Identification of novel common variants associated with chronic pain using conditional false discovery rate analysis with major depressive disorder and assessment of pleiotropic effects of *LRFN5*.

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Abstract

29   Chronic pain is highly prevalent worldwide, with a significant socioeconomic burden, and

30   also contributes to excess mortality. Chronic pain is a complex trait that is moderately heritable and

31   genetically, as well as phenotypically, correlated with major depressive disorder (MDD). Use of the

32   Conditional False Discovery Rate (cFDR) approach, which leverages pleiotropy identified from

33   existing GWAS outputs, has been successful in discovering novel associated variants in related

34   phenotypes. Here, genome-wide association study outputs for both von Korff chronic pain grade as a

35   quasi-quantitative trait and for MDD were used to identify variants meeting a cFDR threshold for

36   each outcome phenotype separately, as well as a conjunctional cFDR (ccFDR) threshold for both

37   phenotypes together. Using a moderately conservative threshold, we identified a total of 11 novel

38   single nucleotide polymorphisms (SNPs), six of which were associated with chronic pain grade and

39   nine of which were associated with MDD. Four SNPs on chromosome 14 were associated with both

40   chronic pain grade and MDD. SNPs associated only with chronic pain grade were located within

41   *SLC16A7* on chromosome 12. SNPs associated only with MDD were located either in a gene-dense

42   region on chromosome 1 harbouring *LINC01360*, *LRRIQ3*, *FPGT* and *FPGT-TNNI3K*, or

43   within/close to *LRFN5* on chromosome 14. The SNPs associated with both outcomes were also

44   located within *LRFN5*. Several of the SNPs on chromosomes 1 and 14 were identified as being

45   associated with expression levels of nearby genes in the brain and central nervous system. Overall,

46   using the cFDR approach, we identified several novel genetic loci associated with chronic pain and

47   we describe likely pleiotropic effects of a recently identified MDD locus on chronic pain.

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Author Summary

52   Genetic variants explaining variation in complex traits can often be associated with more than

53   one trait at once ('pleiotropy'). Taking account of this pleiotropy in genetic studies can increase

54   power to find sites in the genome harbouring trait-associated variants. In this study we used the

55   suspected underlying pleiotropy between chronic pain and major depressive disorder to discover

56   novel variants associated with chronic pain, and to investigate genetic variation that may be shared

57   between the two disorders.

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Introduction

60   Chronic pain is defined as pain lasting longer than 12 weeks. It affects around 30% of the

61   global adult population (Elzahaf, Tashani, Unsworth, & Johnson, 2012), imposes significant

62   socioeconomic burden, and contributes to excess mortality (Hocking, Morris, Dominiczak, Porteous,

63   & Smith, 2012; Vos et al., 2015). Chronic pain is often associated with both specific and non-specific

64   medical conditions (such as cancers and HIV/AIDS, fibromyalgia and musculoskeletal conditions),

65   and with a range of injuries (Greene, 2010; Merskey & Bogduk, 1994). It is also commonly co-

66   morbid with mood disorders, such as major depressive disorder (MDD; Flint & Kendler, 2014;

67   McIntosh et al., 2016). MDD is a common and serious mood disorder involving psychological

68   symptoms such as persistent low mood and anhedonia, and physical symptoms such as changes in

69   appetite and sleep disturbance (American Psychiatric Association 2013). In common with chronic

70   pain, MDD also imposes a significant socioeconomic burden worldwide and is now the leading cause

71   of disability globally (Vos et al., 2015). The causal direction of factors underlying the association

72   between chronic pain and mood disorders is unclear. Chronic pain is a complex trait with moderate

73   heritability (Hocking et al., 2012) and chronic pain and MDD are genetically correlated (McIntosh et

74   al., 2016), suggesting that pleiotropic variants exist that predispose to both conditions. To date,

75   genome-wide association studies (GWAS) have not identified any genome-wide significant variants

76   associated with chronic pain at any site (Mogil, 2012; Zorina-Lichtenwalter, Meloto, Khoury, &

77   Diatchenko, 2016).

78   An alternative strategy for identifying genetic variation contributing to complex traits is to

79   make use of existing GWAS summary statistic outputs within more powerful discovery approaches,

80   such as the conditional false discovery rate (cFDR) approach (Andreassen, Thompson, et al., 2013).

81   The cFDR approach makes better use of the genetic overlap between traits or conditions to discover

82   loci based on their pleiotropic effects in each phenotype separately, as the strength of evidence for

83   involvement of a locus in a primary trait may be enhanced by consideration of the strength of

84   evidence for the same locus in an associated secondary trait. In the case of chronic pain, the

85   association with mood disorders and mood-related traits is of substantial interest, as improved

86   understanding of the biological underpinnings of this overlap may stimulate the development of novel

87   treatment strategies.

88   cFDR analyses have been used to find novel variants associated with schizophrenia, type 2 diabetes,

89   Alzheimer disease, bipolar disorder and systolic blood pressure (Andreassen, Djurovic, et al., 2013;

90   Andreassen et al., 2014; Andreassen, Thompson, et al., 2013; Wang et al., 2016). This therefore

91   represents a promising and potentially more cost-effective method for identifying new SNPs

92   associated with complex traits by maximising the utility of existing GWAS outputs. We aimed to find

93   chronic pain-associated SNPs using cFDR analysis, with MDD as the secondary trait. In addition, we

94   sought to discover loci with pleiotropic effects on these two phenotypes. Our findings revealed six

95   novel chronic pain-associated SNPs and a locus within the *LRFN5* gene where the nature of the

96   pleiotropic effects is consistent with major depression risk being mediated by genetic effects on risks

97   of chronic pain. These findings contribute to our understanding of the biological underpinnings of

98   chronic pain and a component of its shared biology with major depressive disorder.

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Methods

Phenotype definition and source data

For chronic pain in the cFDR analysis, summary statistics from a GWAS carried out collaboratively with Pfizer-23andMe Inc (McIntosh et al., 2016) were used. In that study, chronic pain severity was modelled as a quasi-quantitative trait, defined by von Korff and colleagues as 'chronic pain grade' (CPG; Von Korff, Ormel, Keefe, & Dworkin, 1992), on a scale from 0 (no chronic pain reported) to 4 (high intensity, high disability, severely limiting chronic pain). The GWAS was carried out using data from 23, 301 unrelated individuals of white European descent (10, 543 individuals with CPG levels 1-4 combined, 12, 758 individuals with CPG level 0; Supplementary Table 1). For Major Depressive Disorder (MDD), summary statistics from a recent case-control GWAS meta-analysis (Wray et al., 2018) were provided by the Psychiatric Genomics Consortium (PGC) after removal of data from 23andMe and UK Biobank participants, yielding a dataset originating from an analysis using 43,028 cases and 87, 522 controls. Thus, none of the participants contributing to the CPG summary statistics overlapped with those contributing to the MDD summary statistics. Phenotype definitions, study population demographics and meta-analysis procedures for the MDD GWAS have been described previously (Wray et al., 2018).

Data Preparation & LD Pruning

A dataset of SNPs for which a *p*-value for association, chromosome position data and rsID were available in both MDD and CPG datasets was compiled. This was then LD pruned as follows. Firstly, PLINK-format genotype data, for each SNP in the newly compiled CPG-MDD summary-statistic dataset, was extracted from the UK Biobank genotype data (approved application 6553). Pruning was carried out using command line PLINK (version 1.9) --indep-pairwise function. From each SNP-pair with $r^2 > 0.2$ within a 50-SNP window of the lead SNP, one was removed according to PLINK's greedy pruning algorithm, the window slid along 5 SNPs, and the pruning repeated. This resulted in an LD-pruned dataset of 774,292 SNPs with association data available for both MDD and CPG.

Conditional False Discovery Rate (cFDR) analyses

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128   cFDR is an extension of local-area false-discovery rate (FDR), which is in turn a re-thinking of

129   Benjamini & Hochberg's 'tail-end' false discovery rate procedure (Benjamini & Hochberg, 1995;

130   Efron, 2007; Liley & Wallace, 2015; Storey, 2002). The tail-end FDR procedure is concerned with

131   controlling the FDR at a pre-defined level and deciding the maximum test statistic value from a list of

132   ordered test statistic values that allows for this (Benjamini & Hochberg, 1995), which becomes the

133   cut-off value for deciding significance. Local FDR reframes the FDR as a Bayesian posterior

134   probability that the SNP in question is not associated with the disease or trait, given its association test

135   statistic (usually its p value) (Efron, 2007; Storey, 2002).

136   cFDR analysis of GWAS summary statistics simply extends local FDR, with the result being the

137   posterior probability that the SNP in question is not associated with the primary phenotype, given its

138   association test statistic value for both the primary phenotype and for a secondary, related phenotype.

139   This allows for exploitation of any underlying pleiotropic genetic architecture, believed to be

140   ubiquitous in human complex disease (Gratten & Visscher, 2016; Sivakumaran et al., 2011), along

141   with an increase in power compared to traditional Bonferroni correction of GWAS summary statistic

142   output.

143   cFDR and conjunctional cFDR (ccFDR) values for each SNP for CPG given MDD and vice versa

144   were calculated (Formula 1) as previously detailed (Liley & Wallace, 2015) using the statistical

145   software R (version 3.3.3).

146 $$cFDR = \Pr\left(H_{0(i)} \middle| p_i \leq P_i, p_j \leq P_j\right) = \frac{p_i}{\Pr(p_i \leq P_i \mid p_j \leq P_j)} \qquad (1)$$

147   The cFDR value for a SNP obtained from the above formula is the probability that the SNP is not

148   associated with the primary phenotype, given its strength of association with the secondary

149   phenotype. The ccFDR was obtained via taking the higher of the two cFDR values obtained for each

150   SNP. The significance threshold chosen was cFDR (and ccFDR) ≤0.01.

151   **Genomic Context Analyses**

152   The genomic context for SNPs with significant cFDR values in either analysis was examined. The R

153   package 'rsnps' (Chamberlain et al 2016) was used to extract data from records in NCBI dbSNP

154   (https://www.ncbi.nlm.nih.gov/snp). Gene context for each SNP was examined in the UCSC Genome

155   Browser (build GRCh38/hg38) (Kent, Sugnet, Furey, & Roskin, 2002), using a window of 0.5Mbp

156   around each SNP and data from the GENCODE v24 track, validated or reviewed by either Refseq or

157   SwissProt staff. Thepresence of cis-eQTLs close to the significant SNPs was investigated using the

158   IGV eQTL Browser (Aguet et al., 2017) web interface.

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Further Exploration of Pleiotropy in *LRFN5*

161   Regression models were run to examine associations between genotype at a SNP identified as

162   pleiotropic in the ccFDR analysis and relevant phenotypes in data from the UK Biobank (chronic

163   pain, MDD, age attended assessment centre and sex; approved applications 10302, 6553). Genotype at

164   rs11846556 (the SNP with the lowest ccFDR) in UK Biobank individuals was coded as number of

165   effect-associated alleles (0, 1, 2 copies of the A allele).

166   Chronic pain was assessed via the question 'pain types experienced in the past month', with possible

167   answers as follows: each of 7 different body sites (multiple sites allowed), or 'all over the body', or

168   'do not know', or 'prefer not to answer'. In a separate question, the duration of any pain at the

169   reportable sites/all over the body was assessed. A dichotomous chronic pain variable was defined as

170   the presence of chronic pain in at least 1 site (or all over the body) for longer than 3 months. Those

171   who did not report pain of that duration were assigned to a control group.

172   In addition to this dichotomous 'presence of chronic pain' variable, a chronic pain variable capturing

173   information about the number of sites of chronic pain was also created (chronic pain category; treated

174   as an ordinal variable in regression models), again employing the 3 month minimum duration

175   criterion: 0 = no chronic pain, 1 = single site, 2 = 2-3 sites, 3 = 4-7 sites, 4 = all over the body

176   (Nicholl et al 2014). Individuals giving 'prefer not to answer' and 'do not know' answers were

177   excluded from all analyses.

178   MDD cases were ascertained according to Davis et al 2018 from a subset of UK Biobank participants

179   who completed a detailed the mental health questionnaire assessment (N = 157, 366). Controls

180   consisted of those with no mood disorder; those with bipolar disorder were excluded from analyses.

181   An ordinal MDD phenotype (MDD severity) was also obtained by classifying MDD by number of

182   episodes: 0 = no mood disorder, 1 = single episode MDD, 2 = recurrent MDD.

183   A UK Biobank dataset where all individuals had complete information on age, sex, rs11846556

184   genotype and chronic pain variables was assembled (N = 469, 253). Logistic regression of chronic

185   pain (case-control) on rs1186556 genotype (adjusted for age and sex) and ordinal regression of

186   chronic pain category on rs1186556 genotype (adjusted for age and sex) were then carried out to

187   assess the relationship between SNP genotype and chronic pain.

188   A second dataset where all individuals had complete information on age, sex, rs11846556 genotype

189   and MDD variables was assembled (N = 122,286). Logistic regression of MDD (case-control) on

190   rs11846556 genotype (adjusted for age and sex), and ordinal regression of MDD severity on

191   rs11846556 genotype (adjusted for age and sex) were then performed to assess the relationship

192   between SNP genotype and MDD.

193   A final dataset, where all individuals had complete information on age, sex, genotype, chronic pain

194   and MDD variables was assembled (N = 121,246). Logistic regressions of MDD (case-control) on

195   chronic pain (case-control) and genotype (adjusted for age and sex), and of chronic pain (case-control)

196   on MDD (case-control) and genotype (adjusted for age and sex) were then carried out, to assess

197   whether any relationship between MDD and SNP genotype was attenuated by chronic pain, and

198   whether any relationship between SNP genotype and chronic pain was attenuated by MDD.

199   P values for ordinal regression estimates were obtained via comparing the t value obtained to that of a

200   normal t-distribution. Standard errors were used to calculate 95% CI values for ordinal regression

201   output. All models were adjusted for age and sex, both of which were highly significant in all cases.

202   Some models were additionally adjusted for the phenotype (pain or MDD) not being tested as the

203   outcome variable.

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Results

208   [Table 1]

cFDR and ccFDR analyses

The conditional false discovery approach was used to identify variants associated with chronic pain grade, MDD, or both together in a pleiotropic fashion. Eleven SNPs in total were found at cFDR ≤ 0.01 (Table 1), six of which, located on chromosomes 12 and 14, were associated with CPG and nine of which, located on chromosomes 1 and 14, were associated with MDD. Four of these 11 SNPs, all located within a 131 kbp region on chromosome 14, were found to be pleiotropic (ccFDR ≤0.01).

Genomic Context

The SNPs associated with CPG only were located close to *SLC16A7* on chromosome 12 (Supplementary Table 2a, 2b), while the SNPs associated with MDD only were located within a gene-dense region on chromosome 1 containing *LINC01360, LRRIQ3, FPGT, FPGT-TNNI3K,* amongst other genes (Supplementary Table 2b) or close to (upstream of) or within *LRFN5* on chromosome 14 (Supplementary Table 2a, 2b). The SNPs found to be pleiotropic were also located within *LRFN5* on chromosome 14 (Supplementary Table 2a, 2b). The pleiotropic *LRFN5* SNPs were all located just upstream of the 5'-most promoter, or within a large intron close to the 5'-end of the gene. The SNPs associated with MDD only were also located within this intron, or were located a little further upstream of the gene. The CPG-only SNPs were all located downstream of *SLC16A7*. One of the pleiotropic SNPs on chromosome 14, rs11157241, is located approx. 30 kbp upstream of *LRFN5*.

227   GTeX eQTL lookups revealed that some of these phenotype-associated SNPs were also associated

228   with expression levels of nearby genes. A SNP associated only with MDD, on chromosome 1

229   (rs35641559), was found to be significantly associated with expression of a long non-coding RNA

230   gene *LINC01360* in the testis (FDR < 0.05, Supplementary Table 2c). The MDD-associated and

231   pleiotropic SNPs on chromosome 14 are all significantly associated with expression of *LRFN5* in a

232   range of tissues, including brain, heart, adipose tissue and spleen (Supplementary Table 2c). The

233   CPG-associated SNPs on chromosome 12 were not significantly associated with expression of any

234   gene in the eQTL database (Supplementary Table 2c).

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236   **Association between rs11846556 genotype and MDD and chronic pain in UK Biobank**

237   **[Table 2]**

238   To investigate the nature of the pleiotropy revealed for variants within *LRFN5,* regression models

239   were used to assess the strength of association between rs11846556 genotype and each of the two

240   phenotypes of interest, chronic pain and MDD. Genotype at this SNP was associated with

241   significantly increased risk for chronic pain (Table 2a; FDR-adjusted $p = 0.0008$), with each

242   additional copy of the A allele increasing the odds of having chronic pain by 2% (OR = 1.02).

243   rs11846556 genotype was also associated with chronic pain category (Table 2b), with each additional

244   copy of the A allele associated with an OR of 1.02 per chronic pain category (FDR-adjusted $p =$

245     $4.4x10^{-5}$). Genotype at rs11846556 was not significantly associated with MDD (Table 2a) or with

246   MDD severity (Table 2b). rs11846556 genotype accounted for 0.29% of the variance in chronic pain

247   presence and 0.25% of the variance in chronic pain category (estimated using McFadden's R^2,

248   adjusting for age & sex). rs11846556 genotype was no longer associated with presence of chronic

249   pain after adjustment for MDD status (FDR-adj $p = 0.096$), and with a larger effect size (per allele

250   betas were 0.017 vs 0.015 in the MDD-adjusted and non-adjusted models, respectively).

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254   # Discussion

255   **Genetics of Chronic Pain & Related Disorders**

256   The genetics of pain have hitherto mostly been investigated using candidate gene and animal-model

257   approaches. No genome-wide significant loci have been reported from GWAS of presence of chronic

258   pain at any site, or of chronic pain severity, although GWAS have been carried out for disorders with

259   chronic pain as a symptom, and loci have been reported for particular subtypes of chronic or regular

260   pain e.g. migraine, back pain and other musculoskeletal disorders (Suri et al., 2018; Zorina-

261   Lichtenwalter et al., 2016). Chronic pain reported at particular sites may be triggered by

262   environmental insults (such as surgery or physical trauma) or by long-term inflammatory processes,

263   but the mechanisms that allow pain to persist are thought to be largely neurogenic in origin, with

264   aberrant feedback between the spinal cord and brain strongly implicated (Apkarian, Hashmi, & Baliki,

265   2011; Q. Xu & Yaksh, 2011). Thus, exploration of the molecular mechanisms underlying chronic pain

266   is likely to benefit from studies focussing on phenotypes relating to severity and other measures of

267   overall susceptibility to chronic pain.

268   In this study, the power to detect CPG-associated SNPs was increased by leveraging the additional

269   information coming from the correlation between predisposing loci for CPG and for MDD. Overall,

270   we found six CPG-associated and nine MDD-associated SNPs. In addition, pleiotropic effects of four

271   *LRFN5* SNPs were observed.

CPG-Associated SNPs

273   The SNPs associated with CPG only were located close to *SLC16A7,* which encodes monocarboxylate

274   transporter 2 (MCT2). In the central nervous system, MCT2 is involved in high affinity, proton-

275   coupled transport of metabolites (particularly lactate) into neurons and may play a role in neuronal

276   uptake of energy substrates released by glia (Itoh et al., 2003; Pellerin, 2003). MCT2 is localised to

277   the post-synaptic compartment in many human neurons and may have a specialised role in synaptic

278   functioning Chiry et al., 2008, Pierre et al., 2009,). Regulation of *SLC16A7* has also been linked to

279   disorders of the brain: loss or under-expression has been associated with temporal-lobe epilepsy

280   (Lauritzen et al., 2012) and it may be expressed and methylated at different levels in psychotic

281   patients versus controls (Chen et al., 2014).

MDD-Associated SNPs

283   The SNP on chromosome 1 associated with MDD only was located close to *LRRIQ3* and *FPGT*.

284   *LRRIQ3* encodes leucine-rich repeat (LRR) and IQ motif containing protein 3, a calcium-channel

285   component. LRR-domain containing proteins in general are involved in cell-cell communication,

286   including processes involved in innate immunity and neuronal development (Bella, Hindle, McEwan,

287   & Lovell, 2008; Ng et al., 2011). *FPGT* encodes fucose-1-phosphate guanylyltransferase, a protein

288   involved in the alternative (salvage) pathways of fucose metabolism (Becker & Lowe, 2003). Fucose

289   metabolism is important in a variety of cell-cell communication and host-microbe interaction

290   situations, but is also important during neuronal development (Becker & Lowe, 2003). Variants in the

291   *LRRIQ3* region have been previously associated with schizophrenia (Ripke et al., 2014),

292   neurodevelopmental disorders (Reuter et al., 2017) and migraine (Gormley et al., 2016).

Pleiotropic SNPs in *LRFN5*

294   The significantly associated SNPs on chromosome 14 found within or close to *LRFN5* were either

295   associated with MDD only or were pleiotropic and associated with both CPG and MDD. Due to the

296   LD-based pruning carried out before the cFDR analysis, the MDD-only and pleiotropic SNPs are not

297   in strong linkage disequilibrium and may thus be tagging different functional variants, potentially

298   acting on risk in different ways. *LRFN5* encodes leucine-rich repeat (LRR) and fibronectin type 3

299   domain-containing protein 5. Proteins in the LRFN family span the plasma membrane, and their

300   extracellular domains are thought to participate in the cell-cell interactions necessary for both

301   neuronal development (Morimura, Inoue, Katayama, & Aruga, 2006; Nam, Mah, & Kim, 2011) and

302   synapse formation (Choi et al., 2016). Lrfn5, along with another member of the Lrfn protein family,

303   Lrfn2, may induce both inhibitory and excitatory presynaptic differentiation in nearby.(Lin et al

304   2018), a process that may play a critical role in brain development and function (Cordova-Palomera et

305   al 2016). As a family, these genes are primarily expressed in the central nervous system. Polymorphic

306   markers within or close to *LRFN5* have been reported to be associated with progressive autism and

307   familial schizophrenia (De Bruijn et al., 2010; B. Xu et al., 2009). Reduced expression of Lrfn5 has

308   also been reported to contribute to neuro-inflammation (Zhu et al., 2016). Each of the four pleiotropic

309   SNPs has opposing directions of effect in MDD and CPG. For example, the effect allele at

310   rs11846556 is associated with an increase in CPG but with reduced risk of MDD. This may be

311   explained by theories whereby structural and connectivity-related changes in the brain which facilitate

312   development and maintenance of chronic pain involve neurogenesis and synaptic plasticity (Apkarian

313   et al., 2011; Baliki, Mansour, Baria, & Apkarian, 2014; Vasic & Schmidt, 2017), but impaired

314   neurogenesis is associated with depression (Fang, Demic, & Cheng, 2018; Jacobs, van Praag, & Gage,

315   2000). Additionally, differing expression patterns of *LRFN5* in the brain and CNS vs the periphery

316   may be involved in opposing direction of effect associated with pleiotropic SNPs.

317   **Cis-eQTLs**

318   SNPs within and close to *LRFN5* on chromosome 14, and in the region close to long non-coding RNA

319   gene *LINC01360* on chromosome 1, were found to be cis-eQTLs. rs35641559 on chromosome 1,

320   associated with MDD only, was found to be significantly associated with *LOC105378800* expression

321   levels in the testis. All four pleiotropic SNPs on chromosome 14, were found to be significantly

322   associated with *LRFN5* expression levels in a range of tissues, including the brain. Further

323   investigation of potential regulatory roles for these or other nearby variants is warranted.

324   **Role of rs11846556 in the biology of chronic pain and depression**

325   Number of A alleles at rs11846556, one of the pleiotropic SNPs identified here, was found to be

326   associated with risk of chronic pain (and with higher values of the chronic pain category phenotype),

327   but not with MDD risk or severity (in the UK Biobank cohort), and the effect size for the chronic pain

328   association was not attenuated by inclusion of MDD in the regression model. This relationship is

329   consistent with mediated pleiotropy rather than biological pleiotropy, i.e. a pathway in which

330   genotype influences chronic pain risk, which in turn affects MDD risk, rather than influencing both by

331   separate mechanisms. Formal mediation analyses was beyond the scope of this study primarily due to

332   probable sequential ignorability violation and unmeasured confounders (Daniel, De Stavola, Cousens,

333   & Vansteelandt, 2015; Imai, Keele, & Tingley, 2010).

334   As discussed above, each of the 4 SNPs tagged as pleiotropic, including rs11846556, are also cis-

335   eQTLs for *LRFN5*. The SNP we explored in more detail, rs11846556, is a cis-eQTL of *LRFN5* in the

336   cerebellum and cerebral hemisphere, along with tibial artery (GTEx single-tissue eQTL lookup). The

337   number of A alleles at this SNP is significantly associated with increased expression of *LRFN5* in

338   CNS tissues, but with a trend towards decreased expression in peripheral tissues (Supplementary

339   Figures 1a-d), suggesting the existence of tissue-specific regulatory effects. This SNP is also a cis-

340   eQTL for expression of a long intergenic non-coding RNA (Gencode ID: ENSG00000258636.1) on

341   the reverse strand with respect to *LRFN5*, but only in spleen and aorta.

342   Alterations in synaptic plasticity and neurogenesis in the hippocampus, which is often non-normal in

343   cases of neuropathic pain, may underlie some of the cognitive and affective deficits seen in patients

344   with major depression (Fasick et al 2015). However, in cases where depression is a downstream

345   consequence of chronic pain, its onset may be influenced by lifestyle and other 'above-the-skin'

346   factors that also operate downstream of chronic pain, rather than as a more direct result of synaptic

347   changes related to *LRFN5* expression levels.

348   Our data therefore suggest that rs11846556 genotype is significantly associated with chronic pain, but

349   not with MDD, and that the relationship between chronic pain and genotype is not attenuated by

350   MDD - pleiotropic effects of rs11846556 (or the functional variant it is tagging) on chronic pain and

351   MDD appear to be mediated rather than biological. Possession of more copies of the A allele at this

352   locus is associated with increased *LRFN5* expression levels in the CNS, which may exert its effect on

353   transition to a chronic pain state after a prior insult through consequent alterations to brain network

354   connectivity.

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356   **Strengths and Limitations**

357   A key strength of this study lies in its enhanced power, through the use of the cFDR approach, to

358   detect the contribution of genetic variants to chronic pain relative to previous genome-wide

359   approaches. Limitations include the self-reported nature of the chronic pain phenotype and the

360   somewhat general phrasing of the questions used to elicit data about this phenotype in the 23&Me and

361   UK Biobank studies, which precluded a finer dissection of the nature and severity of the pain being

362   reported. In addition, the questions asked in the two studies were slightly different, generating chronic

363   pain measures that may be capturing somewhat different aspects of the overall phenotype. 'Chronic

364   pain grade' as assessed in the Pfizer-23andMe GWAS may be capturing a more direct severity-related

365 phenotype, whereas 'chronic pain category' as assessed in UKB is likely to be capturing a different

366 aspect of chronic pain susceptibility related to sensitivity of the response to multiple insults, or to

367 propensity to report. Despite this subtle distinction, we were able to demonstrate that an *LRFN5* SNP

368 is associated with both these phenotypic pain measures. Future studies building on these findings

369 would benefit from using clinically validated or supported phenotyping data, however.

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Conclusions

372 To date no common variants have been associated with presence of chronic pain at any site in the

373 body or with number of sites affected or pain severity. In this study six novel SNPs were found to be

374 associated with chronic pain grade, a measure of pain severity. cFDR analyses also increased power to

375 find MDD-associated variants in comparison to genome-wide significance thresholds. Conjunctional

376 cFDR (ccFDR) analyses revealed evidence of pleiotropic effects of variants in *LRFN5*. The regions

377 around the significant SNPs contain genes involved in, amongst other processes, neuronal cell

378 metabolism and development, innate immunity and cell-cell interaction. These regions have also been

379 previously implicated in a range of neurodevelopmental and psychiatric disorders. One of the

380 pleiotropic SNPs identified on chromosome 14 (rs11846556), which is a cis-eQTL of *LRFN5* in

381 cerebellum and cerebral hemisphere, was found to be associated with chronic pain but not MDD in

382 UK Biobank. This provides intriguing preliminary evidence that the pleiotropy associated with

383 variation in *LRFN5* may be mediated rather than horizontal.

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Acknowledgements

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591   **Tables & Figures**

592   Table 1: Loci identified from cFDR analysis.

593   **Trait = trait with which SNP is associated at cFDR ≤0.01. Position = position given as chromosome:base**

594   **pair location. cFDR (CPG) = cFDR for CPG conditioning on MDD; Beta (CPG)/p (CPG) = effect size and**

595   **p value from the CPG GWAS; cFDR (MDD) = cFDR for MDD conditioning on CPG; OR (MDD)/p**

596   **(MDD) = effect size (odds ratio for the effect allele) and p value from the MDD GWAS. Alleles are given**

597   **as effect allele/other; effect allele is defined as the allele for which association with the trait was tested in**

598   **the original (CPG or MDD) GWAS. Significant p-values and cFDR/ccFDR values are shown in bold.**

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Trait	rsID	Position	Alleles (CPG)	Beta (CPG)	P (CPG)	cFDR (CPG)	Alleles (MDD)	OR (MDD)	P (MDD)	cFDR (MDD)	ccFDR
MDD	rs35641559	1:73760104	C/T	0.02	0.03	0.1	T/C	1.04	2.08E-06	8.83E-03	0.11
CPG	rs147573737	12:60231575	C/T	-0.2	2.09E-07	2.21E-03	T/C	1.09	0.023	0.023	0.023
CPG	rs149981001	12:60264802	C/T	0.2	6.24E-08	1.06E-03	T/C	0.92	0.0181	0.018	0.023
MDD	rs10872954	14:41948768	A/G	-0.026	6.45E-03	0.053	A/G	1.04	7.68E-06	7.02E-03	0.053
MDD	rs10138559	14:41975989	C/T	-0.02	0.03	0.1	T/C	0.96	1.04E-06	5.25E-03	0.1
Both	rs11157241	14:42051771	C/T	0.035	2.91E-04	5.83E-04	T/C	1.06	4.44E-09	1.28E-06	5.83E-04
Both	rs8015100	14:42095232	A/T	-0.033	6.67E-04	6.67E-04	A/T	1.06	1.50E-09	9.27E-07	6.67E-04
Both	rs10131184	14:42166111	A/G	0.035	2.82E-04	8.46E-04	A/G	0.95	2.53E-08	7.10E-06	8.46E-04
Both	rs11846556	14:42183025	A/G	-0.037	1.11E-04	5.57E-04	A/G	1.05	2.98E-07	3.76E-05	5.57E-04
MDD	rs1584317	14:42213816	C/G	0.028	4.48E-03	0.029	C/G	0.96	4.59E-06	3.57E-03	0.03
MDD	rs4904790	14:42242623	C/T	-0.03	1.44E-03	0.02	T/C	0.96	1.37E-05	3.58E-03	0.02

611 **Table 2: Analysis of associations between rs11846556 genotype and chronic pain/MDD.] a)**

	Beta	SE	OR	*p*	FDR-adj. *p*	Additional adjuster
CP (dichot.)	0.015	0.004	1.02	2.63E-04	7.89E-04	
CP (dichot.)	0.017	0.008	1.02	0.048	0.096	**MDD (dichot)**
MDD	0.014	0.009	1.01	ns		
MDD	0.011	0.010	1.01	ns		**CP (dichot)**

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613   b)

	Beta	SE	*p*	FDR-adj. *p*
CPC	0.018	0.004	7.26E-06	4.36E-05
MDD severity	0.014	0.009	ns	

614   **Legend: a) results of logistic regression models with dichotomous chronic pain (CP(dichot.)) and**

615   **major depressive disorder (MDD) variables as outcomes and SNP genotype as predictor. SE =**

616   **standard error of the beta coefficient value, OR = odds ratio. Ns = non-significant (p > 0.05).b)**

617   **results of ordinal regression models with chronic pain category and MDD severity variables as**

618   **outcomes and SNP genotype as predictor. SE = standard error of the beta coefficient, ns = non-**

619   **significant (p > 0.05).**

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