Identification and replication of six new loci associated with gallstone disease

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Background and Aim:

Up to 20% of people in Western populations have gallstones. One in five patients with gallstones develop symptoms often requiring removal of the gallbladder.

Approximately 25% of the risk of gallstone disease is determined genetically. So far, seven distinct loci have been found through genome-wide association studies.

Aim: To identify new loci associated with gallstone disease.

Method:

Identification

UK Biobank

N = 337,208

Gallstone cases = 14,940

$P < 5 \times 10^{-8}$

Replication

CGPS&CCHS

N = 19,788

Gallstone cases = 1,522

$P < 0.05$

Results:

Gene	Consequence	Allele frequency	UK Biobank Odds ratio (95% CI)
New associations replicated in CCHS&CGPS			
<i>HNF4A</i>	p.Thr139Ile	0.03	1.30 (1.23-1.38)
<i>FUT2</i>	p.Trp154Ter	0.35	1.11 (1.08-1.14)
<i>SERPINA1</i>	p.Glu366Lys	0.02	1.36 (1.27-1.46)
<i>JMJD1C</i>	intron	0.37	1.08 (1.06-1.10)
<i>ACO74212.3</i>	p.Thr388Asn	0.47	1.08 (1.05-1.11)
<i>SLC10A2</i>	p.Pro290Ser	0.01	1.33 (1.21-1.47)
Known associations			
<i>ABCG8</i>	p.Asp19His	0.07	2.01 (1.94-2.08)
<i>SULT2A1</i>	intron	0.19	1.17 (1.13-1.21)
<i>CYP7A1</i>	gene regulation	0.57	1.11 (1.09-1.14)
<i>TM4SF4</i>	intron	0.60	1.11 (1.08-1.14)
<i>GCKR</i>	p.Pro446Leu	0.48	1.09 (1.06-1.12)
<i>ABCB4</i>	p.Arg590Gln	0.01	1.37 (1.23-1.52)
<i>TTC39B</i>	intron	0.21	1.09 (1.06-1.12)
<i>UGT1A1</i>	intron	0.40	1.07 (1.05-1.10)
New associations not replicated in CCHS&CGPS			
<i>LRBA</i>	p.Ser2809Leu	0.37	1.13 (1.10-1.16)
<i>MARCH8</i>	intron	0.30	1.13 (1.10-1.16)
<i>HNF1A</i>	intron	0.49	1.09 (1.06-1.12)
<i>FADS2</i>	non-coding exon	0.46	1.07 (1.05-1.09)
<i>DAGLB</i>	intron	0.35	1.08 (1.05-1.11)

Loci associated with gallstone disease in UK Biobank and their association in CGPS&CCHS. Yellow font: new loci.

Biology of new loci:

HNF4A Liver and pancreas specific transcription factor.

FUT2 Enzyme that modifies glycans.

SERPINA1 Encodes alpha-1-antitrypsin.

JMJD1C Has a role in histone demethylation. In proximity to *NRBF2*, a liver specific nuclear receptor of unknown function.

ACO74212.3 Testis-specific gene with unknown function.

SLC10A2 Mediates bile acid reabsorption in the ileum.

Conclusion:

We identified and replicated six loci associated with gallstone disease.