# Central serous chorioretinopathy : from pathogenesis to treatment

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# ASSOCIATION OF A HAPLOTYPE IN THE *NR3C2* GENE, ENCODING THE MINERALOCORTICOID RECEPTOR, WITH CHRONIC CENTRAL SEROUS CHORIORETINOPATHY

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## ABSTRACT

**Importance:** Chronic central serous chorioretinopathy (cCSC) is a chorioretinal disease with unknown disease etiology. The glucocorticoid receptor and the mineralocorticoid receptor, 2 glucocorticoid-binding receptors, might be involved in the pathogenesis of cCSC.

**Objective:** To assess the association of functional variants and haplotypes in the glucocorticoid receptor (*NR3C1*) and mineralocorticoid receptor genes (*NR3C2*) with cCSC.

**Design:** Case-control genetic association study. Selected variants in *NR3C1* (rs56149945, rs41423247, rs6198) and *NR3C2* (rs2070951, rs5522) were genotyped using KASP genotyping.

**Setting:** General community, 3 referral university medical centers, outpatient care.

**Participants:** Three hundred thirty-six cCSC patients and 1314 unaffected controls.

**Main outcome measure:** Genetic associations of 3 *NR3C1* variants and 2 *NR3C2* variants with cCSC.

**Results:** After correction for multiple testing, rs2070951 in the *NR3C2* gene was significantly associated with cCSC (p=0.004, OR=1.29, 95% confidence interval (CI) [1.08-1.53]). Moreover, the GA haplotype of single nucleotide polymorphisms rs2070951 and rs5522 in *NR3C2* conferred risk for cCSC (p=0.004, OR=1.39, 95% CI [1.15-1.68]), whereas the CA haplotype decreased risk for cCSC (p<0.001, OR=0.72, 95% CI [0.60-0.87]). Three known variants in *NR3C1* that alter the activity of the glucocorticoid receptor (rs56149945, rs41423247, rs6198) were not associated with cCSC.

**Conclusions and Relevance:** In this study, the variant rs2070951 and the GA haplotype in *NR3C2* are associated with an increased risk for cCSC. This is the first genetic study supporting a possible role for the mineralocorticoid receptor in the pathogenesis of cCSC. Since these haplotypes have previously been associated with perceived stress, this study provides a clue bridging clinical risk factors for cCSC to underlying genetic associations.

## INTRODUCTION

In central serous chorioretinopathy (CSC), it has been suggested that dysfunction of the retinal pigment epithelium (RPE) due to congestion, thickening, and hyperpermeability of the underlying choroid leads to subretinal fluid accumulation with an associated detachment of the neuroretina.[1-5] The exact etiology of the disease is currently unknown, but clinical associations point towards an involvement of steroid signaling. Endogenous hypercortisolism (Cushing's syndrome), exogenous glucocorticoid exposure, and possibly stress and type A personality are associated with CSC.[6-11] It has been hypothesised that the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), 2 glucocorticoid-binding receptors, may also be involved in the pathogenesis of CSC.[2]

The involvement of the MR in the pathogenesis of CSC has been suggested based on the results of studies in rats, in which choroidal findings similar to those seen in CSC occurred after intravitreal injection of either corticosterone or aldosterone.[12] MR involvement was further supported by ophthalmological findings in patients with primary hyperaldosteronism (Conn's syndrome).[13] Moreover, studies evaluating the administration of MR antagonists in patients have shown possible beneficial effects.[12, 14-17] However, clinical results were variable and non-permanent, and no prospective randomised placebo-controlled trials have been performed to date to study the role of MR antagonists in CSC treatment.[2, 16]

The GR is the most widely expressed cortisol receptor in the body, it regulates metabolism and the cardiovascular system, and it plays a role in immune suppression and stress response.[18] As stress and both exogenous and endogenous hypercortisolism may be involved in the etiology of CSC,[4, 7, 10, 11] the GR may also be an interesting player in the pathogenesis of CSC.

There are several genetic variants in the genes encoding the MR and GR that are known to alter the MR and GR protein activity.[19-26] The MR is encoded by the *NR3C2* gene, consisting of 10 exons, with 2 alternative 5'-UTR exons 1$\alpha$ and 1$\beta$ allowing tissue-specific promoter activation.[27] The GR is encoded by the *NR3C1* gene, consisting of 10 exons of which 1-9$\alpha$ are translated into the functional GR$\alpha$ receptor.[22] In this study we assessed whether genetic variants in *NR3C2* (rs2070951 and rs5522) and *NR3C1* (rs56149945, rs41423247, and rs6198) are associated with cCSC.

## MATERIALS AND METHODS

We included 336 cCSC patients in this study. Phenotyping of cCSC patients was performed by an experienced retina specialist (CJFB) and was based on a complete ophthalmological examination, including fundoscopy, optical coherence tomography (OCT), fluorescein angiography (FA), and indocyanine green angiography (ICGA). The patients showed the most typical clinical cCSC characteristics (serous subretinal fluid affecting the fovea on OCT, with a disease period of >3 months, ≥ 1 area of 'hot spot' leakage or diffuse leakage in combination with irregular RPE window defects on FA, and corresponding hyperfluorescence on ICGA), described as phenotypic subgroup 1 in a previous paper on genetic associations in cCSC.[28] Patients with high myopia, evidence of choroidal neovascularisation, polypoidal choroidal vasculopathy, and other atypical findings were excluded. For this study, neither previous nor current steroid use was considered an exclusion criterion.The patient cohort consisted of 234 patients from the Radboud University Medical Center (Nijmegen, the Netherlands), 72 patients from the Leiden University Medical Center (Leiden, the Netherlands), and 30 patients from the University Hospital of Cologne (Cologne, Germany). Unaffected individuals enrolled in the European Genetic Database (EUGENDA; www.eugenda.org) were used as controls (n=1314). Controls had no signs of CSC and age-related macular degeneration, when evaluated by multimodal imaging. The study adhered to the tenets of the Declaration of Helsinki, and was approved by the institutional review boards and the ethics committees of all centers involved. Written informed consent was received from all participants.

Genotyping of selected variants was performed using KASP assays (LGC Genomics; Berlin, Germany) according to manufacturer's instructions. Specific primers with FAM and VIC labels were designed per variant (*NR3C1*: rs6198, rs5614994, rs41423247; *NR3C2*: rs5522, rs2070951) and PCR conditions per primer pair were provided by LGC. Data was read out with the 7900HT Fast Real-Time PCR system (Applied Biosystems by Life Technologies, Austin, TX, USA) and was analysed with SDS (version 2.4, Applied Biosystems).

In IBM SPSS Statistics (version 22; SPSS Inc., Chicago, IL, USA), Pearson's Chi-square test was used to compare both the genotype and allele frequencies between cases and controls. Bonferroni correction for multiple testing was performed for 5 variants and p-values <0.01 were considered statistically significant. Logistic regression was performed for the associated rs2070951 variant with Firth's bias-corrected likelihood ratio test implemented in EPACTS (Efficient and Parallelizable Association Container Toolbox, http://genome.sph.umich.edu/wiki/EPACTS, v3.2.6), correcting for gender.[29]

**Table 1.** Demographic characteristics of the cCSC patients and controls

| | n | Mean age ± SD (years) | Males (%) |
|---|---|---|---|
| **cCSC cases** | | | |
| Nijmegen | 234 | 52 ± 9 | 188 (80%) |
| Cologne | 30 | 50 ± 9 | 24 (80%) |
| Leiden | 72 | 52 ± 10 | 62 (86%) |
| Total | 336 | 52 ± 10 | 274 (81,5%) |
| **Controls** | 1314 | 70 ± 7 | 549 (42%) |

Abbreviations: cCSC: chronic central serous chorioretinopathy; SD: standard deviation

Using a haplotype analysis, the combined effect of the 2 variants in *NR3C2* was assessed. Haplotype analysis was performed using R (version 3.0.2) using the haplo.stats package (version 1.6.8). The 2 most frequent haplotypes were separately used as a reference in the haplo.cc command, to determine odds ratios (ORs) for both haplotypes. A logistic regression analysis (haplo.glm) including gender and haplotypes was performed using the most common haplotype as a reference. Only haplotypes with a frequency of >5% are shown. P-values <0.05 were considered to be statistically significant. Power analysis was performed with CaTS (version 0.0.2), using a multiplicative model in a joint analysis.[30] The power per variant was calculated based on the minor allele frequency in controls, a disease prevalence of 0.0001, and a variable genotype relative risk (1-2.6), and the graph was created with Graphpad Prism (version 5.03, Graphpad Software, La Jolla, California, USA,).

## RESULTS

The demographic characteristics of the patients and controls enrolled in this study are summarised in Table 1. All described variants were in Hardy-Weinberg equilibrium, both for controls and CSC patients. No statistically significant associations between cCSC and variants in the *NR3C1* gene (rs56149945, rs41423247, rs6198) were found (Table 2). After correction for multiple testing (p<0.01), a significant association between cCSC and the rs2070951 variant in the *NR3C2* gene was observed (p=0.004, OR=1.29, 95% confidence interval (CI) [1.08-1.53]). No association between the variant rs5522 in *NR3C2* and cCSC was found (Table 2).

**Table 2.** Association analysis of variants in NR3C1 and NR3C2 in cCSC patients

| | Gene | Location | Major/ Minor allele | MAF controls | MAF patients | Genotype p-value | Allelic p-value | OR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| rs56149945 | *NR3C1* | Exon 2 | A/G | 0.0415 | 0.0357 | 0.37 | 0.50 | 0.86 (0.55-1.34) |
| rs41423247 | *NR3C1* | Intron 2 | C/G | 0.360 | 0.390 | 0.16 | 0.15 | 1.14 (0.95-1.35) |
| rs6198 | *NR3C1* | Exon 9 UTR | A/G | 0.169 | 0.158 | 0.334 | 0.48 | 0.92 (0.73-1.16) |
| rs2070951 | *NR3C2* | c.-2 | C/G | 0.464 | 0.527 | 0.008 | 0.0040 | 1.29 (1.08-1.53) |
| rs5522 | *NR3C2* | Exon 2 | A/G | 0.129 | 0.137 | 0.84 | 0.57 | 1.08 (0.83-1.38) |

Abbreviations: cCSC: chronic central serous chorioretinopathy; CI, confidence interval; MAF: Minor allele frequency; OR: odds ratio; UTR: untranslated region
Bonferroni correction for multiple testing was performed for 5 variants and p-values < 0.01 were deemed significant

Haplotype analysis of the *NR3C2* SNPs rs2070951 and rs5522 showed a significant association with a decreased risk for cCSC for the CA haplotype (p<0.001, OR=0.72, 95% CI [0.60-0.87]) and an increased risk for the GA haplotype (p=0.004, OR=1.39, 95% CI [1.15-1.68]) (Table 3). To account for potential confounding effects of gender between cases and controls we corrected for this factor in a logistic regression model. When including this variable in the model, the association of rs2070951 was independent of gender (p=0.009, OR=1.28, 95% CI [1.16-1.41]). Similarly, when correcting for gender in the haplotype analysis, setting the most common haplotype (GA) as reference, the association of the CA haplotype remained significantly associated with cCSC (p=0.002, OR=0.73, 95% CI [0.66-0.81]).

A multiplicative model was used to calculate the power of the study, since this model produces a genetic relative risk score that is an estimation of the OR of an allelic model.[31] For each variant the power of detecting an association was calculated for the current cohort size. For all variants genotype relative risks <2 could be detected with 80% power using this cohort. The detection limits of the genetic relative risk at 80% power were 1.35, 1.36, 1.46, 1.52, and 1.95 for rs2070951, rs41423247, rs6198, rs5522, and rs56149945, respectively (Figure 1).

**Table 3.** Haplotype analysis of *NR3C2* in cCSC patients

| Haplotype | rs2070951 | rs5522 | p-value | Freq Controls | Freq Patients | OR (95% CI) | | OR (95% CI) | |
|---|---|---|---|---|---|---|---|---|---|
| H1 | C | A | 0.00069 | 0.408 | 0.336 | Base | NA | Protective | 0.72 (0.60-0.87) |
| H2 | C | G | 0.54 | 0.127 | 0.137 | NS | 1.32 (1.00-1.75) | NS | 0.95 (0.73-1.24) |
| H3 | G | A | 0.0037 | 0.463 | 0.527 | Risk | 1.39 (1.15-1.68) | Base | NA |

Abbreviations: cCSC: chronic central serous chorioretinopathy; CI: confidence interval; Freq: frequency; NA: not annotated; NS: not significant; OR: odds ratio

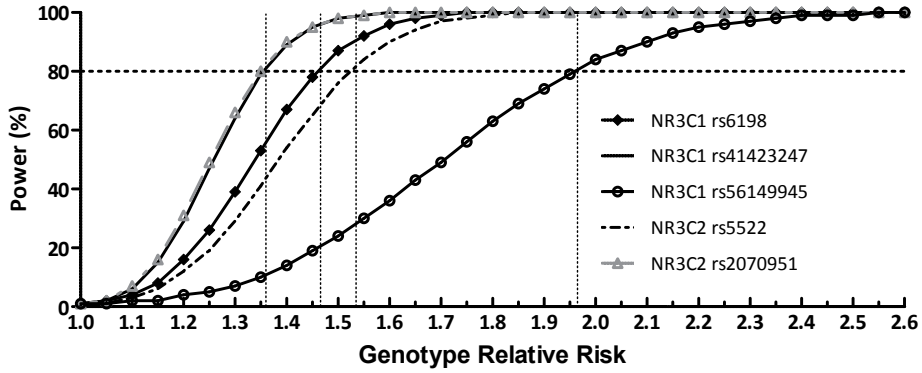


**Figure 1.** Power calculation for each variant analysed in a cohort of 336 chronic central serous chorioretinopathy patients.
For each variant the power to detect a certain genotype relative risk was assessed with CaTS using a multiplicative model, with minor allele frequency in controls and disease frequency of 0.0001 as input. The 80% power detection limits per variant were 1.35, 1.36, 1.46, 1.52, and 1.95 for rs2070951, rs41423247, rs6198, rs5522, and rs56149945, respectively.

## DISCUSSION

In this study, we analysed a possible association of 3 known functional variants in *NR3C1* and 2 known functional variants in *NR3C2* with cCSC. The rs2070951 variant in *NR3C2* was significantly associated with cCSC, whereas the rs5522 variant was not associated with cCSC. The *NR3C2* CA and GA haplotypes were both significantly associated with cCSC, with a protective and a risk-conferring effect, respectively. Odds ratios of the associated *NR3C2* variant and the haplotypes were similar to previously described associations for the *CFH* and *ARMS2* genes, and lower compared to the previously described associations in the *C4* and *CDH5* genes.[28, 32-34] The 3 variants in the *NR3C1* gene (encoding the GR) were not associated with cCSC, which may suggest that MR functionality is more relevant than GR functionality in cCSC disease etiology. However, a larger cohort size is required to exclude the involvement of the 4 variants that were not associated with cCSC in this study.

An abnormal response to the administration of corticosteroids in a subset of (chronic) CSC patients is the strongest risk factor for the disease with described ORs of up to 37.[9] However, the precise mechanism of action of steroids in cCSC disease pathogenesis is unknown. One study showed that both mineralocorticoids and glucocorticoids can activate the MR on choroidal endothelial cells in a rat model.[12] In this animal model, MR activation resulted in vessel dilation via upregulation of the endothelial vasodilatory calcium-dependent potassium channel KCa2.3,[2, 12] producing choroidal thickening that is also commonly observed in cCSC

patients.[2] The MR is also present on RPE cells, and clearance of retinal fluid through the RPE towards the choriocapillaris may be influenced by differences in MR haplotypes.[35] Additionally, on Müller glial cells the MR regulates water homeostasis in the eye, and dysregulation of this mechanism may contribute to the intraretinal fluid observed in a subset of cCSC patients.[2, 36] However, direct GR overactivation without MR involvement seems to be sufficient to induce (chronic) CSC in some patients, since synthetic glucocorticoids with strong selectivity for GR over MR have also described to be a risk factor for the disease.[7, 9]

Both variants in *NR3C2* tested in this study influence the transactivational capacity of the MR after exposure to both cortisol and dexamethasone,[21] and have been shown to affect salivary cortisol levels, especially during the morning cortisol awakening peak.[9, 21, 37] Strikingly, the rs2070951 G-variant, which is associated with cCSC in this study, leads to lower expression of MR and reduced transactivation. One study found that male carriers of the rs2070951 GG genotype in *NR3C2* had a higher systolic blood pressure.[20] This is particularly relevant in the context of cCSC as hypertension is a described risk factor for the disease.[38, 39] The effect of this genetic variant on systolic blood pressure was only observed in male patients, which is interesting since cCSC is much more common in men than in women.[40] In our dataset, the association for rs2070951 was also observed only in male cCSC patients when the data was stratified for gender (p-value in males: 0.020 versus p-value in females: 0.309, data not shown). However, this is likely due to the limited number of female cCSC patients included in the analysis, and based on the current data we therefore cannot definitively conclude that gender differences exist in this genetic association.

Haplotypes in *NR3C2* have previously been associated with differences in perceived chronic stress,[26] another postulated risk factor for cCSC.[11, 41-43] We found that the haplotype (GA) of SNPs rs2070951 and rs5522, which has been previously associated with increased susceptibility to stress,[26] confers risk for developing cCSC in our cohort. The haplotype (CA) that was associated with an optimistic attitude with tendency to recover from or adjust easily to misfortune or change,[44] was protective for the development of cCSC. This could indicate that in cCSC patients with the GA haplotype, both the MR(-mediated pathways) and chronic stress are of significant importance, whereas other not yet identified factors could play a bigger role in cCSC patients with the CA haplotype. Additionally, there is a likelihood that patients with the different haplotypes carry additional unknown genetic variants that might also contribute to an increased or decreased cCSC risk.

Clinical studies that tested the potential of MR antagonists in the treatment of cCSC have yielded mixed results.[14-17] Our findings may partly explain this variable response to MR antagonists, because carriers of different MR haplotypes may respond differently to MR antagonists. The results of our study may lead to the stratification of cCSC patients into subgroups, based on

MR haplotype. Treatment of these stratified patient subgroups with MR antagonists could result in group-specific effects. In patients with the CA haplotype, other (thus far unknown) factors could contribute to the development of CSC to a greater extent. The results of this study may therefore indicate that a more personalised treatment approach in cCSC may be useful. Further studies on the response to treatment in cCSC patients with different MR genotypes are needed to test this hypothesis.

In conclusion, in this study rs2070951 in the *NR3C2* gene, encoding the MR receptor, is significantly associated with cCSC. Additionally, haplotypes of *NR3C2* that have previously been associated with perceived stress also associate with cCSC in this study, which may be a first clue bridging clinical risk factors for cCSC to underlying genetic associations. Functional effects of this variant and the associated haplotype in the MR gene may contribute to the disease mechanisms of cCSC.

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