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A genome-wide association study of sodium levels and drug metabolism in an epilepsy cohort treated with carbamazepine and oxcarbazepine

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Summary

Objective: To ascertain the clinical and genetic factors contributing to carbamazepine- and oxcarbazepine-induced hyponatremia (COIH), and to carbamazepine (CBZ) metabolism, in a retrospectively collected, cross-sectional cohort of people with epilepsy.

Methods: We collected data on serum sodium levels and antiepileptic drug levels in people with epilepsy attending a tertiary epilepsy center while on treatment with CBZ or OXC. We defined hyponatremia as Na+ ≤134 mEq/L. We estimated the CBZ metabolic ratio defined as the log transformation of the ratio of metabolite CBZ-diol to unchanged drug precursor substrate as measured in serum.

Results: Clinical and genetic data relating to carbamazepine and oxcarbazepine trials were collected in 1141 patients. We did not observe any genome-wide significant associations with sodium level in a linear trend or hyponatremia as a dichotomous trait. Age, sex, number of comedications, phenytoin use, phenobarbital use, and sodium valproate use were significant predictors of CBZ metabolic ratio. No genome-wide significant associations with CBZ metabolic ratio were found.

Significance: Although we did not detect a genetic predictor of hyponatremia or CBZ metabolism in our cohort, our findings suggest that the determinants of CBZ metabolism are multifactorial.

KEYWORDS

adverse effects, antiepileptic drugs, EpiPGX Consortium, GWAS, hyponatremia

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1 | INTRODUCTION

Carbamazepine (CBZ) and its keto-analogue, oxcarbazepine (OXC), are routinely used as antiepileptic drugs (AEDs) and are also used in the treatment of chronic pain conditions and bipolar disorder. Although effective, their use is limited by adverse drug reactions (ADRs), including hyponatremia and hypersensitivity. Carbamazepine- and oxcarbazepine-induced hyponatremia (COIH) is reported in up to half of drug exposures. This is often assumed to be asymptomatic but it can lead to difficulties ranging from unsteadiness and mild confusion to seizures and coma. Careful dose titration and monitoring of sodium levels are recommended for reducing the risk of COIH, while individual differences in drug metabolism can make titration difficult.

*HLA-B*1502* is strongly associated with CBZ-induced Stevens-Johnson syndrome (SJS) in people of Han Chinese ethnicity, increasing the risk about 100-fold.[1] In individuals of European descent, *HLA-A*3101* is a clinically relevant predictor of the full spectrum of CBZ-induced hypersensitivity reactions.[2,3] To date, no genetic risk factors have been associated with COIH. Thiazide-induced hyponatremia is associated with 2 polymorphisms in the *KCNJ1* gene, encoding the renal outer medullary potassium

Key Points

- No large, clinically relevant genetic predictors of carbamazepine- or oxcarbazepine-induced hyponatremia
- Age and concurrent phenytoin, phenobarbital, or sodium valproate use was significantly associated with carbamazepine metabolic ratio
- No large, clinically relevant genetic predictors of carbamazepine metabolic ratio

channel (ROMK), which plays an important role in sodium reabsorption along the thick ascending limb of the loop of Henle.[4] CBZ and OXC seem to influence water reabsorption, independent of salt retention, via stimulation of the vasopressin 2 receptor/aquaporin (AVPR2) pathway.[5] Mutations in the *AVPR2* gene, a regulator of water reabsorption, can cause a nephrogenic syndrome of inappropriate antidiuresis (NSIAD) with physiologic similarities to the inappropriate antidiuresis induced by CBZ and OXC.[6] Studies of *AVPR2* copy number variation, however, did not explain variation in sodium levels in non-Hispanic Caucasian populations.[7]

We attempted to determine the clinical and genetic factors contributing to COIH and drug metabolism in a retrospectively collected, cross-sectional cohort of people with epilepsy of European descent treated with CBZ and OXC, which characteristics were previously described.[8]

2 | METHODS

2.1 | Study design and phenotypes

We followed a retrospective cohort study design. The majority of the patients were recruited at a Dutch tertiary epilepsy referral center (SEIN), whereas the remainder were recruited around European tertiary referral clinics associated with the EpiPGX Consortium. Clinical information from medical records, with an emphasis on AED history, was recorded in an electronic database designed for retrospective pharmacogenomics studies.[9] The database was used to identify all individuals who were prescribed CBZ or OXC and who had a recorded serum sodium level during therapy. Most individuals had several measurements, and the lowest sodium level recorded was selected for analysis. Our primary analyses were structured to test genetic variants for association with this lowest recorded sodium level per subject (mEql/L). Secondary analyses tested for genetic association with the following: (a) COIH (combined and per causal drug) and (b) CBZ metabolic ratio. In a subset of CBZ users for which we had concurrently measured CBZ-10,11-diol (CBZ-diol) levels, we calculated the metabolic ratio defined as the log transformation of the ratio of metabolite CBZ-diol to unchanged drug precursor substrate as measured in serum. COIH cases were defined as having a blood sodium level ≤134 mmol attributed to CBZ or OXC as determined by their clinician. COIH controls trialed CBZ or OXC for at least 3 months with a sodium level ≥135 mmol. Epilepsy-specific cohort demographics are presented in Table 1.

2.2 | Sampling and genotype analysis

Serum drug and metabolite concentrations were measured during the course of routine monitoring in the morning before drug intake. For each sodium level measurement, we recorded patient age, serum level of CBZ or OXC, and concomitant use of other drugs. Genotyping of all patients was performed at deCODE Genetics on Illumina OmniExpress-12 v1.1 and OmniExpress-24 v1.1 single nucleotide polymorphism (SNP) arrays. Genotyping quality control was performed as described previously.[10] Principal components analysis (PCA) was performed with European-ancestral samples from the HapMap Project to assess cohort substructure and identify population outliers (Figure S1). Eigenvectors were computed in the genome-wide complex trait analysis tool (GCTA) for each subject for inclusion as covariates in genetic-association testing.[11] Subjects were identified as outliers and removed if greater than 3 standard deviations (SD) from the first 8 principal components. We used the functional mapping and annotation of genome-wide association studies platform (FUMA) to generate Manhattan and quantile-quantile (Q-Q) plots.[12]

2.3 | Study power

We estimated from our recruited sample size that our study had 80% power to detect a genetic predictor of relative risk

TABLE 1 CBZ and OXC cohort characteristics

Description	CBZ	OXC	Combined
Subjects	1031	297	1252[a]
% male	51.4%	48.1%	51.2%
Mean age (±SD)	42.9 ± 15.1	38.1 ± 15.9	41.9 ± 15.6
No. AED comedications (max)[b]	1.0 (5)	0.9 (4)	1.0 (5)
Hyponatremia (Na <135 mEq/L)	331 (32%)	170 (57%)	448[c]
Mean case serum sodium (mEq/L)	129.5 ± 4.1	127.5 ± 4.2	129.0 ± 4.2
Mean control serum sodium (mEq/L)	139.8 ± 2.5	139.4 ± 2.7	139.7 ± 2.5
Mean serum AED level (mg/L) (±SD)[b]	8.7 ± 2.3	17.8 ± 8.2	—
Metabolic ratio (±SD)[d]	0.35 ± 0.21	—	—

[a]Seventy-nine subjects trialed both CBZ and OXC.
[b]Calculated from SEIN subcohort (n = 1074).
[c]Fifty-three subjects experienced hyponatremia on both CBZ and OXC.
[d]Metabolic ratio calculated on a subset of subjects with serum CBZ-diol level readings (n = 468).

(approximated to odds ratio) ≥ 3 with an allele frequency $\geq 2\%$ and an alpha level of 1.0×10^{-8}, using the power calculator for case-control genetic association analyses PGA.[13]

2.4 | Statistical analyses

Clinical cofactors influencing sodium levels and COIH in this cohort were reported previously and used as covariates in our models.[8] Association analyses were conducted using additive linear or logistic regression models in PLINK, including clinical covariates where appropriate and 8 principal components from PCA. Dosage, number of comedications, and AED levels were excluded from the genetic analyses due to missing information in the EpiPGX subcohort. We also analyzed the significance of clinical variables influencing CBZ metabolic ratio using a stepwise linear regression model in SPSS statistical software. As before, significant clinical cofactors from the linear regression model were included as covariates along with 8 principal components from PCA. For each association test, SNPs with <90% call rate were excluded. The threshold for genome-wide statistical significance was set at 1.0×10^{-8}, reflecting an empirical Bonferroni correction for 5 tests, of the standard 5×10^{-8} genome-wide significance threshold.

2.5 | Ethical considerations

All study participants provided written, informed consent for genetic analysis. Study protocols were approved by the research ethics committees listed in Table S1.

3 | RESULTS

We collected clinical and genetic data relating to CBZ (n = 1031 subjects) and OXC (n = 297 subjects) trials. A subset (n = 79 subjects) were trialed on CBZ and OXC. Of the total 1252 patients, 1047 were recruited at SEIN while 201 were recruited through EpiPGX partner sites. Data on drug levels and compliance were available for 98% of the SEIN cohort, but not for the EpiPGX partner sites. In 5% of our SEIN cohort the drug levels or dosage was below therapeutic values (for CBZ <4 mmol/L or <400 mg/d, for OXC <10 mmol/L or <900 mg/d). We report 448 cases with COIH and 804 controls with normal serum sodium measurement. Within our cases there was a subset of 61 subjects with extreme hyponatremia. The incidence of OXC-induced hyponatremia (57%) was almost twofold higher than that of CBZ (32%). Characteristics of our cohort are described in Table 1. A total of 25 subjects were removed after genotyping quality control.
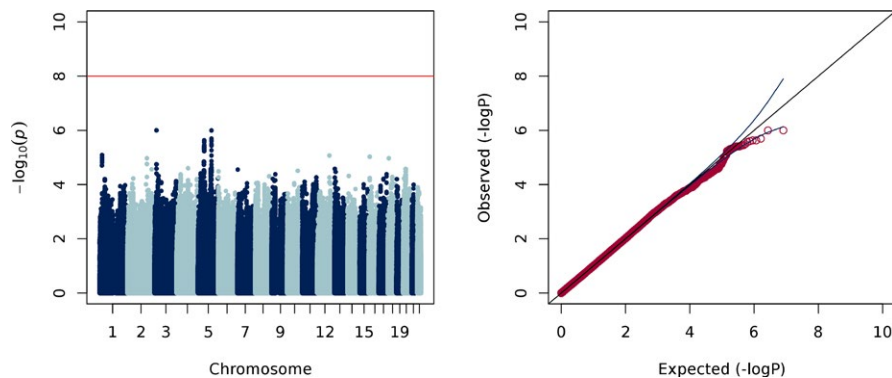
To test whether common genetic variants predict sodium levels, we performed a genome-wide linear regression adjusted for age, clobazam use, sex, plus 8 principal components. We did not observe any genome-wide significant associations with sodium level (Figure 1).

To test whether common genetic variants predict COIH, defined as a serum sodium level <135 mEq/L, we performed a case-control genome-wide logistic regression adjusted for sex, age <40, plus 8 principal components. We did not observe any genome-wide significant associations when we considered COIH as a dichotomous trait (Figure 2). There was a suggestive association signal ($P < 1 \times 10^{-6}$) from chromosome 5, in an intergenic region approximately 500 Mb downstream of the gene *ANKRD55*, evident in the quantitative and dichotomous analyses of sodium. Furthermore, we did not detect evidence for a genetic signal in a subset of 61 severe COIH cases, defined as a serum sodium ≤ 125 mEq/L, when compared to controls. Neither did we did observe any significant associations when we differentiated hyponatremia by causal drug (see Figures S2-S4). Given prior reports of an association with thiazide-induced hyponatremia, we looked closely within the *KCNJ1* and *AVPR2* genes, yet we did not observe any signals of association in our data.

Next, we explored whether clinical cofactors or genetic variants could predict the ratio of active drug to metabolite in our CBZ-exposed subjects. We modeled the contribution of clinical cofactors to CBZ metabolic ratio and found that age, sex, number of comedications, phenytoin use, phenobarbital
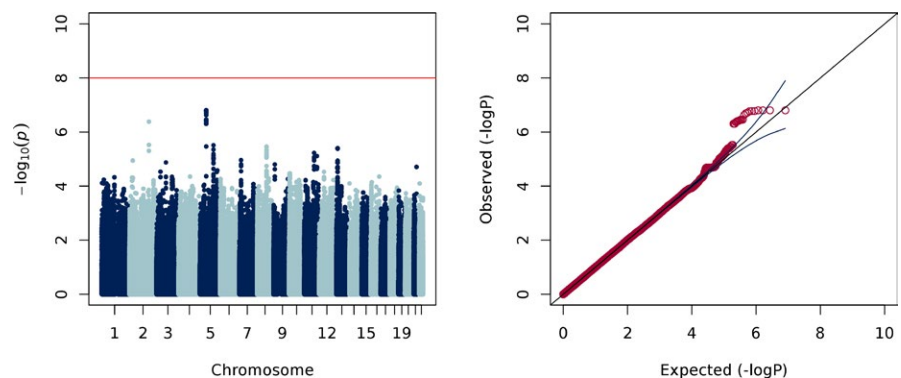
FIGURE 1 Manhattan and Q-Q plots of sodium levels ($\lambda = 1.00$)

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FIGURE 2 Manhattan and Q-Q plots of COIH ($\lambda = 1.00$)
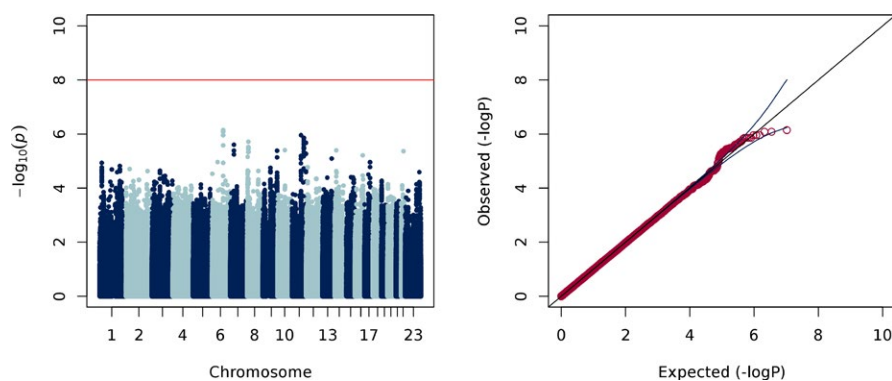
FIGURE 3 Manhattan and Q-Q plots of carbamazepine metabolic ratio ($\lambda = 0.98$)

use, and sodium valproate use were significantly predictive of outcome (adjusted $r^2 = 0.236$, Model 5 in Table 2).

To test whether common genetic variants predict CBZ metabolic ratio, we then performed a genome-wide linear regression adjusted for the covariates in Model 5, plus 8 principal components. We did not observe any genome-wide significant associations with CBZ metabolic ratio (Figure 3). The top 10 most significant GWAS markers for each analysis are listed in Tables S1-S5. Polymorphisms in *CYP3A4* and *EPHX1* have been shown to associate with interindividual variability of CBZ metabolism.[14,15] We did not observe even nominally significant associations between SNPs in *CYP3A4* and CBZ metabolic ratio. It had been reported that homozygous carriers of the *EPHX1*

c.416A>G SNP (rs2234922) seemingly show a reduced CBZ metabolism, as measured by a significantly decreased metabolic ratio.[16] We did not replicate this finding (rs2234922; $P = 0.303$) but we observed a nominally significant association between an intronic *EPHX1* SNP (c.365-2139T>C) and CBZ metabolic ratio (rs4653689; $P = 1.1 \times 10\text{-}4$).

4 | DISCUSSION

Although we did not detect a genetic predictor of hyponatremia in our cohort, we have demonstrated that the determinants of CBZ metabolism are multifactorial. Modeling the

TABLE 2 Stepwise linear regression of carbamazepine metabolic ratio

Model	Factors	R	R^2	Adjusted R^2	Std. error
1	PHT	.363[a]	0.132	0.130	0.196
2	PHT, NoCoMed	.421[b]	0.177	0.174	0.191
3	PHT, NoCoMed, age	.458[c]	0.210	0.205	0.188
4	PHT, NoCoMed, age, PHB	.486[d]	0.236	0.230	0.185
5	PHT, NoCoMed, age, PHB, VPA	.493[e]	0.243	0.236	0.184

NoCoMed, number of comedications; PHB, phenobarbital; PHT, phenytoin; VPA, sodium valproate.

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contribution of clinical variables showed there were strong nongenetic predictors of CBZ metabolism. Subject age, total number of comedications, and the concurrent use of phenytoin, phenobarbital, or sodium valproate were significantly associated with a higher CBZ-diol to CBZ ratio. Much of this can be explained by the induction of the cytochrome P450 enzyme CYP3A4. CBZ is metabolized in the liver by CYP3A4 to carbamazepine-10,11-epoxide, which is further metabolized by microsomal epoxide hydrolase (mEH) to carbamazepine-10,11-diol.[17] Phenytoin and phenobarbital induce CYP3A4 and thus can lower plasma CBZ levels but leave the metabolite levels unaltered, which results in the observed higher metabolic ratio.[18,19] Sodium valproate inhibits epoxide hydrolase, potentiating higher levels of the active metabolite CBZ-10,11-epoxide, which is associated with toxicity and adverse events,[20] but this was not directly measured in this study. Valproate has been shown to increase dose ratios between CBZ and its metabolites, for both the diol and epoxide forms.[21] Age has been found previously to contribute to pharmacokinetic variability in individuals using CBZ with increasing clearance until age 33 and a gradual decrease toward older age.[22]

A limitation of the study is that AED dosage was not reliably recorded in our cohort and we had to make an assumption that the measurement of CBZ metabolic ratio was independent of the individual subject's dosage. In the subset of subjects for whom serum CBZ-diol and CBZ dosage information was available (n = 40) we did not detect a significant effect of CBZ dose on the metabolic ratio ($P = 0.41$).

CBZ and OXC are widely prescribed but their use coincides with a high prevalence of COIH. Within our cohort OXC-induced hyponatremia has a much higher prevalence than that of CBZ, which is consistent with previous estimates.[23,24] From clinical experience, susceptibility to COIH is individually variable. Experimental studies and a recent clinical report suggest that COIH is caused by a direct effect of CBZ/OXC on the kidney by stimulating the vasopressin receptor.[25,26] Mutations in the V2R/AQP2 pathway regulating water reabsorption can cause disorders clinically similar to the syndromes of inappropriate secretion of antidiuresis associated with CBZ/OXC use. Meanwhile thiazide-induced hyponatremia has been associated with polymorphisms in the gene *KCNJ1* and a suggestive association with a variant in *SLCO2A1*, encoding a prostaglandin transporter; these signals did not show even nominal significance in our data.[4,27] We further looked for an effect from these markers within the subset of 53 subjects who experienced hyponatremia on both CBZ and OXC independently, but there was no significant enrichment.

Previously described clinical predictors of serum sodium levels explain only 11%-14% of the variance in the SEIN cohort.[8] Therefore, it is hypothesized that genetic variation could in part explain the variation in susceptibility to COIH. Yet, after analyzing sodium levels in a linear trend and hyponatremia as a dichotomous trait, we did not find genetic predictors for COIH. A recent report of variants in *NFAT5* and *SLC4A10* with suggestive association with plasma osmolality further imply a genetic component to hyponatremia, but these variants showed no evidence for effect on serum sodium measurements in our study, albeit we were not as powered as the original discovery cohort.[28]

In summary, our study rules out common genetic variants of clinically relevant effect size; however, genetic susceptibility for COIH cannot be ruled out completely, as rare variants and combinations of genetic variants of smaller effect size (polygenic risk) may contribute to overall risk. Further study, ideally in a prospective cohort with baseline sodium level and CBZ-diol measurements, is warranted to investigate the genetic contribution to CBZ- and OXC-induced hyponatremia.

DISCLOSURE

None of the authors has any conflict of interest to disclose in relation to this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

APPENDIX 1

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Krishna Chinthapalli, Mojgansadat Borghei, Antonietta Coppola, Antonio Gambardella, Stefan Wolking, Felicitas Becker, Sarah Rau, Christian Hengsbach, Yvonne G. Weber, Bianca Berghuis, Wolfram S. Kunz, Mark McCormack, Norman Delanty, Ellen Campbell, Lárus J. Gudmundsson, Andres Ingason, Kári Stefánsson, Reinhard Schneider, Rudi Balling, Pauls Auce, Ben Francis, Andrea Jorgensen, Andrew Morris, Sarah Langley, Prashant Srivastava, Martin Brodie, Marian Todaro, Slave Petrovski, Jane Hutton, Fritz Zimprich, Martin Krenn, Hiltrud Muhle, Karl Martin Klein, Rikke Moller, Marina Nikanorova, Sarah Weckhuysen, Zvonka Rener-Primec, Gianpiero L. Cavalleri, John Craig, Chantal Depondt, Michael R. Johnson, Bobby P. C. Koeleman, Roland Krause, Holger Lerche, Anthony G. Marson, Terence J. O'Brien, Josemir W. Sander, Graeme J. Sills, Hreinn Stefansson, Pasquale Striano, Federico Zara and Sanjay M. Sisodiya