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Genome-wide association identifies a novel locus for delirium risk

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Abstract

We aimed to identify common genetic variations associated with delirium through genome-wide association testing in a hospital biobank. We applied a published electronic health record based definition of delirium to identify cases of delirium, and control individuals with no history of delirium, from a biobank spanning two Boston academic medical centers. Among 6,035 individuals of Northern European ancestry, including 421 with a history of delirium, we used logistic regression to examine genome-wide association. We identified one locus spanning multiple genes, including three interleukin-related genes, associated with p=1.41e-8, and five other independent loci with p<5e-7. Our results do not support previously reported candidate gene associations in delirium. Identifying common-variant associations with delirium may provide insight into the mechanisms responsible for this complex and multifactorial outcome. Using standardized claims-based phenotypes in biobanks should allow the larger-scale investigations required to confirm novel loci such as the one we identify.

Keywords

genetic association; delirium; consultation psychiatry; attention; biobank

1. Introduction

Delirium is a common and consequential clinical syndrome characterized by fluctuations in mental status. Although reported rates of delirium vary widely with diagnostic method and clinical cohort, it is generally thought to occur in 20-30% of general hospital admissions and up to 80% of intensive care admissions (Francis et al., 1990; Ryan et al., 2013; Siddiqi et al.,

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2006; van den Boogaard et al., 2012; Vasilevskis et al., 2012). Emergence of delirium is associated with increased length of stay, exacerbation of other disorders, and greater in- and post-hospital morbidity and mortality (Bellelli et al., 2007; Ely et al., 2004; Girard et al., 2010; Leslie et al., 2005; MacLullich et al., 2009; Maldonado, 2013; McCusker et al., 2001; O'Keeffe and Lavan, 1997; Pandharipande et al., 2013; Pauley et al., 2015; Pisani et al., 2009; Salluh et al., 2015).

Delirium has been recognized to be complex and multifactorial, but multiple contributing mechanisms have been identified (Maldonado, 2013). These include direct and indirect effects of inflammatory, neuroendocrine, and gross anatomic or neurodegenerative mechanisms (Maclullich et al., 2008). The complexity of this biology is not unexpected given that delirium often arises in the context of systemic illness without overt brain involvement, which implies a level of causal indirection. A wide range of peripheral- and cerebrospinal fluid-based biomarkers have been suggested based on the various hypotheses of delirium pathogenesis, although none are in widespread clinical use (Chu et al., 2011; Stoicea et al., 2014).

Across medicine, genome-wide association studies have been employed as an unbiased means of deriving support for hypothesized disease mechanisms, or identifying novel disease mechanisms. There is a developed literature on delirium genetics focusing on candidate genes and the clinical significance thereof; however, we are not aware of a delirium focused GWAS study (Ely et al., 2007; Stoicea et al., 2014; van Munster et al., 2009). In an effort to gain insight into the biological basis of delirium, we applied a validated definition of delirium drawn from electronic health records to the biobank of two large health systems, and conducted a genome-wide association study.

2. Material and methods

2.1 Overview and Data Set Generation

We used a standard case-control association design, contrasting individuals with delirium and individuals with no history of delirium. Specifically, we accessed electronic health records data from the initial ~15,000 individuals genotyped as part of an academic medical center based biobank initiative drawing on two large Boston area hospitals. Among individuals age 60-90 years, delirium was defined according to a previously-described set of ICD9 diagnostic codes: 290.(11,3,41), 293.(0,1,9), or 780.09, excluding from both case and control groups individuals with delirium owing to substance code (ICD9 291.[0,3], 292.81) based on experience at this site (McCoy et al., 2017a, 2017b). A matched set of control individuals was identified from individuals age 60-90 years with no history of any of these codes.

We generated a datamart incorporating these clinical data using i2b2 server software (i2b2 v1.6, Boston, MA, USA), a computational framework for managing human health data (Murphy et al., 2009, 2007, 2010). The biobank study protocol was approved by the Partners Institutional Review Board, with deidentified data accessed using a Data Use Agreement with Partners HealthCare.

2.2 Genotyping and quality control

As previously described, DNA extracted from buffy coat was genotyped on one of three versions of the Illumina Multi-Ethnic Global (MEG) array (MEGA n=4,927, MEGA EX n=5,353, and MEG n=4,784; mappable variants available for each were 1,411,334; 1,710,339; and 1,747,639 respectively) (McCoy Jr et al., 2017). Each of these arrays incorporates content from the 1000 Genomes Project Phase 3 (1000G Phase 3). SNP coordinates were remapped based on the TopGenomicSeq provided from Illumina based on build 142 of dbSNP. To determine the forward strand of the SNP, we aligned both SNP sequences (alleles A and B) to hg19 using BLAT with default parameters set by UCSC Genome Browser (Kent, 2002).

The cohorts run on each array were cleaned, imputed, and analyzed separately to avoid batch effects. Each cohort included subjects with genotyping call rates exceeding 99% no related individuals based on identity by descent (IBD) were included (Henn et al., 2012). From these individuals, any genotyped SNP with a call rate of at least 95% and Hardy-Weinberg equilibrium P value $<1\times10^{-6}$ was included. Imputation used the Michigan Imputation Server implementing Minimac3 (Fuchsberger et al., 2015, n.d.; “Minimac3,” n.d.). Imputation used all population subsets from 1000G Phase 3 v5 as reference panel; haplotype phasing was performed using SHAPEIT (Delaneau et al., 2012).

For each genotyping cohort, we applied principal components analysis (PCA) of a linkage-disequilibrium-pruned set of genotyped SNPs to characterize population structure, based on EIGENSTRAT as implemented in PLINK v1.9. We plotted these components with superimposition of HapMap samples in order to confirm the location of individuals of Northern European ancestry, and only included those individuals as a means of minimizing risk for confounding by ancestry (i.e., population stratification) (Chang et al., 2015; Price et al., 2006; Purcell et al., 2007).

2.3 Analysis

Single-locus associations were examined using logistic regression assuming an additive allelic effect as implemented in PLINK 1.9, covarying for the first 10 principal components of ancestry a priori (Purcell and Chang, 2013), which yielded lambda=0.995. (In other biobank investigations, analyses incorporating five or 20 components have not yielded meaningfully different results.) In all analyses, only bi-allelic SNPs with minor allele frequencies of at least 1% were retained. We combined individual cohort results in inverse-variance-weighted fixed-effects meta-analysis. (In sensitivity analysis, excluding 336 individuals (78 cases and 258 controls) with a diagnostic code reflecting dementia did not meaningfully change results.) Association results are presented in terms of independent loci after pruning using the clump command in PLINK 1.9, with a 250kb window and $r^2=0.2$ (Purcell and Chang, 2013). Locus plots were generated using locuszoom (Pruim et al., 2010).

3. Results

A total of 6,035 individuals age 60-90 of Northern European ancestry were analyzed, including 421 cases and 5,614 controls (113 versus 1,878; 167 vs 1,846; and 141 vs 1,890 in each batch). Individuals with delirium were older on average (73.44 years SD 7.95) than the control group (71.02 years SD 7.25; t=-6.56, p<0.001), and more likely to be male (59.86% versus 50.86%; Fisher's exact p<0.001).

Results of genome-wide analysis are summarized in the Manhattan and Q-Q plot in Figure 1.

A single locus on chr2, spanning multiple genes, including two sodium/hydrogen exchange pumps (SLC9A4 and SLC9A2) and three interleukin-related genes (IL1RL1,IL18R1, and IL18RAP), exceeded a standard genome-wide threshold for association (p=1.41e-8); Figure 2. A further five independent loci were associated with p<5e-7 (Table 1).

We examined loci previously associated with delirium in candidate gene association studies, including APOE, SLC6A3, and GRIN3A (Supplemental Table 2). None of these demonstrated robust evidence of association (p>0.001 for SLC6A3 and GRIN3A, p>0.01 for APOE).

4. Discussion

By examining more than 6,000 participants in a large biobank, we identified a locus associated with delirium liability at a standard genome-wide threshold, as well as five other loci meriting further investigation. Further characterization will be required to confirm and refine these associations, but our results represent an initial step in clarifying the neurobiology of a common and costly hospital outcome.

Specifically, the strongest association lies in an intronic SNP in SLC9A4, a little-studied sodium/hydrogen exchange pump (Pathak et al., 1996). While primarily investigated as a regulator of pH in the gut [see, e.g., Roginiel 2013] recent evidence also suggests expression in rat hippocampus and frontal cortex and regulation by sex hormones (Karimi et al., 2013; Roginiel et al., 2013).

Notably, the same linkage disequilibrium block also contains three genes related to interleukin signaling - interleukin 1 receptor-like 1, interleukin 18 receptor-1 (IL18R1), and interleukin 18 receptor associated protein (IL18RAP). Null mice for IL1RL1 are more susceptible to polymicrobial sepsis and fail to produce proinflammatory cytokines when stimulated (Sims et al., 1995; Xu et al., 2008). IL18RAP variants have previously been associated with celiac disease in humans (Hunt et al., 2008). Taken together, then, multiple genes under this locus may point at gut immune function as a risk factor for delirium. Although the gut is not emphasized in delirium literature today the potential role of immune response in general is among the most frequently implicated (Maclullich et al., 2008; Maldonado, 2013; Stoicea et al., 2014).

We also examined loci previously associated with delirium in smaller candidate gene studies (Stoicea et al., 2014). The majority of studies have investigated either dopaminergic signaling, or apolipoprotein E. After initial association with ApoE, follow-up studies failed to detect this effect in postoperative patients, confirmed by a recent meta-analysis (Abelha et al., 2012; Adamis et al., 2016; Cunningham et al., 2017; Oldenbeuving et al., 2013; van Munster et al., 2007; Vasunilashorn et al., 2015). Conversely, a meta-analysis of dopaminergic genes (dopamine transporter, SLC6A3, and the D2 dopamine receptor DRD2) identified significant association for a SNP in the former. A SNP in the glutamate receptor GRIN3A was also nominally associated with delirium in a single study (Kazmierski et al., 2014). In the present study, which includes more individuals than in all prior investigations, we did not detect robust evidence of association for any of these candidates (Supplemental Table 2) (Adamis et al., 2016).

We note multiple important caveats in considering these results. First, the use of electronic health records requires acceptance of a phenotype determined with substantially less precision than traditional longitudinal cohort studies. In particular, the inclusion of age-matched controls rather than, for example, postoperative controls or others at high risk for delirium, may decrease our power to detect association by misclassifying some individuals who would be at high risk as controls. While we applied a definition previously published, complementary studies incorporating specific assessment for delirium based on non-code data elements will be valuable (Inouye et al., 2005; Kim et al., 2017; McCoy et al., 2017a). Further, groups have operationalized delirium using similar but not identical code definitions (Bui et al., 2017; Hope et al., 2014; Katznelson et al., 2010). Moreover, while this cohort is substantially larger than those previously reported, power is likely to be modest in the absence of single loci of large effect. We present these results in the hopes they will spur others to consider investigation of biobanks or registries in the same manner. Finally, we note that such studies are likely to be most useful in proposing rather than confirming hypotheses; that is, follow-up investigation of specific mechanisms in vivo or in vitro will be required.

5. Conclusions

In sum, we applied a health claims-based definition of delirium to identify a novel locus associated with delirium risk, suggesting the relevance of gut-associated inflammatory response. More generally, we demonstrate the utility of large biobanks for investigating this important contributor to in-hospital morbidity and mortality. Given the importance of delirium as a clinical concept and the extent to which the pathophysiology of delirium is poorly understood, we hope others will attempt to replicate and extend this work.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Delirium biology can be studied using electronic health records and biobanks.
- One genomic region was associated with delirium at a genome-wide level.
- These analyses do not support prior candidate gene associations.

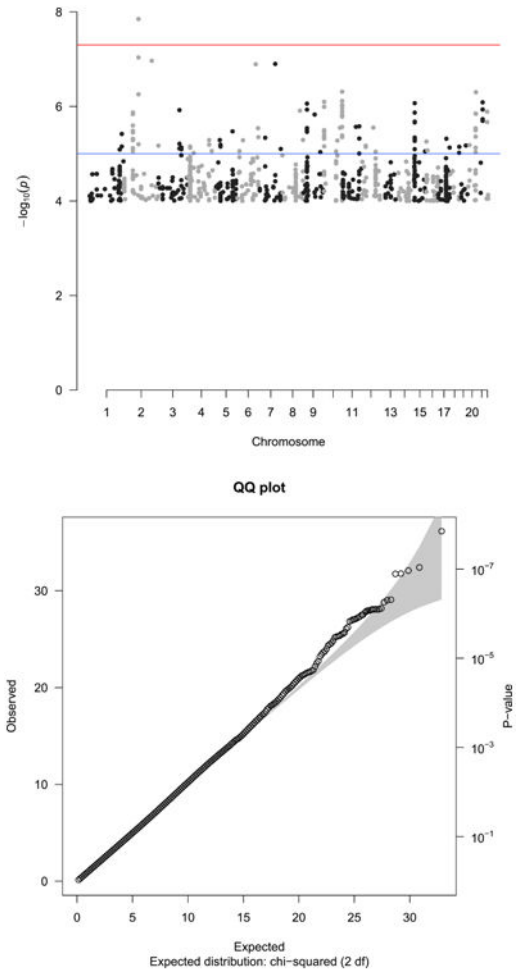

Figure 1. Manhattan plots from genome-wide association for delirium

Figure 1 (inset). Q-Q plot of genome-wide association results for delirium

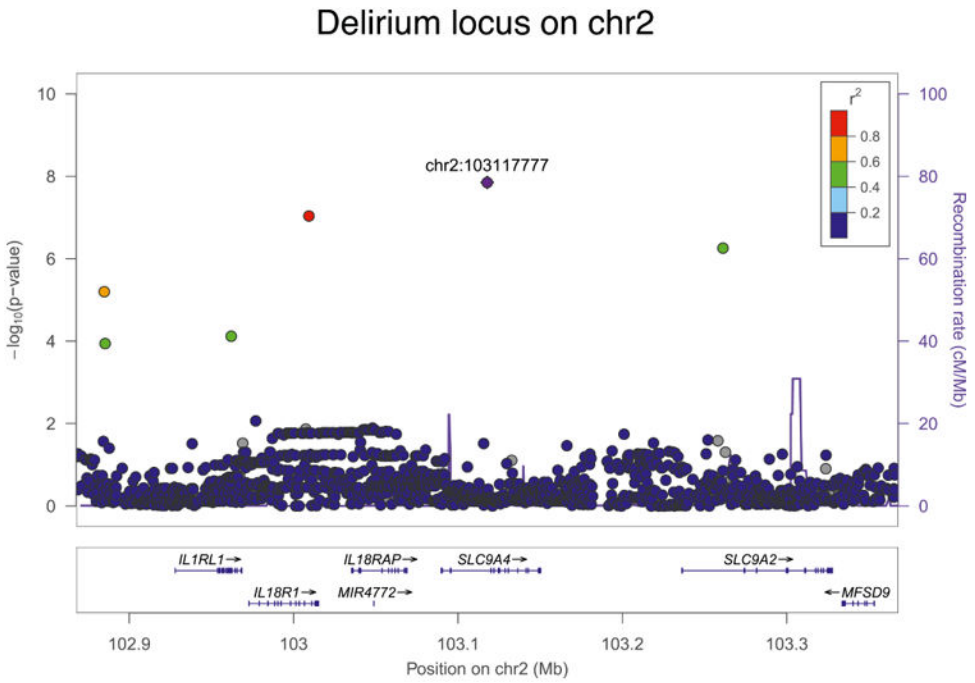

Figure 2. Locus plot of chr2 region most associated with delirium risk

Table 1

Independent loci with strongest evidence of association with delirium

CHR	SNP	P	N SNPs	Locus Position	Locus Size	Genes in Locus
2	2:103117777	1.41E-08	6	chr2:102885986..103262373	376.388	[IL1RL1,IL18R1,IL18RAP,MIR4772,SLC9A2,SLC9A4]
2	2:195210106	1.08E-07	1	chr2:195210106..195210106	0.001	[LOC101927406]
7	7:112660783	1.26E-07	2	chr7:112547190..112660783	113.594	[C7orf60,LOC101928036]
6	6:136207021	1.28E-07	9	chr6:136093841..136220111	126.271	[PDE7B]
10	10:132654411	4.85E-07	50	chr10:132600622..132671267	70.646	[]
20	20:58629940	4.98E-07	5	chr20:58429802..58653458	223.657	[C20orf197,CDH26,FAM217B,PPP1R3D,SYCP2]