptococcal Glomerulonephritis in the Northern Territory of Australia: A Review of Data from 2009 to 2016 and Comparison with the Literature. Am J Trop Med Hyg. 2018;99(6):1643-8.
81. Eke FU, Eke NN. Renal disorders in children: a Nigerian study. Pediatric nephrology. 1994;8(3):383-6.
82. Rodriguez-Iturbe B, Haas M. Post-Streptococcal Glomerulonephritis. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. Streptococcus pyogenes: Basic Biology to Clinical Manifestations. Oklahoma City (OK)2016.
83. Lawrence JG, Carapetis JR, Griffiths K, Edwards K, Condon JR. Acute rheumatic fever and rheumatic heart disease: incidence and progression in the Northern Territory of Australia, 1997 to 2010. Circulation. 2013;128(5):492-501.
84. Murray RC, Chennupati SK. Chronic streptococcal and non streptococcal pharyngitis. Infect Disord Drug Targets. 2012;12(4):281-5.
85. Katzenellenbogen JM, Bond-Smith D, Seth RJ, Dempsey K, Cannon J, Stacey I, et al. Contemporary Incidence and Prevalence of Rheumatic Fever and Rheumatic Heart Disease in Australia Using Linked Data: The Case for Policy Change. J Am Heart Assoc. 2020;9(19):e016851.
86. Wyber R, Noonan K, Halkon C, Enkel S, Cannon J, Haynes E, et al. Ending rheumatic heart disease in Australia: the evidence for a new approach. Med J Aust. 2020;213 Suppl 10:S3-S31.
87. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005;5(11):685-94.
88. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. Lancet. 2012;379(9819):953-64.
89. Tschernoster N, Erger F, Walsh PR, Mc Nicholas B, Fistrek M, Habbig S, et al. Unraveling Structural Rearrangements of the CFH Gene Cluster in Atypical Hemolytic Uremic Syndrome Patients Using Molecular Combing and Long-Fragment Targeted Sequencing. J Mol Diagn. 2022;24(6):619-31.
90. Bossingham D. Systemic lupus erythematosus in the far north of Queensland. Lupus. 2003;12(4):327-31.
91. Foreman J, Xie J, Keel S, Ang CS, Lee PY, Bourne R, et al. Prevalence and Causes of Unilateral Vision Impairment and Unilateral Blindness in Australia: The National Eye Health Survey. JAMA Ophthalmol. 2018;136(3):240-8.

Disease profiles in the Indigenous Australian population are suggestive of a common complement control haplotype

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HIGHLIGHTS

- Indigenous Australians are disparately impacted by disease, with a profile as below
- high frequency of SLE and low frequency of AMD and IgA nephropathy
- increased *S.pyogenes* and *N. meningitidis* infections - organisms that evade complement
- This disease burden reflects that seen in ethnicities with the CFHR3-1Δ complotype
- We propose Indigenous Australians may have CFHR3-1Δ, which contributes to disease

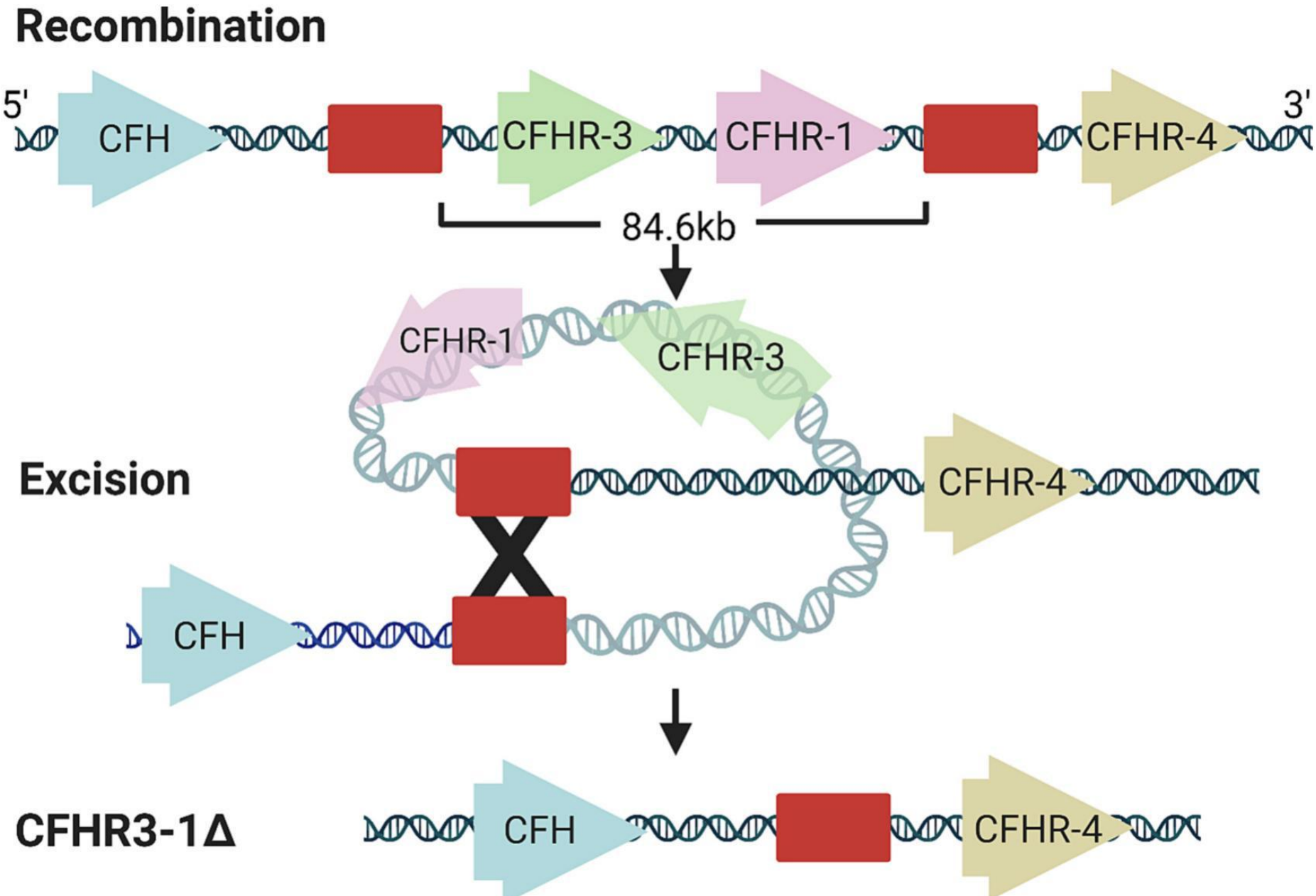
Recombination
5'
CFH
CFHR-3
CFHR-1
CFHR-4
3'
84.6kb
CFHR-1
CFHR-3
Excision
CFHR-4
CFH
CFHR3-1Δ
CFH
CFHR-4

Figure 1

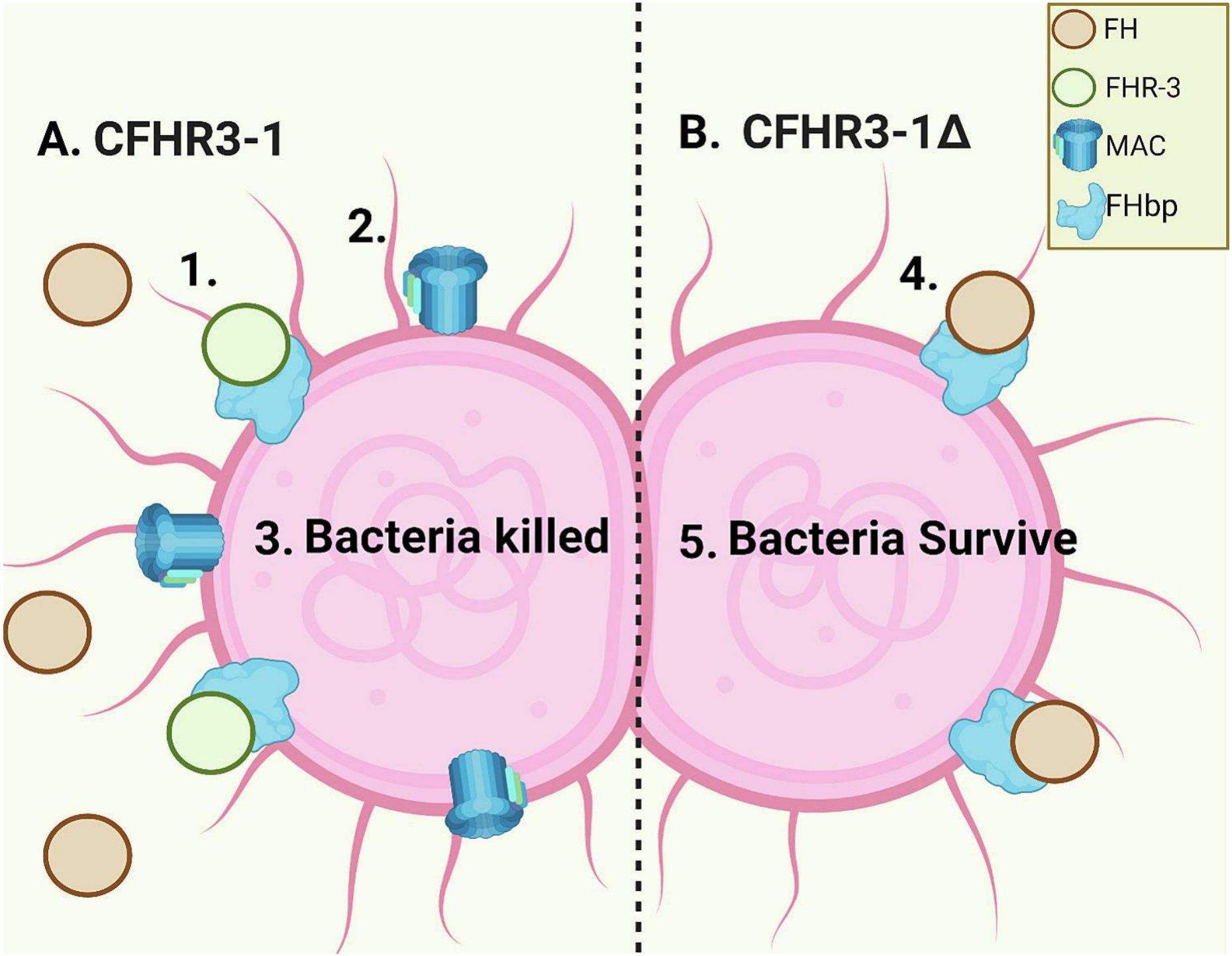
A. CFHR3-1
B. CFHR3-1Δ
FH
FHR-3
MAC
FHbp
1.
2.
3. Bacteria killed
4.
5. Bacteria Survive

Figure 2