The spectrum of central serous chorioretinopathy: clinical characteristics, genetic associations and outcome of treatment

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بسم الله الرحمن الرحيم

CHAPTER 3

Genetic characteristics of CSC phenotypes

بسم الله الرحمن الرحيم

Chapter 3.1

Genetic risk factors in acute central serous chorioretinopathy

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ABSTRACT

Purpose: To investigate genetic associations in white patients with acute central serous chorioretinopathy (aCSC), and to assess genetic differences between aCSC and chronic CSC (cCSC).

Methods: A total of 135 aCSC patients, 272 cCSC patients, and 1385 control individuals were included. Eight single nucleotide polymorphisms (SNPs) were genotyped for *ARMS2* (rs10490924), *CFH* (rs800292, rs1061170, rs1065489, rs1329428, rs2284664, rs3753394), and *NR3C2* (rs2070951). Also, *C4B* gene copy numbers were analyzed.

Results: Three SNPs in the *CFH* gene were significantly associated with aCSC: rs800292 ($P = 0.003$, OR = 1.53 [95% CI = 1.15-2.03]), rs1061170 ($P = 0.002$, OR = 0.64 [95% CI = 0.48-0.86]), and rs1329428 ($P = 5.87 \times 10^{-6}$, OR = 1.83 [95% CI = 1.40-2.38]). A significant difference was found in the distribution of *C4B* gene copy numbers in aCSC patients compared to controls ($P = 0.0042$). No differences could be found among the selected variants between aCSC and cCSC patients.

Conclusions: Three variants in the *CFH* gene and copy number variations in *C4B* were found to be significantly associated with the risk of aCSC development. Despite the differences in clinical presentation, acute and chronic CSC may share a similar genetic predisposition based on our present analysis. Other genetic and/or non-genetic risk factors may be more influential in the differentiation toward an acute or a chronic phenotype of CSC.

INTRODUCTION

Acute central serous chorioretinopathy (aCSC) is a sudden-onset and relatively common macular disease.[1] It is characterized by a neuroretinal detachment with serous subretinal fluid (SRF) accumulation as seen on optical coherence tomography (OCT).[2] Patients with aCSC characteristically show a single focal "hot spot" of leakage on fluorescein angiography (FA).[3] This leakage occurs because of a small defect in a focally detached retinal pigment epithelium (RPE), which normally constitutes the outer blood-retina barrier.[3, 4] Acute CSC has been described to be a self-limiting condition and visual acuity recovers completely in most cases.[5]

In contrast to aCSC, the phenotype of chronic CSC (cCSC) is characterized by prolonged and usually persistent SRF accumulation, larger and/or multiple RPE detachments, often more diffuse RPE leakage, and more extensive multifocal atrophic RPE changes.[1] A timely diagnosis and treatment is required in order to accelerate SRF resolution, and to prevent irreversible photoreceptor damage, vision loss and decreased vision-related quality of life.[6] It is hypothesized that a congested and hyperpermeable choroid lies at the pathophysiological basis of CSC, as part of the pachychoroid spectrum.[1, 7] Dysfunction of the RPE, secondary to these choroidal abnormalities, would then result in SRF leakage and neuroretinal detachment, but the exact etiology of the disease is still unknown.[7, 8] There is ongoing debate about whether aCSC and cCSC form two distinct entities, or whether they belong to a continuum of the same disease.[9, 10]

Recently, single nucleotide polymorphisms (SNPs) in the *ARMS2* gene and the *CFH* gene (involved in the complement system) were found to be significantly associated with cCSC.[11-13] An association of these SNPs was previously identified in age-related macular degeneration (AMD), pointing to a genetic and pathophysiologic overlap between CSC and AMD. An important role for the choroid has been postulated in both diseases, which both manifest at the choriocapillaris-Bruch's membrane-RPE-neuroretina interface. Interestingly, some risk-conferring alleles in *ARMS2* and *CFH* in AMD were found to be protective in cCSC and vice versa.[11] We also identified an association of a SNP in the *NR3C2* gene that encodes the mineralocorticoid receptor in cCSC.[14] Furthermore, genomic copy number variations in the *complement component 4* (*C4B*) gene were shown to be associated with cCSC.[15] To the best of our knowledge, no genetic studies have been performed to date in patients with an acute phenotype of CSC characterized by only a single focal leak on FA and without any other signs of chronicity. Additionally, clinically distinct aCSC and cCSC phenotypes have not been compared genetically thus far.

In the present study, we therefore assessed whether SNPs in *ARMS2* (rs10490924), *CFH* (rs800292, rs1061170, rs1065489, rs1329428, rs2284664, rs3753394), and *NR3C2* (rs2070951), and the copy numbers of *C4B* gene are associated with aCSC in a white patient cohort. Furthermore, these genetic variants were compared between white aCSC and cCSC patients, to assess whether there are significant differences in these genetic risk factors that could indicate that these disease subtypes are (patho)genetically distinct.

METHODS

A total of 135 white subjects with aCSC was included in the study. Subjects were selected from a large cohort of CSC patients from three referral centers: 47 patients from the Department of Ophthalmology at Leiden University Medical Center (Leiden, the Netherlands), 72 patients from the Rotterdam Eye Hospital (Rotterdam, the Netherlands), and 16 patients from University Hospital of Cologne (Cologne, Germany).

Phenotyping of aCSC patients was performed by two experienced retina specialists (SY, CJFB), who had to agree on the aCSC phenotype being typical, which was based on findings on fundoscopy, OCT, FA, and indocyanine green angiography (ICGA) when available. For purposes of comparison to chronic CSC strict criteria for the diagnosis of aCSC were used. Also, only patients who met the definition of aCSC were included when there was at least one follow-up visit and complete resolution of SRF during the first CSC episode (Figure 1). For this study, aCSC was identified on multimodal imaging as a combination of: 1. Documented serous SRF accumulation on OCT; 2. A single focal leakage point ("hot spot") on FA; 3. Atrophic RPE alterations (including RPE detachments) limited to less than one optic disc diameter in size in the affected eye. Also, the contralateral eyes were not allowed to show any signs of chronicity, such as presence of atrophic RPE changes or chronic SRF leakage. Patients with other possible causes of SRF accumulation such as choroidal neovascularization, or polypoidal choroidal vasculopathy were excluded. In this study, previous steroid use was not an exclusion criterion.

The control group consisted of white individuals enrolled in the European Genetic Database (EUGENDA; www.eugenda.org), in whom no signs of maculopathy were found when evaluated by multimodal imaging, and 176 subjects from the blood bank of the Radboud University Medical Center (Nijmegen, the Netherlands). The control group for the analysis of *ARMS2* and *CFH* included 826 controls, whereas the analysis of *NR3C2* and *C4B* included 1385 and 250 controls, respectively. Additionally, to assess the genetic difference between aCSC and cCSC we included a cohort of 272 white patients with typical cCSC (Figure 1), as described in a previous genetic analysis on cCSC by our group.[11] Both controls and a subgroup of the cCSC patients were genotyped in previous studies.[11, 14, 15] Approval for this study was obtained at the local institutional review boards in all participating centers and the study was in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to blood collection for genetic analysis.

SNP and copy number genotyping

DNA was isolated from peripheral blood by using standard procedures. The choice of the most relevant genetic variants to be analyzed was based on findings in earlier studies.[12-15] Genotyping of the selected SNPs was performed using KASP assays (LGC Genomics; Berlin, Germany) as described previously according to the manufacturer's instructions. Data were read out with the 7900HT Fast Real-Time PCR system (Applied Biosystems *by Life*

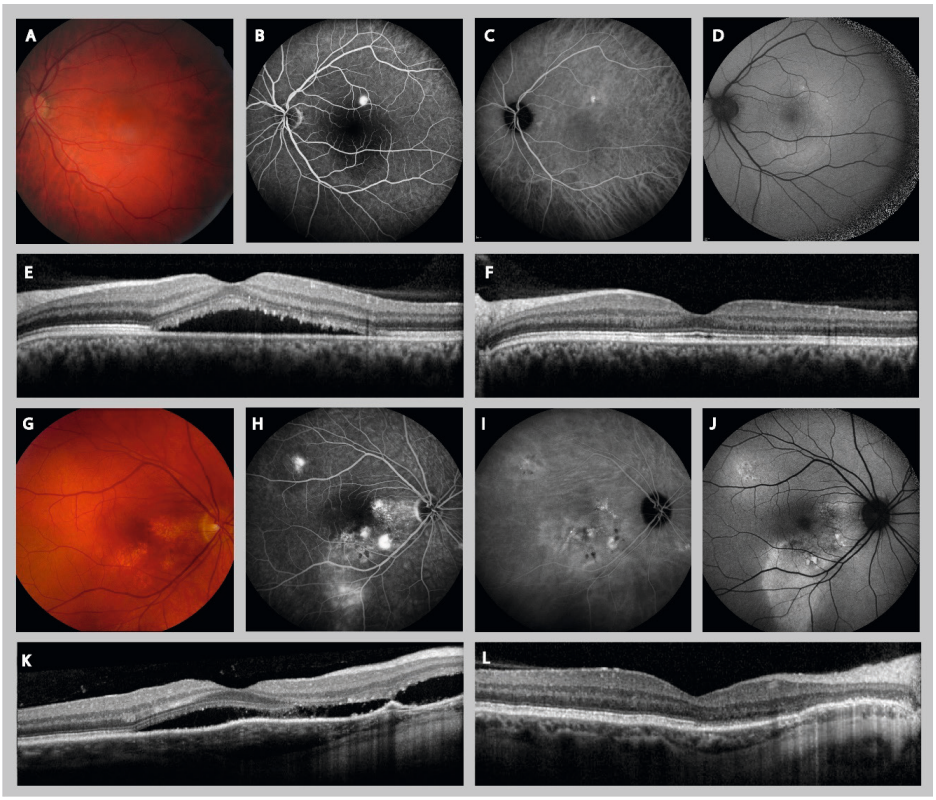


Figure 1. Clinical features visible on multimodal imaging of the left eye of a 41-year-old male patient (A-F) with acute central serous chorioretinopathy (aCSC) and the right eye of a 40 year-old male patient (G-L) with chronic CSC (cCSC). (B) Fluorescein angiography (FA) revealed a single "hot spot" of leakage and no atrophic retinal pigment epithelium (RPE) changes in the aCSC patient. (C) On mid-phase indocyanine green angiography (ICGA) a small hyperfluorescent lesion was observed at the location of the "hot spot" on FA. (D) Fundus autofluorescence (FAF) imaging showed granular hyper-autofluorescent changes at the site of the serous neuroretinal detachment. (E and F) Optical coherence tomography (OCT) scan at first presentation revealed a subretinal serous fluid (SRF) accumulation (E), which resolved after four weeks (F). (H) FA imaging in the cCSC patient revealed a large area of atrophic RPE changes and multiple leakage spots. (I) ICGA imaging in this patient revealed diffuse choroidal hyperpermeability which was slightly larger than the area of leakage visible on FA, and FAF imaging showed a mixture of intense areas of hyper-autofluorescence together with granular hypo-autofluorescent changes. At diagnosis, foveal SRF and a small RPE detachment were observed on the OCT scan of the cCSC patient (K), which both resolved within three weeks after treatment with half-dose photodynamic therapy (L).

Technologies, Austin, TX, USA) and were analyzed with SDS (version 2.4, Applied Biosystems). *C4B* copy numbers were measured as previously described using a TaqMan genotyping assay (Hs07226350_cn, Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA) with RNaseP as a reference assay.[15]

Statistical analysis

The allele frequency of the SNPs was compared between aCSC and unaffected controls or cCSC patients using a 2-sided Pearson's chi-square test (IBM SPSS Statistics, version 22, SPSS Inc., Chicago, IL, USA). The *C4B* copy numbers distribution was compared with a 2-sided Fisher's exact test and a logistic model correcting for gender was performed setting two copies of *C4B* as a reference, as previously described.[15] Bonferroni correction for multiple testing was performed for nine variants and *P*-values <0.0056 were considered statistically significant. The combined effect of the selected six variants in *CFH* was assessed using a haplotype analysis correcting for gender. Haplotype analysis was performed using R (v3.0.2) using the haplo.stats package (v1.6.8). The two most frequent haplotypes were separately used as a reference in the haplo.glm command to determine odds ratios (ORs) for the haplotypes with a frequency >5% and the aggregate of the haplotypes with a frequency <5%.

RESULTS

Of the 135 aCSC patients included, 92 patients (68%) were men, with a mean age of 47 ± 10 years (Table 1). Fifty-six aCSC patients (41%) underwent ICGA imaging and in none of them signs of a CNV were detected. Recent steroid use (< 3 months prior to diagnosis) was reported in 29 aCSC patients (21%). The demographic characteristics of aCSC patients, cCSC patients and controls are summarized in Table 1.

Table 1 Demographic characteristics of the study population

	aCSC patients	cCSC patients	Controls ARMS2 & CFH	Controls C4B	Controls NR3C2
No. of subjects	135	272	826	250	1385
No. of males	92 (68%)	216 (79%)	424 (51%)	198 (79%)	635 (46%)
Mean age ± SD (years)	47 ± 10	51 ± 10	64 ± 12	51 ± 10	51 ± 10

Association of SNPs in ARMS2, NR3C2, and CFH genes with aCSC

No association could be found with the rs10490924 variant in *ARMS2* in aCSCs (Table 2). An initial significant association in the rs2070951 variant in *NR3C2* was lost after correction for multiple testing (Table 2). Among the six tested variants in *CFH* gene, five variants showed an association with aCSC. Among these, two variants, rs1065489 ($P = 0.019$, odds ratio (OR) = 0.63 [95% confidence interval (CI) = 0.43-0.93]) and rs2284664 ($P = 0.013$, OR = 1.44 [95% CI = 1.08-1.93]) showed an association, which was lost after correction for multiple testing (Table 2). Three variants were significantly associated with aCSC after correction for multiple testing: rs800292 ($P = 0.003$, OR = 1.53 [95% CI = 1.15-2.03]), rs1061170 ($P = 0.002$, OR = 0.64 [95% CI = 0.48-0.86]), and rs1329428 ($P = 5.87 \times 10^{-6}$, OR = 1.83 [95% CI = 1.40-2.38]).

Table 2 Analysis of eight single nucleotide polymorphisms in acute central serous chorioretinopathy

SNP (gene)	Alleles in controls (Major/Minor)	aCSC (n)	MAF aCSC	Controls (n)	MAF controls	Unadjusted allelic P	Allelic odds ratio (95% CI)
rs10490924 (*ARMS2*)	G/T	132	0.174	812	0.217	0.111	0.76 (0.54-1.07)
rs2070951 (*NR3C2*)	C/G	132	0.538	1385	0.468	0.0287	1.33 (1.03-1.71)
rs800292 (*CFH*)	G/A	133	0.320	798	0.235	**3.06×10^{-3}**	1.53 (1.15-2.03)
rs1061170 (*CFH*)	T/C	133	0.259	803	0.353	**2.82×10^{-3}**	0.64 (0.48-0.86)
rs1065489 (*CFH*)	G/T	134	0.119	794	0.177	0.0199	0.63 (0.43-0.93)
rs1329428 (*CFH*)	C/T	133	0.579	787	0.429	**5.87×10^{-6}**	1.83 (1.40-2.38)
rs2284664 (*CFH*)	C/T	134	0.287	805	0.219	0.0132	1.44 (1.08-1.93)
rs3753394 (*CFH*)	C/T	131	0.263	800	0.293	0.324	0.86 (0.64-1.16)

$P < 0.0055$ was considered significant.
MAF = minor allele frequency.

Association of CFH haplotypes with aCSC

Haplotype analysis corrected for gender identified five haplotypes in the *CFH* gene with a frequency above 5% and an aggregate of the haplotypes with a frequency lower than 5%. When using the most common haplotype (H1) as a reference, an association with aCSC was found for the risk-conferring H2 (P = 0.003, OR = 1.75 [95% CI = 1.21-2.53]), H4 (P = 0.0180, OR = 1.69 [95% CI = 1.09-2.6]) and H5 (P = 0.001, OR = 2.3 [95% CI = 1.39-3.83]), of which H2 and H5 were significant after correction for multiple testing (Table 3). Using the H2 haplotype as a reference, a protective effect for the H1 (P = 0.003 OR = 0.57 [95% CI = 0.39-0.83]) and H3 (P = 0.010, OR = 0.54 [95% CI 0.33-0.86]) haplotypes was identified, but only the association with H1 remained after correction for multiple testing.

C4B copy number determination in aCSC

Carriers of two copies of the *C4B* gene were more frequent in the aCSC group (68%) compared to the control group (57%), whereas carrying three *C4B* gene copies was observed less frequently in the aCSC group (5.3% versus 18% in controls) (see Figure 2, which demonstrates the *C4B* gene copy distribution). The distribution of *C4B* in aCSC patients compared to controls was significantly different after correction for multiple testing (P = 0.0042). The effect size of different *C4B* copy numbers on aCSC was assessed by a logistic regression model corrected for gender. The overall model was not significant (P = 0.051) (Table 4), but carriers of three *C4B* copies appeared to have a reduced risk of aCSC (P = 0.002, OR = 0.27 [95% CI = 0.12-0.63]) (Table 4).

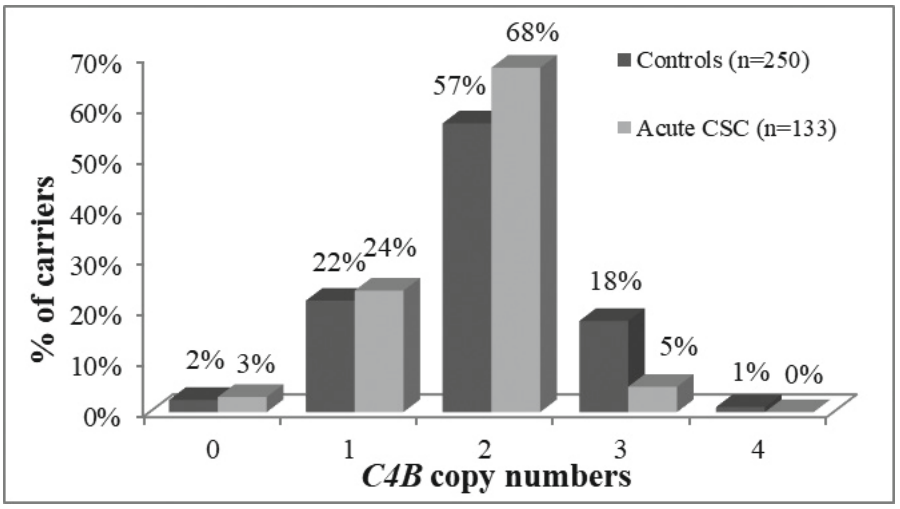
Differences between aCSC and cCSC

The minor allele frequencies of the tested *ARMS2, NR3C2*, and *CFH* variants were not significantly different between aCSC and cCSC patients (See Table 5, which demonstrates minor allele frequencies in aCSC versus cCSC). Haplotype H4 in *CFH* showed a higher frequency in aCSC compared to cCSC (0.164 in aCSCs versus 0.111 in cCSCs, P = 0.0250, OR = 1.78 [95% CI = 1.08-2.95]), but this was not significant after correction for multiple testing (See Table 6, which demonstrates *CFH* haplotypes in aCSC versus cCSC). The distribution of *C4B* copy numbers was not significantly different between aCSC and cCSC patients (P = 0.345), and the logistic regression model was also not significant (P = 0.472) (See Table 7, which demonstrates logistic regression model for *C4B* load in aCSC versus cCSC).

Table 3 *Complement factor H* (*CFH*) gene haplotypes in aCSC

Haplotypes	Variants											
	rs3753394	rs800292	rs1061170	rs2284664	rs1329428	rs1065489	HF aCSC	HF controls	Unadjusted allelic P	Allelic odds ratio (95% CI)	Unadjusted allelic P	Allelic odds ratio (95% CI)
H1	C	G	C	C	C	G	0.249	0.329	Base	Base	**0.003**	0.57 (0.39-0.83)
H2	C	A	T	T	T	G	0.272	0.209	**0.003**	1.75 (1.21-2.53)	Base	Base
H3	T	G	T	C	C	T	0.102	0.158	0.799	0.94 (0.58-1.52)	0.010	0.54 (0.33-0.86)
H4	C	G	T	C	T	G	0.164	0.133	0.018	1.69 (1.09-2.6)	0.859	0.96 (0.64-1.46)
H5	T	G	T	C	T	G	0.114	0.072	**0.001**	2.3 (1.39-3.83)	0.280	1.32 (0.8-2.17)
Rare	*	*	*	*	*	*	0.100	0.098	0.107	1.52 (0.91-2.52)	0.578	0.87 (0.53-1.43)

$P < 0.0083$ was considered significant.
HF = haplotype frequency; MAF = minor allele frequency.



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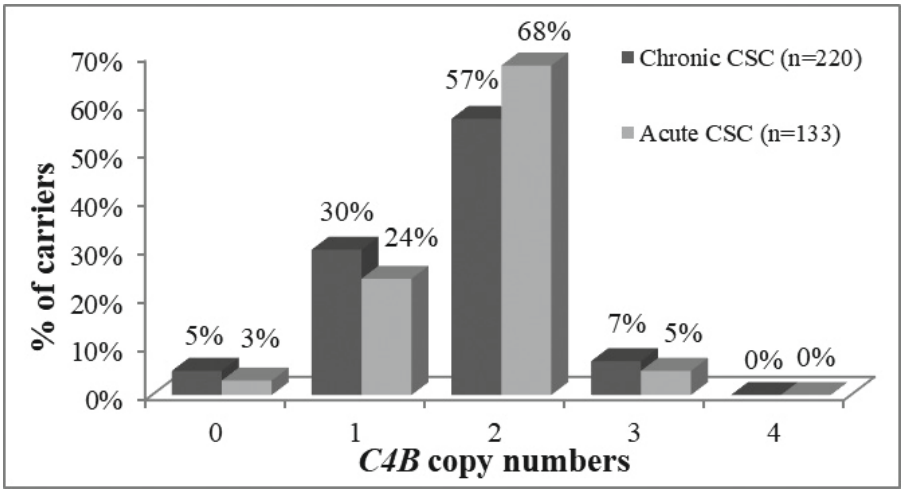

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Figure 2. Distribution of *C4B* copy numbers among acute central serous chorioretinopathy (CSC), chronic CSC, and controls.

Table 4 Logistic regression model for *C4B* load

Overall significance model P = 0.051				
	Controls (n = 250)	**aCSC patients (n = 133)**	**P**	**Odds ratio (95% CI)**
Male sex	198 (79%)	91 (68%)	0.066	1.58 (0.97-2.57)
C4B copy number				
0	6 (2.4%)	4 (3.0%)	0.788	1.20 (0.33-4.39)
1	55 (22%)	32 (24%)	0.704	0.91 (0.54-1.51)
2	142 (57%)	90 (68%)	Base	Base
3	44 (18%)	7 (5.3%)	**0.002**	0.27 (0.12-0.63)
4	3 (1.2%)	0	0.999	NA

P <0.0055 was considered significant.
NA = not annotated.

Table 5 Comparison of allele frequencies in aCSC versus cCSC

SNP (gene)	**aCSC (n)**	**MAF aCSC**	**cCSC (n)**	**MAF cCSC**	**Unadjusted allelic P**	**Allelic odds ratio (95% CI)**
rs10490924 (*ARMS2*)	132	0.174	243	0.193	0.520	0.88 (0.60-1.30)
rs2070951 (*NR3C2*)	132	0.538	269	0.520	0.642	1.07 (0.80-1.44)
rs800292 (*CFH*)	133	0.320	245	0.296	0.500	1.12 (0.81-1.54)
rs1061170 (*CFH*)	133	0.259	245	0.320	0.0801	0.74 (0.53-1.04)
rs1065489 (*CFH*)	134	0.119	244	0.133	0.587	0.88 (0.56-1.39)
rs1329428 (*CFH*)	133	0.579	244	0.510	0.0707	1.32 (0.98-1.78)
rs2284664 (*CFH*)	134	0.287	244	0.275	0.709	1.07 (0.76-1.48)
rs3753394 (*CFH*)	131	0.263	242	0.273	0.783	0.95 (0.68-1.34)

P < 0.0055 was considered significant.
MAF = minor allele frequency.

Table 6 *Complement factor H* (*CFH*) gene haplotypes in aCSC versus cCSC

Haplotypes	Variants											
	rs3753394	rs800292	rs1061170	rs2284664	rs1329428	rs1065489	HF aCSC	HF cCSC	Unadjusted allelic P	Allelic odds ratio (95% CI)	Unadjusted allelic P	Allelic odds ratio (95% CI)
H1	C	G	C	C	C	G	0.249	0.301	Base	Base	0.219	0.77 (0.51-1.16)
H2	C	A	T	T	T	G	0.272	0.262	0.219	1.29 (0.86-1.94)	Base	Base
H3	T	G	T	C	C	T	0.102	0.104	0.408	1.28 (0.71-2.30)	0.976	0.99 (0.57-1.73)
H4	C	G	T	C	T	G	0.164	0.111	0.025	1.78 (1.08-2.95)	0.201	1.38 (0.84-2.26)
H5	T	G	T	C	T	G	0.114	0.115	0.373	1.28 (0.75-2.18)	0.963	0.99 (0.59-1.66)
Rare	*	*	*	*	*	*	0.100	0.108	0.515	1.21 (0.68-2.16)	0.822	0.94 (0.54-1.64)

$P < 0.0083$ was considered significant.
MAF = minor allele frequency.

Table 7 Logistic regression model for *C4B* load aCSC versus cCSC

Overall significance model P = 0.472				
	cCSC patients (n = 220)	**aCSC patients (n =133)**	**P**	**Odds ratio (95% CI)**
Male sex	216 (79%)	91 (68%)	0.026	1.75 (1.07-2.88)
C4B copy number				
0	12 (5.4%)	4 (3.0%)	0.247	0.50 (0.16-1.61)
1	66 (30%)	32 (24%)	0.142	0.69 (0.41-1.14)
2	126 (57%)	90 (68%)	Base	Base
3	15 (6.8%)	7 (5.2%)	0.361	0.64 (0.25-1.66)
4	1 (0.4%)	0 (0%)	1.000	NA

P <0.0055 was considered significant.
NA = not annotated.

DISCUSSION

To the best of our knowledge, this is the first study to analyze potential genetic associations specifically in aCSC patients, and to compare them with known genetic associations that were previously identified in cCSC. We have found a significant association between three variants in the *CFH* gene and copy numbers of the *C4B* gene in patients with aCSC compared to healthy individuals. Among these *CFH* variants, two SNPs were risk-conferring and one was protective. Additionally, the H1 haplotype in the *CFH* gene was protective, whereas H2 and H5 were risk-conferring for aCSC. Three copy numbers of *C4B* conferred a protective effect for aCSC. No association was found between polymorphisms in *ARMS2* or *NR3C2* and the risk of aCSC. Finally, no significant differences were identified in these variants between aCSC and cCSC patients.

Genetic variation in different components of the complement system, which is an essential part of innate immunity,[16] such as factor H (FH) and complement component 4B (C4B) proteins, have previously been associated with cCSC. Of the six tested variants in the *CFH* gene, five variants were associated with aCSC of which three were significant after correction for multiple testing. When comparing our findings in aCSC patients with available literature in cCSC patients, our data confirmed the protective effect of rs1061170, and the risk-conferring effects of rs1329428 and rs800292. However, for these variants the observed effect size in aCSC was larger than previously described in white cCSC patients, respectively, rs1061170 (OR = 0.64 versus 0.83), rs1329428 (OR = 1.83 versus 1.47) and rs800292 (OR = 1.53 versus 1.50).[11]

Additionally, as observed in cCSC patients, the H1 haplotype in *CFH* was found to be protective for aCSC. Similar to the single variants, the protective effect of the H1

haplotype was stronger for aCSC compared to cCSC (OR = 0.57 versus 0.83).[11] The H2 and H5 haplotypes which were previously reported to increase the risk of cCSC, showed the same association in aCSC patients and their effect size was again larger in aCSC patients compared to cCSC (OR = 1.75 versus 1.33 and OR = 2.30 versus 1.37, respectively).[11] It has been suggested that factor H, which is encoded by the *CFH* gene, can influence the choroidal hemodynamic properties.[17] Also, it has been suggested that an altered activity of factor H protein could cause RPE damage and dysfunction,[11, 17] but the exact mechanism of factor H in the etiology of CSC is still unknown. Both an absence and low copy numbers of *C4B* are known to increase the risk of cCSC, whereas carrying three copies is protective against cCSC.[15] In our study, this protective effect was confirmed in aCSC patients, with an even larger effect size (OR = 0.27) compared to previous reports of cCSC.[15]

Exogenous administration of glucocorticoids, or an endogenous excess (Cushing syndrome) was previously found as an important risk factor in development of CSC.[18] The glucocorticoid receptor and mineralocorticoid receptor are the most important targets for glucocorticoids, and therefore their involvement in the pathogenesis of CSC is conceivable.[1] We have previously found a significant association of a genetic variant in the *NR3C2* gene, encoding the mineralocorticoid receptor, with an increased risk of cCSC.[14] In the present study, we did not find a significant association between the rs2070951 SNP in *NR3C2* with aCSC patients after correction for multiple testing, which could have occurred due to a lack of statistical power. Future larger studies can shed a light on whether this finding is indeed due to a lack of power or if it reflects a true difference in *NR3C2* rs2070951 risk SNP load between aCSC and healthy individuals.

In a previous study, we have found an association between genetic variations in the *ARMS2* gene and cCSC.[11] A possible mechanistic explanation for this association was speculated to be the potential interaction of the ARMS2 protein with the extracellular matrix at the level of the choroid and RPE, which are also primarily affected in CSC.[11] Although the mechanism of action is not fully understood, presence of the rs10490924 variant in the *ARMS2* gene was shown to be protective against cCSC development.[11, 12] This association with the rs10490924 SNP in *ARMS2* was not found in the current aCSC cohort. Again, this may be due to a lack of power, but could also indicate a difference in genetic predisposition between aCSC and healthy controls.

Acute CSC and cCSC generally show contrasting clinical presentations in terms of extent of retinal abnormalities and final visual outcome.[1, 19] There is currently no consensus on the classification of CSC, the definition of chronicity, and the exact period of time after which CSC should be considered chronic differs between studies, ranging from two to six months.[20-23] Besides a time based definition, cCSC is usually distinguished from aCSC by its more extensive retinal abnormalities on multimodal imaging, which includes multiple focal or diffuse leakage spots and widespread bilateral RPE alterations.[2, 9] A typical aCSC, on the other hand, presents with a single leakage spot, with only very few RPE changes.

Although some patients with cCSC have a history of aCSC, many patients present with a chronic phenotype at the first presentation.[9, 24] Therefore, it is still unclear whether these two are part of a continuum with the same pathophysiological background, or if they are essentially different entities. A combination of genetic and non-genetic risk factors such as steroid use, hypertension, and pregnancy,[25-27] may play a role in the aspect and severity of CSC, and the risk of progression of aCSC towards a chronic disease course.

Our data suggest a genetic overlap between aCSC and cCSC. No genetic difference could be found when comparing the selected variants in the cCSC and aCSC cohort. However, the effect size of the genetic variants associated with both aCSC and cCSC appears to be systematically larger in aCSC compared to cCSC. The lack of a significant difference between aCSC and cCSC with regard to the associated genetic variants may be partially caused by the small sample size of the current aCSC cohort, and thus a limited power. The larger effect size observed for aCSC suggests that genetic risk factors may play a larger role in the development of aCSC. It has been previously suggested that in multifactorial retinal diseases with genetic involvement such as age-related macular degeneration, patients who develop the disease at a younger age have a stronger genetic predisposition.[28, 29] A similar mechanism could explain the larger genetic predisposition among aCSC patients, who are generally younger than cCSC patients.[9] Other limitations in the present study are the different sample sizes in the control groups, and the possible ethnical differences between German and Dutch patients, whom we considered equal as one white population.

In conclusion, variants rs800292 and rs1329428 in *CFH* gene were found to be significantly associated with a higher risk of aCSC, whereas variant rs1061170 in this gene was protective against aCSC. Three copy numbers of the *C4B* gene was protective against aCSC, and copy number of the gene differed between aCSC patients and controls. These specific *CFH* SNPs and the *C4B* copy numbers showed an even stronger association with aCSC than previously reported for cCSC. Our findings indicate that despite the differences in clinical presentation, acute and chronic CSC might share genetic risk and protective factors, at least among the currently known variants. Presumably, other non-genetic risk factors, or other currently unknown genetic variants are more influential in the differentiation toward an acute or a chronic disease course in CSC. Future genotype-phenotype correlation analyses in larger cohorts may provide important clues about interaction between these different risk factors.

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Conflict of interest

The authors report no conflicts of interest.

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