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ABCB1/4 gallbladder cancer risk variants identified in India also show strong effects in Chileans

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Abbreviations: CI, 95 % confidence interval; GBC, gallbladder cancer; LD, linkage disequilibrium; OR, per-allele odds ratio; RAF, risk allele frequency; SNP, single nucleotide polymorphisms

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ABSTRACT

Background: The first large-scale genome-wide association study of gallbladder cancer (GBC) recently identified and validated three susceptibility variants in the *ABCB1* and *ABCB4* genes for individuals of Indian descent. We investigated whether these variants were also associated with GBC risk in Chileans, who show the highest incidence of GBC worldwide, and in Europeans with a low GBC incidence.
Methods: This population-based study analysed genotype data from retrospective Chilean case-control (255 cases, 2042 controls) and prospective European cohort (108 cases, 181 controls) samples consistently with the original publication.
Results: Our results confirmed the reported associations for Chileans with similar risk effects. Particularly strong associations (per-allele odds ratios close to 2) were observed for Chileans with high Native American (=Mapuche) ancestry. No associations were noticed for Europeans, but the statistical power was low.
Conclusion: Taking full advantage of genetic and ethnic differences in GBC risk may improve the efficiency of current prevention programs.

1. Introduction

Each year, gallbladder cancer (GBC; ICD-10 diagnosis code C23) kills more than 70,000 people worldwide (globocan.iarc.fr). Most GBC diagnoses occur in low- and middle-income countries, and research into this aggressive disease has been largely neglected. In some areas of high GBC incidence, prophylactic cholecystectomy is offered to gallstone patients to prevent GBC [1]. Accurate predictions of an individual's GBC risk would permit personalized indications for elective cholecystectomy.

Mhatre et al. recently identified and validated three GBC susceptibility variants in the *ABCB1* and *ABCB4* genes in a genome-wide association study of the northern Indian population [2]. GBC shows considerable differences in incidence by geography and ethnicity: it represents the second most common cause of cancer-related death among Chilean women, but is relatively rare among Europeans. We set out to investigate the association between the three newly identified variants and GBC risk in Chileans and Europeans.

The genome of modern Chileans is a genetic admixture between Europeans, Africans, and Native Americans from two major indigenous peoples: ancestral groups from southern Chile (e.g. Mapuche) and Andean populations from the north (e.g. Aymara and Quechua). We previously showed that each increase of 1 % in the proportion of Mapuche ancestry translates into a 3.7 % increase in the GBC mortality risk for Chileans [3].

2. Material and methods

The present multicentre, population-based, candidate variant association study included 255 GBC cases and 2042 controls from a Chilean retrospective study, and 108 GBC cases and 181 controls from a consortium of large European prospective cohorts. The genetic structure of the investigated Chilean controls has been previously investigated by Lorenzo Bermejo et al. [3] We analysed our data as consistently as possible with the original publication by Mhatre et al. [2] Logistic regression was applied to assess the association between GBC and the three candidate variants. The models considered the GBC case–control status as response variable, the count of high-risk alleles as main explanatory variable, and the covariates age in intervals (<20 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years and >60 years), sex, and five principal components to adjust for population stratification (see Supplementary Material for details on the principal component analysis). Probability values were calculated from a trend score test with one degree of freedom on the high-risk allele counts.

In addition to overall analyses, calculations for Chileans were stratified by the quarters of estimated Mapuche proportions. For each stratum, the genetic principal components were recalculated and the associations between the three variants and GBC risk was separately tested as indicated above. In order to test the interaction between the three variants and Mapuche ancestry on GBC risk, the null model (H0) considered the count of high-risk alleles, age in intervals, sex and individual continuous Mapuche proportions. The alternative model (H1) additionally included an interaction term between Mapuche proportions and high-risk allele counts for each susceptibility variant. A likelihood ratio test was used to determine whether the interaction term in H1 resulted in a statistically significant fit improvement compared with H0.

The variance in GBC liability explained by the investigated single nucleotide polymorphisms (SNP) was calculated based on a liability threshold model [4]. Calculations relied on the estimated risk allele frequencies and per-allele odds ratios, together with the lifetime risk of GBC in Chile (0.017, globocan.iarc.fr). We refer to the Supplementary Material for additional details on the study design, ethics committee approval, genotyping, data quality control, data preparation and sensitivity analyses (Supplementary Material).

3. Results

The Figure shows principal component analyses results from Chilean and European genotype data (Fig. 1). For Chileans, the first

[1] These authors contributed equally to this work.

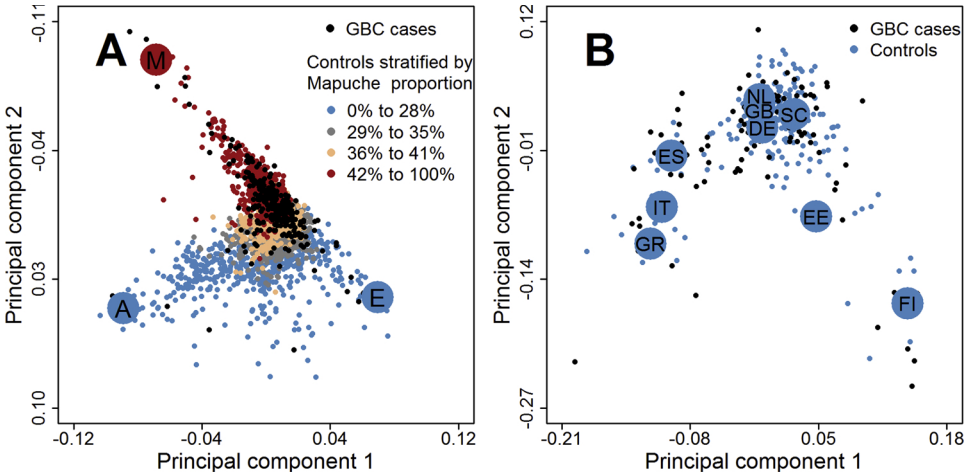

Fig. 1. The first two principal components from a principal component analysis of Chilean (A) and European (B) genome-wide genotype data.
Small dots represent individuals. Chilean controls are coloured according to the estimated proportions of Mapuche ancestry. Large dots in Panel A represent the medians of the first two eigenvalues for individuals with at least 90 % Mapuche (M), Aymara (A), and European (E) ancestry. In Panel B, large dots represent the medians for each country: DE, Germany; EE, Estonia; ES, Spain; FI, Finland; GB, Great Britain; GR, Greece; IT, Italy; NL, Netherlands; SC, Scandinavian countries (Denmark, Norway, Sweden).

principal component separated European and Native American ancestry, while the second principal component distinguished between Mapuche and Aymara ancestry. The association between GBC risk and large proportions of Mapuche ancestry was striking. For Europeans, the first principal component reflected the north–south geographic axis and the second principal component reflected the east–west axis.

The majority of the Chilean cases were women (76 %) and in average 32 years younger than the predominantly male (59 %) Chilean controls (Table 1). Estimated adjusted per-allele odds ratios (OR) and risk allele frequencies (RAFs) for Chileans were similar to the reported Indian estimates: OR = 1.38 and RAF = 0.79 for rs1558375, OR = 1.43 and RAF = 0.82 for rs4148808, and OR = 1.47 and RAF = 0.82 for rs17209837 (Table 2). Chilean women showed higher per-allele ORs than Chilean men (OR = 1.53 for rs1558375, OR = 1.47 for rs4148808 and OR = 1.53 for rs17209837), but gender-differences did not reach statistical significance (overlapping 95 % confidence intervals). Stratified analyses by the quarters of Mapuche proportions revealed particularly strong associations (OR 1.70 or higher) for Chileans with over

Table 1
Demographic characteristics of the Chilean and European study populations.

Chileans	Cases (n = 255)	Controls (n = 2042)
Gender: males (%) / females (%)	61 (24 %) / 194 (76 %)	1202 (59 %) / 840 (41 %)
Age (years): median / 5 % quantile / 95 % quantile	61 / 38 / 78	29 / 21 / 70
Mapuche proportion (%): median / 5 % quantile / 95 % quantile	41 / 22 / 66	36 / 15 / 52
European proportion (%): median / 5 % quantile / 95 % quantile	49 / 20 / 64	49 / 24 / 64
Chileans (43%–100% Mapuche proportion)	**(n = 111)**	**(n = 478)**
Gender: males (%) / females (%)	27 (24 %) / 84 (76 %)	351 (73 %) / 127 (27 %)
Age (years): median / 5 % quantile / 95 % quantile	60 / 35 / 79	30 / 22 / 73
Mapuche proportion (%): median / 5 % quantile / 95 % quantile	48 / 42 / 93	46 / 42 / 67
European proportion (%): median / 5 % quantile / 95 % quantile	44 / 0 / 53	46 / 26 / 52
Chileans (36%–42% Mapuche proportion)	**(n = 63)**	**(n = 554)**
Gender: males (%) / females (%)	17 (27 %) / 46 (73 %)	343 (62 %) / 211 (38 %)
Age (years): median / 5 % quantile / 95 % quantile	61 / 38 / 74	30 / 22 / 72
Mapuche proportion (%): median / 5 % quantile / 95 % quantile	40 / 36 / 42	39 / 36 / 42
European (%): median / 5 % quantile / 95 % quantile	51 / 41 / 57	51 / 39 / 58
Chileans (29%–35% Mapuche proportion)	**(n = 54)**	**(n = 451)**
Gender: males (%) / females (%)	9 (17 %) / 45 (83 %)	256 (57 %) / 195 (43 %)
Age (years): median / 5 % quantile / 95 % quantile	60 / 38 / 76	28 / 21 / 70
Mapuche proportion (%): median / 5 % quantile / 95 % quantile	34 / 30 / 36	33 / 30 / 36
European proportion (%): median / 5 % quantile / 95 % quantile	56 / 37 / 63	53 / 38 / 63
Chileans (0%–28% Mapuche proportion)	**(n = 27)**	**(n = 559)**
Gender: males (%) / females (%)	8 (30 %) / 19 (70 %)	252 (45 %) / 307 (55 %)
Age (years): median / 5 % quantile / 95 % quantile	65 / 42 / 78	26 / 20 / 56
Mapuche proportion (%): median / 5 % quantile / 95 % quantile	24 / 0 / 28	22 / 05 / 29
European proportion (%): median / 5 % quantile / 95 % quantile	63 / 0 / 87	46 / 14 / 78
Europeans	**(n = 108)**	**(n = 181)**
Gender: males (%) / females (%)	22 (20 %) / 86 (80 %)	64 (35 %) / 117 (65 %)
Age (years): median / 5 % quantile / 95 % quantile	69 / 54 / 82	70 / 55 / 82

Table 2
Association results for the three recently identified common GBC risk variants in Chileans[†] and Europeans.

Population	Mapuche proportion	Locus	SNP ID	Cases	Controls	RAF	OR[‡]	95 %	CI	Trend p-value
Chileans	0%–100%	*ABCB4*	rs1558375	255	2042	0.79	**1.38**	1.05	1.83	0.02
		ABCB4	rs4148808			0.82	**1.43**	1.07	1.92	0.02
		ABCB1	rs17209837			0.82	**1.47**	1.09	1.97	0.01
Chileans	42%–100%	*ABCB4*	rs1558375	111	478	0.76	**1.70**	1.08	2.66	0.02
		ABCB4	rs4148808			0.78	**1.95**	1.21	3.13	0.006
		ABCB1	rs17209837			0.78	**1.95**	1.21	3.13	0.006
Chileans	36%–41%	*ABCB4*	rs1558375	63	554	0.80	1.59	0.92	2.74	0.10
		ABCB4	rs4148808			0.83	1.47	0.83	2.59	0.18
		ABCB1	rs17209837			0.84	1.41	0.78	2.53	0.26
Chileans	29%–35%	*ABCB4*	rs1558375	54	451	0.80	1.00	0.52	1.92	0.99
		ABCB4	rs4148808			0.84	0.99	0.51	1.92	0.99
		ABCB1	rs17209837			0.84	1.00	0.52	1.94	0.99
Chileans	0%–28%	*ABCB4*	rs1558375	27	559	0.78	0.85	0.33	2.19	0.73
		ABCB4	rs4148808			0.84	0.82	0.29	2.31	0.71
		ABCB1	rs17209837			0.84	1.04	0.37	2.89	0.95
Europeans	–	*ABCB4*	rs1558375	108	181	0.84	1.06	0.65	1.74	0.80
		ABCB4	rs4148808			0.87	1.32	0.78	2.24	0.31
		ABCB1	rs17209837			0.86	1.27	0.74	2.16	0.39

SNP = Single nucleotide polymorphism, ID = identification, RAF = risk allele frequency (risk allele = Adenin), OR = per-allele odds ratio adjusted for age, sex and first five principal components, CI = confidence interval.

[†] Chilean analyses are also stratified by the estimated proportion of Mapuche ancestry, with each group containing one quarter of the Chilean individuals.

[‡] Per-allele odds ratios adjusted for age, sex and the first five genetic principal components. Bold type denotes associated 95 % confidence intervals that do not include 1.

42 % Mapuche ancestry. By contrast, no association was noticed for Chileans with less than 35 % Mapuche ancestry. The effect on GBC risk of interactions between continuous Mapuche proportions and the variants rs1558375 and rs4148808 attained statistical significance (p-values from likelihood ratio tests equal to 0.02 and 0.04, respectively). We did not find genetic associations for Europeans, but the statistical power was only 34 % (RAF = 0.80, reported per-allele OR in India, $\alpha = 0.05$, trend test) [5]. The UK Biobank includes 22 additional GBC cases among 337,000 unrelated individuals of British ancestry (ukbiobank.ac.uk), but combination of the available summary statistics had practically no effect on the results (**Supporting Table S1**).

4. Discussion

In their genome-wide association study, Mhatre et al. investigated GBC cases and controls recruited in the north and northeast of India, where the incidence of GBC is 2–8 times higher than in other parts of the country. The validation of the three strong GBC risk associations in Chile, the country with the highest incidence of GBC worldwide, a different genetic background and much higher rates of gallstone disease (86 % for the Chilean compared with 33 % for the Indian GBC patients) is non-trivial. By way of illustration, assuming that heritability of GBC accounts for 23 % of the risk, the variance in GBC liability explained by the variant rs4148808 in Chileans was 0.4–1.6 %. The present study also suggests that individual proportions of Mapuche ancestry modulate the risk effects conferred by the three GBC susceptibility variants. No genetic association was found in the European cohort, probably due to the low statistical power, but the estimated ORs for Europeans and also the decrease in association effect sizes with increasing proportions of European ancestry suggest weaker effects, if any, of the identified GBC risk variants in individuals of European descent. It is important to consider that GBC is a rare disease in most European countries. To put numbers into context, the present results for Europeans rely on 108 GBC cases in comparison with the 22 cases of white British ancestry among the 500,000 participants in the UK Biobank. Although the statistical power for Europeans was small, we consider that the present findings may motivate collaborative research to raise the available sample sizes.

The function of the *ABCB4* gene is to translocate phosphatidylcholine (PC) from the inner to the outer leaflet of the canalicular membrane of the hepatocyte [6]. The resulting phospholipids become available for excretion into bile, where they form – together with bile salts and ABCG5/G8 driven cholesterols – mixed micelles. Individuals with an *ABCB4* deficiency suffer severe liver diseases like progressive familial intrahepatic cholestasis type 3 and knockout of the *ABCB4* gene in mice results in hepatic inflammation [7,8]. The *ABCB4* gene has also been linked to gallstone disease [9]. When too little PC is translocated the solubility of cholesterol in mixed micelles is reduced. Cholesterol-enriched micelles may cause precipitation of cholesterol crystals that subsequently build gallstones [10]. Accordingly, two *ABCB4* mutations were found to be significantly associated with gallstones in Icelandic patients, indicating a potential mechanistic link between gallstone disease and GBC risk. The *ABCB1* gene is an efficient ATP-dependent efflux pump regulating the metabolism of anticancer drugs and other xenobiotics [11]. Some studies detected associations between *ABCB1* polymorphisms and blood lipids, but a meta-analysis evaluating potential determinants for gallstone formation found no significant association between blood lipids and incident gallstones [12–14].

In order to reduce the incidence of GBC, the Chilean government financially supports prophylactic cholecystectomy for gallstone patients aged between 35 and 49 years [15]. Persons with “at least one Mapuche surname” are considered at high risk of GBC. In the present investigation, individual proportions of Mapuche ancestry were estimated relying on genome-wide genotype data, which provide more accurate quantifications of ethnicity than family names. For example, the Mapuche proportions of investigated Chileans without Mapuche surnames

varied from 0 % to 100 %. The ability to predict individual GBC risk accurately would eventually translate into a reduction in the number of unnecessary cholecystectomies while simultaneously forecasting GBC development with high sensitivity.

Unravelling the links between genetic ancestry and GBC development, together with taking full advantage of the identified risk differences by type and magnitude of Native American ancestry, may improve the efficiency of current GBC prevention policies. In contrast to other hepatobiliary cancers, cholecystectomy can be offered to persons at high risk of GBC. Low- and middle-income countries with high GBC incidences and limited financial and health resources would particularly benefit from accurate GBC risk prediction based on established risk factors (gallstones, overweight, ethnicity) and newly identified risk biomarkers.

Contributions of the authors

Boekstegers and Marcelain contributed equally to this work and are co-lead authors. Rothhammer and Lorenzo Bermejo contributed equally to this work and are co-senior authors. Boekstegers and Lorenzo Bermejo had full access to all the data in the manuscript and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Boekstegers, Lorenzo Bermejo

Data acquisition: Lorenzo Bermejo, Marcelain, Baez Benavides, Barahona Ponce, Ahumada, Müller, Retamales, Fuentes Guajardo, Barajas, Bertrán, Morales, Rojas, Sanhueza, Loader, de Toro, Rivera, Gutiérrez, Bernal, Ortega, Montalvo, Portiño, Gabler, Spencer, Gonzalez-Jose, Bedoya, Bortolini, Canizales, Gallo, Ruiz Linares, Olloquequi, Krista Fischer, Bossers, Brenner, Hveem, Jenab, Eklund, Völker, Waldenberger, Aleksandrova, Katzke, Weiderpass, Moradi

Quality control of data and algorithms: Boekstegers

Data analysis and interpretation: Lorenzo Bermejo, Boekstegers, Barahona Ponce, Marcelain

Statistical analysis: Boekstegers

Manuscript preparation: Boekstegers

Manuscript editing: Lorenzo Bermejo

Manuscript review: All Authors

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Declaration of Competing Interest

None.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.101643.

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