European Review for Medical and Pharmacological Sciences 2023; 27: 9987-10000

Clinical research advances of CFHR5 nephropathy: a recent review

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Abstract. – CFHR5 nephropathy is a type of clinical C3 glomerulopathy, which is a monogenic genetic disease caused by the internal replication of CFHR5 gene, a protein related to the complement regulatory factor H family. The disease seems to be prevalent only in people of Greek Cypriot descent. Because of the special variation of the internal replication of exon 2 and exon 3 of CFHR5 protein in the occurrence of disease, it has had a serious impact on local residents. At present, the mechanism of glomerular damage caused by CFHR5 protein mutations is still unclear. The purpose of this article is to review the clinical research advances of this disease in the past 10 years, including the study of mutant genes, the analysis of mutant proteins and the role of alternative pathways in glomerular injury. It covers the progress in diagnosis and clinical treatment of the disease and looks forward to the future development prospects of its treatment. It is hoped that the recent results will be summarized for the follow-up in-depth study of CFHR5 nephropathy.

Key Words:
C3 glomerulopathy, CFHR5 nephropathy, Cyprus, Factor H-related protein, CFHR5 protein.

Introduction

CFHR5 nephropathy is a rare disease dominated by autosomal dominant inheritance. Its clinical features are persistent microscopic hematuria, synpharyngitic macroscopic hematuria, renal failure, C3 glomerulonephritis, and proteinuria in some patients. So far, the disease has only appeared in patients of Greek Cypriot descent, with a penetration rate of 90%, belonging to the endemic cause of kidney disease, which is presumed to originate from the Troodos mountains of Cyprus[1-4]. Previously, due to the limitation of the technical level, there had been no clear results for some isolated hematuria or familial hematuria, and patients could only withstand various clinical diagnoses from doctors. It was not until 2009, when molecular techniques became available, that CFHR5 nephropathy, another manifestation of C3 glomerulonephritis, was discovered[5]. In 2010, Gale et al[1] reported the first familial glomerulopathy caused by the founder mutation of *CFHR5* gene in Greek Cypriots living in the United Kingdom. By analyzing the DNA sequences of these two groups of families by molecular technology, it was found that there was internal replication of exon 2 (*SCR1*) and exon 3 (*SCR2*) in the related protein 5 (*CFHR5*) gene of the complement regulator H family, forming a mutant protein (CFHR1212-9) different from the wild type (CFHR12-9)[6]. The mutant protein interferes with complement regulation inside the kidney, leading to complement accumulation in the glomerulus and kidney damage[7]. This leads to family C3G called CFHR5 nephropathy[1]. It has been reported in the literature that CFHR5 colocalizes in kidney tissue together with other immune deposits containing complement. The pathogenic role of this protein is not fully understood, and it is hypothesized that it may play a physiological role in complement activation in kidneys. However, there is a lack of large observation studies, and further clinical analysis is still needed[8-10]. Interestingly, Gale et al[1] showed that isolated microhematuria may be a feature of progressive kidney disease in Cypriot families. In addition, analysis of the data showed that familial isolated microhematuria attributable to heterozygous mutations in *COL4A3* and *COL4A4* was also associated with progressive chronic kidney

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disease. Therefore, this also emphasizes the importance of any history of kidney disease in the family and the value of kidney biopsy and genetic studies in this context[1,11].

At present, there is no special treatment for CFHR5 nephropathy, but more doctors are keen to use an anticomplement C5 monoclonal antibody eculizumab[2,12]. However, according to a previous report[13] on the use of eculizumab in a Turkish girl patient who only showed urinary protein, the eculizumab did not yield any efficacy. Therefore, its use in the treatment of CFHR5 nephropathy needs further research. This review shows the clinical progress of CFHR5 nephropathy developed in more than ten years and provides the latest clinical results for follow-up studies about this disease.

CFHR5 Protein

CFHR5 is a novel human plasma protein with a molecular mass of 65kDa synthesized by the liver. In 2001[8], CFHR5 was identified by a monoclonal antibody raised using pathologic human glomerular preparations as the immunogen. CFHR5 was purified by affinity chromatography from complement-lysed erythrocytes, and the peptide sequence was obtained. It is a member of the complement factor H-related protein family (CFHR1, CFHR2, CFHR3, CFHR4, CFHR5) and is inferred to be a 551 amino acid protein consisting of nine short consensus repeat (SCR) domains. Because of its linear arrangement, it is also the longest protein in the CFHR family. However, in blood circulation, the concentration is very low, only about 3-6 MCG/ML, and it is also the least abundant of the CFHR. Since CFHR5 forms a homodimer through its two N-terminal domains SCR-1/2, it is classified as a factor H family I histone, along with CFHR1 and CFHR2. Among its 9 SCR1-9, SCR1, and SCR2 are homologous to the first two SCR of CFHR1 and CFHR2, SCR3-7 has significant homology to SCR10-14 of CFH, and SCR8-9 is comparable to SCR19 and 20 of CFH[8,14-20]. Although highly homologous to CFH, CFHR5, like the other four related eggs, lacks a CFH-associated protein responsible for the domain of CFH complement regulatory activity[15]. Compared with the monovalent factor H, the saturation of C3b/C3d increases. Although earlier studies using superphysiological concentrations of CFHR5 showed that there was weak (compared to factor H) evidence of complement regulatory activity[16], recent studies have shown that, at physiological concentrations, CFHR5 competitively antagonizes factor H, thereby relaxing complement[17,18]. In addition, CFHR5 can bind to heparin, c-reactive protein, pentoxin-3, and extracellular matrix[16,21] and according to previous studies[16,22,23], it can also inhibit C3 and C5 convertase. Mutant CFHR5 has been described as a causative agent of the C3G subtype[1,7,24] (Figure 1).

The gene encoding *CFHR5* protein and the factor *H* gene are located on the fragment of human chromosome 1q32 in the *RCA* gene family[25]. *CFHR5* gene is located downstream of the factor *H* gene. Deletion, duplication and insertion of genes or chromosomes will cause changes in sequence and copy number, resulting in mutant structures different from normal ones, affecting the regulation of the normal complement system and leading to various diseases[23,26]. CFHR5 nephropathy, precisely because of the heterozygous internal replication of its gene, leads to the duplication of exons encoding the first two domains of the CFHR5 protein. Affected individuals possess both a wild-type nine-domain CFHR5 protein (CFHR12-9) and an unusually large mutant CFHR5 protein in which the first two protein domains are replicated (CFHR1212-9), a variant currently found only in Cypriot ancestry[1,6]. According to the recent deregulation hypothesis, it has been speculated that CFHR5 nephropathy may be the result of CFH deregulation enhanced by mutant CFHR1212-9 and CFH failure to regulate C3 activation in the glomerular basement membrane[6,27]. However, the specific mechanism is still unclear and further clinical studies are needed (Figure 1).

CFHR5 Nephropathy

CFHR5 nephropathy is a disease endemic only to Cyprian origin, which greatly increases the burden of local patients due to its endemic variation[1]. According to Athanasiou et al[5] statistics of clinical cases, microscopic hematuria was observed in both men and women under 30 years of age. Among men, 80% develop chronic kidney disease and end-stage kidney disease between 51 and 85 years of age. In contrast, only 20% of women develop chronic kidney disease by the age of 88, and most exhibit only microscopic hematuria during their lifetime. In addition, data from another study also suggest that the range of protein differences between the sexes is highly infor-

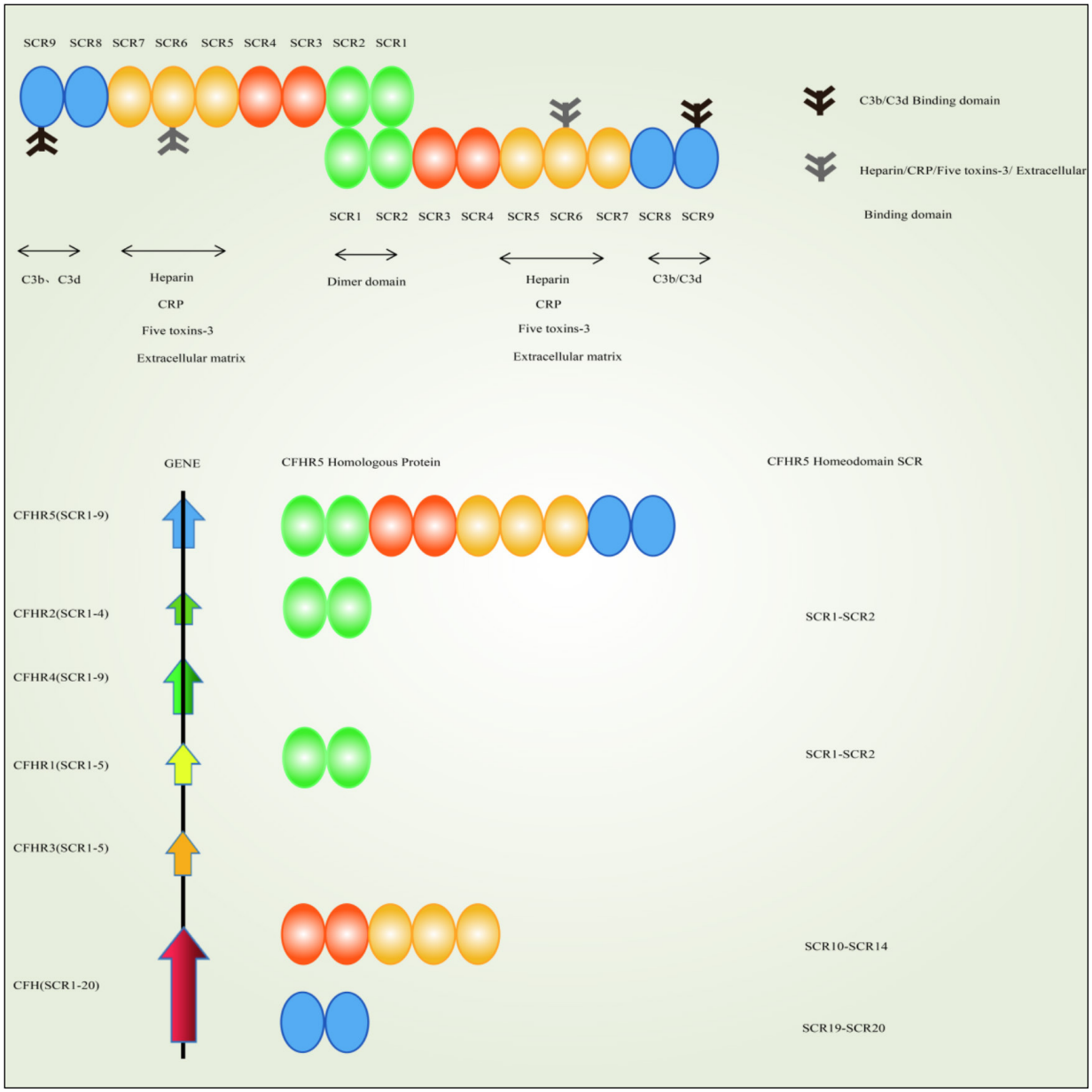

Figure 1. CFHR5 is composed of nine short consensus repeat (SCR) domains. Figure I is the structural diagram of CFHR5 protein. The green SCR corresponds to the dimer domain. "Toxins" -3 and Extracellular matrix are associated with yellow SCR. The blue SCR corresponds to the C3b/C3d binding region. Figure II is the location map of complement factor H and its family related proteins on human chromosome 1q32 in the RCA gene family. Six colored arrows represent the gene arrangement order of different proteins. The SCR1 and SCR2 domains corresponding to green proteins in CFHR1 and CFHR2 are homologous to SCR1 and SCR2 domains of CFHR5 protein. The SCR10-14 domain corresponding to the orange and yellow proteins in CFH is homologous to the SCR3-7 domain in CFHR5, and the SCR19-20 domain corresponding to the blue protein in CFH is homologous to the SCR8-9 domain in CFHR5.

mative with respect to the major functional gain role of the mutant protein in glomerular C3 deposition. There is a significant gender difference in the incidence of renal failure in CFHR5 nephropathy (much higher in men), but the reason for the predominance of males in CFHR5 nephropathy in chronic renal failure remains unclear[7].

Since 2012, a consensus meeting on C3 glomerulopathy has been organized in Cambridge, UK. MPGN in membranoproliferative glomeru-

lonephritis was divided into two groups: MPGN caused by polyclonal or monoclonal IgG-induced immune complexes (IC-MPGN) and complement C3 mediated glomerulonephritis with almost no detectable immunoglobulin in glomerular deposits[28]. Shortly thereafter, Pickering et al[29] and Cook et al[30] divided C3 glomerulopathy into three main subgroups: Type I was dense sediment disease (DDD). Type II is C3 glomerulonephritis (C3 GN). Type III is CFHR5 glomerulopathy (CFHR5 GP). CFHR5 GP often presents as C3 glomerulonephritis. Therefore, CFHR5 GP is also known as C3 glomerulonephritis subtype of familial C3 glomerulonephritis. Different from C3 glomerulonephritis, CFHR5 GP has special genetic variants, namely, internal duplication of *CFHR5* gene, which can be detected by PCR screening using genomic DNA[1,28]. Therefore, special molecular techniques can be used to diagnose CFHR5 GP.

CFHR5 GP Genetic Analysis

Mutation, deletion, duplication and rearrangement of *CFHR5* gene are closely related to many glomerular diseases, such as IgA nephropathy[31], atypical hemolytic uremic syndrome[20], type III collagen glomerulopathy[32], lupus nephropathy[33]. Among these mutations, the most abundant position changes of *CFHR5* gene were at 278 and 356 positions in patients with IC-MPGN or C3G (and atypical hemolytic uremic syndrome). Among them, glycine at position 278 is easily mutated to serine, and arginine at position 356 is easily mutated to histidine[10]. In CFHR5 GP, the *CFHR5* gene is also mutated, which is involved in the heterozygous internal replication of *CFHR5* exons 2-3[1,2]. This variant is unique in patients of Cypriot descent with CFHR5 GP. However, it is worth noting that the formation of this mutant protein is not unique due to the different locations of the genomic breakpoints. Currently, more than two genomic breakpoints have been found to form the same mutant protein as CFHR5 GP[1,6].

In 2010, Gale et al[1] tested individuals for kidney disease and extracted DNA from blood or saliva from two families of Cypriot origin. EasyLINKAGE[34], PEDCHECK[35], GENEHUNTER version 2.1[36] and HAPLOPAINTER[37] were used to analyze the genotypes and haplotypes of 6008 SNPs in these two families. After PCR amplification, the exons of candidate genes were sequenced in two directions. Internal duplication of *CFHR5* was assessed by multiplex ligation-dependent probe amplification (MLPA). The result is that all affected members of both families share a haplotype of 17 SNPs spanning 8.74 *CM*, which is consistent with alleles from a common ancestor at this locus. MLPA analysis revealed heterozygous duplications of *CFHR5* exons 2 and 3 in families 1 and 2 affected individuals. Internal replication of *CFHR5* was confirmed by southern hybridization of genomic DNA with *CFHR5* exon 2[1]. Unfortunately, the study did not clarify how the mutant causes glomerular damage.

CFHR5 GP Protein Analysis

The complement factor H-associated 5 protein (CFHR5) was first found co-with C3 in glomerular immune deposits in patients with glomerulonephritis. Protein analysis of CFHR5 deposited in mesangial and basement membranes was carried out. The mesangial and basement membranes are also the two most susceptible sites for activation due to the lack of additional complement modulators[7,38]. Previously, CFHR5 was often thought to have nine SCR domains in flexible linear conformations[1,17,39-41]. Recent studies[7] have shown that CFHR5 is a dimeric compact domain conformation. This structure readily leads to the formation of CFHR5 oligomers in the presence of the mutant CFHR5 protein. This structure modifies our understanding of how CFHR5 interacts with its target ligand C3b and its C3d fragment, as well as other fragments, such as heparin-like analogues, explaining the molecular defect behind CFHR5 GP[40,42].

CFHR5 is composed of nine repetitive consensus SCRs, each of which is about 4 nm in length, and the predicted length of the fully extended CFHR5 domain is 64 nm. However, the maximum length of the actual CFHR5 in one experiment was 20-21 nanometers. This indicates that CFHR5 has a similar folding domain structure, which reflects the compact domain conformation phenomenon in CFHR5[27]. After the error in the coding of the gene base inside *CFHR5*, the mutation of *CFHR5* will be formed in the human body. The heterozygous repeat of SCR-1/2 results in a more elongated CFHR5 molecule than wild-type CFHR5. Other heterozygous genomic rearrangements lead to the production of a more elongated CFHR5 protein with an additional N-terminal SCR-1/2 domain, the formation of which has been

described as autosomal dominant C3 glomerular disease. In addition, the longer the length of the macromolecule containing the mutant CFHR5, the lower the density of C3d and C3b on the host cell surface required for polyvalent binding. When passing through high blood flow glomeruli, C3d and C3b deposits are higher, making mutant CFHR5 preferentially bind to C3d and C3b compared with factor H, thereby causing factor H to relax the regulation of complement and causing renal injury[1,27]. Interestingly, even the additional ability to regulate complement did not prevent the direct effect of the mutant on C3d and C3b binding[7] (Figure 2).

Analysis of CFHR5 GP Alternative Pathway

The complement system is one of the oldest parts of the innate immune system, such as microbial elimination, immune complex clearance, tissue regeneration and angiogenesis[43]. It is characterized by multiple variations in protein structure, abundance, and activation, and its prevalence is often ethnically related[44]. The complement system is a protein cascade composed of more than 50 proteins that are present both in the fluid phase and bound to cell membranes, including soluble components, soluble and cell-binding regulatory molecules, and cell-surface receptors. Complement acts as an efficient effector of the innate immune system to remove pathogens and other dangerous particles, such as immune complexes, cell debris, and dead cells. At the same time, the complement system connects innate and adaptive immunity in the inflammatory processes and activation of various cells[43,45-47]. Proteins of the complement system can be rapidly converted to active forms by proteolytic cascades triggered by any of the three activation pathways: classical pathway, lectin, and alternative pathway[46-48]. According to relevant studies, immunofluorescence analysis of glomerular deposits in CFHR5 GP revealed that the deposits were mainly C3 fragments and did not show any deposits of immunoglobulin or early components of classical or lectin pathways, especially C1q and C4c. Accordingly, it is inferred that it is caused by dysfunction of the alternative complement pathway, leading to abnormal complement activation, deposition and degradation in the glomeruli[2,27].

Alternative pathway (AP) activation under normal physiology does not require specific protein activators. AP is continuously activated at low levels in plasma by a process called "tickover". Tickover is a process in which plasma water spontaneously hydrolyzes circulating C3 to form a molecule called C3 (H_2O) and exposes the thioester domain binding site. C3 (H_2O) can bind to AP protein factor B. The attached factor B is then cleaved by factor D (a circulating serine protease) to produce a weak C3 converting enzyme [C3(H2O)Bb]. The C3 converting enzyme cleaves more C3 to the activated C3b. The C3b thioester domain binds adjacent surfaces by covalent attachment to hydroxyl and amine groups on carbohydrates and proteins. The C3b immobilized on the target surface can then combine with factor B to generate the immobilized form of C3bB. Factor D cleaves factor B in this complex to produce AP converting enzyme (C3bBb)[44,46,49]. In this process,

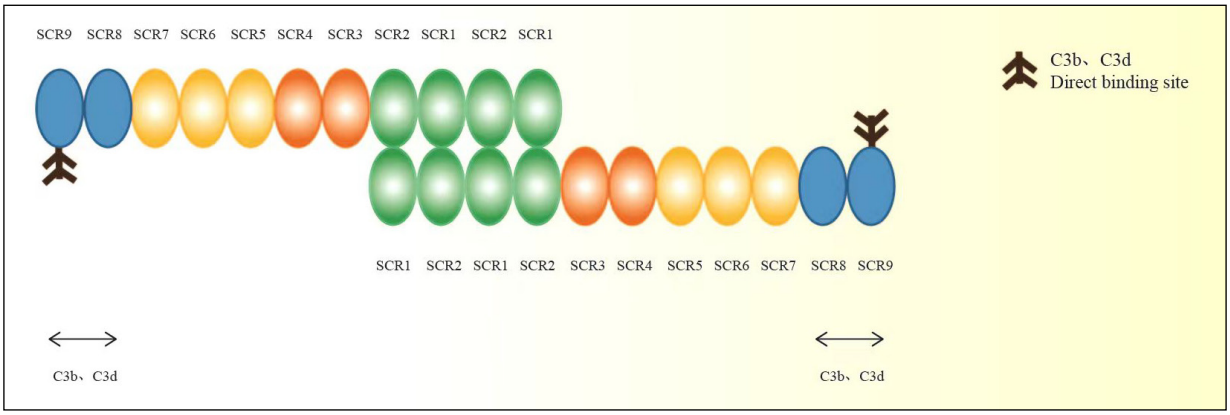

Figure 2. It is the structure diagram of mutant CFHR5 protein. The green region represents the mutant region, which is the duplicated SCR1 and SCR2 structure caused by the internal replication of exon 2 and exon 3. The protein changed from SCR1-9 to SCR1212-9. The latter can directly bind to C3b/C3d.

the C3b released into the liquid phase is rapidly inactivated by factor I, and the C3bBb formed is not efficient or stable. Factor H can replace Bb in the C3bBb complex to dissociate C3b from Bb. The dissociated or dissociated C3b is immediately inactivated by factor I. Because this process is constrained by factors I and H, a large amount of AP converting enzyme cannot be produced. Therefore, the AP will not be activated. When CFHR5 is mutated, it forms a more elongated CFHR5 protein with an extra N-terminal SCR-1/2 domain, which has a stronger affinity for C3bBb or C3b, impeding its replacement by factor H into Bb, resulting in the production of

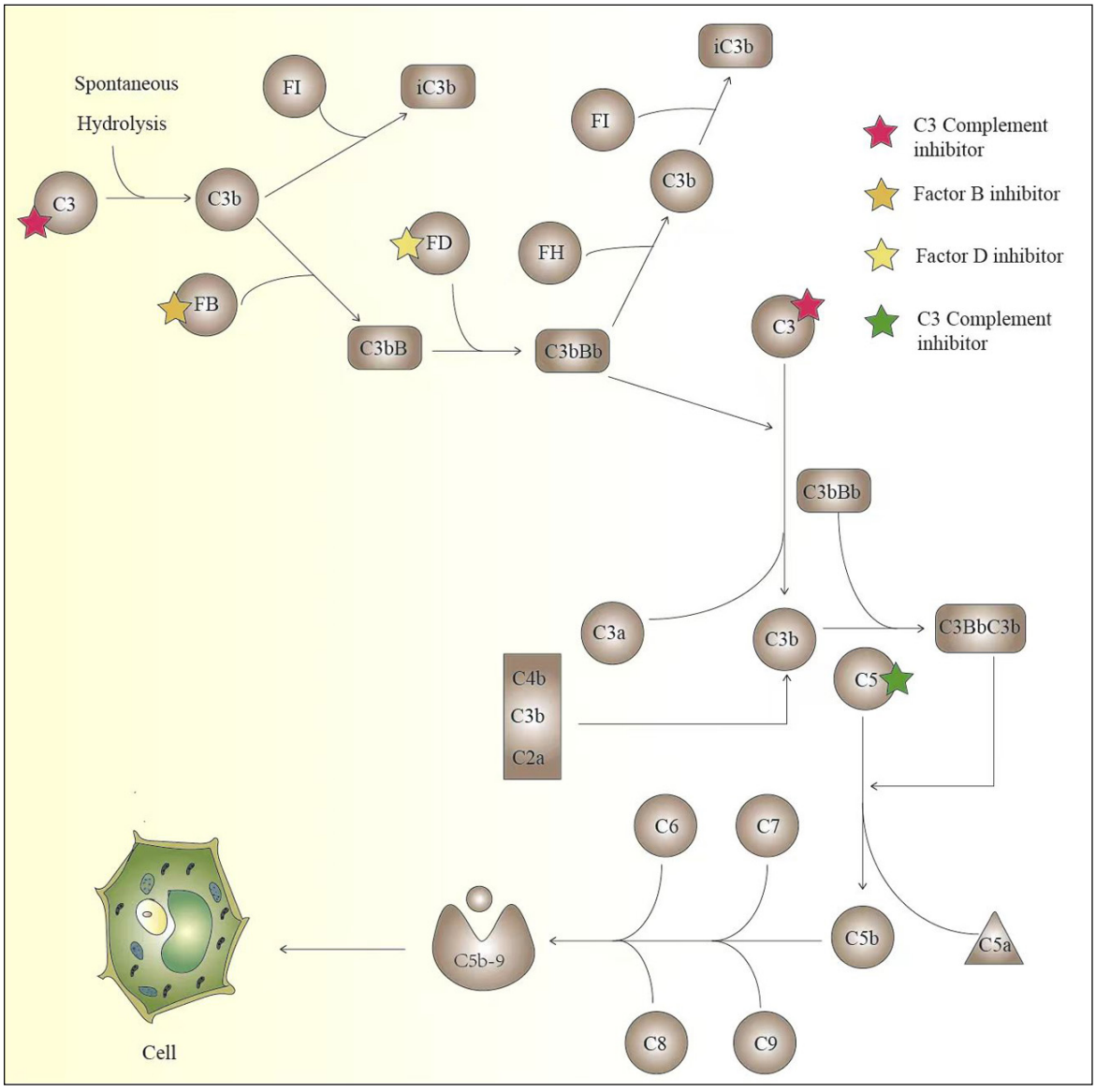

Figure 3. It is a schematic representation of activation of the alternative pathway. C3 is slowly hydrolyzed into C3b, and part of the C3b released in the phase solution is decomposed into inactive C3b(iC3b) by factor I, and part of the C3b is combined with factor B to generate the fixed form of C3bB. Factor B in this complex (C3bB) is cleaved by factor D to produce AP converting enzyme (C3bBb). However, the formed C3bBb is not efficient or stable. Factor H can replace Bb in C3bBb complex, dissociating C3b from Bb, and the dissociated C3b is immediately inactivated by factor I in the phase liquid. In the absence of alternative pathway regulation, multiple C3 molecules are cleaved and activated to further form C3 converting enzymes and enhance complement activity. As the density of active C3b increases, C3 convertase binds to C3b to form C5 convertase. C5 convertase cleaves C5 into the anaphylaxis toxin C5a and fragment C5b. C5b binds to C6-C9 to form the membrane attack complex (C5b-9). The membrane attack complex is a pore-like structure that inserts into the cell membrane and can damage normal glomerular cells. The four different colored star icons in Figure 3 represent different inhibitors.

large amounts of C3b and C3bBb (C3 convertase) in the blood. The C3 converting enzyme cleaves more C3 to the activated C3b. As the density of active C3b increases, C3 convertase binds to C3b to form C5 convertase. C5 convertase cleaves C5 into the anaphylaxis toxin C5a and fragment C5b. C5b binds to C6-C9 to form the membrane attack complex (C5b9). The membrane attack complex is a pore-like structure inserted into the cell membrane that promotes lysis in anucleated cells and gram-negative bacteria and damages pathways in nucleated cells[44,46] (Figure 3).

The Diagnosis

First, family history and ethnic information are important in diagnosing CFHR5 kidney disease, which can provide valuable evidence for rare genetic disorders. Therefore, in a modern multicultural society, family history should include disease and ethnic information[2], which is also the first step in screening for the disease.

Second, familial clinical features associated with C3 glomerulonephritis, such as persistent familial microscopic hematuria, intermittent synpharyngeal gross hematuria (generally present after infection), familial hematuria with progressive renal injury, and proteinuria in some patients[1,4,5].

Third, because CFHR5 GP is a special familial C3 glomerulonephritis, the results of immunofluorescence staining can be referred to C3 glomerulonephritis, which shows the immune deposits of C3 found in the mesangial, subepithelial, and subepithelial layers. The unique (or at least dominant) glomerular immunofluorescence staining intensity of C3 is at least two orders of magnitude higher than that of any other immunoreactant, and there are no deposits of C1q, C4c, or immunoglobulin (IgA, IgM, IgG)[1,50,51]. It is important to note that CFHR5 GP needs to be identified with

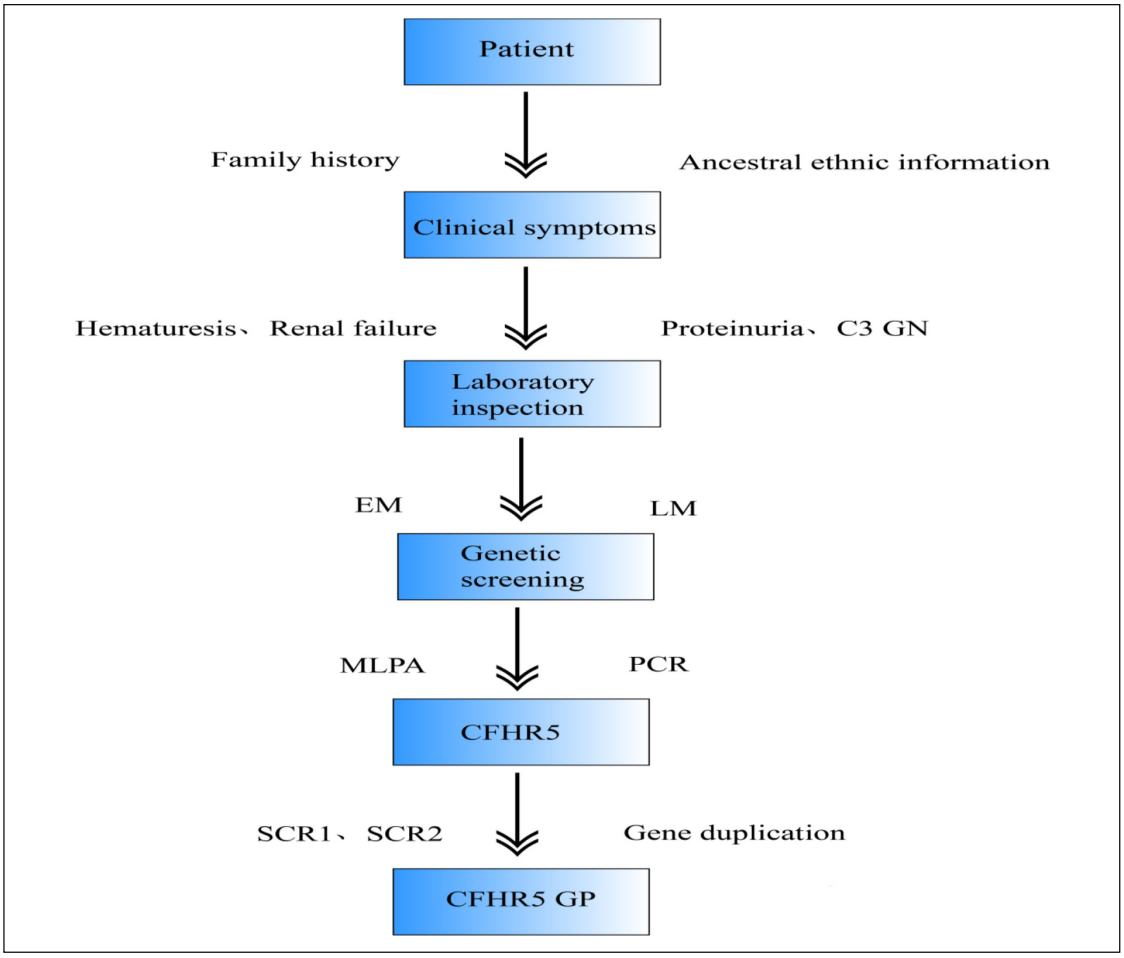

Figure 4. It is a guide chart for the diagnosis of CFHR5 nephropathy.

DDD. Electron microscopy (EM) was used. In C3GN, discrete C3 deposits are located along the mesangial and capillary walls, whereas in DDD, C3 deposits are more intense in the mesangial and glomerular basement membrane (GBM), forming distinctive zonal bands[52,53].

Through molecular genetic analysis technology, the evidence of gene internal replication in exon 2 and exon 3 of CFHR5 mutant protein was found, and finally, CFHR5 GP could be diagnosed[1]. Of note, since CFHR5 GP is a subtype of C3 glomerulonephritis, demonstrating the presence of intra-gene duplication in exon 2 and exon 3 of the CFHR5 mutant protein is a critical step in the diagnosis of CFHR5 GP (Figure 4).

Treatment

Currently, there are no specific detailed guidelines for the clinical treatment of CFHR5 nephropathy. Since it is a subtype of C3 glomerulopathy in clinical practice, the treatment options for C3 glomerulopathy can be referred to, including supportive therapy, immunotherapy, complement inhibitor therapy, transplantation surgery, and other treatments.

Supportive Treatment

For patients with hematuria accompanied by proteinuria and normal renal function, ACE inhibitors, ARBs, and statins can be used as supportive therapy[5,30,54]. Inhibitors of the renin-angiotensin system have both nephroprotective and antiproteinuria effects. However, a recent study found that renin has an intrinsic ability to cleat C3 molecules into C3a and C3b, thereby accelerating the activation of the alternative complement pathway. The use of the direct renin inhibitor "Aliskiren" resulted in a significant reduction in complement activation, resulting in lower C3 and C5B-9 deposition in three patients with DDD[55].

Immunological Therapy

The efficacy of immunosuppressive agents in the treatment of CFHR5 nephropathy has not been described sufficiently. A nationwide collaborative study coordinated by the Spanish Glomerular Disease Study Group (GLOSEN) was the first to describe the effects of corticosteroid hormone plus "mycophenolate mofetil" (MMF) treatment in 2015, by recruiting 61 patients with C3GN and regularly following them to help analyze clinical features, response to treatment, and outcome. After comparing patients who received conservative treatment, this beneficial effect was found to be more pronounced in those treated with corticosteroid hormone and MMF[56]. Although CFHR5 nephropathy was not mentioned, clinical progressive testing of its efficacy in the treatment of CFHR5 nephropathy could be attempted. Although immunosuppressive therapy has the potential to suppress the cellular immune response associated with C3 glomerulopathy by reducing the production of autoantibodies and limiting allergic reactions to C3a and C5a, the effectiveness of this approach has been mixed. According to a recent study analysis[57], in a study involving 21 patients with DDD and 59 patients with C3GN4, the 10-year renal survival rate of the two groups was less than 50%, and 29% of the patients entered end-stage renal disease (ESRD) after only 28 months. Although 32 patients received immunosuppressive therapy, either with corticosteroid hormone alone (22 patients) or with corticosteroid hormone plus other drugs (10 patients), univariate and multivariate analyses showed that these treatments failed to reduce progression to ESRD.

Complement Inhibitor Therapy

Because complement dysregulation plays an important role in C3 glomerular disease, the study of complement inhibitors has become a popular endeavor. By inhibiting the abnormal activation of the complement system, it has also become the main goal of disease treatment.

Eculizumab, a humanized anti-complement C5 monoclonal antibody, blocks C5a and C5b-9 production. The US Food and Drug Administration (FDA) approved Eculizumab for the treatment of aHUS in 2011. Studies have shown that it can inhibit the terminal complement pathway and effectively treat paroxysmal nocturnal hemoglobinuria[58,59]. In several case studies and small trials, eculizumab improved proteinuria, serum creatinine, and kidney biopsy results[12,60-63]. Anticomplement therapies such as eculizumab have been proposed as specific treatments for C3 glomerulopathy. This may have therapeutic effects on CFHR5 nephropa-

thy, and clinical studies are needed to address this issue[1,2]. Interestingly, Nomacopan (another C5 inhibitor) and OMS721 (a MASP2 inhibitor) have already started clinical trials in aHUS. Although a NomacopAN trial was planned for HSCT-associated TMA, both trials appear to be currently on hold[64]. Zilucoplan is a drug that is structurally completely different from the antibodies mentioned above but has the same main function. It is a synthetic macrocyclic peptide inhibitor that is used as a subcutaneous autoradient and functions primarily in the same way as eculizumab, blocking C5 cleavage[65-67]. It is currently undergoing phase III clinical trials. Fortunately, the introduction of anti-C5 therapies demonstrated the efficacy of complement regulation in human disease and increased confidence in this approach, thus ushering in a new era of complement drug discovery[68].

Due to the limitations of C5 therapy, this drug can only inhibit the terminal pathway and cannot block the production of C3. Therefore, interception targeting C3 has emerged as a promising therapeutic intervention as it is expected to have a broader impact on the disease process underpinning C3G179. In this regard, both the European Medicines Agency and the FDA have endorsed the clinical potential of C3-based inhibitors for C3G. Two drug candidates, AMY-101 and APL-2, are novel inhibitors that block C3 production in clinical practice[68].

APL-2 is designed to inhibit the complement cascade in C3 and may be more effective than partial complement inhibitors in the treatment of various complement-mediated diseases. APL-2 is a synthetic cyclic peptide that binds to polyethylene glycol (PEG) polymers, specifically to C3 and C3b, and effectively blocks all three pathways of complement activation (classical, lectin, and alternative pathways). To date, APL-2 has generally been well tolerated. No major infections have been observed in trials involving systemic administration of APL-2, including those in PNH, AIHA or other trials[69].

AMY-101 is a novel peptide complement inhibitor being developed by AMYNDAS based on Cp40, a third-generation compstatin analog. AMY-101 is a selective inhibitor of complement activation in humans and NHP. It binds to complement component C3, a central "functional hub" that controls upstream complement activation/amplification and downstream effector function. By binding to C3, AMY-101 inhibits the cleavage of native C3 to its active fragments C3a and C3b. Thus, C3b deposition, amplification *via* alternative pathways, and all downstream complement responses are prevented. AMY-101 is being developed to treat complement-mediated diseases that are primarily driven by aberrant C3 activation[70].

Factor D and factor B also play important roles in the early process of AP activation. Recently, inhibitors of factor D and factor B have also been quietly studied. Danicopan (ACH-4471, ACH-044471, ALXN2040) is a first-in-class oral, small-molecule factor D inhibitor that prevents the formation of new AP C3 converting enzymes. This study identified Danicopan at 200 mg thrice daily as a safe and effective dose[71-73].

Known factor B covalent inhibitors include Nafamostat and peptide aldehydes. But there is a lack of specificity and, so far, no factor B inhibitor can be used for treatment. The high abundance of latent factor B poses an additional challenge for drug discovery, as complete blockade would require high systemic drug levels if inhibitors could not distinguish between active and latent factor B forms[74-76].

Transplantation Surgery

When CFHR5 nephropathy reaches the end stage, kidney transplantation becomes an effective and feasible treatment for patients. According to Athanasiou et al[5], kidney transplantation was performed when 5 people reached ESRD. Both transplant patients still had normal kidneys seven and nine years later, respectively. Kidney biopsies were performed in three patients, all showing typical C3 mesangial deposits. Vernon reported the first documented case of recurrent CFHR5 nephropathy in a 53-year-old Cypriot man undergoing kidney transplantation. Strikingly, histological changes in CFHR5 nephropathy were evident in donor kidneys 46 days after transplantation. This unique case demonstrates that the kidney-derived CFHR5 protein cannot prevent the development of CFHR5 nephropathy[19]. Since CFHR5 protein is produced in the liver, it is speculated that liver transplantation could be attempted, but there are no specific clinical data reported, and further studies are needed.

Other Treatments

In a retrospective cohort analysis of 60 patients with C3GN, combination therapy with steroids

and mycophenolate mofetil improved renal survival compared with other immunosuppressive regimens and untreated patients. However, none of these therapies have been specifically targeted for patients with CFHR5 kidney disease. However, the rapid development and characterization of treatment modalities for C3 glomerulopathy make it a candidate therapeutic space for significant change in the coming years[5,56]. Plasma exchange is also a treatment option, but strong data supporting the use of plasma therapy in patients with CFHR5 nephropathy are lacking. It has only been reported sporadically in C3 glomerulopathy. For example, a 15-year-old girl with recurrent DDD after kidney transplantation underwent plasma exchange three times a week and successfully removed circulating C3 nephrotic factor. However, when this treatment was discontinued (after more than 100 exchanges), the allograft failed. These data suggest that the exact role of plasma therapy in patients with C3 glomerulopathy remains to be determined[50,77]. In addition, it remains to be noted that tonsillectomy can be considered for gross hematuria caused by recurrent suppurative tonsillitis. According to a previous report[5], after the removal of purulent tonsils, the patient's hematuria was effectively controlled and the long-term effect was better.

Conclusions

CFHR5 nephropathy is another type of kidney disease caused by a mutant gene in Cyprus. Although the mechanism of how the mutation causes the disease is not clear in clinical practice. With the development of molecular technology and medical technology, we gradually realized that gene plays an important role in the field of nephropathy. In addition, the genetic screening of other types of C3 glomerulopathy also needs to be increased. Is it certain that CFHR5 nephropathy occurs only in Cyprus? It is also necessary to carry out genetic analysis through more clinical similar records. Progress towards earlier intervention in inherited diseases could also be achieved by expanding genetic screening for familial diseases.

Our narrative review of CFHR5 nephropathy suggests that clinically targeted complement inhibitors will hold considerable promise in the treatment of nephropathy in the future. It is worth noting that complement inhibitors increase the risk of infection due to their effect on the immune system. Therefore, in the clinical use of this type of drug, it is still necessary to accurately study its use in treatment and the rationality of dosage, which will be worth further exploration.

Conflict of Interest
The authors declare that they have no conflict of interests.

Acknowledgements
We sincerely acknowledge Shandong University of Traditional Chinese Medicine for the support..

Ethics Approval
Not applicable.

Informed Consent
Not applicable.

Funding
None.

Authors' Contribution
(Z.-G. Fei) Zhenggen Fei wrote the manuscript and draw the pictures; (P.-Y. Liu) Peiyu Liu, (H.-Y. Xu) Haiyu Xu, (H.-H. Chen) Huihui Chen, proofread the manuscript; (F.-J. Zhang) Fengjun Zhang, (K. Zhen) Kun Zhen reviewed and revised the manuscript.

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