Supplementary Methods:

A. Tag- and proxy SNP identification

23 *ABCC8* tag-SNPs (including 2kb at the 5' and 3' ends) were identified using HapMap (HapMap-3 Release-2, NCBI B36, CEU population, http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap3r2_B36/) with the tagger-algorithm pairwise approach, $r^2 \geq 0.8$ and minor allele frequency >0.20. After eliminating tag-SNPs predicted to fail multiplexing, or with a low call-rate (<90%) when genotyped, 15 tag-SNPs were included in the final analysis: rs11024273, rs11024286, rs2074311, rs2237982, rs2237991, rs2299639, rs3758953, rs4148618, rs4148622, rs4148641, rs4757517, rs7105832, rs7124355, rs7947462, rs916827. Eight tag-SNPs were eliminated: rs2283257 was in complete linkage disequilibrium (LD) with rs4148618 and therefore removed to minimize duplication. Rs2188966, rs2283255, rs757110 and rs2283258 were excluded due to predicted primer interactions precluding successful multiplexing on MassARRAY (the latter two were previously evaluated in a smaller whole-exome analysis[4]). Rs7950189 and rs1109591 were excluded due to low call rates. The rs7106053 assay revealed a split heterozygote cluster, low-mass homozygote peak in the no-template-control, and no calls for the high-mass homozygote. Proxy-SNPs associated with tag-SNPs based on LD ($r^2 \geq 0.8$) were identified using SNP annotation and proxy search (SNAP, Broad Institute, Version 2.2)[23].

B. DNA collection and Genotyping

DNA was collected per our previously published methods[4,24]. Three primers were designed for each tag-SNP using MassARRAY Design-3.1 (two amplification primers flanking the polymorphic site for sample amplification, and a single MassExtend primer immediately adjacent to allow for allelic discrimination via single base extension). Genotyping using iPlex-Gold was performed with an Agena Compact MassArray with Nanodispenser by the University of Pittsburgh Genomics Research Core (Supplementary Methods). For stringent quality control, known high-quality DNA and no-template controls were included

for each assay group. Blind technical duplicates were also included. Genotype analysis was performed using Typer-4.0. Assay quality was further verified by visual inspection of cluster plot and poorly performing assays (those with amplification in no-template controls or ambiguous clusters) were excluded from further analysis. Based on this quality control, 75/485 samples were excluded resulting in 410 samples for final analysis. The average call rate for the 15 tag-SNPs analyzed was 96.7± 2%. Research assistants involved in genotyping SNPs were blinded to outcomes.

C. Functional category prediction of *ABCC8* tag and proxy SNPs

Predicted SNP functional effects were investigated using F-SNP (http://compbio.cs.queensu.ca/F-SNP/)[32]. All significant SNPs were evaluated for established clinical significance via PubMed, Embase, and ClinVar searches. Previously reported SNPs associated with glucose metabolism disorders were similarly identified to investigate potential similarities/differences with SNPs associated with cerebral edema/outcomes in sTBI. The following search terms were used without restrictions: "*ABCC8* polymorphisms", "*ABCC8* SNPs", sulfonylurea receptor 1 polymorphisms", "sulfonylurea receptor 1 SNPs", "*ABCC8* polymorphisms diabetes", "*ABCC8* SNPs diabetes", "*ABCC8* polymorphisms glucose", "*ABCC8* SNPs glucose", "*ABCC8* polymorphisms insulin", "*ABCC8* SNPs insulin". Reference lists for major reviews were also scrutinized. References were individually examined for SNPs (identified by their reference-SNP cluster identification, rsID) significantly associated with glucose metabolism disorders. For variants reported using human genome variation society (HGVS) nomenclature, ClinVar was searched using the HGVS identification to obtain the equivalent rsID whenever available. Finally, "*ABCC8*" was searched in ClinVar to identify any additional SNPs associated with disorders of glucose metabolism.

SUPPLEMENTARY RESULTS

Risk-alleles CTGA are associated with average-ICP

Since none of the four tag-SNPs were in LD, risk-allele combinations were analyzed as haplotypes. Risk-alleles CTGA were present in 4.6% of the cohort and was significantly associated with average-ICP (Supplemental Table 1) in multiple models including the global haplotype test (p=0.0008) as well as individual haplotype specific tests using univariate and multivariate generalized linear regression model (Haplo.glm). No risk-allele combinations of the significant tag-SNPs were associated with CT edema or 3-month GOS.

SUPPLEMENTAL TABLE 1: ABCC8 TAG-SNP RISK ALLELE HAPLOTYPE ASSOCIATED WITH AVERAGE INTRACRANIAL PRESSURE IN SEVERE TBI

Outcome	Haplotype*	Haplotype Frequency	Hapscore Model		Univariate Regression		Multivariate Regression	
			Hapscore	*p-value*	*β-coefficient ± SE*	*p-value*	*β-coefficient ±SE*	*p-value*
Average -ICP	CTGA	4.6%	2.652	***0.0008****	4.16± 1.2	***0.001****	3.53± 1.14	***0.002****
Peak ICP	CTGA	4.6%	1.817	0.069	5.98± 4.31	0.17	4.38± 4.03	0.28

*Haplotypes derived from tag-SNPs rs7105832 (A/C), rs2237982 (C/T), rs11024286 (G/A), rs4148622 (G/A). Regression Models Reference Base: ACGG (all major alleles)

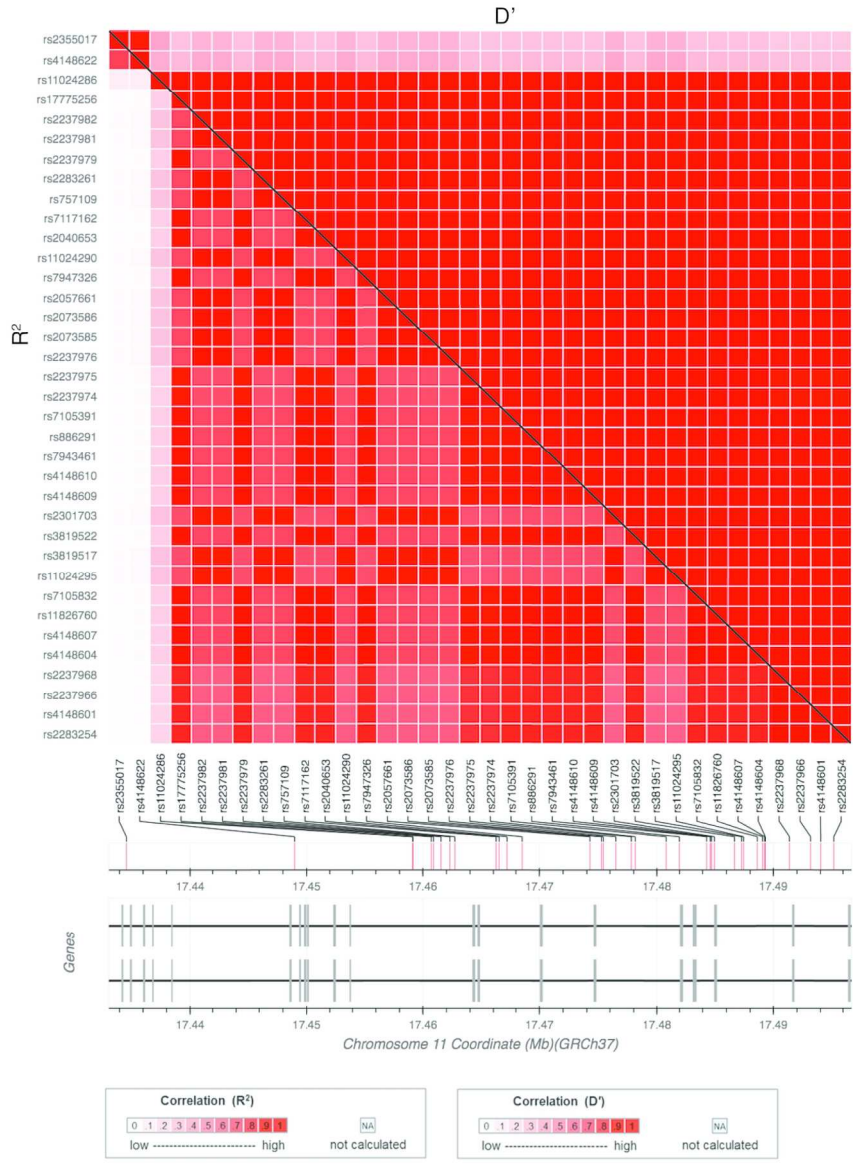
Patients with the CTGA risk-allele combination of tag-SNPs had significantly higher average ICP by 3.53 mmHg (multivariate, p=0.002) or 4.16 mmHg (univariate, p=0.001) versus those without. Maintaining internal consistency, this risk-allele set combines the variant-allele of rs7105832 (C) and the variant allele of rs2237982 (T) that were independently associated with increased CE measures in single locus analyses.

Supplementary Table 2: ABCC8 Tag-and Proxy-SNP chromosome locations and predicted functional implications

#	*SNP ID*	*Tag (T) /Proxy (P)*	*r^2 with Tag-SNP (if proxy)*	*Intron / Exon*	*Predicted Functional Category*	*Predicted Functional Results*	*FS Score*	*Pubmed Reference or ClinVar Reports*
1	rs2355017	Proxy	0.83 rs4148622	I 20	Transcriptional regulation	Changed	0.208	None
2	rs4148622	Tag	NA	I 15	Transcriptional regulation	Changed	0.176	None
3	rs11024286	Tag	NA	I 10	Transcriptional regulation	Changed	0.176	Knuppel et al, 2013: obesity (no association)
4	rs17775256	Proxy	1.0 rs7105832	I 10	Transcriptional regulation	Changed	0.176	None
5	rs2237982	Tag	NA	I 10	Transcriptional regulation	Changed	0.176	None
6	rs2237981	Proxy	1.0 rs2237982	I 10	Transcriptional regulation	Changed	0.176	Feng et al, 2008: diabetes associated with Gliclazide responsiveness
7	rs2237979	Proxy	1.0 rs7105832	I 10	Transcriptional regulation	Changed	0.208	None
8	rs2283261	Proxy	1.0 rs2237982	I 10	Transcriptional regulation	Unchanged	0.05	Jha et al, 2016 (CE)
9	rs757109	Proxy	1.0 rs2237982	I 10	Transcriptional regulation	Changed	0.176	None
10	rs7117162	Proxy	1.0 rs7105832	I 10	Transcriptional regulation	Changed	0.176	None
11	rs2040653	Proxy	1.0 rs7105832	I 10	Transcriptional regulation	Changed	0.176	None
12	rs11024290	Proxy	1.0 rs2237982	I 8	Transcriptional regulation	Changed	0.176	None
13	rs7947326	Proxy	0.93 rs7105832	I 8	Transcriptional regulation	Changed	0.208	None
14	rs6486370	Proxy	0.97 rs2237982	I 7	Transcriptional regulation	Changed	0.176	None
15	rs2057661	Proxy	1.0 rs2237982	I 7	Transcriptional regulation	Changed	0.208	None
16	rs2073586	Proxy	1.0 rs2237982	I 6	Transcriptional regulation	Changed	0.208	None
17	rs2073585	Proxy	1.0 rs2237982	I 6	Transcriptional regulation	Changed	0.208	None
18	rs2237976	Proxy	1.0 rs2237982	I 6	Transcriptional regulation	Changed	0.208	None
19	rs2237975	Proxy	0.97 rs7105832	I 6	Transcriptional regulation	Changed	0.176	None
20	rs2237974	Proxy	0.97 rs7105832	I 6	Transcriptional regulation	Changed	0.0	None
21	rs7105391	Proxy	1.0 rs7105832	I 6	Transcriptional regulation	Unchanged	0.05	None
22	rs886291	Proxy	1.0 rs7105832	I 6	Transcriptional regulation	Unchanged	0.0	None
23	rs7943461	Proxy	1.0 rs7105832	I 4	Transcriptional regulation	Changed	0.176	None
24	rs4148610	Proxy	1.0 rs7105832	I 4	Transcriptional regulation	Changed	0.176	None
25	rs4148609	Proxy	0.97 rs7105832	I 4	Transcriptional regulation	Changed	0.158	Jablonski et al, 2010 diabetes (significant interaction with Metformin)
26	rs2301703	Proxy	0.97 rs2237982	I 4	Transcriptional regulation	Changed	0.176	ClinVar ID 157707: neonatal diabetes and hyperinsulinism (likely benign)
27	rs3819522	Proxy	1.0 rs7105832	I 3	Transcriptional regulation	Unhanged	0.05	None
28	rs3819517	Proxy	0.93 rs7105832	I 3	Transcriptional regulation	Changed	0.176	None
29	rs11024295	Proxy	0.93 rs7105832	I 3	Transcriptional regulation	Changed	0.176	None
30	rs7105832	Tag	NA	I 3	Transcriptional regulation	Changed	0.176	None
31	rs11826760	Proxy	1.0 rs7105832	I 3	Transcriptional regulation	Changed	0.208	None
32	rs4148607	Proxy	0.97 rs7105832	I 3	Transcriptional regulation	Changed	0.208	None
33	rs4148604	Proxy	0.97 rs7105832	I 3	Transcriptional regulation	Unchanged	0.05	None
34	rs2237968	Proxy	0.97 rs7105832	I 3	Transcriptional regulation	Changed	0.176	None
35	rs2237966	Proxy	0.90 rs7105832	I 2	Transcriptional regulation	Changed	0.176	None
36	rs4148601	Proxy	0.93 rs7105832	I 2	Transcriptional regulation	Changed	0.208	None
37	rs2283254	Proxy	0.93 rs7105832	I 2	Transcriptional regulation	Unchanged	0.0	None

I= intron, E= exon, FS= functional significance.

Supplemental Figure 1 Linkage disequilibrium plot of significant tag and proxy SNPs



191x264mm (300 x 300 DPI)