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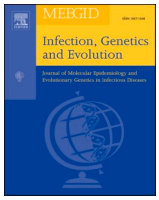

Review

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 >50 soluble and membrane-bound members, which are fundamental in protecting the host from invading pathogens (Melis et al., 2015; Ricklin et al., 2010). 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 (Muller-Eberhard, 1986). 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 (Al-Sharif et al., 1998; Male et al., 2000). 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 (Holmes et al., 2013; Sunyer et al., 1998). For example, European populations have a different haplotype of

Abbreviations: factor H, FH; age-related macular degeneration, AMD; rheumatic heart disease, RHD.

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complement regulatory components when compared to Sub-Saharan African populations, proposedly driven by selective pressures of autochthonous infectious diseases (Ermini et al., 2012; Ireland et al., 2006). 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 (Gracey and King, 2009). 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 (Male et al., 2000; Lucientes-Continente et al., 2023; Skerka et al., 2013). *CFHR3* and *CFHR1* are situated in tandem on chromosome 1, downstream of *CFH* (Male et al., 2000). 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 29 kb duplicated regions (Fig. 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

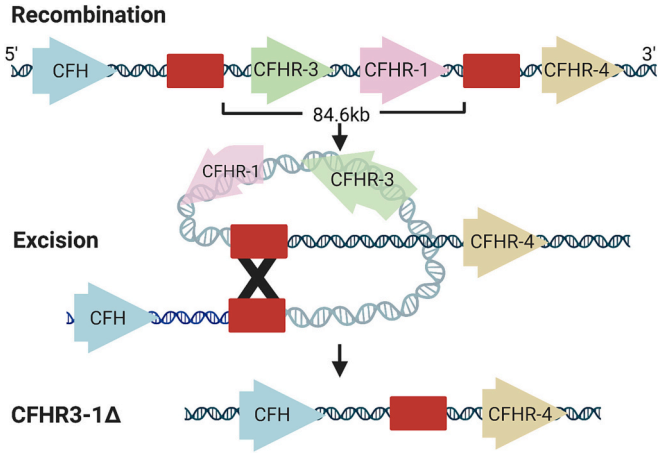

Fig. 1. Mechanism for formation of *CFHR3–1Δ*. Recombination and excision of *CFHR1* and *CFHR3* results in the *CFHR3–1Δ* haplotype: *CFH*, *CFHR3*, *−1* and *− 4*, on chromosome 1q31.3 are flanked by identical 29 kb sequences (red boxes). Homologous sequences across these 29 kb repeat sequences can undergo (Melis et al., 2015) recombination, followed by (Ricklin et al., 2010) excision of *CFHR1* and *− 3* genes, leaving (Muller-Eberhard, 1986) the *CFHR3–1Δ* haplotype, lacking *CFHR1* and *− 3* genes. FHR = factor H related. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

occur and can influence plasma FH levels and contribute to disease outcomes (Piras et al., 2021; Valoti et al., 2019). Characterisation of complotypes has revealed copy number variants of the *CFHR* family grouped by genetic ancestry in a multiethnic study by Holmes et al (Holmes et al., 2013). 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 (Holmes et al., 2013). 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% (Pugach et al., 2013). There is genetic evidence of an association between the migration of early Indian and Australian populations prior to European colonisation. (Pugach et al., 2013; Malaspinas et al., 2016). Hence, genetic elements in early Indian populations have the potential to carry forward into Indigenous Australian populations, including the *CFHR3–1Δ* haplotype (Holmes et al., 2013; Pugach et al., 2013; Malaspinas et al., 2016; Metspalu et al., 2004; Tobler et al., 2017). 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 (Lores-Motta et al., 2021; McHarg et al., 2015). *CFHR3–1Δ* protects against the development of AMD and also IgA nephropathy (IgAN) (Holmes et al., 2013; Cantsilieris et al., 2012; Dhillon et al., 2010; Jullien et al., 2018; Xie et al., 2016; Zhu et al., 2015; Soraru et al., 2020). Conversely, *CFHR3–1Δ* increases the risk of developing rarer autoimmune disorders such as systemic lupus erythematosus (SLE) (Holmes et al., 2013; Soraru et al., 2020; Zhao et al., 2011) and atypical haemolytic uraemic syndrome (a-HUS) (Park et al., 2022; Wilson et al., 2020; Zipfel et al., 2020). The *CFHR3–1Δ* genotype can also occur in a more complex complotype, with case reports describing *CFHR3–1Δ* and *CFI* mutation associated with *Streptococcus pneumoniae* (*S. pneumoniae*)-associated thrombotic microangiopathy (Matsumoto et al., 2022), *CFHR3–1Δ* and a C3 variant associated with complement-mediated kidney disease (Jandal et al., 2023) multiple genetic changes in *CFH/CFHR1* associated with disease, as reviewed for a-HUS (Valoti et al., 2019) and with other complement variants such as those that occur in *CFI* and *CFHR1* also contributing to AMD (de Breuk et al., 2021; den Hollander et al., 2022; Hageman et al., 2006). 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 (Holmes et al., 2013). 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 (Rosa et al., 2016; Silver et al., 2010; Zhang et al., 2014). 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 (Hudson et al., 2020).

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 (Gracey and King, 2009). 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 (Hoy et al., 2016; Hoy et al., 2020). However, analysis of renal biopsies suggests that IgAN is less prevalent among Indigenous Australians with ESKF (between 12.7 and 19.1% Indigenous Australians versus 24.4% for non-Indigenous Australians, $p = 0.001$), despite a predisposition to other kidney diseases (Table 1) (Hoy et al., 2012). 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 (Landers et al., 2010; Taylor et al., 2010). 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 (Mitchell et al., 2018). 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) (Landers et al., 2010; Taylor et al., 2010). 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) (Keel et al., 2017). Hence, AMD-related vision loss and clinical findings of AMD are less common among 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 (Jullien et al., 2018; Zhao et al., 2011; Hughes et al., 2006). Indigenous Australians are disproportionately affected by SLE (Zhao et al., 2011; Anstey et al., 1993; Grennan and Bossingham, 1995; Nigam et al., 2020; Ong et al., 2011; Segasothy and Phillips, 2001; Vincent et al., 2013), 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) (Segasothy and Phillips, 2001). The disparity of SLE prevalence observed in Central Australian Indigenous communities was also observed in other communities from the Northern Territory (Anstey et al., 1993). 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) (Grennan and Bossingham, 1995; Nigam et al., 2020). 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 (Contreras et al., 2006). 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 (Hovingh et al., 2016; Jozsi and Factor, 2017).

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) (Archer et al., 2017; Welfare AIoHa,

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	(Anstey et al., 1993)
	0.07	0.02	3.5		No	Yes	(Segasothy and Phillips, 2001)
	0.09	0.05	1.8		No	Yes	(Bossingham, 2003)
	0.09	0.02*	4.5		No	No	(Bossingham, 2003)
Intermediate AMD	5.7	10.5	0.54	0.31	Yes	Yes	(Keel et al., 2017)
Advanced AMD	0.17	0.96	0.18				
Vision impairing AMD	0.95	10.3	0.092		Yes	Yes	(Foreman et al., 2018)
IgAN**	19.10	24.40	0.78	0.35–0.56	No	Yes	(Hoy et al., 2016)
RHD	0.67	0.0109	61.1	NA	Yes	Yes	(Katzenellenbogen et al., 2020)

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 $\frac{Disease\ Prevalance\left(CFHR3-1^{-/-}\right)}{Disease\ Prevalance\left(CFHR3-1^{+/+}\right)}$.

2016). 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 (Granoff et al., 2009; Jarva et al., 2005). 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 (Davila et al., 2010; Martinon-Torres et al., 2016). Additionally, FHR-3 also binds FHbp (Fig. 2) and competitively inhibits FHbp binding to FH (Caesar et al., 2014; Schneider et al., 2009). 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 (Fig. 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 (Alic et al., 2020). Evidence, however, suggests the depiction in Fig. 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 (Bradley et al., 2015) or only observed links of *CFHR3–1Δ* with *N. meningitidis* risk in the context of other variants in the *CFH/CFHR* cluster (Kumar et al., 2022). 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 (Caesar et al., 2014; Kumar et al., 2022; Hodeib et al., 2020). Further, variations in *N. meningitidis* FHbp expression, driven by strain variation in the promoter region, are associated with invasive meningococcal disease risk (Earle et al., 2021; Spinsanti et al., 2021; Yee et al., 2023). 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.

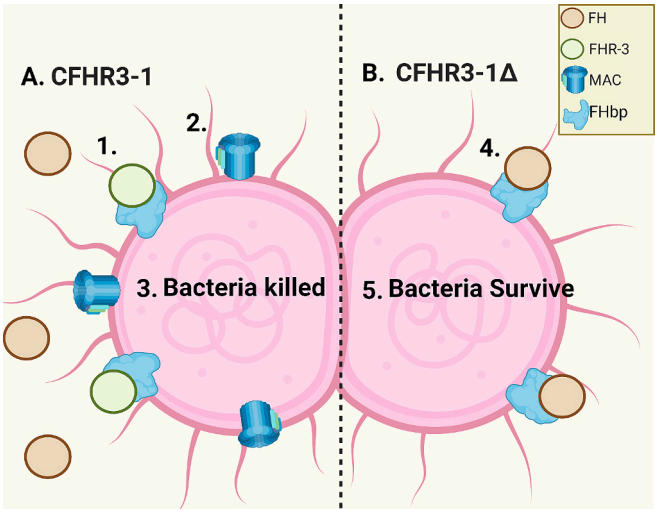

Fig. 2. Mechanism by which FHR-3 contributes to counteracting *Neisseria meningitidis* immune evasion and facilitates bacterial cell killing via the complement system. A. FHR-3 competes with FH for binding to the bacterial FHbp on the bacterial cell surface, allowing complement to deposit, form the MAC 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.

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 (Dowler and Wilson, 2020; Mika et al., 2012; van der Maten et al., 2016). 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 (Sharma and Pangburn, 1997). 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 (Sharma and Pangburn, 1997), 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 (Haapasalo et al., 2008). Interestingly, *CFHR3–1Δ* is in linkage disequilibrium with CFH and occurs with Y402 more frequently than the Hardy-Weinberg equilibrium would estimate (Raychaudhuri et al., 2010). 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 socioeconomic 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 (Katzenellenbogen et al., 2017). 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 (Holt DaG, 2022), 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 (Dowler and Wilson, 2020; Katzenellenbogen et al., 2017). For PSGN, the disproportionate burden is clear; in a 2018 study, 94% of the 323 cases were in Indigenous Australians (Chaturvedi et al., 2018). 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 (Dowler and Wilson, 2020). These data together resemble trends in the Nigerian population, where PSGN is the leading cause of child morbidity linked to renal disease (Eke and Eke, 1994). Significantly, PSGN correlates to chronic renal disease later in life, especially when patients have comorbidities such as diabetes and obesity (Rodriguez-Iturbe and Haas, 2016). 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 (Lawrence et al., 2013; Murray and Chennupati, 2012). In a national registry of newly diagnosed individuals with RHD between 2013 and 2017, 83% (1041 of 1254) were Indigenous Australians (Katzenellenbogen et al., 2020; Wyber et al., 2020). Thus, RHD is clearly a significant and disproportionate problem among Indigenous Australian communities, with rates among 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 (Carapetis et al., 2005; Marijon et al., 2012). 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 (Tschernoster et al., 2022). 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 (Katzenellenbogen et al., 2020; Carapetis et al., 2005; Marijon et al., 2012; Bossingham, 2003). Retrospective improvements for engagement, involvement, translation, and governance of Indigenous Australian genetic research have also been published (Foreman et al., 2018). 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.

Declaration of Competing Interest

None.

Data availability

No data was used for the research described in the article.

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