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The *ABCG8* polymorphism increases the risk of gallbladder cancer in the general population and gallstones in obese patients from Poland

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Abstract

Background: Gallstone disease (GD) is common but remains asymptomatic in most cases. However, gallstones can lead to complications like choledocholithiasis or gallbladder cancer. In this study, we analyse the common genetic risk factor for GD, the p.D19H variant in the sterol transporter *ABCG8*, in Polish patients with gallstones and gallbladder cancer.

Methods: Three adult cohorts were prospectively recruited: 65 patients with gallbladder cancer, 170 obese individuals scheduled for bariatric surgery and 72 patients who underwent endoscopic retrograde cholangiopancreatography due to recurrent choledocholithiasis. The control cohort consisted of 172 gallstone-free adults. The *ABCG8* p.D19H (rs11887534) polymorphism was genotyped using TaqMan assays.

Lukasz Krupa, Piotr Kalinowski and Joanna Ligocka contributed equally to this study.

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Results: The minor allele frequency (MAF) of the *ABCG8* p.D19H polymorphism was significantly ($p = .02$) higher among cases with either gallstones or gallbladder cancer (MAF = 8.4%) as compared to controls (MAF = 4.0%). The highest frequency of the risk allele was detected in patients with gallbladder cancer (18.5%) and obese patients with GD (17.5%), followed by individuals with choledocholithiasis (13.9%). Notably, the p.19H variant was associated with an increased risk of developing gallbladder cancer (OR 2.76, 95% CI 1.16–6.54, $p = .01$) and an increased risk of GD in obese individuals scheduled for bariatric surgery (OR = 2.70, 95% CI 1.05–6.49, $p = .03$), but did not significantly affect the risk of choledocholithiasis.

Conclusions: The *ABCG8* p.D19H common risk variant increases the risk of developing gallbladder cancer in Central Europeans and enhances the risk of gallstones in the obese. Carriers of the p.D19H variant might benefit from personalized preventive strategies, particularly regarding gallbladder cancer.

KEYWORDS

ABCG8 polymorphism, cholesterol, gallbladder, genetic risk, hepatobiliary tumours, obesity

1 | INTRODUCTION

Gallstone disease (GD) is one of the most common gastrointestinal diseases and poses a significant burden on healthcare systems.[1] The prevalence of gallstones in Europe and North America in the adult Caucasian population ranges between 10% and 20%.[2] Over 80% of patients with gallstones remain asymptomatic and live without any complications.[3] However, the risk of developing symptomatic disease or complications requiring surgical or endoscopic intervention ranges from 1% to 2.3% per year.[4] In Western populations, cholesterol gallstones account for 90%–95% of all stones.[5,6] Untreated, long-lasting GD is known to be an important risk factor for gallbladder cancer.[7] The incidence of gallbladder cancer in a population with gallstones ranges from .3% to 3%.[7]

The interplay of genetic predisposition and environmental factors contributes to gallstone formation.[8] This is consistent with a fivefold increased risk for gallbladder stones among first-degree relatives of stone carriers.[9] Genetic factors were found to contribute to approximately 25% of total gallstone risk.[10] Among common genetic risk factors for GD, the *ABCG8* p.D19H polymorphism appears to be the most prevalent. ABCG8 composes together with ABCG5 a hepatobiliary sterol transporter, and carriers of the risk variant (i.e., *ABCG8* p.19H) have an approximately two-fold increased risk of gallstones.[11] This variant has also been associated with an increased risk of biliary tomours.[12–14] Although this variant was identified as a risk factor for GD more than 15 years ago,[11] the mechanisms by which carriers of this variant develop stones, as well as other gallbladder pathologies, have not yet been fully elucidated.

Environmental risk factors strongly associated with the formation of cholesterol stones include female sex, age over 40 years and obesity.[8] Rapid weight loss after bariatric surgery is one of many known risk factors for gallstone development.[15] Even following cholecystectomy or endoscopic ductal stone removal, recurrence of choledocholithiasis is observed in a significant number of patients, potentially leading to serious complications such as biliary sepsis and pancreatitis. The risk of recurrent GD after endoscopic bile duct clearance is well investigated,[16,17] but there is limited data available on common bile duct (CBD) stone recurrence after cholecystectomy. Known factors for recurrent bile duct stones include dilatation and angulation of CBD, biliary stricture, prior open cholecystectomy and periampullary diverticulum.[17,18] Von Schönfels et al.[19] analysed a cohort of Northern Germans and reported that gallstone recurrence after cholecystectomy might be associated with the presence of the *ABCG8* p.D19H polymorphism. However, the main limitation of that study was that the data was collected via mail and provided by patients.

To date, there is a lack of data regarding the *ABCG8* p.D19H variant in adult patients with GD and gallbladder cancer from Poland. In this study, we genotyped the *ABCG8* p.D19H polymorphism in three Polish cohorts: gallbladder cancer patients, obese patients undergoing bariatric surgery and individuals with recurrent bile duct stones to determine the role of this polymorphism in the risk of GD and gallbladder cancer. This selection of

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patients encompasses the spectrum of GD providing crucial insights into genetic influences and the variable clinical outcomes of GD.

2 | PATIENTS AND METHODS

2.1 | Patients and controls

We prospectively recruited three cohorts of adult patients. The first cohort included 65 patients with gallbladder cancer. In all of these patients, the diagnosis was based on the evaluation of intraoperatively-collected specimens of tumour tissue. The second cohort consisted of 170 patients scheduled for bariatric surgery, specifically sleeve gastrectomy. Within this group, 20 patients had gallbladder stones at the moment of bariatric surgery and another 20 had previously undergone cholecystectomies due to gallbladder stones. The third cohort consisted of 72 patients with recurrent choledocholithiasis. The patients in this cohort underwent endoscopic retrograde cholangiopancreatography (ERCP) at least 1 year post-cholecystectomy for stone disease (the vast majority) or required a second ERCP at least 1 year after an ERCP with successful complete stone removal from the bile ducts. In this cohort, the presence of stones in the CBD was confirmed during the ERCP procedure. The control cohort consisted of 172 adults without gallstones, as confirmed by abdominal sonography. Obese patients without stones were included in the control cohort for the analysis concerning patients scheduled for bariatric surgery. All samples were collected at the Medical University of Warsaw and at the Medical Department of the University of Rzeszów, Poland. Blood tests were determined by standard clinical-chemical assays in the central laboratories of the participating centres. Age below 18 years, pregnancy and tumours other than gallbladder cancer were regarded as exclusion criteria. Informed consent was obtained from all patients and controls, and the study protocol follows the ethical guidelines of the Declaration of Helsinki as reflected in an a priori approval by the Research Ethics Committees of the participating centres (39/KBE/2012, 110/B/2015, KB/48/2015, KB/140/2015 and KB/237/2015).

2.2 | Genotyping

Genotyping of the *ABCG8* p.D19H (rs11887534) polymorphism in the cases and controls was performed in the genetic laboratory of the Department of Medicine II at Saarland University Medical Center in Homburg by technicians blinded to the phenotype of patients. DNA was extracted from peripheral blood using the DNeasy Blood and Tissue Kit (Qiagen, Hilden, Germany). The concentrations of DNA were measured using a NanoDrop ND-1000 spectrophotometer (PeqLab, VWR, Germany). The studied variant was genotyped using TaqMan assays (C_26135643_10, ThermoFisher, Germany). PCR reactions contained 5–50 ng DNA, 1 × *TaqMan* Universal Master Mix and 1 × TaqMan assay (C___26135643_10, Thermo Fisher Scientific, Germany) in 5 μL-reactions. The amplification process involved an initial step at 95°C for 20 s, followed by 30 cycles of heating at 95°C for 3 s and then cooling at 60°C for 30 s. The post-read was carried out at 25°C for 1 min. Quality control for genotyping was maintained by including both negative controls and DNA samples with established *ABCG8* genotypes as internal standards. Fluorescence data were analysed with allelic discrimination software 7500 v.2.3 (Applied Biosystems, Germany).

2.3 | Statistical analyses

All tests were performed using with GraphPad Prism 10.1.1 (GraphPad Software, Boston, Massachusetts USA) or SPSS 28.0 (IBM Corp., Armonk, New York USA). Phenotypic quantitative data are expressed as medians and ranges. The Kolmogorov–Smirnov test was used to determine the normality of the distribution. For normally distributed continuous variables, comparisons between groups were performed using Student's *t*-tests or ANOVA tests. Non-normally distributed traits were compared using Mann–Whitney rank sum or Kruskal-Wallis tests. Frequencies of qualitative phenotypes were analysed using contingency table statistics. Hardy–Weinberg equilibrium (HWE) in cases and controls was checked with exact tests using an online available tool (Finetti v.3.0.8). The distribution of the genotypes in cases and controls was analysed in contingency tables using the χ^2 test in a dominant model. A two-sided $p < .05$ was considered statistically significant.

3 | RESULTS

Table 1 presents the baseline characteristics of the study cohorts. The gallbladder cancer patient cohort consisted of 77% women, and their median age was 62 (range 31–77) years. Among these, 54 patients also presented with GD. In the group of 170 patients who underwent bariatric surgery, 68% were women, with a median age of 42 years (range 19–65 years). All had body mass index (BMI) above 34 kg/m^2, and 40 of these patients suffered from GD. The cohort of individuals with recurrent

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TABLE 1 Baseline characteristics of the patients included in the analysis.

Variable	Patients with gallbladder cancer	Obese patients	Patients with recurrent choledocholithiasis
N (females/males)	65 (50/15)	170 (115/55)	72 (50/22)
Age (years)	62 (31–77)	42 (19–65)	68 (26–94)
Patients with gallstones (*n*)	54 (83.1%)	40 (23.5%)	72 (100%)
BMI (kg/m^2)	26.4 (18.4–38.8)	43.9 (34.2–64.3)	27.7 (25.1–54.1)
GGT (U/L)	77 (11–1863)	31 (12–296)	181 (13–4886)
Bilirubin (mg/dL)	.87 (.22–59.0)	.56 (.14–1.87)	1.20 (.47–9.77)
ALP (U/L)	121 (40–2153)	72 (25–133)	166 (51–904)
Cholesterol (mg/dL)	189 (124–592)	184 (97–273)	177 (21–274)
Triglycerides (mg/dL)	150 (26–653)	151 (58–779)	113 (17–299)

Note: All results are presented as medians and ranges, unless stated otherwise.

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; GGT, gamma-glutamyl transferase.

gallstones consisted of 69% women, with a median age of 68 years (range 26–94 years). In the control cohort of 172 individuals (102 women), all were older than 40 years, with the majority being older than 50 years (range 40–92). Patients with choledocholithiasis were significantly older ($p = .03$) than controls, whereas the obese patients scheduled for bariatric surgery were significantly younger ($p < .01$) than controls without stones. There was no difference in terms of age between gallstone-free controls and patients with gallbladder cancer. In terms of gender distribution, we detected a significantly ($p = .01$) higher frequency of female patients in the gallbladder cancer cohort as compared to controls. Significant differences were observed between the three groups of patients in terms of age, BMI, liver function tests, and serum triglyceride levels (all $p < .05$). For instance, patients with recurrent bile duct stones were the oldest and had the highest serum gamma-glutamyl transferase activities (all $p < .05$). Conversely, patients scheduled for bariatric surgery were the youngest ones and had the lowest serum bilirubin levels (all $p < .05$).

In all patient groups and in controls, the genotype frequencies were within HWE (all $p > .05$). Table 2 presents the minor allele frequencies of the *ABCG8* p.D19H genotypes in both cases. The minor allele frequency (MAF) of the risk allele was significantly ($p = .02$) higher among cases with either gallstones or gallbladder cancer (MAF = 8.4%) compared to controls (MAF = 4.0%). As presented in Table 2, the highest frequency of individuals carrying at least one copy of the p.19H risk allele was detected among patients with gallbladder cancer (18.5%), followed by obese patients with GD (17.5%), and patients with choledocholithiasis (13.9%). The frequency of carriers of the *ABCG8* p.D19H allele was higher in all patient cohorts as compared to controls (7.5%).

Table 2 summarizes the results of case-control association tests. The p.D19H variant was associated with an increased risk of developing gallbladder cancer (OR 2.76, 95% CI 1.16–6.54, $p = .01$). Additionally, the variant was associated with an increased risk of GD in obese individuals in comparison to all controls (OR = 2.70, 95% CI 1.05–6.49, $p = .03$) and in the analysis restricted only to individuals scheduled for bariatric surgery (OR 2.85, 95% CI 1.07–8.01, $p = .04$). However, there was no association with recurrent choledocholithiasis (OR = 1.97, 95% CI .82–4.86, $p > .05$).

4 | DISCUSSION

Previous genetic studies have demonstrated that the *ABCG8* p.D19H polymorphism increases the risk of developing gallstones and biliary tumours.[14,20] In our study, we expand these associations to Polish patients and show that this variant might play an essential role in gallstone formation in obese patients, but also in the development of gallbladder cancer. Figure 1 presents the summary of the key findings of our study, also listing additional risk factors that might modulate the risk of developing gallstones and gallbladder cancer.

The finding that the *ABCG8* p.D19H variant increases the risk of gallbladder cancer in individuals from Poland is one of the major novelties in our study. Gallbladder cancer might result from a longstanding GD. Despite being curable by surgery, only about 10% of patients are eligible for radical surgical treatment.[21] The incidence rates of gallbladder cancer are the highest in Eastern Europe, East Asia and Latin America.[22,23] The regional variations in the incidence are likely due to differences in environmental factors and regional intrinsic risk factors, but also genetic predisposition. Bustos et al. previously provided evidence that the *ABCG8* p.D19H polymorphism is associated with

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an increased risk of gallbladder cancer in Chileans.[24] Our findings are also in line with the studies from India[12] and China.[13] Stender et al.[14] analysed the Northern European population and found that 27% of biliary cancers were attributed to the p.D19H variant. We expand these associations to Polish patients, noting that countries like Chile and Poland are characterized by a high incidence of gallbladder cancer.[25]

Obesity, as well as rapid weight loss following bariatric surgery, significantly increases the risk of GD.[26] The necessity of prophylactic cholecystectomy in all patients during bariatric surgery remains a matter of debate, and the risks associated with gallstone complications after bariatric surgery vary widely.[27,28] Analysis of genetic risk modifiers may enable us to identify obese patients at significantly increased risk of GD. This could lead to a more precise risk stratification and possible consideration of preventive cholecystectomy. It could also expand the use of chemoprevention for gallstones, such as the use of ursodeoxycholic acid.[5] Our findings indicate that the p.D19H variant in *ABCG8* is associated with an increased risk of GD in severely obese individuals. Whether this also increases the risk of postoperative gallstone-related complications, such as cholecystitis warrants further studies. Nevertheless, given the annual complication rate of 3% in patients with gallstones,[4] identifying individual risk factors might facilitate a more individualized approach regarding primary prevention in the obese.

Interestingly, contrary to the previous reports,[19] our analysis did not find evidence that the p.D19H variant increases the risk for de novo CBD stone formation after cholecystectomy or post-ERCP. This discrepancy may be due to the predominant role of well-known personal risk factors for de novo stone formation, such as strictures or dilatation of the CBD, as well as insufficient papillotomy. Our study did non analyze these potentially confounding

TABLE 2 Results of the case-control association tests for the *ABCG8* p.D19H polymorphism.

Phenotype	Carriers of the p.19H allele	OR	OR 95% CI	*p*-Value
Gallbladder cancer	18.5%	2.76	1.16–6.54	.01
Gallstone disease in the obese	17.5%	2.70	1.05–6.49	.03
Recurrent choledocholithiasis	13.9%	1.97	.82–4.86	>.05

Note: OR values are given for the carriership of the 19H risk allele. The distribution of the genotypes in cases and in controls was analysed in contingency tables (χ^2 test) in a dominant model.

Abbreviations: *ABCG8*, hepatobiliary cholesterol hemi-transporter; CI, confidence interval; OR, odds ratio; p, protein (amino acid number).

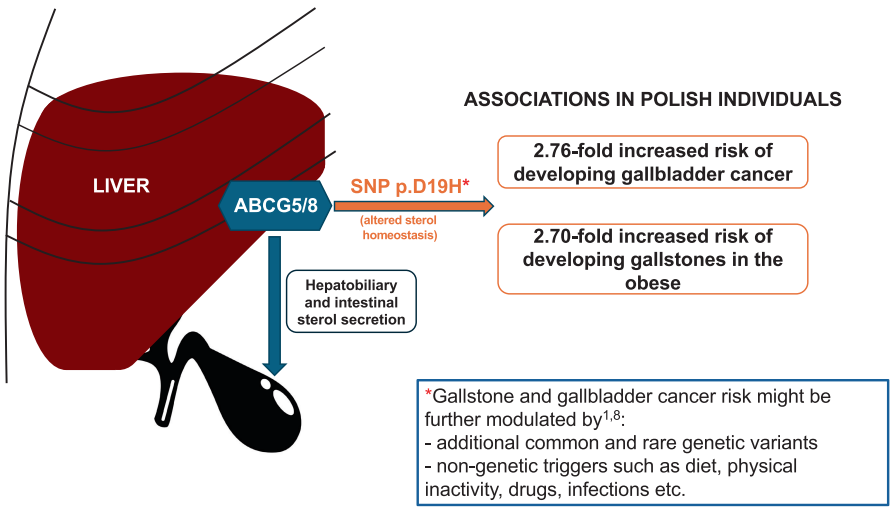

FIGURE 1 The common variant *ABCG8* p.D19H in the hepatobiliary cholesterol transporter increases the odds of developing gallstones (in obese) and gallbladder cancer in Polish individuals. *ABCG5/8* is expressed as a heterodimer in the canalicular membrane and on enterocytes in the intestine, where it transports sterols back into the lumen. Carriers of the *ABCG8* p.D19H variant are at increased risk of stones and gallbladder cancer. This is attributed to altered hepatobiliary cholesterol homeostasis, resulting in bile supersaturation. The risk of gallbladder diseases might be potentiated further by other genetic variants and non-genetic risk factors such as diet, physical inactivity, or drugs.

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factors. We also based our case-control analyses on univariate models, which should be regarded as a limitation of our report. Moreover, the number of patients with recurrent stone disease might have been too small in our cohort to capture the association with the studied variant—notably the number of carriers of the risk variant in this cohort was twice that of the controls.

The prospective recruitment of all analysed patients should be regarded as the strength of this study. However, we focused however only on one, predominant genetic risk factor for GD, namely *ABCG8* p.D19H. Previous GWAS studies have demonstrated additional common and rare variants that likely contribute to gallstones and gallbladder pathology. For example, Joshi et al.[29] in a meta-analysis of genome-wide association studies (GWAS) and Ferkingstad et al.[30] have supported the role of *ABCG8* p.D19H in the gallstone risk, but also identified other variants of moderate to large effect such as *HNF4*, *SERPINA1*, *SLC10A2*, *SULT2A1* and *TM4DF4*. To obtain a more comprehensive assessment it would be required to perform extensive gene sequencing and approaches such as Polygenic Risk Scores including *ABCG8* and other impactful variants.

Overall, our findings demonstrate that the *ABCG8* p.D19H polymorphism contributes to GD in obese patients from Poland. It also increases the risk of developing gallbladder cancer. Further studies will be needed to develop tools for the primary prevention of GD and its complications, as well as gallbladder cancer among carriers of this polymorphism.

AUTHOR CONTRIBUTIONS

LK, PK, JL, KJ, JG, BK, PM, KZ, MK1 and MK2 recruited patients and controls; SNW, FL and MK2 were responsible for the genotyping procedures; LK and MK2 analysed the data; LK, MD and MK2 drafted the first version of the manuscript, which was read and edited by all authors; MK2 supervised the project and prepared the final version of the manuscript together with LK.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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