

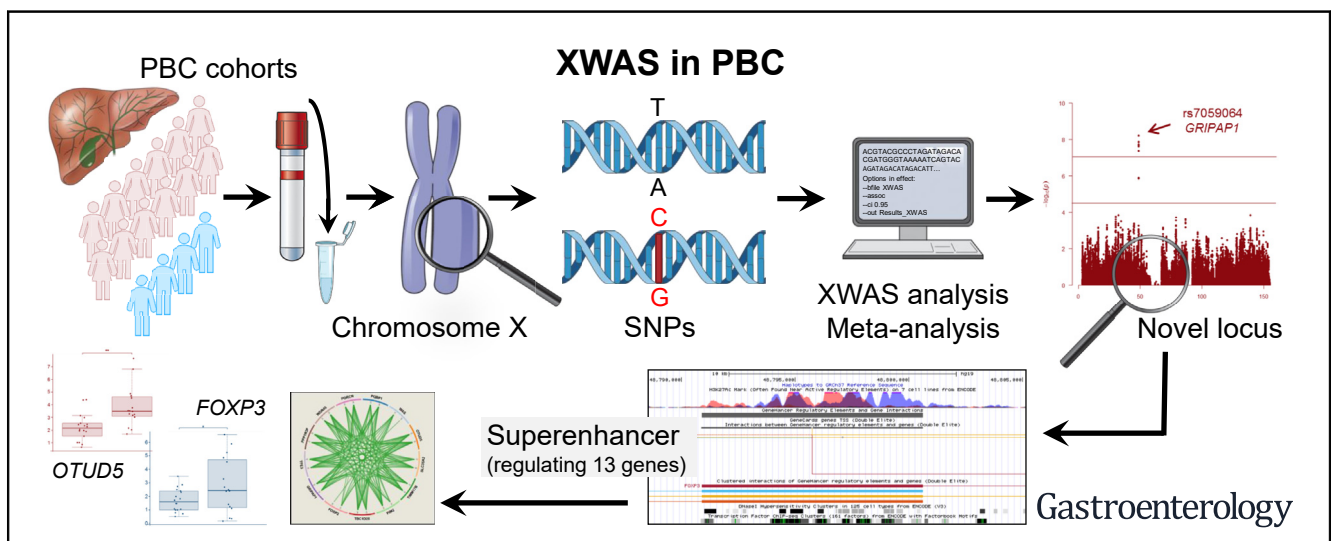
# BASIC AND TRANSLATIONAL—BILIARY

## X Chromosome Contribution to the Genetic Architecture of Primary Biliary Cholangitis



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**BACKGROUND & AIMS:** Genome-wide association studies in primary biliary cholangitis (PBC) have failed to find X chromosome (chrX) variants associated with the disease. Here, we specifically explore the chrX contribution to PBC, a sexually dimorphic complex autoimmune disease. **METHODS:** We performed a chrX-wide association study, including genotype data from 5 genome-wide association studies (from Italy, United Kingdom, Canada, China, and Japan; 5244 case patients and 11,875 control individuals). **RESULTS:** Single-marker association analyses found approximately 100 loci displaying  $P < 5 \times 10^{-4}$ , with the most significant being a signal within the *OTUD5* gene (rs3027490;  $P = 4.80 \times 10^{-6}$ ; odds ratio [OR], 1.39; 95% confidence interval [CI], 1.028–1.88; Japanese cohort). Although the transethnic meta-analysis evidenced only a suggestive signal (rs2239452, mapping within the *PIM2* gene; OR, 1.17; 95% CI, 1.09–1.26;  $P = 9.93 \times 10^{-8}$ ), the population-specific meta-analysis showed a genome-wide significant locus in East Asian individuals pointing to the same region (rs7059064, mapping within the *GRIPAP1* gene;  $P = 6.2 \times 10^{-9}$ ; OR, 1.33; 95% CI, 1.21–1.46). Indeed, rs7059064 tags a unique linkage disequilibrium block including 7 genes: *TIMM17B*, *PQBP1*, *PIM2*, *SLC35A2*, *OTUD5*, *KCND1*, and *GRIPAP1*, as well as a superenhancer (GH0XJ048933 within *OTUD5*) targeting all these genes. GH0XJ048933 is also predicted to target *FOXP3*, the main T-regulatory cell lineage specification factor. Consistently, *OTUD5* and *FOXP3* RNA levels were up-regulated in PBC case patients (1.75- and 1.64-fold, respectively). **CONCLUSIONS:** This work represents the first comprehensive study, to our knowledge, of the chrX contribution to the genetics of an autoimmune liver disease and shows a novel PBC-related genome-wide significant locus.

**Keywords:** X-Wide Association Study; Meta-analysis; Superenhancer.

Primary biliary cholangitis (PBC) is a complex disease in which an inappropriately activated immune response, characterized by high-titer serum anti-mitochondrial autoantibodies (AMAs) and disease-specific antinuclear autoantibodies, leads to progressive damage of the intrahepatic bile ducts, which may eventually cause liver failure.<sup>1,2</sup> The disease is characterized by a striking female predominance (female-to-male prevalence ratio of up to 8:1), with evidence of a significant contribution of X chromosome (chrX) defects to PBC pathogenesis: in fact, women with PBC show a significantly higher frequency of X monosomy in peripheral leukocytes compared to age-matched healthy women.<sup>3,4</sup> However, there is a substantial lack of explanation for female predominance, which is also emphasized by the absence of risk loci mapping on chrX.<sup>5</sup>

PBC is characterized by a strong genetic predisposition, with the major histocompatibility complex (MHC) class II haplotypes (primarily *HLA-DRB1*, *DQB1*, and *DPB1*) showing the strongest association with the disease.<sup>6–10</sup> In addition, genome-wide association studies (GWASs) have identified more than 40 non-MHC loci contributing to the disease risk.

## WHAT YOU NEED TO KNOW

### BACKGROUND AND CONTEXT

Primary biliary cholangitis (PBC) is an autoimmune liver disease showing a relevant female preponderance; however, genetic studies have failed to find X chromosome variants associated with the disease.

### NEW FINDINGS

Using a chromosome X-specific meta-analysis (>5000 case patients and >11,500 control individuals), we identified a novel genome-wide significant locus, characterized by a superenhancer targeting all the genes of the region, including *FOXP3*.

### LIMITATIONS

Further studies will be necessary to replicate the identified signal in independent PBC cohorts and unravel the molecular mechanisms linking the superenhancer, *FOXP3*, and PBC.

### IMPACT

Considering the genetic overlap among autoimmune liver diseases, as well as other autoimmune disorders with a female preponderance, our study suggests that focused studies of the role of *FOXP3* may be useful.

Most of these non-MHC loci implicate genes that contribute to cell-mediated immune mechanisms.<sup>10–17</sup> These GWAS studies show an overlap in susceptibility loci between European and East Asian populations, albeit with some degree of locus heterogeneity.<sup>10–17</sup>

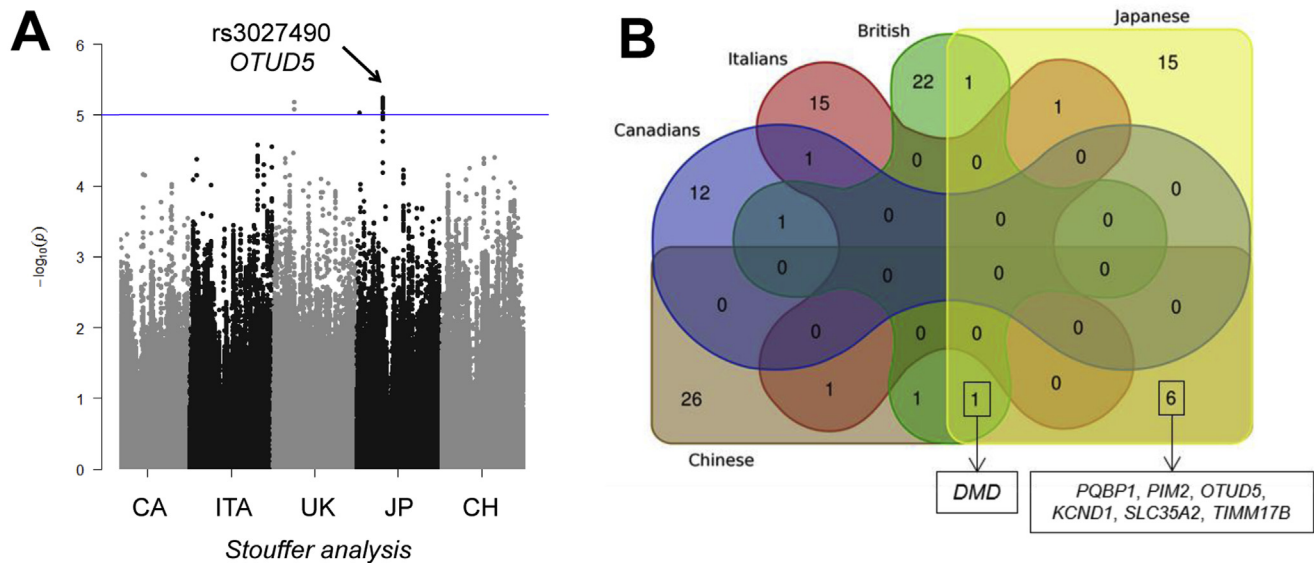
Notwithstanding these efforts, only a modest fraction of PBC heritability (approximately 15%) has been explained.<sup>18</sup> Of note, the role of chrX in PBC still remains largely unknown, with no association signal reported at a genome-wide threshold of significance. This could also be explained by the fact that chrX polymorphisms have not been included in GWAS analysis and, especially in the past, also by the lack of chrX-specific bioinformatics pipelines to be used in the analytic steps.<sup>19</sup> These limitations have, indeed, a more general impact on the genetics of complex diseases: chrX constitutes 5% of the nuclear genome, and mutations in genes mapping on this chromosome account for approximately 10% of mendelian disorders<sup>20</sup>; nevertheless, only 114 chrX susceptibility loci (0.8%) at  $P \leq 5 \times 10^{-8}$  have been described on a total of approximately 15,000 signals identified by GWASs for more than 300 traits.<sup>21</sup>

**Abbreviations used in this paper:**  $\lambda$ , genomic inflation factor; AMA, anti-mitochondrial antibodies; ChrX, X chromosome; CI, confidence interval; eRNA, enhancer RNA; GWAS, genome-wide association studies; IFN, interferon; kb, kilo base pairs; LD, linkage disequilibrium; MAF, minor allele frequency; MHC, major histocompatibility complex; NFAT, nuclear factor of activated T-cells; OR, odds ratio; PBC, primary biliary cholangitis; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; QC, quality check; QQ, quantile-quantile; RT, reverse transcriptase; SE, superenhancer; SNP, single-nucleotide polymorphism; TAD, topologically associating domain; Treg, T regulatory cell; XWAS, X chromosome-wide association study.

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0016-5085/\$36.00

<https://doi.org/10.1053/j.gastro.2021.02.061>



**Figure 1.** SNP association analysis results. (A) Manhattan plots showing the associations of chrX SNPs with PBC in the analyzed cohorts for the Stouffer analysis (test 2). The blue line represents the  $P = 1 \times 10^{-5}$  significance level. SNPs showing the lowest  $P$  values are indicated by an arrow. (B) Venn diagrams show the number of genes mapping in correspondence/proximity of SNPs at  $P < .0005$  for each population. Chinese and Japanese populations show the major number of overlapping signals (genes are listed); the only gene shared by 3 populations is also highlighted. CA, Canadians; CH, Chinese; ITA, Italians; JP, Japanese; UK, British.

Here, we examine the chrX contribution to the genetic architecture of PBC by applying an analysis pipeline accounting for X-specific quality check (QC), imputation, and association tests.<sup>22,23</sup>

## Materials and Methods

### Study Design and Participants

This study included genotype data on chrX principally derived from 5 previously performed GWASs (Supplementary Table 1).<sup>7,11,12,15-17</sup> All participants gave written informed consent for genetic studies. Local institutional review boards approved the respective study protocols.

All case patients met internationally accepted criteria for PBC.<sup>24</sup> Most individuals were positive for serum AMA. Nevertheless, AMA positivity was not used as an inclusion criterion, considering previous data suggesting no effect of AMA status on the profile of disease-associated loci.<sup>7</sup>

### Quality Check of Genotype Data

QC steps were applied with a stepwise procedure separately for each data set. First, we removed individuals (1) showing cryptic relatedness based on identity-by-state status ( $PI_{\text{Hat}} > 0.10$ ), (2) having  $>10\%$  missing genotypes, (3) with reported sex not matching the heterozygosity rates observed on chrX, and (4) with significant differences in the call rate between case patients and control individuals.<sup>25</sup> Next, we excluded single-nucleotide polymorphisms (SNPs) having (1)  $>10\%$  missingness throughout the data set, (2) a minor allele frequency (MAF) of  $<0.005$ , (3) a departure from the Hardy-Weinberg equilibrium in control females ( $P < 1 \times 10^{-4}$ ), (4) significant differences in MAF between male and female control individuals ( $P < .05/\text{number of SNPs}$ ), and (5) a location in pseudoautosomal regions. Finally,

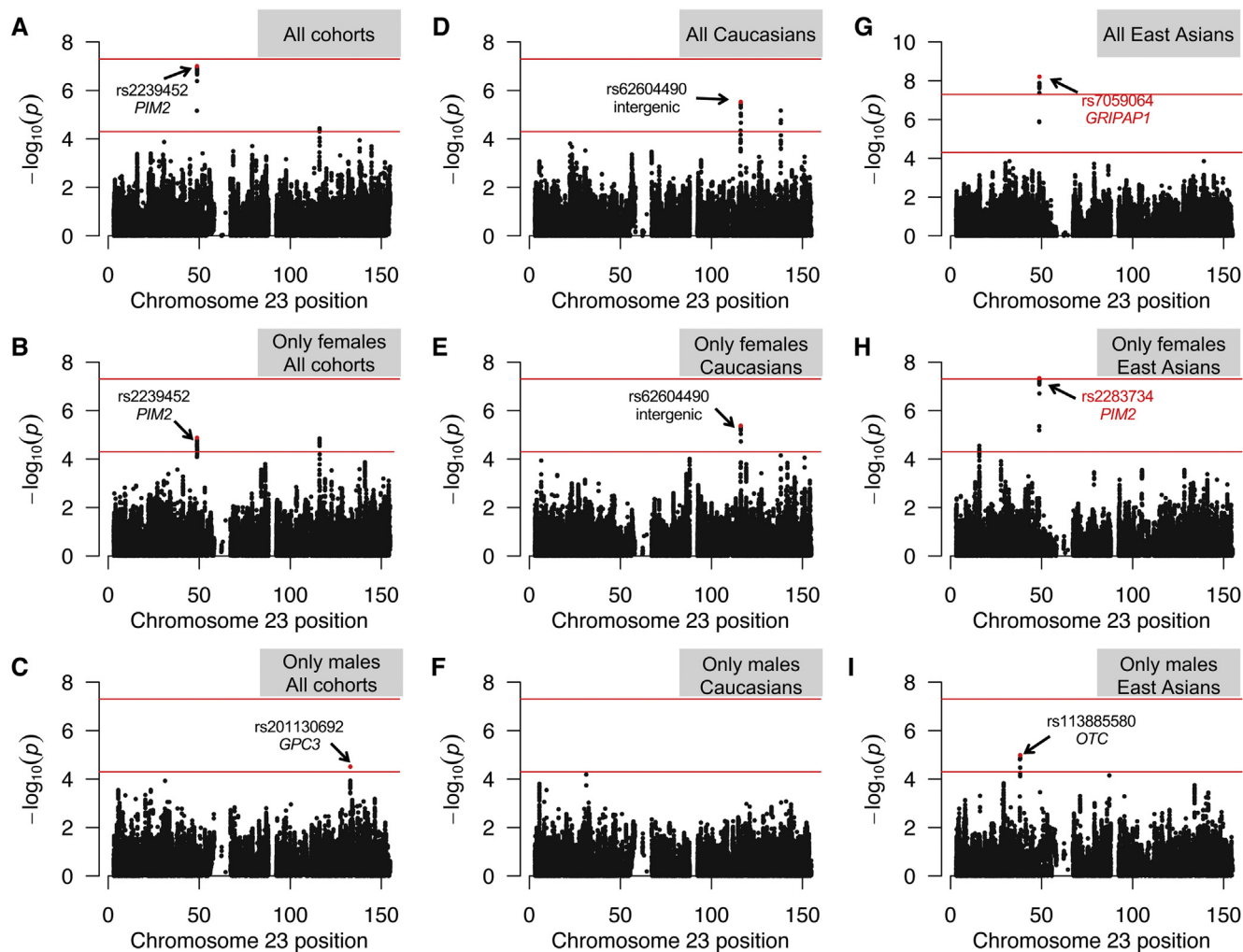
we also removed SNPs exhibiting differential missingness between males and females ( $P < 1 \times 10^{-4}$ ).

### Correction for Population Stratification

We corrected for possible population stratification using chrX-derived principal components, which have been shown to provide a more accurate population stratification correction for chrX-wide association study (XWAS) in admixed populations.<sup>22</sup> This procedure was performed using the principal component analysis method implemented in the EIGENSOFT program ([https://genetics.med.harvard.edu/reich/Reich\\_Lab/Software.html](https://genetics.med.harvard.edu/reich/Reich_Lab/Software.html))<sup>26,27</sup> after pruning for linkage disequilibrium (LD) and removing large LD blocks.<sup>28</sup> For assessment and correction for population stratification, we used the first 10 principal components of each data set<sup>27</sup> and excluded all individuals inferred to be of an ancestry different from that of the specific data set.

### Imputation

Prephasing was performed using SHAPEIT software, version 2.17 ([https://mathgen.stats.ox.ac.uk/genetics\\_software/shapeit/shapeit.html](https://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html)),<sup>29</sup> using the parameters suggested for chrX. Data sets were imputed using IMPUTE2 software, version 2.3.2 ([https://mathgen.stats.ox.ac.uk/impute/impute\\_v2.html#reference\\_5](https://mathgen.stats.ox.ac.uk/impute/impute_v2.html#reference_5)),<sup>30</sup> based on 1000 Genomes Project whole-genome and whole-exome haplotype data (reference panel: 1000Genome Phase3).<sup>31</sup> IMPUTE2 has improved the imputation accuracy on chrX by taking into account the reduced effective population size available for this chromosome by assuming that it is 25% less than that of the autosomes. As recommended by the IMPUTE2 authors,<sup>30</sup> the effective population size was set to 20,000 and the  $k$  value to 1000. Variants with an MAF of  $<0.005$  or with informativeness of  $<0.7$  were considered of low confidence and, hence, were not considered



**Figure 2.** Manhattan plots of meta-analyses. Manhattan plots summarizing the results of (A–C) transethnic, (D–I) population-specific, and (B, C, E, F, H, I) sex-stratified meta-analyses. The horizontal lines represent the suggestive  $P = 5 \times 10^{-5}$  and the genome-wide Bonferroni-corrected  $P = 5 \times 10^{-8}$  significance levels. SNPs showing the lowest  $P$  values are indicated by an arrow (if intragenic, the relevant gene is also indicated); those reported in red survive to the Bonferroni correction for multiple testing.

in further analyses. Imputed data sets were finally submitted to QC steps with PLINK-XWAS, version 1.1, software (<http://keinanlab.cb.bscb.cornell.edu/content/xwas>)<sup>23</sup> using the described criteria.

### Single-Nucleotide Polymorphism Association Analyses

SNP association tests were performed using PLINK-XWAS, version 1.1.<sup>23</sup>

We assumed uniform and complete chrX inactivation in females and a similar effect size between males and females. Hence, females are considered to have 0, 1, or 2 copies of an allele (as in autosomal analyses), whereas males are considered to have 0 or 2 copies of the same allele (ie, male hemizygotes are considered equivalent to female homozygotes). This test was implemented in PLINK under the Model-2 option.

We then performed a second test by analyzing each sex separately (case patients vs control individuals), with males

coded as having either 0 or 2 copies of an allele, as described. The female-only and male-only  $P$  values were then combined using the weighted Stouffer method,<sup>32</sup> which allows the combination of  $P$  values not only accounting for potential effect size and direction between males and females but also weighting the 2 test statistics (by using the square root of the male/female sample size).

All samples recruited in China were processed and analyzed as described on a Chinese server to comply with the Regulation of the People's Republic of China on the Administration of Human Genetic Resources. The summary statistics, with no individual-level data, were used for all subsequent analyses (eg, meta-analysis with other panels).

Quantile-quantile (QQ) plots, genomic inflation factor ( $\lambda$ ) calculations, and Manhattan plots were obtained using the R program (<https://www.r-project.org/>).<sup>33</sup> SNP association results were clumped by PLINK 1.9 software (<https://www.cog-genomics.org/plink/1.9/>), adopting  $P < .001$ ,  $r^2 > 0.5$ , and 250 kilo base pairs (kb) as parameters.

**Table 1.** Meta-analysis Results: List of Top Independent Suggestive Signals ( $P < 5 \times 10^{-5}$ ).

Populations	Software	SNP	ChrX Position <sup>a</sup>	A1/A2	P <sub>Japanese</sub>	P <sub>Chinese</sub>	P <sub>Canadian</sub>	P <sub>Italian</sub>	P <sub>British</sub>	P <sub>meta</sub>	OR (95% CI)	Locus
All cohorts	MR-MEGA	rs2239452	48775572	G/C	7.51e-06	5.41e-04	.97	.59	.012	9.9e-08	1.17 (1.09-1.26)	P/M2
Female, all cohorts	MR-MEGA	rs2239452	48775572	G/C	4.35e-05	4.83e-4	.48	.36	5.11e-3	1.3e-05	1.11 (1.02-1.21)	P/M2
Male, all cohorts	MR-MEGA	rs201130692	132978723	-/A	.015	.88	5e-04	.045	.25	3.1e-05	3.16 (1.8-5.42)	GPC3
East Asian	METAINTER	rs7059064	48837087	G/A	8.1e-06	1.75e-04	—	—	—	6.2e-09	1.33 (1.21-1.46)	GRIPAP1
East Asian, female	METAINTER	rs2283734	8773556	A/G	4.15e-05	2.91e-04	—	—	—	4.64e-08	1.38 (1.23-1.56)	P/M2
East Asian, male	METAINTER	rs113885580	38236645	G/A	.0075	3.84e-04	—	—	—	1.06e-05	2.36 (1.61-3.46)	OTC
White	METAINTER	rs62604490	116104694	G/A	—	—	.36	.0058	6.90e-05	2.98e-06	0.75 (0.66-0.85)	Intergenic
White, female	METAINTER	rs62604490	116104694	G/A	—	—	.47	7.59e-04	1.09e-04	4.24e-06	0.73 (0.63-0.83)	Intergenic

NOTE. Only the top signals of each suggestively/genome-wide associated region are reported (see also Figure 2). For all SNPs presented in this table, directions among cohorts were always consistent, except for rs2239452 (all cohort analyses). A1, tested allele (MAF allele).

<sup>a</sup>According to human genome release February 2009, GRCh37/hg19.

### Meta-analysis

We filtered the SNP lists to include only those polymorphisms for which the association result was available from all cohorts (110,370 SNPs). Meta-analysis was performed both by combining the data of all analyzed populations (transethnic meta-analysis) and by separately considering White and East Asian populations.

The transethnic meta-analysis was carried out by using the MR-MEGA (Meta-Regression of Multi-Ethnic Genetic Association software, which models allelic effects of a variant across data sets, weighted by their corresponding standard errors, in a linear regression framework, including the axes of genetic variation as covariates.<sup>34</sup>

The White- and East Asian-specific meta-analyses were performed using the Stouffer method, taking into account weights and effect directions, as implemented in METAINTER software.<sup>35</sup> This software uses a modified version of the meta-analytic approach based on multivariate generalized least-squares estimation suggested by Becker and Wu<sup>36</sup> and is equivalent to the fixed-effects model. Meta-analysis results were clumped together using SNP effect concordance analysis (SECA) software,<sup>37</sup> extracting subsets of independent SNPs via LD. The procedure was *P* value informed, using  $r^2 > 0.1$  and 1 Mb (in LD with the index SNP) as parameters.

Finally, the genome-wide associated PBC risk locus in Asian individuals was closely examined by considering SNPs in the region surrounding the top hit (ie, rs7059064;  $\pm 200$  kb). Pairwise LD among the SNPs was calculated to detect potential independent signals. SNPs showing  $P_{meta}$  of  $< .01$  and low LD with the rs7059064 SNP ( $r^2 < 0.5$ ) were selected for conditional analysis.

In all our analyses, we considered loci with  $P < 5 \times 10^{-8}$  (genome-wide level) as significant and loci with  $P < 5 \times 10^{-5}$  as suggestive of association. Although,  $P < 1 \times 10^{-5}$  is the threshold at which, under the null hypothesis, 1 false positive result is expected per chrX-wide scan of approximately 100,000 SNPs, we chose the less stringent threshold of  $P < 5 \times 10^{-5}$ , based on the high level of LD characterizing chrX.<sup>38</sup>

### Measurements of Messenger RNA Levels

Peripheral blood mononuclear cells (PBMCs) were isolated by centrifugation on a Lympholyte Cell separation medium (Cederlane Laboratories Limited) gradient. Total RNA was isolated using the EuroGold Trifast kit (Euroclone).

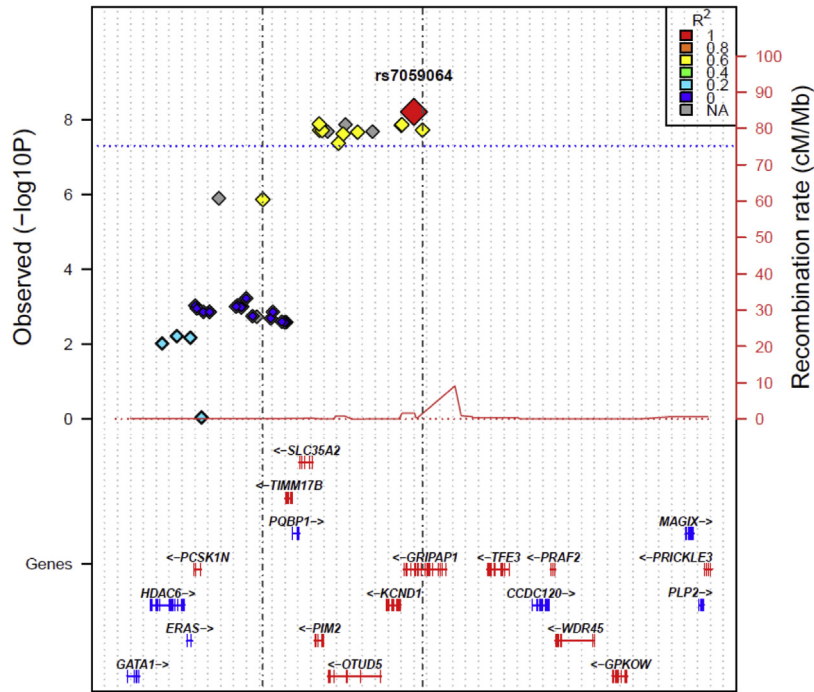
Random examers (Promega) and the Superscript-III Reverse Transcriptase (Thermo Fisher Scientific) were used to perform first-strand complementary DNA synthesis, following the manufacturer's instructions. Semiquantitative real-time reverse-transcriptase polymerase chain reactions (RT-PCRs) were accomplished by using 1  $\mu$ L of the RT reaction, the SYBR Premix Ex Taq II (TaKaRa), and a touchdown thermal protocol on a LightCycler 480 (Roche). *HMBS* (hydroxymethylbilane synthase) was used as the housekeeping gene. Reactions were performed in triplicate, and expression data were analyzed using the GeNorm software.<sup>39</sup> Primer sequences will be provided upon request.

### Results

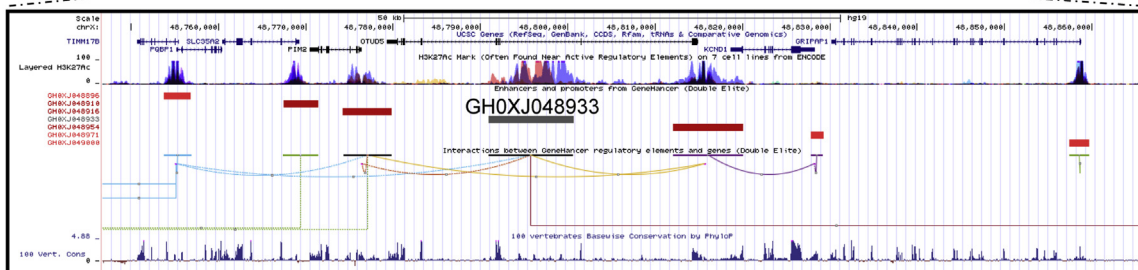
For evaluating the contribution of chrX to the genetic architecture of PBC, we extended the chrX marker sets from

**A**

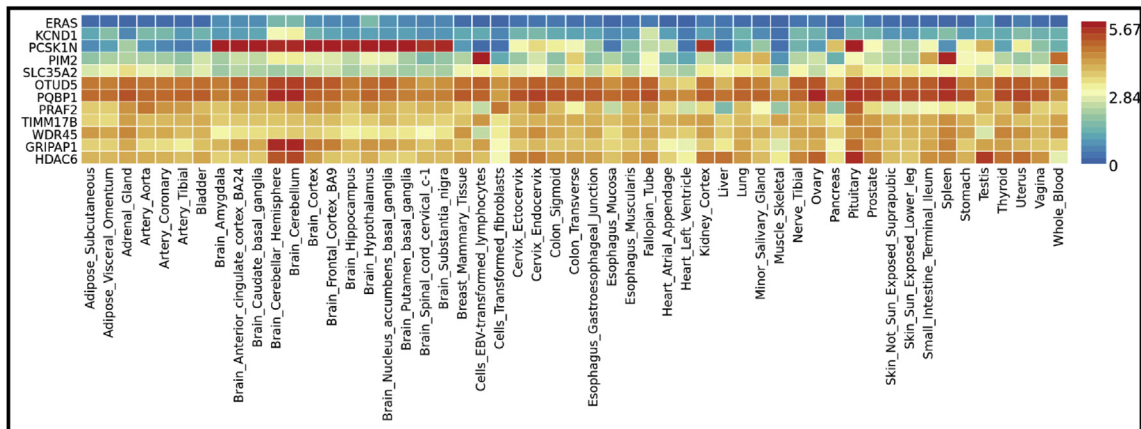
# All East Asians rs7059064



**B**



**C**



**Figure 3.** The *GRIPAP1/PIM2* locus. (A) Plot of the regional association signals surrounding the rs7059064 top hit in East Asian individuals. The plot was built using the LocusTrack site (<https://gump.qimr.edu.au/general/gabrieC/LocusTrack/>).<sup>40</sup> (B) Screenshot from the UCSC Genome browser (<http://genome.ucsc.edu/>; GRCh37/hg19) highlighting the PBC-associated LD region (coordinates chrX: 48,750,000–48,865,000). The following tracks are shown: (1) the ruler with the scale at the genomic level; (2) chrX nucleotide numbering; (3) the UCSC RefSeq track; (4) ENCODE data (<https://www.encodeproject.org/>) for the H3K4Me1, H3K4Me3, and H3K27Ac histone marks, derived from 7 cell lines; (5) enhancers (gray bars) and promoters (red bars) from GeneHancer<sup>41</sup> with the GH0XJ048933 enhancer targets; (6) interactions (curved lines) connecting GeneHancer regulatory elements/genes; and (7) the basewise conservation track. (C) Expression panel across tissues of the genes depicted in A (GTEx data; <https://gtexportal.org/home/>). UCSC, University of California–Santa Cruz. cM/MB, centi Morgan per Mega base.

**Table 2.** Association Data for the Lead rs7059064 Polymorphism in All Analyzed Populations

	Position <sup>a</sup>	Minor Allele/Major Allele	MAF Cases	MAF Controls	OR (95% CI)	P Value	Population	P <sub>meta</sub>	Transethnic P <sub>meta</sub>
rs7059064	48837087	G/A	0.114	0.119	0.99 (0.77–1.25)	.908	Canadian	.350	9.93e–08
			0.111	0.0935	1.21 (0.92–1.59)	.174	Italian		
			0.0973	0.116	0.89 (0.78–1.02)	.0942	British		
			0.162	0.119	1.38 (1.20–1.59)	8.14e–06	Japanese	6.2e–09	
			0.160	0.123	1.28 (1.13–1.46)	1.75e–04	Chinese		

NOTE. Minor allele frequencies (MAF) and *P* values of association tests are given for all populations (model 2 analysis). *P* values are presented for both the population-specific and transethnic meta-analyses.

<sup>a</sup>According to human genome release Feb. 2009, GRCh37/hg19

5 GWAS cohorts by imputing nonpseudoautosomal regions in a total of approximately 17,000 individuals. For the analyses, we obtained up to 240,385 high-quality SNPs (Supplementary Table 1).

### Single-Nucleotide Polymorphism Association Analysis Within Individual Cohorts

We performed 2 different tests: within each cohort, the associations were studied considering males and females together (test 1) or separately. For the separate analysis, males and females were combined using the Stouffer method (test 2). QQ plots for each test, along with the corresponding  $\lambda$  calculations, showed well-calibrated test statistic distributions (Supplementary Figure 1).

Association analyses did not show any genome-wide significant signal (Figure 1A), with the most significant being a signal within the *OTUD5* gene (rs3027490,  $P = 4.80 \times 10^{-6}$ ; odds ratio [OR], 1.39; 95% confidence interval [CI], 1.028–1.88; Japanese cohort, test 1) (Supplementary Table 2). The association signals were consistent between the 2 used association methods within each population (Supplementary Tables 2 and 3). In particular, a total of 115 and 104 SNPs in the 5 cohorts displayed a nominal *P* of <.0005 for test 1 and test 2 analysis, respectively, with 79 overlapping signals; >40% of signals were within gene-desert regions (Supplementary Table 4). Genes pinpointed by these signals showed few overlaps among populations (Figure 1B).

### Transethnic Meta-analysis

Based on SNP association results, we performed transethnic meta-analyses including all 5 of the cohorts by using 2 approaches: (1) results from the test 1 analysis were directly combined, and (2) results from the test 2 analysis were used in a sex-differentiated meta-analysis. The genomic inflation factors for these meta-analyses were between 0.979 and 1.114 (Supplementary Figure 2), indicating only a minimal residual bias.

Adopting the genome-wide significance threshold, the transethnic meta-analysis showed the presence of only 1

interesting signal: the region tagged by the rs2239452 variant, which maps in the *PIM2* gene (suggestive  $P_{\text{meta}} = 9.93 \times 10^{-8}$ ) (Figure 2A and Table 1). This signal was found considering all 5 cohorts together, and it seems to be sustained by the female component of the cohorts (suggestive  $P_{\text{meta-females}} = 1.34 \times 10^{-5}$ ) (Figure 2B and Table 1).

### Population-Specific Meta-analysis Evidenced a Novel Primary Biliary Cholangitis Locus

Because of the evidence for locus heterogeneity in PBC susceptibility among different ethnicities,<sup>10–17</sup> we also performed separate European and East Asian-specific meta-analyses, as well as sex-specific meta-analyses, using the same strategy described; genomic inflation factors for these meta-analyses were well calibrated (Supplementary Figure 3).

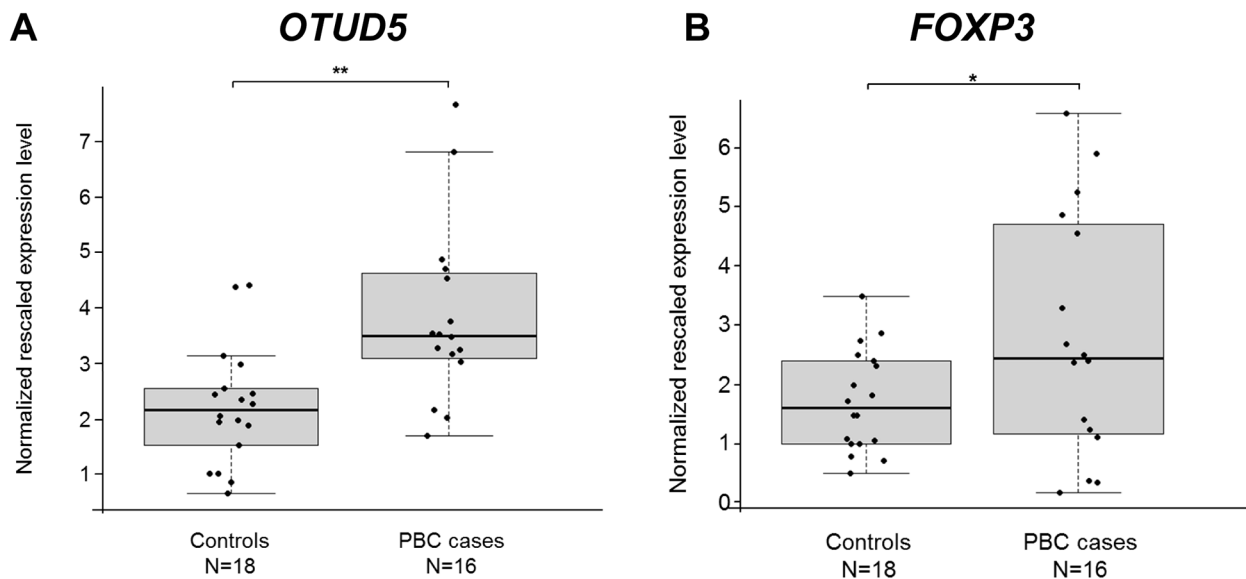
The population-specific meta-analysis evidenced 1 locus with an association signal at genome-wide significance, that is, the region tagged by the rs7059064 polymorphism, which maps within the *GRIPAP1* gene ( $P_{\text{meta}} = 6.17 \times 10^{-9}$ ; OR, 1.33; 95% CI, 1.21–1.46) (Figures 2 and 3, Table 1, and Supplementary Tables 5 and 6). This signal was found in East Asian individuals and corresponds to the top region evidenced by the transethnic meta-analysis (the *GRIPAP1* and *PIM2* genes are only 53 kb apart).

In European individuals, there were only suggestive associations, 1 in an intergenic region (rs62604490;  $P_{\text{meta}} = 2.98 \times 10^{-6}$ ) (Table 1 and Supplementary Figure 4) and a second mapping within the *FGF13* gene (rs73241097;  $P_{\text{meta}} = 6.77 \times 10^{-6}$ ) (Table 1 and Supplementary Figure 5).

The sex-stratified analysis found a novel suggestive signal among East Asian males (ie, rs113885580 mapping within the *OTC* gene;  $P_{\text{meta-males}} = 1.06 \times 10^{-5}$ ) (Figure 2, Table 1, and Supplementary Figure 6) and evidenced that both the signal in the *GRIPAP1* region and the intergenic region pinpointed by the rs62604490 SNP are sustained by the female component ( $P_{\text{meta-females}} = 4.64 \times 10^{-8}$  and  $P_{\text{meta-females}} = 4.24 \times 10^{-6}$ , respectively). The strongest signal among East Asian females corresponded to rs2283734, an SNP mapping in the *PIM2* gene (Figure 2), the same gene highlighted by the transethnic meta-analysis.







**Figure 5.** *OTUD5* and *FOXP3* are overexpressed in PBC. Boxplots show expression levels of (A) *OTUD5* and (B) *FOXP3* measured by semiquantitative real-time RT-PCR in PBMCs of a PBC case-control cohort. Boxes define the interquartile range; thick lines refer to the median. Results were normalized to expression levels of the *HMBS* housekeeping gene and are presented as rescaled values. The number of individuals is indicated (N). Significance levels of *t* tests: \**P* < .05, \*\**P* < .005.

11.4%) vs those observed in East Asian patients (16%–16.2%), thus possibly explaining the lack of association observed among European individuals. The effect of the rs7059064-G allele among East Asian individuals was comparable between males and females (females: OR, 1.50; 95% CI, 1.24–1.81; OR, 1.53; males: 95% CI, 0.99–2.38), thus indicating that the apparent major contribution of females to the association signal simply stems from the higher number of analyzed female patients (Supplementary Table 1).

Within a  $\pm 200$ -kb window centered on the rs7059064 polymorphism, there were 25 SNPs with association signals at  $P_{\text{meta}}$  of < .01. However, after conditional analysis, none of them remained significant, indicating that rs7059064 tagged a single haplotype that could account for the association signal in this region. Indeed, this region is

characterized by a unique LD block including 7 genes (Figure 3A and B<sup>40,41</sup>): *TIMM17B*, *PQB1*, *PIM2*, *SLC35A2*, *OTUD5*, *KCND1*, and *GRIPAP1*. Among these genes, only *PQB1* was previously associated at the genome-wide level with a phenotype (ie, type 2 diabetes mellitus; <https://www.ebi.ac.uk/gwas/>).

With the exception of *KCND1*, each of these genes shows expression in most tissues, including liver and whole blood (Figure 3C). Although this region does not contain significant expression quantitative trait loci (GTEx portal and Expression Quantitative Trait Locus Catalogue at The European Bioinformatics Institute), it is characterized by the presence of a strong epigenetic signature (the activating H3K27Ac histone mark) within *OTUD5* intron 2, associated with the presence of a superenhancer (SE) (element ID: GH0XJ048933) (Figure 3B and 4A). Two SNPs, in perfect LD

**Figure 4.** The GH0XJ048933 SE codes for an eRNA and coregulates the genes of the *GRIPAP1/PIM2* locus. (A) Screenshot from the UCSC Genome browser showing the GH0XJ048933 SE region (chrX: 48,791,000–48,802,000). Listed tracks are (1) the ruler with the scale at the genomic level; (2) chrX nucleotide numbering; (3) the track for eRNAs from the FANTOM5 Human Enhancers project ([http://slidebase.binf.ku.dk/human\\_enhancers/](http://slidebase.binf.ku.dk/human_enhancers/)); (4) the UCSC RefSeq track; (5) ENCODE data for the H3K4Me1, H3K4Me3, and H3K27Ac histone marks, derived from 7 cell lines; (6) the enhancers/promoters track from GeneHancer<sup>41</sup> (the gray bar indicates the GH0XJ048933 enhancer); (7) interactions connecting GeneHancer regulatory elements and genes (interactions with *OTUD5*, *PIM2*, *PQB1*, and *FOXP3* are depicted); (8) the basewise conservation track; and (9) the dbSNP(151) track for common polymorphisms. (B) Integration of gene expression (GE), protein expression (PE), copy number (CN) and methylation (ME) relative to the 13 genes regulated by the GH0XJ048933 SE. Data come from The Cancer Genome Atlas portal (<https://tcga-data.nci.nih.gov/docs/publications/tcga/>). The circle plot was built by using the Zodiac tool (<http://www.compgenome.org/zodiac/>).<sup>42</sup> Only significant intergenic interactions are shown (FDR  $\leq$  0.1). Green lines indicate positive interactions. (C) The tables show expression data (>1%) in organs/cells for the eRNA gene mapping within GH0XJ048933. Red bars indicate a significant overrepresentation of the transcript (FANTOM5 data). (D) TAD structure of the chrX: 47,480,000–50,440,000 region. The central TAD contains all genes of the PBC-associated region tagged by rs7059064. Image produced through the 3D-Genome Browser (<http://3dgenome.org/>),<sup>43</sup> using Hi-C data produced in HepG2 cells (hepatocytes) and generated by the Dekker Laboratory (resolution: 40 kb). (E) *FOXP3* interactome. The best 10 interactions are shown (highest confidence = 90%). Evidence is based on text mining, experiments, databases, coexpression data, gene fusions, and co-occurrences. Image produced using the STRING tool (<https://string-db.org/>). (F) Violin plots show *FOXP3* RNA expression levels in whole blood and liver, obtained through the GTEx portal, stratified by sex (265 males, 142 females). FDR, false discovery rate.

with the top-hit rs7059064, fall within this SE (Supplementary Table 5). GH0XJ048933 is known to target 13 genes, including 6 out of 7 mapping in the PBC-associated region; *KCND1* is the only one not targeted by the SE (Figure 4B<sup>42,43</sup>) (data from the FANTOM5 Human Enhancers project<sup>44</sup>). Among these 13 genes, we found the immunologically relevant transcription factor *FOXP3* (forkhead box P3). Hence, to further study the potential impact of the identified haplotype, we evaluated the expression levels of both *OTUD5* and *FOXP3* by semiquantitative real-time RT-PCR comparing PBMCs from 16 female patients with PBC and 18 healthy female control individuals. Only females were examined because of the possibility of confounding sex effects (especially for *FOXP3*; see “Discussion” section). We found a significant 1.75- and 1.64-fold up-regulation in patients with PBC of *OTUD5* ( $P = .0013$ ) and *FOXP3* ( $P = .046$ ), respectively (Figure 5).

For the other top loci (the intergenic rs62604490 polymorphism, the *FGF13* locus, and the *OTC* gene), the main features are illustrated in Supplementary Figures 4–6.

## Discussion

GWASs have been a fruitful method for disclosing genes/regions involved in the predisposition to complex diseases; however, chrX is notable for the paucity of associated loci.<sup>19</sup> For example, the most recent meta-analysis on multiple sclerosis, another complex disorder with an autoimmune etiology and a marked female preponderance, identified 233 loci associated with the disease at the genome-wide level, but just 1 locus was reported on chrX.<sup>45</sup> In our study, we adopted an analysis pipeline specifically designed for chrX to search for novel potential contributors to PBC heritability and, possibly, to its female preponderance.

Indeed, the best association signal observed both in the transethnic and in the population-specific meta-analyses points to a unique LD region characterized by the presence of 7 genes (*TIMM17B*, *PQBP1*, *PIM2*, *SLC35A2*, *OTUD5*, *KCND1*, and *GRIPAP1*) and an SE, GH0XJ048933 (within *OTUD5*), which presents features with a potential impact on PBC pathogenesis.

First, the enhancer is the site of active transcription of an enhancer RNA (eRNA), which has been described as significantly expressed in blood, thymus, and spleen, as well as in blood cells such as neutrophils and natural killer, T, and B cells (Figure 4A and C; FANTOM5 data). This type of non-coding RNA usually contributes to the enhancer activity and to the *in-cis* regulation of nearby genes.<sup>46</sup>

Second, the enhancer is enriched in binding sites for immune-related nuclear factor of activated T-cells (NFAT) transcription factors (particularly, NFATC1 and NFATC3), thus stressing its possible involvement in an immune-mediated regulation of target genes.

Third, the enhancer targets 13 genes that, by integrating gene expression, protein expression, and methylation data, seem to be strongly coregulated (Figure 4C), which could be predicted for an enhancer having its cognate promoters located in the same topologically associating domain (TAD) (Figure 4D).

Fourth, GH0XJ048933 also targets the *FOXP3* gene. *FOXP3* is a specific marker of T regulatory cells (Tregs), which are critical for the correct maintenance of immune tolerance (especially self-tolerance) and have been implicated in the pathogenesis of many autoimmune diseases.<sup>47–49</sup>

Fifth, *FOXP3* interacts with important determinants of the immune response (Figure 4E), and the transcript is among the few mapping on chrX to show a significant differential expression between males and females (in blood,  $P = .0082$ ) (Figure 4F).<sup>50</sup>

Last, but not least, different *Foxp3* transgenic mouse models have been developed<sup>51–53</sup>; particularly interesting are (1) *Foxp3*<sup>-/-</sup> knockout mice, which developed an intense multiorgan inflammatory response and loss of CD4<sup>+</sup>CD25<sup>+</sup> Treg cells<sup>51</sup>; (2) *Foxp3* conditional-knockout mice (*Foxp3*<sup>-loxR26Cre<sup>ERT2</sup></sup>), which showed increased levels of IgE and autoantibodies<sup>52</sup>; and, more importantly, (3) the so-called Scurfy mice (*Foxp3*<sup>sf</sup> mutant), that is, animals that have a mutation in *Foxp3* that results in the complete abolition of Foxp3<sup>+</sup> Tregs, which are all characterized, at 3–4 weeks of age, by the presence of high-titer serum AMA of all isotypes, by moderate to severe lymphocytic infiltrates surrounding portal areas, and by evidence of biliary duct damage.<sup>53</sup>

Together with *FOXP3*, at least 3 additional genes with potential implications in PBC—*PIM2*, *OTUD5*, and *GRIPAP1*—could be regulated by the GH0XJ048933 SE (Figures 3 and 4). The proviral integration site for Moloney murine leukemia virus 2 (*PIM2*) is a serine/threonine kinase belonging to the PIM family, playing fundamental roles in proliferation/differentiation processes and with known implications in cancer.<sup>54</sup> A growing number of studies have also implicated *PIM2* in regulating the immune response, in particular with the description of a circuit linking the *PIM2* protein with *FOXP3*: *PIM2*, induced by *FOXP3*, was shown to be essential for the expansion of Tregs and, contrariwise, *PIM2* was also described as being able to inhibit the suppressive function of Tregs by phosphorylating *FOXP3*.<sup>55</sup> Concerning the *OTUD5* gene, it codes for a member of the OTU (ovarian tumor) domain-containing cysteine protease superfamily. Also known as DUBA (deubiquitinating enzyme A), the *OTUD5* protein was shown to suppress the type 1 interferon (IFN)–dependent innate immune response by cleaving the polyubiquitin chain from the IFN-1 adaptor protein, thus causing the disassociation of the adaptor from the downstream signaling complex and, ultimately, the interruption of the IFN-1 signaling cascade.<sup>56</sup> As for *GRIPAP1* (GRIP1-associated protein 1), this gene codes for a guanine nucleotide exchange factor for the Ras family of small G proteins.<sup>57</sup> Indeed, in a study aimed at identifying autoantibodies in PBC directed against GWBs (glycine-tryptophan-containing bodies, ie, cytoplasmic domains that are involved in mRNA processing), Stinton et al<sup>58</sup> were able to demonstrate that *GRIPAP1* is one of the most common GWB autoantigen targets, being present in 17% of analyzed patients. Although we showed that *OTUD5* and *FOXP3* are differentially expressed in patients with PBC, a major limitation of our study is the lack of functional studies—from, on one hand, unraveling the molecular mechanisms linking

SE GH0XJ048933 and its molecular targets to, on the other hand, explaining how genetic variants in this region could influence these mechanisms.

In conclusion, from the extensive analysis of chrX, it emerges that a number of genes possibly contribute to PBC, each with a modest effect. This is not trivial, especially considering that chrX can be regarded as an immunologic chromosome. (It contains the largest number of immune-related genes compared to other chromosomes<sup>59</sup>). Our major finding is, however, the identification of a genome-wide significantly associated locus, that is, the one tagged by the rs7059064 polymorphism. This locus is characterized by the presence of different genes and of an SE possibly involved in their coregulation, as well as in the regulation of *FOXP3* (which located in the same TAD). Future studies are mandatory for explaining the role of SE GH0XJ048933 and its targets in PBC.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at <https://doi.org/10.1053/j.gastro.2021.02.061>.

## References

- Kaplan MM, Gershwin ME. Primary biliary cirrhosis. *N Engl J Med* 2005;353:1261–1273.
- Invernizzi P, Selmi C, Gershwin ME. Update on primary biliary cirrhosis. *Dig Liver Dis* 2010;42:401–408.
- Gerussi A, Cristofori L, Carbone M, et al. The immunobiology of female predominance in primary biliary cholangitis. *J Autoimmun* 2018;95:124–132.
- Invernizzi P, Miozzo M, Battezzati PM, et al. Frequency of monosomy X in women with primary biliary cirrhosis. *Lancet* 2004;363(9408):533–535.
- Webb GJ, Hirschfield GM. Using GWAS to identify genetic predisposition in hepatic autoimmunity. *J Autoimmun* 2016;66:25–39.
- Invernizzi P, Selmi C, Poli F, et al. Human leukocyte antigen polymorphisms in Italian primary biliary cirrhosis: a multicenter study of 664 patients and 1992 healthy controls. *Hepatology* 2008;48:1906–1912.
- Hirschfield GM, Liu X, Xu C, et al. Primary biliary cirrhosis associated with *HLA*, *IL12A*, and *IL12RB2* variants. *N Engl J Med* 2009;360:2544–2555.
- Invernizzi P. Human leukocyte antigen in primary biliary cirrhosis: an old story now reviving. *Hepatology* 2011;54:714–723.
- Invernizzi P, Ransom M, Raychaudhuri S, et al. Classical HLA-DRB1 and DPB1 alleles account for HLA associations with primary biliary cirrhosis. *Genes Immun* 2012;13:461–468.
- Joshita S, Umemura T, Tanaka E, et al. Genetics and epigenetics in the pathogenesis of primary biliary cholangitis. *Clin J Gastroenterol* 2018;11:11–18.
- Liu X, Invernizzi P, Lu Y, et al. Genome-wide meta-analyses identify three loci associated with primary biliary cirrhosis. *Nat Genet* 2010;42:658–660.
- Mells GF, Floyd JA, Morley KI, et al. Genome-wide association study identifies 12 new susceptibility loci for primary biliary cirrhosis. *Nat Genet* 2011;43:329–332.
- Liu JZ, Almarri MA, Gaffney DJ, et al. Dense fine-mapping study identifies new susceptibility loci for primary biliary cirrhosis. *Nat Genet* 2012;44:1137–1141.
- Juran BD, Hirschfield GM, Invernizzi P, et al. Immuno-chip analyses identify a novel risk locus for primary biliary cirrhosis at 13q14, multiple independent associations at four established risk loci and epistasis between 1p31 and 7q32 risk variants. *Hum Mol Genet* 2012;21:5209–5221.
- Nakamura M, Nishida N, Kawashima M, et al. Genome-wide association study identifies *TNFSF15* and *POU2AF1* as susceptibility loci for primary biliary cirrhosis in the Japanese population. *Am J Hum Genet* 2012;91:721–728.
- Qiu F, Tang R, Zuo X, et al. A genome-wide association study identifies six novel risk loci for primary biliary cholangitis. *Nat Commun* 2017;8:14828.
- Kawashima M, Hitomi Y, Aiba Y, et al. Genome-wide association studies identify *PRKCB* as a novel genetic susceptibility locus for primary biliary cholangitis in the Japanese population. *Hum Mol Genet* 2017;26:650–659.
- Gulamhusein AF, Juran BD, Lazaridis KN. Genome-wide association studies in primary biliary cirrhosis. *Semin Liver Dis* 2015;35:392–401.
- Wise AL, Gyi L, Manolio TA. eXclusion: toward integrating the X chromosome in genome-wide association analyses. *Am J Hum Genet* 2013;92:643–647.
- Amberger J, Bocchini CA, Scott AF, et al. McKusick's Online Mendelian Inheritance in Man (OMIM). *Nucleic Acids Res* 2009;37(Suppl 1):D793–D796.
- MacArthur J, Bowler E, Cerezo M, et al. The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res* 2017;45:D896–D901.
- Chang D, Gao F, Slavney A, et al. Accounting for eXentricities: analysis of the X chromosome in GWAS reveals X-linked genes implicated in autoimmune diseases. *PLoS One* 2014;9(12):e113684.
- Gao F, Chang D, Biddanda A, et al. XWAS: a software toolset for genetic data analysis and association studies of the X chromosome. *J Hered* 2015;106:666–671.
- Lindor KD, Gershwin ME, Poupon R, et al. Primary biliary cirrhosis. *Hepatology* 2009;50:291–308.
- Laurie CC, Doheny KF, Mirel DB, et al. Quality control and quality assurance in genotypic data for genome-wide association studies. *Genet Epidemiol* 2010;34:591–602.
- Patterson N, Price AL, Reich D. Population structure and eigenanalysis. *PLoS Genet* 2006;2(12):e190.
- Price AL, Patterson NJ, Plenge RM, et al. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet* 2006;38:904–909.
- Novembre J, Johnson T, Bryc K, et al. Genes mirror geography within Europe. *Nature* 2008;456(7218):98–101.

29. Delaneau O, Marchini J, Zagury JF. A linear complexity phasing method for thousands of genomes. *Nat Methods* 2011;9:179–181.
30. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet* 2009; 5(6):e1000529.
31. Auton A, Brooks LD, Altshuler D, et al. A global reference for human genetic variation. *Nature* 2015;526(7571): 68–74.
32. Stouffer SA, Suchman EA, DeVinney LC, et al. *Adjustment during Army life*. Princeton, New Jersey: Princeton University Press, 1949.
33. R Core Team. *R. A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2013.
34. Mägi R, Horikoshi M, Sofer T, et al. Trans-ethnic meta-regression of genome-wide association studies accounting for ancestry increases power for discovery and improves fine-mapping resolution. *Hum Mol Genet* 2017; 26:3639–3650.
35. Vaitsakhovich T, Drichel D, Herold C, et al. METAINTER: meta-analysis of multiple regression models in genome-wide association studies. *Bioinformatics* 2015;31:151–157.
36. Becker BJ, Wu MJ. The synthesis of regression slopes in meta-analysis. *Stat Sci* 2007;22:414–429.
37. Nyholt DR. SECA: SNP effect concordance analysis using genome-wide association summary results. *Bioinformatics* 2014;30:2086–2088.
38. Schaffner SF. The X chromosome in population genetics. *Nat Rev Genet* 2004;5:43–51.
39. Vandesompele J, De Preter K, Pattyn F, et al. Accurate normalization of real-time quantitative RT-PCR data by geometric averaging of multiple internal control genes. *Genome Biol* 2002;3(7). RESEARCH0034.
40. Cuellar-Partida G, Renteria ME, LocusTrack MacGregor S. integrated visualization of GWAS results and genomic annotation. *Source Code Biol Med* 2015;10:1.
41. **Fishilevich S, Nudel R, Rappaport N, et al.** GeneHancer: genome-wide integration of enhancers and target genes in GeneCards. Oxford: Database, 2017. 2017:bax028.
42. **Zhu Y, Xu Y, Helseth DL Jr, et al.** Zodiac: a comprehensive depiction of genetic interactions in cancer by integrating TCGA data. *J Natl Cancer Inst* 2015; 107(8):djv129.
43. Wang Y, Song F, Zhang B, et al. The 3D Genome Browser: a web-based browser for visualizing 3D genome organization and long-range chromatin interactions. *Genome Biol* 2018;19:151.
44. Lizio M, Harshbarger J, Abugessaisa I, et al. Update of the FANTOM web resource: high resolution transcriptome of diverse cell types in mammals. *Nucleic Acids Res* 2017;45:D737–D743.
45. International Multiple Sclerosis Genetics Consortium. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science* 2019;365(6460):eaav7188.
46. **Hnisz D, Shrinivas K, Young RA, et al.** A phase separation model for transcriptional control. *Cell* 2017; 169:13–23.
47. Sakaguchi S, Yamaguchi T, Nomura T, et al. Regulatory T cells and immune tolerance. *Cell* 2008;133:775–787.
48. **Mohr A, Atif M, Balderas R, et al.** The role of FOXP3<sup>+</sup> regulatory T cells in human autoimmune and inflammatory diseases. *Clin Exp Immunol* 2019;197:24–35.
49. **Attias M, Al-Aubodah TA, Piccirillo CA.** Mechanisms of human FoxP3<sup>+</sup> T<sub>reg</sub> cell development and function in health and disease. *Clin Exp Immunol* 2019;197:36–51.
50. Tukiainen T, Villani AC, Yen A, et al. Landscape of X chromosome inactivation across human tissues. *Nature* 2017;550(7675):244–248.
51. Lin W, Truong N, Grossman WJ, et al. Allergic dysregulation and hyperimmunoglobulinemia E in Foxp3 mutant mice. *J Allergy Clin Immunol* 2005;116:1106–1115.
52. **Tai Y, Sakamoto K, Takano A, et al.** Dysregulation of humoral immunity in Foxp3 conditional-knockout mice. *Biochem Biophys Res Commun* 2019;513:787–793.
53. Zhang W, Sharma R, Ju ST, et al. Deficiency in regulatory T cells results in development of antimitochondrial antibodies and autoimmune cholangitis. *Hepatology* 2009; 49:545–552.
54. Narlik-Grassow M, Blanco-Aparicio C, Carnero A. The PIM family of serine/threonine kinases in cancer. *Med Res Rev* 2014;34:136–159.
55. Deng G, Nagai Y, Xiao Y, et al. Pim-2 kinase influences regulatory T cell function and stability by mediating Foxp3 protein N-terminal phosphorylation. *J Biol Chem* 2015;290:20211–20220.
56. Kayagaki N, Phung Q, Chan S, et al. DUBA: a deubiquitinase that regulates type I interferon production. *Science* 2007;318(5856):1628–1632.
57. Ye B, Liao D, Zhang X, et al. GRASP-1: a neuronal RasGEF associated with the AMPA receptor/GRIP complex. *Neuron* 2000;26:603–617.
58. Stinton LM, Swain M, Myers RP, et al. Autoantibodies to GW bodies and other autoantigens in primary biliary cirrhosis. *Clin Exp Immunol* 2011;163:147–156.
59. Bianchi I, Lleo A, Gershwin ME, Invernizzi P. The X chromosome and immune associated genes. *J Autoimmun* 2012;38(2–3):J187–J192.

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Received March 29, 2020. Accepted February 25, 2021.

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#### Acknowledgments

A full list of consortium members appears in the Supplementary Material.

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#### Conflicts of interest

The authors disclose no conflicts.

#### Funding

This study was partly supported by Italian Ministry of Health grants (PE-2016-02363915 and GR-2018-12367794), National Institutes of Health grant R01DK091823, and National Natural Science Foundation of China grants (81830016 and 81620108002 to XM). The authors thank Associazione Malattie Autoimmuni del Fegato (AMAF) Monza Organizzazione non lucrativa di utilità sociale (ONLUS) and Associazione Italiana Ricerca Colangite Sclerosante (AIRCS) for the unrestricted research funding. This work was also supported by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (15K19314 to 17K15924 to Yuki Hitomi; 15K06908 to Minae Kawashima; 15K19357 and 17K09449 to Yoshihiro Aiba; and 23591006, 26293181, and 17H04169 to Minoru Nakamura), a Grant-in-Aid for Clinical Research from the National Hospital Organization (to Minoru Nakamura), a grant from the Research Program of Intractable Disease provided by the Ministry of Health, Labor, and Welfare of Japan to Minoru Nakamura, a grant from the Takeda Foundation (to Yuki Hitomi), and grants from the Japan Agency for Medical Research and Development (JP19km0405205 and JP19km0405501h0001 to Katsushi Tokunaga and Masao Nagasaki). Marco Carbone, Alessio Gerussi, and Pietro Invernizzi are members of the European Reference Network on Hepatological Diseases.

## Supplementary Material

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- <sup>116</sup>Hywel Dda University Health Board, Glangwili General Hospital, Dolgwilli Road, Carmarthen SA31 2AF, United Kingdom.
- <sup>117</sup>Hywel Dda University Health Board, Bronglais Hospital, Caradog Road, Aberystwyth SY23 1ER, United Kingdom.
- <sup>118</sup>Imperial College Healthcare NHS Trust, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, United Kingdom.
- <sup>119</sup>Imperial College Healthcare NHS Trust, Hammer-smith Hospital, Du Cane Road, London W12 0HS, United Kingdom.
- <sup>120</sup>Imperial College Healthcare NHS Trust, St Mary's Hospital, Praed Street, London W2 1NY, United Kingdom.
- <sup>121</sup>Imperial College Healthcare NHS Trust, St Mary's Hospital, Praed Street, London W2 1NY, United Kingdom.
- <sup>122</sup>Ipswich Hospital NHS Trust, Ipswich Hospital, Heath Road, Ipswich IP4 5PD, United Kingdom.
- <sup>123</sup>Isle of Wight NHS Trust, St Mary's Hospital, Parkhurst Road, Newport PO30 5TG, United Kingdom.
- <sup>124</sup>James Paget University Hospitals NHS Foundation Trust, James Paget Hospital, Lowestoft Road, Gorleston, Great Yarmouth NR31 6LA, United Kingdom.
- <sup>125</sup>Kettering General Hospital NHS Foundation Trust, Kettering General Hospital, Rothwell Road, Kettering NN16 8UZ, United Kingdom.
- <sup>126</sup>Kings College Hospital NHS Foundation Trust, King's College Hospital, Denmark Hill, London SE5 9RS, United Kingdom.
- <sup>127</sup>King's College Hospital NHS Foundation Trust, Beckenham Beacon, 395 Croydon Road, Beckenham BR3 3QL, United Kingdom.
- <sup>128</sup>King's College Hospital NHS Foundation Trust, Princess Royal University Hospital, Farnborough Common, Orpington BR6 8ND, United Kingdom.
- <sup>129</sup>Kingston Hospital NHS Foundation Trust, Kingston Hospital, Galsworthy Road, Kingston upon Thames KT2 7QB, United Kingdom.
- <sup>130</sup>Lancashire Teaching Hospitals NHS Foundation Trust, Chorley and South Ribble Hospital, Preston Road, Chorley PR7 1PP, United Kingdom.
- <sup>131</sup>Lancashire Teaching Hospitals NHS Foundation Trust, Royal Preston Hospital, Sharoe Green Lane North, Preston PR2 9HT, United Kingdom.
- <sup>132</sup>Leeds Teaching Hospitals NHS Trust, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, United Kingdom.
- <sup>133</sup>Leeds Teaching Hospitals NHS Trust, St James's University Hospital, Beckett Street, Leeds LS9 7TF, United Kingdom.
- <sup>134</sup>Lewisham and Greenwich NHS Trust, The Queen Elizabeth, Woolwich, Stadium Road, Greenwich SE18 4QH, United Kingdom.
- <sup>135</sup>Lewisham and Greenwich NHS Trust, Lewisham Hospital, High Street, Lewisham SE13 6LH, United Kingdom.
- <sup>136</sup>London North West Healthcare NHS Trust, Central Middlesex Hospital, Acton Lane, Park Royal, London NW10 7NS, United Kingdom.
- <sup>137</sup>London North West Healthcare NHS Trust, Northwick Park and St Mark's Hospitals, Watford Road, Harrow HA1 3UJ, United Kingdom.
- <sup>138</sup>Luton and Dunstable University Hospital NHS Foundation Trust, Luton and Dunstable University Hospital, Lewsey Road, Luton LU4 0DZ, United Kingdom.
- <sup>139</sup>Maidstone and Tunbridge Wells NHS Trust, Maidstone Hospital, Hermitage Lane, Maidstone ME16 9QQ, United Kingdom.
- <sup>140</sup>Maidstone and Tunbridge Wells NHS Trust, Tunbridge Wells Hospital, Tonbridge Road, Pembury, Tunbridge Wells TN2 4QJ, United Kingdom.
- <sup>141</sup>Medway NHS Foundation Trust, Medway Maritime Hospital, Windmill Road, Gillingham ME7 5NY, United Kingdom.
- <sup>142</sup>Mid Cheshire Hospitals NHS Foundation Trust, Leighton Hospital, Middlewich Road, CW1 4QJ, United Kingdom.

- <sup>143</sup>Mid Essex Hospital Services NHS Trust, Broomfield Hospital, Court Road, Chelmsford CM1 7ET, United Kingdom.
- <sup>144</sup>Mid Essex Hospital Services NHS Trust, St Peters Hospital, Spital Road, Maldon CM9 6EG, United Kingdom.
- <sup>145</sup>Mid Yorkshire Hospitals NHS Trust, Dewsbury and District Hospital, Halifax Road, Dewsbury WF13 4HS, United Kingdom.
- <sup>146</sup>Milton Keynes Hospital NHS Foundation Trust, Milton Keynes Hospital, Standing Way, Milton Keynes MK6 5LD, United Kingdom.
- <sup>147</sup>Newcastle upon Tyne Hospitals NHS Foundation Trust, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN, United Kingdom.
- <sup>148</sup>NHS Ayrshire & Arran, University Hospital Crosshouse, Kilmarnock Road, Kilmarnock KA2 0BE, United Kingdom.
- <sup>149</sup>NHS Borders, Borders General Hospital, Melrose TD6 9BS, United Kingdom.
- <sup>150</sup>NHS Dumfries & Galloway, Dumfries and Galloway Royal Infirmary, Bankend Road, Dumfries DG1 4AP, United Kingdom.
- <sup>151</sup>NHS Fife, Queen Margaret Hospital, Whitefield Road, Dunfermline KY12 0SU, United Kingdom.
- <sup>152</sup>NHS Fife, Victoria Hospital, Hayfield Road, Kirkcaldy KY2 5AH, United Kingdom.
- <sup>153</sup>NHS Forth Valley, Forth Valley Royal Hospital, Stirling Road, Larbert FK5 4WR, United Kingdom.
- <sup>154</sup>NHS Forth Valley, Stirling Community Hospital, Livilands, Stirling FK8 2AU, United Kingdom.
- <sup>155</sup>NHS Grampian, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN, United Kingdom.
- <sup>156</sup>NHS Grampian, Dr Gray's Hospital, Elgin IV30 1SN, United Kingdom.
- <sup>157</sup>NHS Grampian, Woolmanhill Hospital, Skene Street, Aberdeen AB25 1LD, United Kingdom.
- <sup>158</sup>NHS Greater Glasgow and Clyde, Gartnavel General Hospital, 1053 Great Western Road, Glasgow G12 0YN, United Kingdom.
- <sup>159</sup>NHS Greater Glasgow and Clyde, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, United Kingdom.
- <sup>160</sup>NHS Greater Glasgow and Clyde, Inverclyde Royal Hospital, Larkfield Road, Greenock PA16 0XN, United Kingdom.
- <sup>161</sup>NHS Greater Glasgow and Clyde, Royal Alexandra Hospital, Corsebar Road, Paisley PA2 9PN, United Kingdom.
- <sup>162</sup>NHS Greater Glasgow and Clyde, Southern General Hospital, 1345 Govan Road, Glasgow G51 4TF, United Kingdom.
- <sup>163</sup>NHS Greater Glasgow and Clyde, Victoria Infirmary, Langside Road, Glasgow G42 9TY, United Kingdom.
- <sup>164</sup>NHS Highland, Caithness General Hospital, Bankhead Road, Wick KW1 5NS, United Kingdom.
- <sup>165</sup>NHS Highland, Raigmore Hospital, Old Perth Road, Inverness IV2 3UJ, United Kingdom.
- <sup>166</sup>NHS Lanarkshire, Hairmyres Hospital, Eaglesham Road, East Kilbride G75 8RG, United Kingdom.
- <sup>167</sup>NHS Lanarkshire, Monklands Hospital, Monkscourt Avenue, Airdrie ML6 0JS, United Kingdom.
- <sup>168</sup>NHS Lanarkshire, Wishaw General Hospital, 50 Netherton Street, Wishaw ML2 0DP, United Kingdom.
- <sup>169</sup>NHS Lothian, Royal Infirmary of Edinburgh, 51 Little France Crescent, Old Dalkeith Road, Edinburgh EH16 4SA, United Kingdom.
- <sup>170</sup>NHS Lothian, St John's Hospital, Howden Road West, Howden, Livingston EH54 6PP, United Kingdom.
- <sup>171</sup>NHS Lothian, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, United Kingdom.
- <sup>172</sup>NHS Tayside, Perth Royal Infirmary, Taymount Terrace, Perth PH1 1NX, United Kingdom.
- <sup>173</sup>NHS Tayside, Ninewells Hospital, Dundee DD1 9SY, United Kingdom.
- <sup>174</sup>Norfolk and Norwich University Hospitals NHS Foundation Trust, Norfolk and Norwich University Hospital, Colney Lane, Norwich NR4 7UY, United Kingdom.
- <sup>175</sup>North Bristol NHS Trust, Frenchay Hospital, Frenchay Park Road, Bristol BS16 1LE, United Kingdom.
- <sup>176</sup>North Cumbria University Hospitals NHS Foundation Trust, Cumberland Infirmary, Newtown Road, Carlisle CA2 7HY, United Kingdom.
- <sup>177</sup>North Cumbria University Hospitals NHS Foundation Trust, West Cumberland Hospital, Hensingham, Whitehaven CA28 8JG, United Kingdom.
- <sup>178</sup>North Tees and Hartlepool NHS Foundation Trust, University Hospital of Hartlepool, Holdforth Road, Hartlepool TS24 9AH, United Kingdom.
- <sup>179</sup>North Tees and Hartlepool NHS Foundation Trust, University Hospital of North Tees, Hardwick, Stockton on Tees TS19 8PE, United Kingdom.
- <sup>180</sup>Northampton General Hospital NHS Trust, Northampton General Hospital, Cliftonville, Northampton NN1 5BD, United Kingdom.
- <sup>181</sup>Northern Devon Healthcare NHS Trust, North Devon District Hospital, Raleigh Park, Barnstaple EX31 4JB, United Kingdom.
- <sup>182</sup>Northern Health and Social Care Trust, Whiteabbey Hospital, Doagh Road, Newtownabbey BT37 9RH, United Kingdom.
- <sup>183</sup>Northern Lincolnshire and Goole NHS Foundation Trust, Diana, Princess of Wales Hospital, Scartho Road, Grimsby DN33 2BA, United Kingdom.
- <sup>184</sup>Northern Lincolnshire and Goole NHS Foundation Trust, Goole and District Hospital, Woodland Avenue, Goole DN14 6RX, United Kingdom.
- <sup>185</sup>Northern Lincolnshire and Goole NHS Foundation Trust, Scunthorpe General Hospital, Cliff Gardens, Scunthorpe DN15 7BH, United Kingdom.
- <sup>186</sup>Northumbria Healthcare NHS Foundation Trust, Hexham General Hospital, Corbridge Road, Hexham NE46 1QJ, United Kingdom.
- <sup>187</sup>Northumbria Healthcare NHS Foundation Trust, North Tyneside Hospital, Rake Lane, North Shields NE29 8NH, United Kingdom.

<sup>188</sup>Nottingham University Hospitals NHS Trust, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB, United Kingdom.

<sup>189</sup>Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Derby Road, Nottingham NG7 2UH, United Kingdom.

<sup>190</sup>Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, United Kingdom.

<sup>191</sup>Pennine Acute Hospitals NHS Trust, Fairfield General Hospital, Rochdale Old Road, Bury BL9 7TD, United Kingdom.

<sup>192</sup>Pennine Acute Hospitals NHS Trust, North Manchester General Hospital, Delaunays Road, Crumpsall M8 5RB, United Kingdom.

<sup>193</sup>Pennine Acute Hospitals NHS Trust, Rochdale Infirmary, Whitehall Street, Rochdale OL12 0NB, United Kingdom.

<sup>194</sup>Pennine Acute Hospitals NHS Trust, The Royal Oldham Hospital, Rochdale Road, Oldham OL1 2JH, United Kingdom.

<sup>195</sup>Peterborough and Stamford Hospitals NHS Foundation Trust, Peterborough City Hospital, Edith Cavell Campus, Bretton Gate, Peterborough PE3 9GZ, United Kingdom.

<sup>196</sup>Peterborough and Stamford Hospitals NHS Foundation Trust, Stamford & Rutland Hospital, Ryhall Road, Stamford PE9 1UA, United Kingdom.

<sup>197</sup>Plymouth Hospitals NHS Trust, Derriford Hospital, Derriford Road, Plymouth PL6 8DH, United Kingdom.

<sup>198</sup>Poole Hospital NHS Foundation Trust, Poole Hospital, Longfleet Road, Poole BH15 2JB, United Kingdom.

<sup>199</sup>Portsmouth Hospitals NHS Trust, Queen Alexandra Hospital, Cosham, Portsmouth PO6 3LY, United Kingdom.

<sup>200</sup>Princess Alexandra Hospital NHS Trust, St Margaret's Hospital, The Plain, Epping CM16 6TN, United Kingdom.

<sup>201</sup>Princess Alexandra Hospital NHS Trust, The Princess Alexandra Hospital, Hamstel Road, Harlow CM20 1QX, United Kingdom.

<sup>202</sup>Queen Elizabeth Hospital King's Lynn NHS Foundation Trust, The Queen Elizabeth Hospital King's Lynn, Gayton Road, King's Lynn PE30 4ET, United Kingdom.

<sup>203</sup>Rotherham NHS Foundation Trust, Rotherham Hospital, Moorgate Road, Rotherham S60 2UD, United Kingdom.

<sup>204</sup>Royal Berkshire NHS Foundation Trust, Royal Berkshire Hospital, Craven Road, Reading RG1 5AN, United Kingdom.

<sup>205</sup>Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, Royal Bournemouth Hospital, Castle Lane East, Bournemouth BH7 7DW, United Kingdom.

<sup>206</sup>Royal Cornwall Hospitals NHS Trust, Royal Cornwall Hospital, Treliske, Truro TR1 3LJ, United Kingdom.

<sup>207</sup>Royal Devon and Exeter NHS Foundation Trust, Royal Devon and Exeter Hospital, Barrack Road, Exeter EX2 5DW, United Kingdom.

<sup>208</sup>Royal Free London NHS Foundation Trust, The Royal Free Hospital, Pond Street, London NW3 2QG, United Kingdom.

<sup>209</sup>Royal Free London NHS Foundation Trust, Barnet Hospital, Wellhouse Lane, Barnet EN5 3DJ, United Kingdom.

<sup>210</sup>Royal Free London NHS Foundation Trust, Chase Farm Hospital, The Ridgeway, Enfield EN2 8JL, United Kingdom.

<sup>211</sup>Royal Liverpool and Broadgreen University Hospitals NHS Trust, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, United Kingdom.

<sup>212</sup>Royal United Hospitals Bath NHS Foundation Trust, Royal United Bath Hospital, Combe Park, Bath BA1 3NG, United Kingdom.

<sup>213</sup>Royal Wolverhampton Hospitals NHS Trust, New Cross Hospital, Wolverhampton Road, Wolverhampton WV10 0QP, United Kingdom.

<sup>214</sup>Royal Wolverhampton Hospitals NHS Trust, Cannock Chase Hospital, Brunswick Road, Cannock WS11 5XY, United Kingdom.

<sup>215</sup>University Hospitals of North Midlands NHS Trust, County Hospital, Weston Road, Stafford ST16 3SA, United Kingdom.

<sup>216</sup>Salisbury NHS Foundation Trust, Salisbury District Hospital, Salisbury SP2 8BJ, United Kingdom.

<sup>217</sup>Sandwell and West Birmingham Hospitals NHS Trust, Sandwell General Hospital, Lyndon, West Bromwich B71 4HJ, United Kingdom.

<sup>218</sup>Sheffield Teaching Hospitals NHS Foundation Trust, Northern General Hospital, Herries Road, Sheffield S5 7AU, United Kingdom.

<sup>219</sup>Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, United Kingdom.

<sup>220</sup>Sherwood Forest Hospitals NHS Foundation Trust, King's Mill Hospital, Mansfield Road, Sutton in Ashfield NG17 4JL, United Kingdom.

<sup>221</sup>Sherwood Forest Hospitals NHS Foundation Trust, Newark Hospital, Boundary Road, Newark NG24 4DE, United Kingdom.

<sup>222</sup>Shrewsbury and Telford Hospital NHS Trust, Princess Royal Hospital, Apley Castle, Telford TF1 6TF, United Kingdom.

<sup>223</sup>Shrewsbury and Telford Hospital NHS Trust, Royal Shrewsbury Hospital, Mytton Oak Road, Shrewsbury SY3 8XQ, United Kingdom.

<sup>224</sup>South Devon Healthcare NHS Foundation Trust, Torbay Hospital, Lowes Bridge, Torquay TQ2 7AA, United Kingdom.

<sup>225</sup>South Eastern Health and Social Care Trust, Lagan Valley Hospital, 39 Hillsborough Road, Lisburn BT28 1JP, United Kingdom.

<sup>226</sup>South Eastern Health and Social Care Trust, Ulster Hospital, Upper Newtownards Road, Dundonald, Belfast BT16 1RH, United Kingdom.

<sup>227</sup>South Tees Hospitals NHS Foundation Trust, The James Cook University Hospital, Marton Road, Middlesbrough TS4 3BW, United Kingdom.

<sup>228</sup>South Tees Hospitals NHS Foundation Trust, Friarage Hospital, Northallerton DL6 1JG, United Kingdom.

- <sup>229</sup>South Tyneside NHS Foundation Trust, South Tyneside District Hospital, Harton Lane, South Shields NE34 0PL, United Kingdom.
- <sup>230</sup>South Warwickshire NHS Foundation Trust, Warwick Hospital, Lakin Road, Warwick CV34 5BW, United Kingdom.
- <sup>231</sup>Southend University Hospital NHS Foundation Trust, Southend Hospital, Prittlewell Chase, Westcliff-on-Sea SS0 0RY, United Kingdom.
- <sup>232</sup>Southport & Ormskirk Hospital NHS Trust, Ormskirk District General Hospital, Wigan Road, Ormskirk L39 2AZ, United Kingdom.
- <sup>233</sup>Southport & Ormskirk Hospital NHS Trust, Southport and Formby District General Hospital, Town Lane, Kew, Southport PR8 6PN, United Kingdom.
- <sup>234</sup>St George's University Hospitals NHS Foundation Trust, St George's Hospital, Blackshaw Road, Tooting, London SW17 0QT, United Kingdom.
- <sup>235</sup>St Helens and Knowsley Teaching Hospitals NHS Trust, St Helens Hospital, Marshalls Cross Road, St Helens WA9 3DA, United Kingdom.
- <sup>236</sup>St Helens and Knowsley Teaching Hospitals NHS Trust, Whiston Hospital, Warrington Road, Prescott L35 5DR, United Kingdom.
- <sup>237</sup>Surrey and Sussex Healthcare NHS Trust, East Surrey Hospital, Canada Avenue, Redhill RH1 5RH, United Kingdom.
- <sup>238</sup>Tameside Hospital NHS Foundation Trust, Tameside General Hospital, Fountain Street, Ashton-under-Lyne OL6 9RW, United Kingdom.
- <sup>239</sup>United Lincolnshire Hospitals NHS Trust, Lincoln County Hospital, Greetwell Road, Lincoln LN2 5QY, United Kingdom.
- <sup>240</sup>United Lincolnshire Hospitals NHS Trust, Grantham and District Hospital, 101 Manthorpe Road, Grantham NG31 8DG, United Kingdom.
- <sup>241</sup>United Lincolnshire Hospitals NHS Trust, Pilgrim Hospital Boston, Sibsey Road, Boston PE21 9QS, United Kingdom.
- <sup>242</sup>University College London Hospitals NHS Foundation Trust, University College Hospital, 235 Euston Road, London NW1 2BU, United Kingdom.
- <sup>243</sup>University Hospital of South Manchester NHS Foundation Trust, Wythenshawe Hospital, Southmoor Road, Wythenshawe, Manchester M23 9LT, United Kingdom.
- <sup>244</sup>University Hospital Southampton NHS Foundation Trust, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, United Kingdom.
- <sup>245</sup>University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Mindelsohn Way, Edgbaston, Birmingham B15 2GW, United Kingdom.
- <sup>246</sup>University Hospitals Bristol NHS Foundation Trust, Bristol Royal Infirmary, Upper Maudlin Street, Bristol BS2 8HW, United Kingdom.
- <sup>247</sup>University Hospitals Coventry and Warwickshire NHS Trust, University Hospital, Clifford Bridge Road, Coventry CV2 2DX, United Kingdom.
- <sup>248</sup>University Hospitals of Leicester NHS Trust, Glenfield Hospital, Groby Road, Leicester LE3 9QP, United Kingdom.
- <sup>249</sup>University Hospitals of Leicester NHS Trust, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, United Kingdom.
- <sup>250</sup>University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW, United Kingdom.
- <sup>251</sup>University Hospitals of Morecambe Bay NHS Foundation Trust, Royal Lancaster Infirmary, Ashton Road, Lancaster LA1 4RP, United Kingdom.
- <sup>252</sup>University Hospitals of North Midlands NHS Trust, Royal Stoke University Hospital, Newcastle Road, Stoke-on-Trent ST4 6QG, United Kingdom.
- <sup>253</sup>Walsall Healthcare NHS Trust, Walsall Manor Hospital, Moat Road, Walsall WS2 9PS, United Kingdom.
- <sup>254</sup>Warrington and Halton Hospitals NHS Foundation Trust, Warrington Hospital, Lovely Lane, Warrington WA5 1QG, United Kingdom.
- <sup>255</sup>West Hertfordshire Hospitals NHS Trust, Hemel Hempstead General Hospital, Hillfield Road, Hemel Hempstead HP2 4AD, United Kingdom.
- <sup>256</sup>West Hertfordshire Hospitals NHS Trust, St Albans City Hospital, Waverley Road, St Albans AL3 5PN, United Kingdom.
- <sup>257</sup>West Hertfordshire Hospitals NHS Trust, Watford General Hospital, Vicarage Road, Watford WD18 0HB, United Kingdom.
- <sup>258</sup>West Middlesex University NHS Trust, West Middlesex University Hospital, Twickenham Road, Isleworth TW7 6AF.
- <sup>259</sup>West Suffolk NHS Foundation Trust, Walnut Tree Hospital, Walnut Tree Lane, Sudbury CO10 1BE, United Kingdom.
- <sup>260</sup>West Suffolk NHS Foundation Trust, West Suffolk Hospital, Hardwick Lane, Bury St Edmunds IP33 2QZ, United Kingdom.
- <sup>261</sup>Western Sussex Hospitals NHS Foundation Trust, Worthing Hospital, Lyndhurst Road, Worthing BN11 2DH, United Kingdom.
- <sup>262</sup>Western Sussex Hospitals NHS Foundation Trust, St Richard's Hospital, Spitalfield Lane, Chichester PO19 6SE, United Kingdom.
- <sup>263</sup>Weston Area Health NHS Trust, Weston General Hospital, Grange Road, Uphill, Weston super Mare BS23 4TQ, United Kingdom.
- <sup>264</sup>Whittington Hospital NHS Trust, The Whittington Hospital, Magdala Avenue, London N19 5NF, United Kingdom.
- <sup>265</sup>Wirral University Teaching Hospital NHS Foundation Trust, Arrowe Park Hospital, Upton CH49 5PE, United Kingdom.
- <sup>266</sup>Wirral University Teaching Hospital NHS Foundation Trust, Victoria Central Hospital, Mill Lane, Wallasey CH44 5UF, United Kingdom.
- <sup>267</sup>Worcestershire Acute Hospitals NHS Trust, Alexandra Hospital, Woodrow Drive, Redditch B98 7UB, United Kingdom.
- <sup>268</sup>Worcestershire Acute Hospitals NHS Trust, Kidderminster Hospital and Treatment Centre, Bewdley Road, Kidderminster DY11 6RJ, United Kingdom.

<sup>269</sup>Worcestershire Acute Hospitals NHS Trust, Worcestershire Royal Hospital, Charles Hastings Way, Worcester WR5 1DD, United Kingdom.

<sup>270</sup>Wrightington, Wigan and Leigh NHS Trust, Royal Albert Edward Infirmary, Wigan Lane, Wigan WN1 2NN, United Kingdom.

<sup>271</sup>Wye Valley NHS Trust, The County Hospital, Stonebow Road, Hereford HR1 2BN, United Kingdom.

<sup>272</sup>Yeovil District Hospital NHS Foundation Trust, Yeovil District Hospital, Higher Kingston, Yeovil BA21 4AT, United Kingdom.

<sup>273</sup>York Teaching Hospital NHS Foundation Trust, Bridlington Hospital, Bessingby Road, Bridlington YO16 4QP, United Kingdom.

<sup>274</sup>York Teaching Hospital NHS Foundation Trust, Scarborough Hospital, Woodlands Drive, Scarborough YO12 6QL, United Kingdom.

<sup>275</sup>York Teaching Hospital NHS Foundation Trust, The York Hospital, Wigginton Road, York YO31 8HE, United Kingdom.

<sup>276</sup>Great Western Hospitals NHS Foundation Trust, Marlborough Road, Swindon, Wiltshire SN3 6BB, United Kingdom.

<sup>277</sup>Abertawe Bro Morgannwg University Health Board, Morriston Hospital, Heol Maes Eglwys, Morriston, Swansea SA6 6NL, United Kingdom.

<sup>278</sup>Abertawe Bro Morgannwg University Health Board, Singleton Hospital, Sketty Lane, Sketty, Swansea SA2 8QA, United Kingdom.

<sup>279</sup>Abertawe Bro Morgannwg University Health Board, Neath Port Talbot Hospital, Baglan Way, Port Talbot SA12 7BX, United Kingdom.

<sup>280</sup>Abertawe Bro Morgannwg University Health Board, Princess of Wales Hospital, Coity Road, Bridgend CF31 1RQ, United Kingdom.

<sup>281</sup>Hywel Dda University Health Board, Prince Philip Hospital, Bryngwyn Mawr, Dafen, Llanelli SA14 8QF, United Kingdom.

<sup>282</sup>Hywel Dda University Health Board, Glangwili General Hospital, Dolgwilli Road, Carmarthen SA31 2AF, United Kingdom.

<sup>283</sup>Aintree University Hospitals NHS Foundation Trust, Aintree University Hospital, Longmoor Lane, Liverpool L9 7AL, United Kingdom.

<sup>284</sup>Airedale NHS Foundation Trust, Airedale General Hospital, Skipton Road, Steeton, Keighley BD20 6TD, United Kingdom.

<sup>285</sup>Aneurin Bevan University Health Board, Nevill Hall Hospital, Brecon Road, Abergavenny NP7 7EG, United Kingdom.

<sup>286</sup>Aneurin Bevan University Health Board, Royal Gwent Hospital, Cardiff Road, Newport NP20 2UB, United Kingdom.

<sup>287</sup>Aneurin Bevan University Health Board, Ysbyty Ystrad Fawr, Ystrad Fawr Way, Ystrad Mynach, Hengoed CF82 7EP, United Kingdom.

<sup>288</sup>Ashford & St Peter's Hospitals NHS Foundation Trust, Ashford Hospital, London Road, Ashford TW15 3AA, United Kingdom.

<sup>289</sup>Ashford & St Peter's Hospitals NHS Foundation Trust, St Peter's Hospital, Guildford Road, Chertsey KT16 0PZ, United Kingdom.

<sup>290</sup>Barnsley Hospital NHS Foundation Trust, Barnsley Hospital, Gawber Road, Barnsley S75 2EP, United Kingdom.

<sup>291</sup>Betsi Cadwaladr University Health Board, Glan Clwyd Hospital, Rhyl LL18 5UJ, United Kingdom.

<sup>292</sup>Betsi Cadwaladr University Health Board Ysbyty Gwynedd, Penrhosgarnedd, Bangor LL57 2PW, United Kingdom.

<sup>293</sup>Betsi Cadwaladr University Health Board, Llandudno General Hospital, Hospital Road, Llandudno LL30 1LB, United Kingdom.

<sup>294</sup>Betsi Cadwaladr University Health Board, Wrexham Maelor Hospital, Croesnewydd Road, Wrexham LL13 7TD, United Kingdom.

<sup>295</sup>Blackpool Teaching Hospitals NHS Foundation Trusts, Blackpool Victoria Hospital, Whinney Heys Road, Blackpool FY3 8NR, United Kingdom.

<sup>296</sup>Bolton NHS Foundation Trust, Royal Bolton Hospital, Minerva Road, Farnworth, Bolton BL4 0JR, United Kingdom.

<sup>297</sup>Bradford Teaching Hospitals NHS Foundation Trust, Bradford Royal Infirmary, Duckworth Lane, Bradford BD9 6RJ, United Kingdom.

<sup>298</sup>Buckinghamshire Healthcare NHS Trust, Amersham Hospital, Whielden Street, Amersham HP7 0JD, United Kingdom.

<sup>299</sup>Buckinghamshire Healthcare NHS Trust, Stoke Mandeville Hospital, Mandeville Road, Aylesbury HP21 8AL, United Kingdom.

<sup>300</sup>Buckinghamshire Healthcare NHS Trust, Wycombe Hospital, Queen Alexandra Road, High Wycombe HP11 2TT, United Kingdom.

<sup>301</sup>Burton Hospitals NHS Foundation Trust, Queen's Hospital, Belvedere Road, Burton upon Trent DE13 0RB, United Kingdom.

<sup>302</sup>Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge Biomedical Campus, Hills Road, Cambridge CB2 0QQ, United Kingdom.

<sup>303</sup>Cardiff and Vale University Health Board, University Hospital Llandough, Penlan Road, Llandough, Penarth CF64 2XX, United Kingdom.

<sup>304</sup>Cardiff and Vale University Health Board, University Hospital of Wales, Heath Park, Cardiff CF14 4XW, United Kingdom.

<sup>305</sup>Chelsea and Westminster Hospital NHS Foundation Trust, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, United Kingdom.

<sup>306</sup>Chesterfield Royal Hospital NHS Foundation Trust, Chesterfield Royal Hospital, Calow, Chesterfield S44 5BL, United Kingdom.

<sup>307</sup>City Hospitals Sunderland NHS Foundation Trust, Sunderland Royal Hospital, Kayll Road, Sunderland SR4 7TP, United Kingdom.

<sup>308</sup>Colchester Hospital University NHS Foundation Trust, Colchester General Hospital, Turner Road, Colchester CO4 5JL, United Kingdom.

- <sup>309</sup>Countess of Chester Hospital NHS Foundation Trust, Countess of Chester Hospital, Countess of Chester Health Park, Liverpool Road, Chester CH2 1UL, United Kingdom.
- <sup>310</sup>County Durham and Darlington NHS Foundation Trust, Darlington Memorial Hospital, Hollyhurst Road, Darlington DL3 6HX, United Kingdom.
- <sup>311</sup>County Durham and Darlington NHS Foundation Trust, University Hospital of North Durham, North Road, Durham DH1 5TW, United Kingdom.
- <sup>312</sup>Cwm Taf University Health Board, Prince Charles Hospital, Gurnos, Merthyr Tydfil CF479DT, United Kingdom.
- <sup>313</sup>Cwm Taf University Health Board, Royal Glamorgan Hospital, Ynysmaerdy, Llantrisant, Pontyclun CF72 8XR, United Kingdom.
- <sup>314</sup>Cwm Taf University Health Board, Ysbyty Cwm Cynon, New Road, Mountain Ash, Rhondda Cynon Taff CF45 4BZ, United Kingdom.
- <sup>315</sup>Dartford And Gravesham NHS Trust, Darent Valley Hospital, Darenth Wood Road, Dartford DA2 8DA, United Kingdom.
- <sup>316</sup>Derby Hospitals NHS Foundation Trust, Royal Derby Hospital, Uttoxeter Road, Derby DE22 3NE, United Kingdom.
- <sup>317</sup>Doncaster and Bassetlaw Hospitals NHS Foundation Trust, Bassetlaw Hospital, Blyth Road, Worksop S81 0BD, United Kingdom.
- <sup>318</sup>Doncaster and Bassetlaw Hospitals NHS Foundation Trust, Doncaster Royal Infirmary, Armthorpe Road, Doncaster DN2 5LT, United Kingdom.
- <sup>319</sup>Dorset County Hospitals NHS Foundation Trust, Dorset County Hospital, Williams Avenue, Dorchester DT1 2JY, United Kingdom.
- <sup>320</sup>East and North Hertfordshire NHS Trust, Lister Hospital, Coreys Mill Lane, Stevenage SG1 4AB, United Kingdom.
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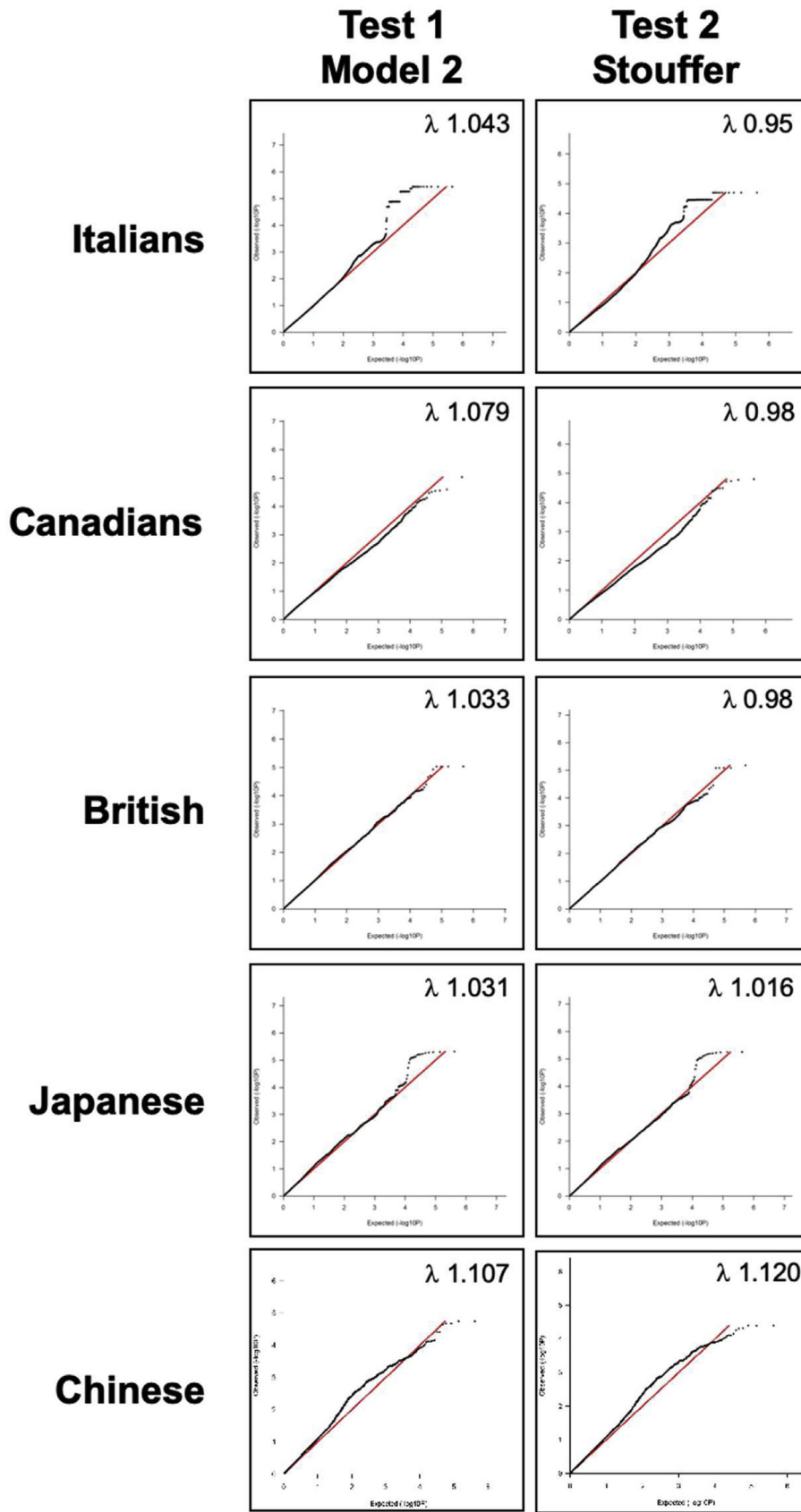
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### Supplementary References

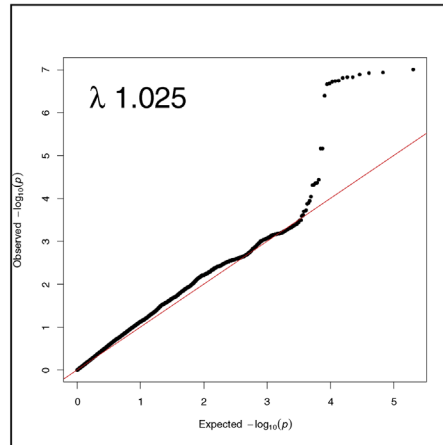
1. Cuellar-Partida G, Renteria ME, LocusTrack MacGregor S. integrated visualization of GWAS results and genomic annotation. *Source Code Biol Med* 2015;10:1.
2. Fishilevich S, Nudel R, Rappaport N, et al. GeneHancer: genome-wide integration of enhancers and target genes in GeneCards. Oxford: Database, 2017. 2017:bax028.
3. Wang Y, Song F, Zhang B, et al. The 3D Genome Browser: a web-based browser for visualizing 3D genome organization and long-range chromatin interactions. *Genome Biol* 2018;19:151.
4. Wang C, Hennessey JA, Kirkton RD, et al. Fibroblast growth factor homologous factor 13 regulates Na<sup>+</sup> channels and conduction velocity in murine hearts. *Circ Res* 2011;109:775–782.
5. Sakamoto T, Morishita A, Nomura T, et al. Identification of microRNA profiles associated with refractory primary biliary cirrhosis. *Mol Med Rep* 2016;14:3350–3356.
6. Hirschfield GM, Liu X, Xu C, et al. Primary biliary cirrhosis associated with *HLA*, *IL12A*, and *IL12RB2* variants. *N Engl J Med* 2009;360:2544–2555.
7. Liu X, Invernizzi P, Lu Y, et al. Genome-wide meta-analyses identify three loci associated with primary biliary cirrhosis. *Nat Genet* 2010;42:658–660.
8. Mells GF, Floyd JA, Morley KI, et al. Genome-wide association study identifies 12 new susceptibility loci for primary biliary cirrhosis. *Nat Genet* 2011;43:329–332.
9. Nakamura M, Nishida N, Kawashima M, et al. Genome-wide association study identifies *TNFSF15* and *POU2AF1* as susceptibility loci for primary biliary cirrhosis in the Japanese population. *Am J Hum Genet* 2012;91:721–728.
10. Kawashima M, Hitomi Y, Aiba Y, et al. Genome-wide association studies identify *PRKCB* as a novel genetic susceptibility locus for primary biliary cholangitis in the Japanese population. *Hum Mol Genet* 2017;26:650–659.
11. Qiu F, Tang R, Zuo X, et al. A genome-wide association study identifies six novel risk loci for primary biliary cholangitis. *Nat Commun* 2017;8:14828.



**Supplementary Figure 1.** QQ plots for single marker association tests of observed vs expected  $P$  values resulting from the application of the 2 association tests (model 2 and Stouffer tests; see “Materials and Methods” section) in the 5 analyzed cohorts.  $P$  values are reported as  $-\log_{10}$  transformed. The genomic inflation factor ( $\lambda$ ) is also shown.

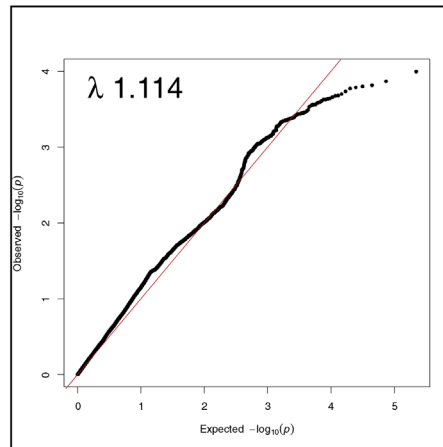
### Transethnic meta-analysis (Test 1, Model 2)

**All  
cohorts**

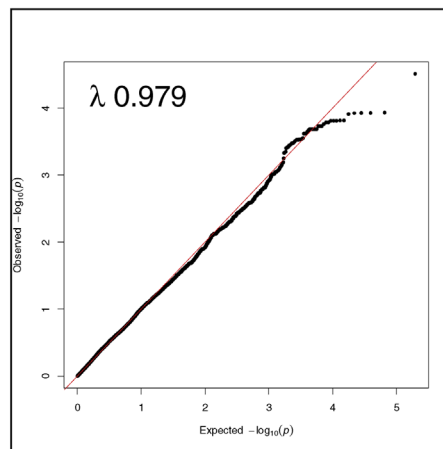


### Transethnic sex-stratified meta-analysis (Test 2, Stouffer)

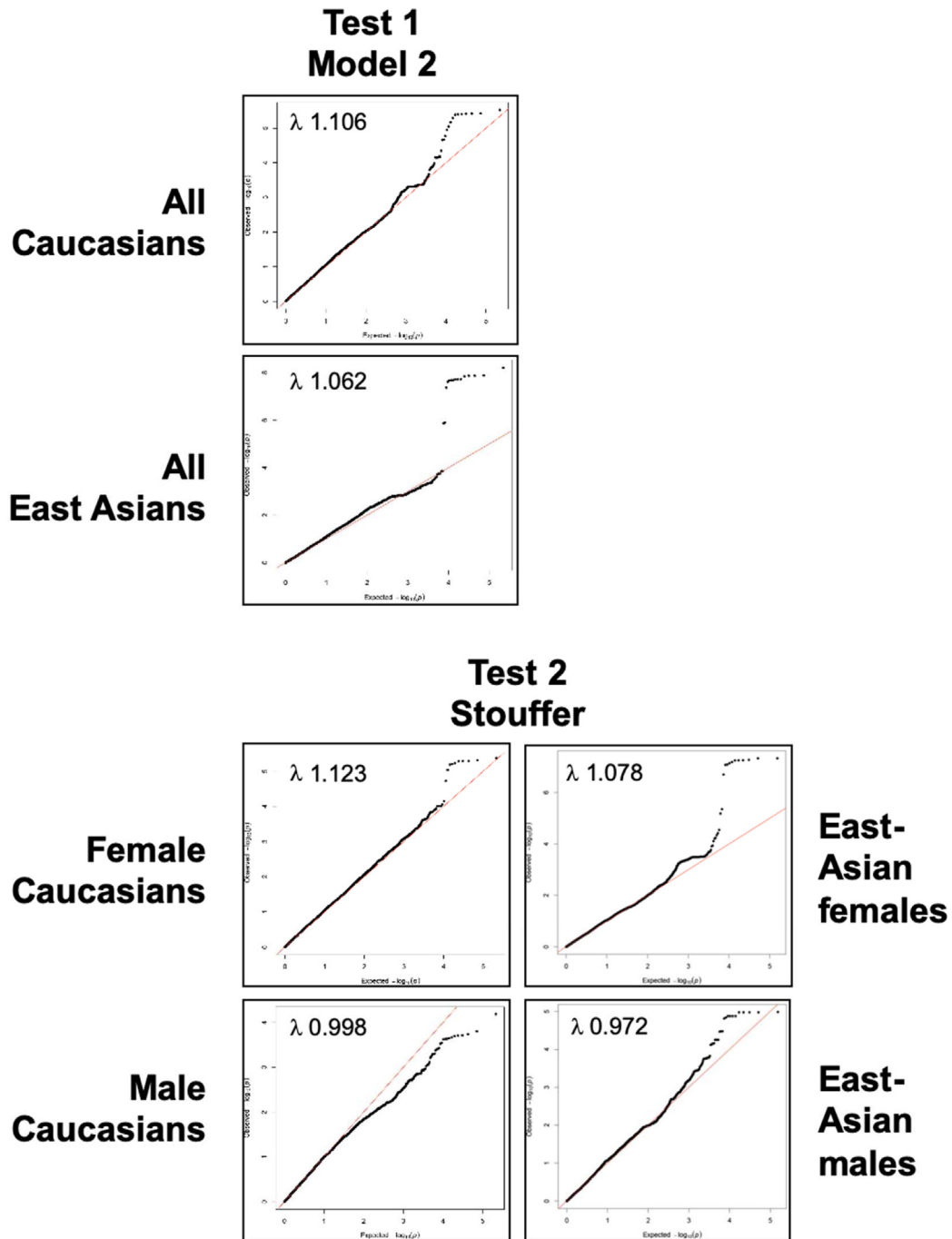
**Females  
All cohorts**



**Males  
All cohorts**



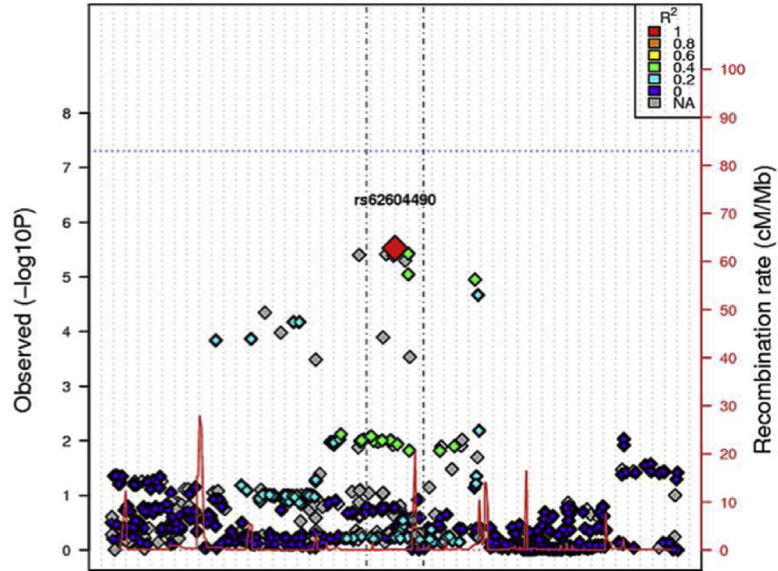
**Supplementary Figure 2.** Transethnic meta-analyses: QQ plots of the observed vs expected  $P$  values resulting from the application of the different meta-analyses (model 2 association analyses combined for all ethnicities; Stouffer analyses combined for females or males).  $P$  values are reported as  $-\log_{10}$  transformed. The genomic inflation factor ( $\lambda$ ) is also shown.



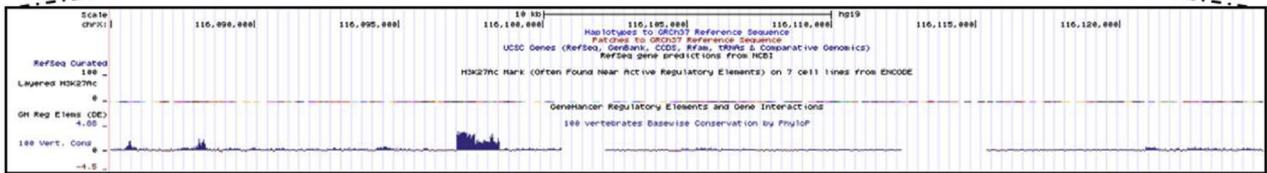
**Supplementary Figure 3.** Population-specific meta-analyses: QQ-plots of observed vs expected  $P$  values resulting from the application of the different meta-analyses (model 2 association analyses combined for White and East Asian individuals; Stouffer analyses combined for females or males, subdivided as Caucasian and East Asian).  $P$  values are reported as  $-\log_{10}$  transformed. The genomic inflation factor ( $\lambda$ ) is also shown.

**A**

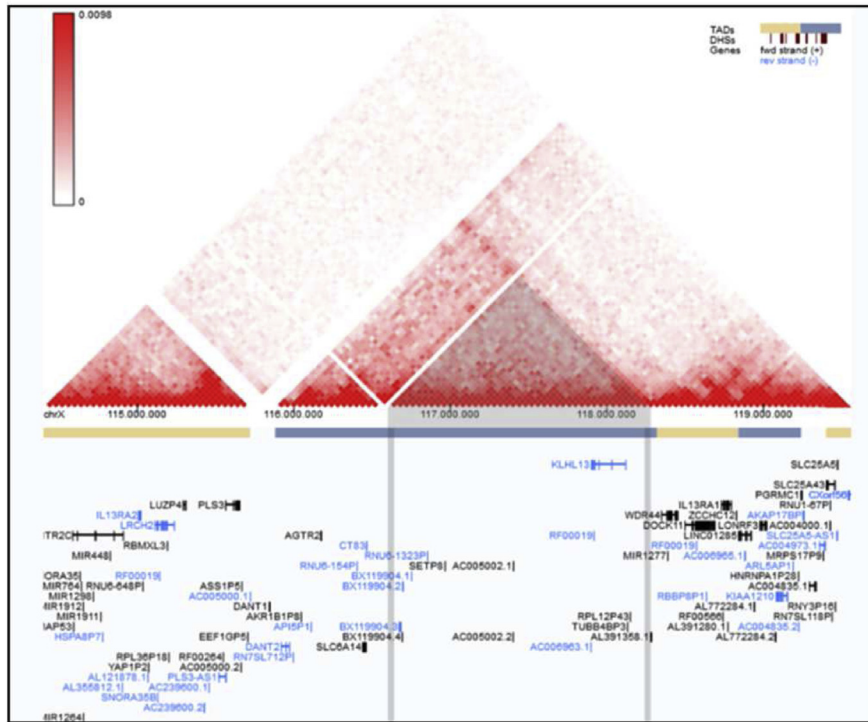
# All Caucasians rs62604490



**B**



**C**



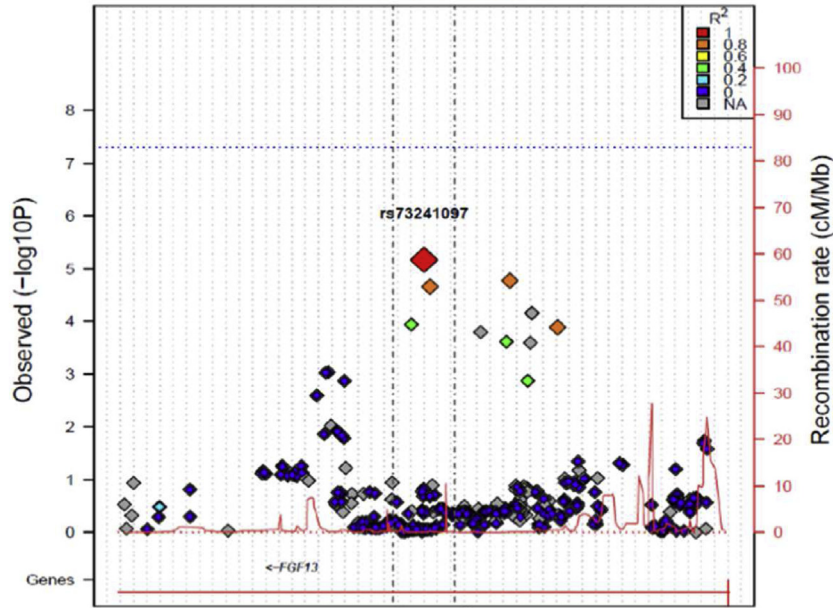
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**Supplementary Figure 4.** The intergenic locus rs62604490. (A) Plot of the regional association signals surrounding the rs62604490 top hit in White individuals. The plot was built using the LocusTrack web site (<https://gump.qimr.edu.au/general/gabrieC/LocusTrack>).<sup>1</sup> The locus does not present any particular feature. (B) Screenshot from the UCSC Genome browser (<http://genome.ucsc.edu/>; release February 2009, GRCh37/hg19) specifically highlighting the region surrounding the rs62604490 polymorphism (coordinates chrX: 116,085,000–116,125,000). Shown, in order, are the following tracks: (1) the ruler with the scale at the genomic level; (2) chrX nucleotide numbering; (3) the UCSC RefSeq track; (4) ENCODE data (<https://www.encodeproject.org/>) for the H3K4Me1, H3K4Me3, and H3K27Ac histone modifications marks, all derived from 7 cell lines; (5) the GeneHancer regulatory elements track<sup>2</sup>; and (6) the basewise conservation track. (C) TAD structure of the genomic region corresponding to coordinates chrX: 114,500,000–119,500,000. The central TAD contains the region tagged by rs62604490 and contains only a few noncoding genes (eg, the pseudogene *SETP8*) and the protein-coding *KLHL13* and *TUBB4BP3* genes. Image produced through the 3D Genome Browser (<http://3dgenome.org>),<sup>3</sup> using Hi-C data produced in HepG2 cells (hepatocytes) and generated by the Dekker Laboratory (at a resolution of 40 kb).

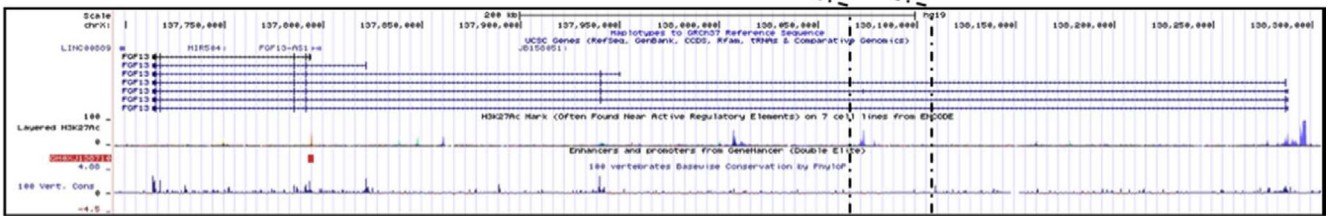


**A**

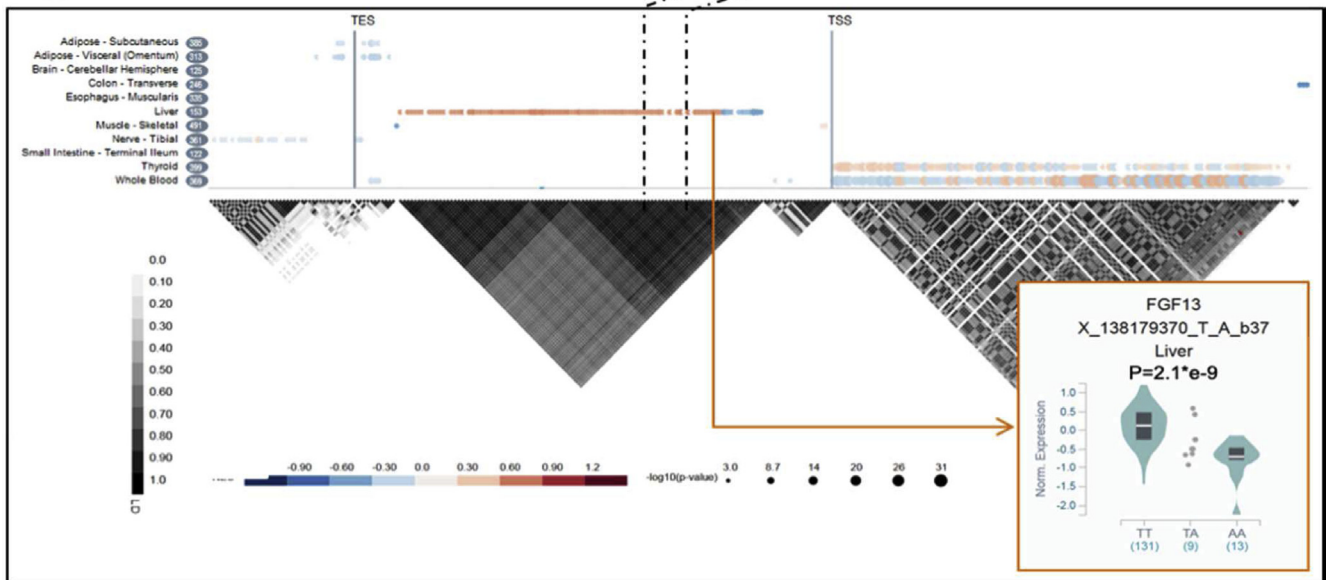
# All Caucasians rs73241097



**B**

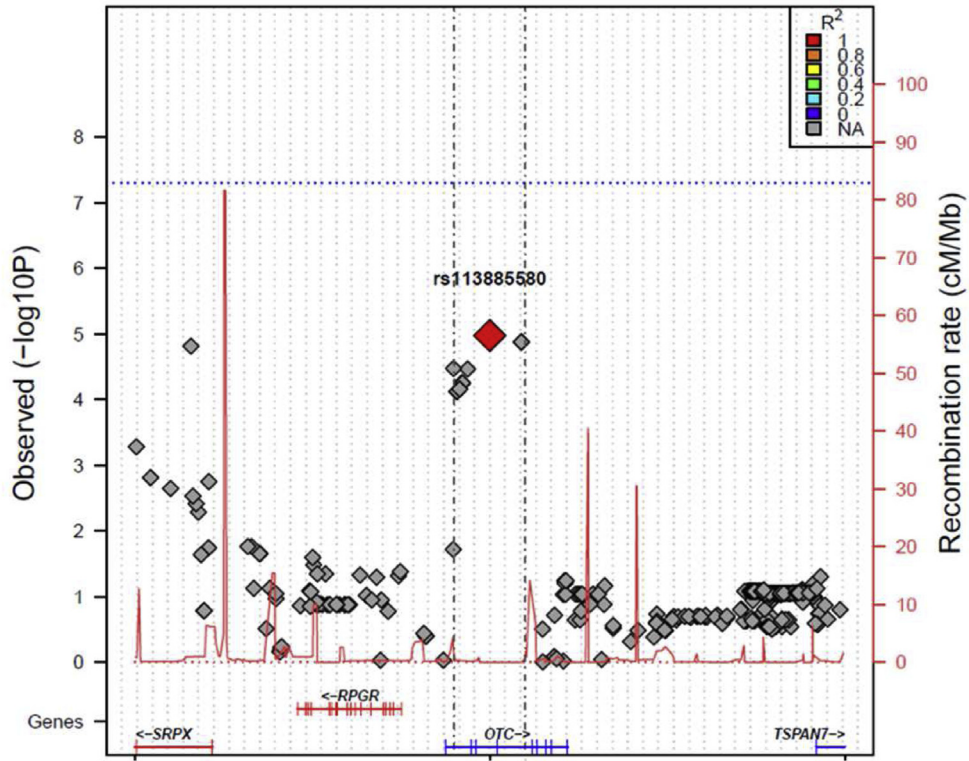


**C**

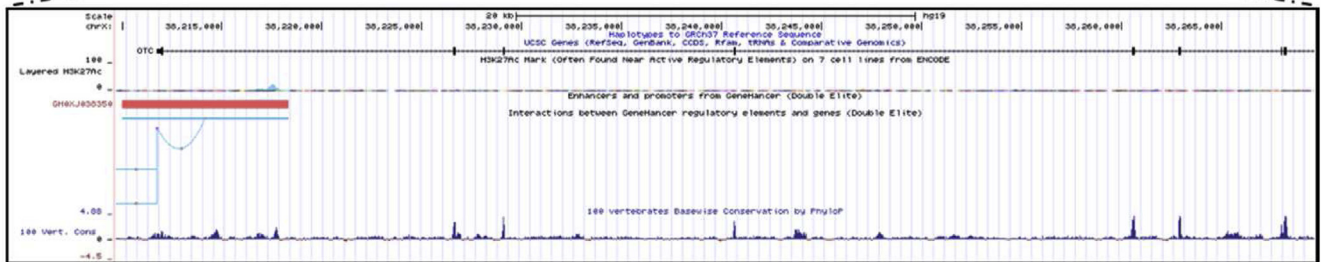


**Supplementary Figure 5.** The *FGF13* locus. The strongest intragenic signal evidenced by the meta-analysis in White individuals maps within the *FGF13* (fibroblast growth factor 13) gene.<sup>4</sup> This is a large gene (573 kb) characterized by the presence of 2 well-defined LD blocks. This locus also shows the presence of a micro-RNA (miR), hsa-miR-504, which is significantly up-regulated (1.35-fold increase) in the serum of patients with PBC.<sup>5</sup> The enhancer GH0XJ138710, located in *FGF13* intron 3, is described as targeting *FGF13* itself, its antisense transcript *FGF13-AS*, and the *MIR504* gene. (A) Plot of the regional association signals surrounding the rs73241097 top hit in White individuals. The plot was built using the LocusTrack website (<https://gump.qimr.edu.au/general/gabrieC/LocusTrack/>).<sup>1</sup> (B) Screenshot from the UCSC Genome browser (<http://genome.ucsc.edu/>; release February 2009, GRCh37/hg19) highlighting the entire *FGF13* gene (coordinates chrX: 137,710,000–138,300,000). The image shows, in order, the following tracks: (1) the ruler with the scale at the genomic level; (2) chrX nucleotide numbering; (3) the UCSC RefSeq track; (4) ENCODE data (<https://www.encodeproject.org/>) for the H3K4Me1, H3K4Me3, H3K27Ac histone modifications marks, derived from 7 cell lines; (5) enhancers (gray bars) and promoters (red bars) from GeneHancer<sup>2</sup>; the GH0XJ138710 element targets *FGF13-AS1*, *FGF13*, *MIR504*, *GC0XM138741*, and *GC0XP138598*; and (7) the basewise conservation track. (C) *FGF13* LD structure and position of significant expression quantitative trait loci (eQTLs). The panel was obtained through the GTEx portal (<https://gtexportal.org/home/>). TSS and TES indicate the transcriptional starting and ending points, respectively, for the *FGF13* gene, which is characterized by 2 LD blocks. Significant eQTLs are plotted (all showing  $-\log P$  value of  $\geq 5$ ). The vast majority of significant eQTLs were found in liver and whole blood; the most significant eQTL in liver corresponds to SNP rs58004267. (Inset) Violin plots for *FGF13* levels in the liver stratified according the rs58004267 genotypes (data based on 153 donors).

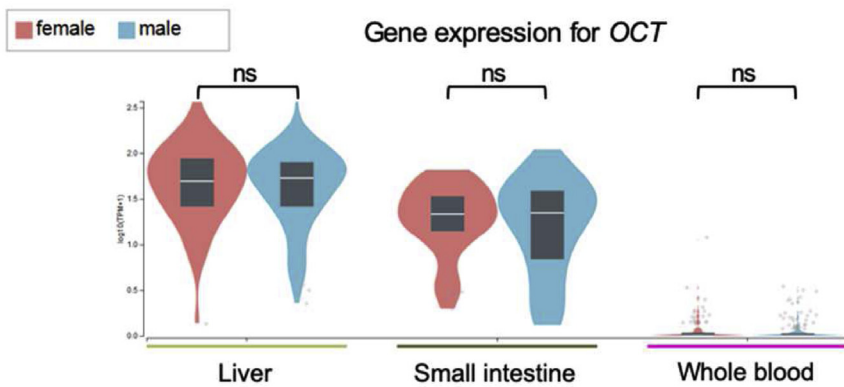
# A East-Asian males rs113885580



## B



## C



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**Supplementary Figure 6.** The *OTC* locus. (A) Plot of the regional association signals surrounding the rs113885580 top hit in East Asian males. The plot was built using the LocusTrack website (<https://gump.qimr.edu.au/general/gabrieC/LocusTrack/>).<sup>1</sup> The rs113885580 polymorphism maps within intron 3 of the *OTC* gene, which codes for the ornithine carbamoyltransferase mitochondrial matrix enzyme. Mutations in this gene are known to cause OTC enzyme deficiency, leading to hyperammonemia (Online Mendelian Inheritance in Man no. 311250). (B) Screenshot from the UCSC Genome browser (<http://genome.ucsc.edu/>; release February 2009, GRCh37/hg19) specifically highlighting the *OTC* region (coordinates chrX: 38,210,000–38,270,000). The panel shows, in order, the following tracks: (1) the ruler with the scale at the genomic level; (2) chrX nucleotide numbering; (3) the UCSC RefSeq track; (4) ENCODE data (<https://www.encodeproject.org/>) for the H3K4Me1, H3K4Me3, H3K27Ac histone modifications marks, all derived from 7 cell lines; (5) promoters (red bar) from GeneHancer<sup>2</sup>; the GH0XJ038350 regulatory element targets the *OTC*, *RPGR*, *SRPX*, and *TDGF1P1* genes; (6) interactions connecting GeneHancer regulatory elements and genes; and (7) the basewise conservation track. (C) Violin plots show *OTC* RNA expression levels in liver, small intestine (the only tissues in which *OTC* is expressed), and whole blood (for comparison), obtained through the GTEx portal (<https://gtexportal.org/home/>). Data are stratified according to gender.

**Supplementary Table 1.** Characteristics of the Analyzed Cohorts and SNP Data

Cohort	Case Patients, <sup>a</sup> n	Control Individuals, <sup>a</sup> n	Female Case Patients, n (%)	Control Females, n (%)	Genotyping Platform	SNPs After Imputation and QC, n	Reference
Canadian	503	1503	470 (93.4)	799 (53.2)	Illumina HumanHap370 BeadChip	219,134	Hirschfield et al <sup>6</sup>
Italian	446	928	412 (92.4)	446 (41.4)	Illumina 610K array or 1Mb array	219,677	Liu et al <sup>7</sup>
British	1816	5161	1663 (91.6)	2552 (49.4)	Illumina 660W-Quad array or Human1M-Duo	240,385	Mells et al <sup>8</sup>
Japanese	1361	1495	1196 (87.9)	840 (56.2)	Affymetrix Axiom Genome-wide ASI 1 array	208,364	Nakamura et al <sup>9</sup> and Kawashima et al <sup>10</sup>
Chinese	1118	2788	974 (87.1)	2113 (75.8)	Illumina HumanOmniZhongHua-8	207,728	Qiu et al <sup>11</sup>
Total	5244	11,875	4715 (89.9)	6750 (56.8)	—	—	—

<sup>a</sup>After QC filtering.**Supplementary Table 2.** Best Association Signals ( $P < .0005$ ) in the XWAS Model 2 Association Analysis (Test 1)

Cohort	SNP	ChrX Position <sup>a</sup>	Variant	MAF		Model 2 Analysis		
				Case Patients	Control Individuals	OR (95% CI)	$P$	Gene(s)
Canada	rs183870982	69129411	G>A	0.01791	0.006165	3.537 (1.092–11.46)	9.18e–06	<i>EDA</i>
	rs2285577	9558968	G>A	0.3467	0.2856	1.409 (1.016–1.955)	2.52e–05	<i>TBL1X</i>
	rs112801406	71510071	C>G	0.01927	0.007293	3.134 (1.050–9.354)	2.77e–05	<i>PIN4, ERCC6L</i>
Italy	rs73556360	126797765	A>T	0.02342	0.006569	4.045 (1.133–14.44)	3.60e–06	Desert
	rs73549132	126495213	A>G	0.02113	0.005831	3.88 (1.071–14.056)	2.02e–05	Desert
	rs10126824	152108084	C>T	0.1054	0.06984	1.781 (1.014–3.128)	5.50e–05	<i>ZNF185</i>
UK	rs192961663	38579456	G>T	0.01158	0.006772	2.192 (1.056–4.551)	9.21e–06	<i>TSPAN7</i>
	rs79313454	22920071	A>C	0.04318	0.02669	1.549 (1.023–1.955)	1.95e–05	<i>LOC100873065</i>
	rs71777981	30558898	TAA>T	0.292	0.3322	0.8369 (0.7031–0.9962)	6.05e–05	Desert
Japan	rs3027490	48799318	C>T	0.1677	0.1224	1.39 (1.028–1.88)	4.80e–06	<i>OTUD5</i>
	rs199498815	7461987	GT>G	0.043	0.06499	0.603 (0.367–0.99)	6.44e–05	Desert
	rs11092966	86811338	C>T	0.3031	0.2598	1.26 (1.004–1.581)	6.56e–05	<i>KLHL4</i>
China	rs141281542	80999222	G>A	0.181	0.146	1.31 (1.16–1.488)	1.75e–05	Desert
	rs376902940	100749576	G>T	0.013	0.004	2.856 (1.76–4.64)	2.25e–05	<i>ARMCX4</i>
	rs184774753	100593280	C>G	0.012	0.004	2.78 (1.71–4.53)	3.84e–05	<i>TAF7L, NANOGNBP3, RPL21P132, TIMM8A, BTK, Y-RNA, RNU6-934P</i>

NOTE. ORs and CIs refer to the model 2 association analysis. SNPs are defined as intragenic (in yellow), in proximity to genes (within a range of  $\pm 50$  kb), or mapping within a gene desert (no genes in a range of  $\pm 50$  kb).<sup>a</sup>According to human genome release February 2009, GRCh37/hg19.

**Supplementary Table 3.** Best Association Signals ( $P < .0005$ ) in the XWAS Stouffer Association Analysis (Test 2)

Cohort	SNP	ChrX Position <sup>a</sup>	Variant	MAF, Males		MAF, Females		Stouffer Analysis		$P_{meta}$ (Stouffer)	Gene(s)
				Case Patients	Control Individuals	Case Patients	Control Individuals	OR males/OR females	$P_{males}/P_{females}$		
Canada	rs2285577	9558968	G>A	0.4848	0.3114	0.3408	0.2741	2.36/1.397	.018/.00028	1.56e-05	TBL1X
	rs183870982	69129411	G>A	0.1212	0.008584	0.01419	0.005089	14.1/2.599	.000118/.03889	7.00e-05	EDA
Italy	rs112801406	71510071	C>G	0.09375	0.01297	0.01663	0.004667	8.692/3.548	.002558/.006972	7.06e-05	PIN4, ERCC6L
	rs56661704	126831980	G>A	0.1316	0.006198	0.01838	0.006772	24.29/2.78	2.22e-05/.0362	2.01e-05	Desert
	rs73549132	126495213	A>G	0.1053	0.006198	0.0172	0.005631	18.86/3.128	.0001797/.03004	5.89e-05	Desert
UK	rs10126824	152108084	C>T	0.2162	0.09302	0.10	0.05663	2.69/1.914	.02127/.001067	6.44e-05	ZNF785
	rs150995504	38641373	T>A	0.0719	0.009988	0.01422	0.01045	7.303/1.367	1.46e-07/0.1228	6.58e-06	TSPAN7
	rs79313454	22920071	A>C	0.05263	0.0259	0.04274	0.02709	2.034/1.597	.06673/.0001498	4.12e-05	LOC100873065
Japan	rs2867192	30544859	A>G	0.2039	0.2863	0.2491	0.2814	0.626/0.8446	.02407/.001013	7.07e-05	Desert
	rs3027490	48799318	C>T	0.1878	0.1337	0.1661	0.1178	1.534/1.496	.06104/2.73e-05	5.66e-06	OTUD5
	rs11092966	86811338	C>T	0.3812	0.2685	0.2968	0.2563	1.767/1.23	.001778/.005776	5.92e-05	KLHL4
China	rs199498815	7461987	GT>G	0.01695	0.05945	0.04502	0.06725	0.266/0.6272	.02961/.001182	9.44e-05	Desert
	rs376902940	100749576	G>T	0.035	0.004	0.011	0.004	7.998/2.879	.004742/.001551	4.01e-05	ARMCX4
	rs141281542	80999222	G>A	0.280	0.154	0.173	0.145	2.138/1.244	4.20e-04/0.005102	4.05e-05	Desert
	rs139439999	55471232	A>C	0.101	0.061	0.063	0.040	1.727/1.593	.09336/2.44e-04	5.60e-05	MAGEH1, USP51, hsa-mir-4536-2

NOTE. ORs and confidence intervals CIs refer to the Stouffer association analysis. SNPs are defined as intragenic (in yellow), in proximity to genes (within a range of ±50 kb), or mapping within a gene desert (no genes in a range of ±50 kb).  
<sup>a</sup>According to human genome release February 2009, GRCh37/hg19.

**Supplementary Table 5.** Characteristics of the Top-Hit rs7059064 Polymorphism

Polymorphism	Database	Frequency of the G Allele (Number of Alleles)	URL
rs7059064	TOPMED	0.279 (125568)	<a href="https://www.nhlbiwgs.org/">https://www.nhlbiwgs.org/</a>
	GnomAD	0.259 (20380)	<a href="https://gnomad.broadinstitute.org/">https://gnomad.broadinstitute.org/</a>
	European (Finnish)	0.0994 (2486)	
	East Asian	0.125 (911)	
	European (non-Finnish)	0.128 (9970)	
	Other	0.160 (752)	
	Ashkenazi Jewish	0.160 (162)	
	Latino	0.175 (600)	
	African	0.615 (5499)	
	1000Genomes	0.327 (3775)	<a href="https://www.internationalgenome.org/">https://www.internationalgenome.org/</a>
	TwinsUK	0.115 (3708)	<a href="https://twinsuk.ac.uk/">https://twinsuk.ac.uk/</a>
	ALSPAC	0.123 (2889)	<a href="http://www.bristol.ac.uk/alspac/">http://www.bristol.ac.uk/alspac/</a>
	Vietnamese Genomes	0.100 (48)	<a href="https://genomes.vn/">https://genomes.vn/</a>

NOTE. Shown are the frequencies of the rs7059064 polymorphism across different populations, as retrieved from different publicly available databases. Data were accessed through the dbSNP database on September 13, 2019 ([https://www.ncbi.nlm.nih.gov/snp/rs7059064#seq\\_hash](https://www.ncbi.nlm.nih.gov/snp/rs7059064#seq_hash)). Alleles were sequenced in the vast majority of cases by next-generation whole-genome sequencing. (The rs7059064 polymorphism maps within intron 21 of the *GRIPAP1* gene.)

**Supplementary Table 6.** Association Data for 2 SNPs Mapping Within the GH0XJ048933 Superenhancer in Perfect LD With the rs7059064 Polymorphism (Chinese and Japanese Populations)

SNP	Position <sup>a</sup>	$r^2$ Value (Referred to rs7059064)	$P_{\text{Japanese}}$	$P_{\text{Chinese}}$
rs201894148	48791182	1	5.25e-06	.000514
rs3027490	48799318	1	4.80e-06	.000833

<sup>a</sup>According to human genome release February 2009, GRCh37/hg19.