Published in final edited form as:

Nature. 2014 September 18; 513(7518): E1–E3. doi:10.1038/nature13629.

***GATM* locus does not replicate in rhabdomyolysis study**

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All HMG-CoA reductase inhibitors (statins) can cause muscle injury ranging from asymptomatic elevations in creatine kinase (CK) levels to severe muscle breakdown (rhabdomyolysis) leading to kidney failure and death,¹ and the genetic variants responsible for this uncommon adverse drug reaction remain largely undiscovered. Mangravite *et al.* reported a new locus in the gene *GATM* (rs9806699) that was associated with a decreased risk of muscle injury in two case-control studies of myopathy (odds ratio [OR], 0.60).² In a larger case-control study of statin-related rhabdomyolysis, a more severe form of muscle injury, we were unable to replicate this finding. This failure to replicate raises questions about the role of *GATM* in statin-related muscle injury.

Mangravite *et al.* used differential gene expression profiling of lymphoblastoid cell lines exposed to simvastatin to identify *cis*-eQTLs for the gene *GATM* as candidate loci for pharmacogenomic associations with muscle injury, which they evaluated in two case-control studies of myopathy. Variation at their most significant *cis*-eQTL for *GATM*, rs9806699, was associated with a decreased risk of muscle injury (OR 0.60, 95% confidence interval [CI] 0.39–0.95) in a study with 72 mild myopathy cases (blood CK levels > 3x the upper limit of normal [ULN] with muscle symptoms) recruited from a healthcare organization (Marshfield). In a second study with 39 mild and 61 severe myopathy cases (CK > 10x ULN with muscle symptoms) using simvastatin during the SEARCH clinical trial, variation at two single-nucleotide polymorphisms (SNPs) in linkage disequilibrium with rs9806699 (r^2 0.7) was also associated with a decreased risk of muscle injury (rs1719247, OR 0.61, 95% CI 0.42–0.88; rs1346268, OR 0.62, 95% CI 0.43–0.90). On the basis of these epidemiologic findings and the results of functional studies in hepatocyte-derived cell lines, the authors identified *GATM* as a new genetic locus for statin-induced myopathy.

We attempted to replicate these findings in a case-control study of rhabdomyolysis (CK > 10x ULN and muscle symptoms) related to the use of cerivastatin,^{3,4} which was removed from the market in 2001 because of a high incidence of this adverse drug reaction.⁵ 175

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Author contributions: JCB and JSF performed the analyses. BMP obtained the funding for this work. All authors contributed to the design of the analyses and the drafting and revision of the manuscript.

Competing financial interests: BMP serves on the DSMB for a clinical trial of a device funded by the manufacturer (Zoll LifeCor).

rhabdomyolysis cases (94.9% of European ancestry) were compared with 645 statin-using control subjects from the Cardiovascular Health Study without rhabdomyolysis (99.7% of European ancestry). Variation at rs9806699 was not associated with the risk of rhabdomyolysis (OR 1.01, 95% CI 0.70–1.45), and variation at the other two SNPs was weakly associated with an increased risk (rs1719247, OR 1.37, 95% CI 0.98–1.90; rs1346268, OR 1.25, 95% CI 0.90–1.73). 99 rhabdomyolysis cases used fibrates, which can cause drug-drug interactions with statins, and excluding fibrate users also resulted in null associations (Table 1). Combining our results (all subjects) with results by Carr *et al.* and Mangravite *et al.* in a fixed effects meta-analysis resulted in null associations at rs9806699 (OR 0.88, 95% CI 0.72–1.08, $P = 0.22$), rs1719247 (OR 0.86, 95% CI 0.69–1.07, $P = 0.17$), and rs1346268 (OR 0.85, 95% CI 0.68–1.05, $P = 0.12$). There was statistical heterogeneity at rs1719247 ($\tau^2 = 0.22$, $P = 0.001$) and rs1346268 ($\tau^2 = 0.14$, $P = 0.009$).

Although most cases from the SEARCH trial involved severe myopathy, it is possible that the *GATM* variants identified by Mangravite *et al.* protect against mild but not severe statin-related muscle injury. Other differences in the study populations could also result in heterogeneity of the effects of these variants. An alternative explanation for the discrepant findings is that *GATM* is not related to this adverse drug reaction. By contrast, a nonsynonymous variant in the drug transporter gene *SLCO1B1* (rs4149056) that decreases the clearance of statins^{6,7} has been associated with statin-related muscle injury of various severity and statin types.^{8–11} The odds ratio for the rs4149056 minor allele in our rhabdomyolysis study (2.0)³ was similar to the odds ratios in a study of less-severe myopathy cases related to simvastatin use (2.1) and a in recent meta-analysis (2.2).¹¹ In other words, the drug transporter encoded by *SLCO1B1* is a widely replicated finding.⁶

The approach by Mangravite *et al.* of identifying potential new pharmacogenomic interactions through differential gene expression profiling is innovative. However, the failure to replicate their findings in a large study of rhabdomyolysis raises questions about whether *GATM* represents a genuine genetic locus for this adverse drug reaction.

Methods

Case subjects were recruited through attorneys representing cerivastatin users who developed rhabdomyolysis. Trained abstractors reviewed medical records to validate rhabdomyolysis events. Because cerivastatin comprised a small fraction of statin use during its market life (March 1998–August 2001), it was not practicable to assemble a broad sample of cerivastatin users who did not develop rhabdomyolysis. Instead, the control group comprised statin-using participants of the Cardiovascular Health Study, a prospective cohort study of older adults.^{12,13}

Acknowledgments

Grant acknowledgement: This work was funded by a grant from the NHLBI, HL078888.

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Table 1

Association of *GATM* loci with the risk of cerivastatin-related rhabdomyolysis.

SNP	All Subjects					Excluding fibrate users				
	Cases (N=175), MAF	Controls (N=645), MAF	OR	95% CI	P value	Cases (N=76), MAF	Controls (N=643), MAF	OR	95% CI	P value
rs9806699	0.27	0.28	1.01	0.70–1.45	0.96	0.24	0.28	0.84	0.52–1.36	0.49
rs1719247	0.29	0.25	1.37	0.98–1.90	0.07	0.24	0.25	1.00	0.64–1.57	0.99
rs1346268	0.29	0.27	1.25	0.90–1.73	0.18	0.24	0.27	0.88	0.52–1.36	0.57

Rhabdomyolysis case subjects had creatine kinase levels > 10x the upper limit of normal and used cerivastatin at the time of onset of symptoms of muscle pain or weakness. Control subjects did not experience rhabdomyolysis and used the following statins: lovastatin (44%), simvastatin (19%), pravastatin (18%), atorvastatin (13%), fluvastatin (6%), or cerivastatin (1%). CI = confidence interval, OR = odds ratio, MAF = minor allele frequency, SNP = single nucleotide polymorphism.