

1 **Genome-wide study identifies association between HLA-B*55:01 and penicillin**
2 **allergy**

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54

55 **Abstract**

56 **Background**

57 Hypersensitivity reactions to drugs are often unpredictable and can be life-
58 threatening, underscoring a need for understanding the underlying mechanisms and
59 risk factors. The extent to which germline genetic variation influences the risk of
60 commonly reported drug allergies such as penicillin allergy remains largely unknown.

61 **Methods**

62 We extracted data from the electronic health records of 52,000 Estonian and
63 500,000 UK biobank participants to study the role of genetic variation in the
64 occurrence of penicillin hypersensitivity reactions. We used imputed SNP to HLA
65 typing data from up to 22,554 and 488,377 individuals from the Estonian and UK
66 cohorts, respectively, to further fine-map the human leukocyte antigen (HLA)
67 association and replicated our results in two additional cohorts involving a total of
68 1.14 million individuals.

69 **Results**

70 Genome-wide meta-analysis of penicillin allergy revealed a significant association
71 located in the HLA region on chromosome 6. The signal was further fine-mapped to
72 the HLA-B*55:01 allele (OR 1.47 95% CI 1.37-1.58, P-value 4.63×10^{-26}) and
73 confirmed by independent replication in two cohorts. The meta-analysis of all four
74 cohorts in the study revealed a strong association of HLA-B*55:01 allele with self-
75 reported penicillin allergy (OR 1.33 95% CI 1.29-1.37, P-value 2.23×10^{-72}). *In silico*
76 follow-up suggests a potential effect on T lymphocytes at HLA-B*55:01.

77 **Conclusion**

78 We present the first robust evidence for the role of an allele of the major
79 histocompatibility complex (MHC) I gene HLA-B in the occurrence of penicillin
80 allergy.

81

82 **MAIN**

83

84 Adverse drug reactions (ADRs) are common in clinical practice and are associated
85 with high morbidity and mortality. A meta-analysis of prospective studies in the US
86 revealed the incidence of serious ADRs to be 6.7% among hospitalized patients, and
87 the cause of more than 100,000 deaths annually ¹. In Europe, ADRs are responsible
88 for 3.5% of all hospital admissions, with 10.1% of patients experiencing ADRs during
89 hospitalization and 197,000 fatal cases per year ^{2,3}. In the US, the cost of a single
90 ADR event falls between 1,439 to 13,462 USD ⁴.

91

92 ADRs are typically divided into two types of reactions. Type A reactions are more
93 predictable and related to the pharmacological action of a drug, whereas type B
94 reactions are idiosyncratic, less predictable, largely dose-independent, and typically
95 driven by hypersensitivity reactions involving the immune system ⁵. Although type B
96 reactions are less frequent (<20%) than type A reactions, they tend to be more
97 severe and more often lead to the withdrawal of a drug from the market ⁶. Based on
98 the timing of onset, drug allergy can be further divided into immediate or delayed
99 effects ⁷. One of the most common causes of type B reactions are antibiotics ⁵,
100 typically from the beta-lactam class, with the prevalence of penicillin allergy
101 estimated to be as high as 25% in some settings ^{8,9}. Despite the relative frequency of
102 such reactions, there are very few studies of the genetic determinants of penicillin

103 allergy^{10,11}. This underscores the need for a better understanding of the
104 mechanisms and risk factors, including the role of genetic variation, that contribute to
105 hypersensitivity reactions.

106

107 The increasing availability of genetic and phenotypic data in large biobanks provides
108 an opportune means for investigating the role of genetic variation in drug-induced
109 hypersensitivity reactions. In the present study, we sought to identify genetic risk
110 factors underlying penicillin-induced hypersensitivity reactions by harnessing data
111 from the Estonian (EstBB) and UK Biobanks (UKBB), with further replication in large
112 population-based cohorts.

113

114 **RESULTS**

115 **GENOME-WIDE ASSOCIATION ANALYSIS OF PENICILLIN HYPERSENSITIVITY**

116 To discover genetic factors that may predispose to penicillin allergy, we conducted a
117 genome-wide association study (GWAS) of 19.1 million single-nucleotide
118 polymorphisms (SNPs) and insertions/deletions in UKBB and EstBB (minor allele
119 frequency filter in both cohorts MAF > 0.1%). Cases were defined as participants
120 with a Z88.0 ICD10 code (“Allergy status to penicillin”) for a reported history of
121 penicillin allergy. In total, we identified 15,690 unrelated individuals (4.2% of the total
122 cohort size of 377,545) in UKBB with this diagnostic code. However, the
123 corresponding number of cases in EstBB was only 7 (0.02% of the total cohort size
124 of 32,608) suggesting heterogeneity in the use of the Z88.0 ICD10 code in different
125 countries. We therefore also identified participants that had self-reported drug allergy
126 at recruitment in EstBB and categorized the EstBB self-reported reactions by drug
127 class J01C* (beta-lactam antibacterials, penicillins) to match this to the respective

128 Z88.0 diagnostic code, resulting in 961 (2.9%) unrelated cases with penicillin allergy
129 in EstBB. We validated the approach in EstBB by evaluating the association between
130 the number of penicillin (using the Anatomical Therapeutic Chemical (ATC)
131 Classification System code J01C*) filled prescriptions per person and self-reported
132 penicillin allergy. Using Poisson regression analysis, we identified a negative effect
133 on the number of filled penicillin prescriptions among individuals with self-reported
134 allergy in EstBB (P-value 2.41×10^{-15} , Estimate -0.18 i.e. prescription count is 16%
135 lower for individuals with penicillin allergy).

136 We then meta-analyzed the results of the GWASes in these two cohorts separately,
137 weighing effect size estimates using the inverse of the corresponding standard
138 errors. We identified a strong genome-wide significant ($p < 5 \times 10^{-8}$) signal for
139 penicillin induced allergy (defined as ICD10 code Z88.0 or reported allergy to drugs
140 in ATC J01C* class) on chromosome 6 in the major histocompatibility complex
141 (MHC) region (lead variant rs114892859, MAF(EstBB) = 0.7%, MAF(UKBB) = 2%, P
142 = 2.21×10^{-28} , OR 1.02 95% CI 1.016-1.023) (**Figure 1 Table S1 in the**
143 **Supplementary Appendix**).

144

145 FINE-MAPPING THE PENICILLIN ALLERGY-ASSOCIATED HLA LOCUS

146 To further fine-map the causal variant of the identified association with penicillin
147 allergy, we performed a functional annotation analysis with FUMA (Functional
148 Mapping and Annotation of Genome-Wide Association Studies) ¹². We detected an
149 independent intronic lead SNP for the penicillin allergy meta-analysis (GWAS top
150 variant rs114892859, P-value 2.21×10^{-28}) in the *MICA* gene (**Figure 1, B**). When
151 testing the SNP for expression quantitative trait locus (eQTL) associations in blood
152 based on data from the eQTLGen Consortium ¹³, the variant appeared to be

153 associated with the expression levels of several nearby genes, with the most
154 significant being *PSORS1C3* (P-value 8.10×10^{-62}) and *MICA* (P-value 1.21×10^{-52})
155 (**Table S2 in the Supplementary Appendix**). We further performed an *in silico*
156 investigation of the lead SNP rs114892859 and its best proxy (only proxy with $r^2 > 0.9$
157 in UKBB and EstBB; rs144626001) in HaploReg v4 to explore annotations and
158 impact of the non-coding variant¹⁴. In particular rs114892859 had several
159 annotations indicative of a regulatory function, including its location in both promoter
160 and enhancer marks in T-cells and evidence of RNA polymerase II binding^{14,15}.
161 Interestingly, its proxy is more likely to be deleterious based on the scaled Combined
162 Annotation Dependent Depletion (CADD) score (scaled score of 15.78 for
163 rs144626001 (C/T) and 4.472 for rs114892859 (G/T))^{16,17}.

164

165 Due to the high LD in the MHC region, we used imputed SNP to HLA typing data
166 available at four-digit resolution¹⁸ for up to 22,554 and 488,377 individuals from the
167 Estonian and UK cohorts, respectively, to further fine-map the identified HLA
168 association with penicillin allergy. In both cohorts a shared total of 103 alleles at four-
169 digit level were present for all of the MHC class I genes (*HLA-A*, *HLA-B*, *HLA-C*) and
170 59 alleles for three of the classical MHC class II genes (*HLA-DRB1*, *HLA-DQA1*,
171 *HLA-DQB1*). To assess the variation in the frequencies of the HLA alleles in different
172 populations, we compared the obtained allele frequencies in both cohorts (**Table S3**
173 **in the Supplementary Appendix**) with the frequencies of HLA alleles in different
174 European, Asian and African populations reported in the HLA frequency database
175 (**Figure S2 and S3, Table S4 in the Supplementary Appendix**).

176

177 We then used an additive logistic regression model to test for associations between
178 different four-digit HLA alleles and penicillin allergy in UKBB and EstBB. The results
179 of both cohorts were meta-analyzed and P-values passing a Bonferroni correction
180 ($0.05/162 = 3.09 \times 10^{-4}$, where 162 is the number of meta-analyzed HLA alleles) were
181 considered significant (**Table S5 in the Supplementary Appendix**). One of the
182 three results that surpassed the significance threshold had discordant effects in the
183 two cohorts and one had a marginally significant association (P-value 2.81×10^{-4} ,
184 **Table S5 in the Supplementary Appendix**). The strongest association we detected
185 for penicillin allergy was the HLA-B*55:01 allele (P-value 4.63×10^{-26} ; OR 1.47 95%
186 CI 1.37-1.58).

187

188 REPLICATION OF HLA-B*55:01 ASSOCIATION WITH PENICILLIN ALLERGY

189 To further confirm association with penicillin allergy we analyzed the association of
190 the HLA-B*55:01 allele with self-reported penicillin allergy among 87,996 cases and
191 1,031,087 controls from the 23andMe research cohort. We observed a strong
192 association (P-value 1.00×10^{-47} ; OR 1.30 95% CI 1.25-1.34; **Figure 2**) with a similar
193 effect size as seen for the HLA-B*55:01 allele in the meta-analysis of the EstBB and
194 UKBB. We obtained further confirmation for this association from the published
195 dataset of Vanderbilt University's biobank BioVU, where the HLA-B*55:01 allele was
196 associated with allergy/adverse effect due to penicillin among 58 cases and 23,598
197 controls (P-value 1.79×10^{-2} ; OR 2.15 95% CI 1.19-6.5; **Figure 2**)¹⁹. Meta-analysis of
198 results from discovery and replication cohorts demonstrate a strong association of
199 HLA-B*55:01 allele with self-reported penicillin allergy (P-value 2.23×10^{-72} ; OR 1.33
200 95% CI 1.29-1.37; **Figure 2**).

201

202 FURTHER ASSOCIATIONS AT HLA-B*55:01

203 Finally, we used the Open Targets Genetics platform's UKBB PheWAS data²⁰ to
204 further characterize the association of GWAS top variant rs114892859 that is also a
205 strongly correlated tag-SNP ($r^2 > 0.95$) of the HLA-B*55:01 allele (**Table S6 in the**
206 **Supplementary Appendix**) with other traits, and found strong associations with
207 lower lymphocyte counts (P-value 9.21×10^{-14} , estimate -0.098 cells per nanoliter per
208 allergy-increasing T allele) and lower white blood cell counts (P-value 3.17×10^{-9} ,
209 estimate -0.078 cells per nanoliter per allergy-increasing T allele). To confirm this
210 association, we extracted data on lymphocyte counts from the electronic health
211 record (EHR) data of 4,567 EstBB participants, and observed the same inverse
212 association of the HLA-B*55:01 allele with lymphocyte counts (Estimate -0.148
213 number of cells per nanoliter per T allele; P-value=0.047).

214

215 DISCUSSION

216

217 In the present study, we identify a strong genome-wide significant association of the
218 HLA-B*55:01 allele with penicillin allergy using data from four large cohorts: UKBB,
219 EstBB, 23andMe and BioVu.

220

221 Hypersensitivity or allergic reactions to medications are type B adverse drug
222 reactions that are known to be mediated by the immune system. One major driver of
223 hypersensitivity reactions is thought to be the HLA system, which plays a role in
224 inducing the immune response through T cell stimulation, and is encoded by the
225 most polymorphic region in the human genome.²¹ Genetic variation in the HLA
226 region alters the shape of the peptide-binding pocket in HLA molecules, and enables

227 their binding to a vast number of different peptides – a crucial step in the adaptive
228 immune response²². However, this ability of HLA molecules to bind a wide variety of
229 peptides may also facilitate binding of exogenous molecules such as drugs,
230 potentially leading to off-target drug effects and immune-mediated ADRs²³. The
231 precise mechanism of most HLA-drug interactions remains unknown, but it seems
232 that T cell activation is necessary for the majority of HLA-mediated ADRs^{7,23,24}.
233 Despite the increasing evidence for a role of the HLA system in drug-induced
234 hypersensitivity, much is still unclear, including how genetic variation in the HLA
235 region predisposes to specific drug reactions.

236

237 Penicillin is the most common cause of drug allergy, with clinical manifestations
238 ranging from relatively benign cutaneous reactions to life-threatening systemic
239 syndromes^{8,9}. There is a previous GWAS on the immediate type of penicillin allergy,
240 where a borderline genome-wide significant protective association of an allele of the
241 MHC class II gene *HLA-DRA* was detected and further replicated in a different cohort
242²⁵. Here we detect a robust association between penicillin allergy and an allele of the
243 MHC class I gene *HLA-B*. The allele and its tag-SNP were also associated with
244 lower lymphocyte levels and overlapped with T cell regulatory annotations, which
245 suggests that the variant may predispose to a T-cell-mediated, delayed type of
246 penicillin allergy. MHC I molecules are expressed by almost all cells and present
247 peptides to cytotoxic CD8+ T cells, whereas MHC II molecules are expressed by
248 antigen-presenting cells to present peptides to CD4+ T helper lymphocytes^{7,22}.
249 There are several examples of MHC I alleles associated with drug-induced
250 hypersensitivity mediated by CD8+ T cells^{7,26,27}. The involvement of T cells in
251 delayed hypersensitivity reactions has been shown by isolating drug reactive T cell

252 clones²⁸, and cytotoxic CD8+ T cells have been shown to be relevant especially in
253 allergic skin reactions^{29–31}. More than twenty years ago, CD8+ T cells reactive to
254 penicillin were isolated from patients with delayed type of hypersensitivity to penicillin
255³². The association with the HLA-B*55:01 allele detected in our study might be a
256 relevant factor in this previously established connection with CD8+ T cells. The HLA-
257 B*55:01 allele, together with other HLA-B alleles that share a common "E pocket
258 sequence", has previously been associated with increased risk for eosinophilia and
259 systemic symptoms, Stevens-Johnson Syndrome and toxic epidermal necrolysis
260 (SJS/TEN) among patients treated with nevirapine³³. The underlying mechanism in
261 penicillin allergy remains a question and various models have been proposed for T-
262 cell-mediated hypersensitivity^{26,31}. For example, the hapten model suggests that
263 drugs may alter proteins and thereby induce an immune response^{26,34} – penicillins
264 have been shown to bind proteins^{34,35} to form hapten–carrier complexes, which may
265 in turn elicit a T cell response³⁶. Drugs may also bind with MHC molecules directly.
266 For example, abacavir has been shown to bind non-covalently to the peptide-binding
267 groove of HLA-B*57:01, leading to a CD8+ T cell-mediated hypersensitivity response
268³⁷. Although we detect strong evidence for the involvement of HLA-B*55:01 in
269 penicillin allergy, and a marginally significant association in the MHC II gene DRB1,
270 both need further functional investigation to explore their exact roles and
271 mechanisms in the induced response.

272

273 The frequency of the HLA-B*55:01 allele was slightly lower (0.7%) in EstBB than in
274 UKBB (1.9%), however our comparison between European and Asian populations
275 indicated a similar frequency (P-value 0.97) between these populations. It is

276 therefore possible that the HLA-B*55:01 allele may be a common contributor to
277 penicillin allergy among Asians as well, but this needs further investigation.
278 It is being increasingly recognized that the involvement of HLA variation in
279 hypersensitivity reactions goes beyond peptide specificity. Other factors, such as
280 effects on HLA expression that influence the strength of the immune response have
281 also been described³⁸. The analysis of eQTLs based on the data of the eQTLGen
282 Consortium¹³ revealed that the T allele of the lead SNP rs114892859 identified in
283 our GWAS of penicillin allergy appears to be associated with the expression of
284 several nearby genes, including lower expression of both *HLA-B* and *HLA-C*, and an
285 even stronger effect on RNA levels of *PSORS1C3* and *MICA* (**Table S2 in the**
286 **Supplementary Appendix**). Interestingly, variants in the *PSORS1C3* gene have
287 been associated with the risk of allopurinol, carbamazepine and phenytoin induced
288 SJS/TEN hypersensitivity reactions³⁹. *MICA* encodes the protein MHC class I
289 polypeptide-related sequence A⁴⁰ which has been implicated in immune surveillance
290^{41,42}. Our findings therefore support the observation that variants associated with
291 expression of HLA genes may contribute to the development of hypersensitivity
292 reactions.

293

294 The main limitation of this study is the unverified nature of the phenotypes extracted
295 from EHRs and self-reported data in the biobanks. Previous work has found that
296 most individuals labeled as having beta-lactam hypersensitivity may not actually
297 have true hypersensitivity^{8,43,9}. Nevertheless, despite the possibility that some cases
298 in our study may be misclassified, we detect a robust HLA association that was
299 replicated in several independent cohorts against related phenotypes. The increased
300 power arising from biobank-scale sample sizes therefore mitigates some of the

301 challenges associated with EHR data. The robustness of the genetic signal across
302 cohorts with orthogonal phenotyping methods, ranging from EHR-sourced in UKBB
303 to various forms of self-reported data in EstBB and 23andMe, also supports a true
304 association. Finally, the modest effect size of the HLA-B*55:01 allele (OR 1.33),
305 particularly when compared to effect sizes of HLA alleles with established
306 pharmacogenetic relevance^{44–46}, suggests that this variant in isolation is unlikely to
307 have clinically meaningful predictive value. Our work does provide the foundation for
308 further studies to investigate the application of a polygenic risk score⁴⁷ (which
309 combines the effects of many thousands of trait-associated variants into a single
310 score), possibly in combination with phenotypic risk factors, in identifying individuals
311 at elevated risk of penicillin allergy.

312 In summary, our results provide novel evidence of a robust genome-wide significant
313 association of HLA and the HLA-B*55:01 allele with penicillin allergy.

314

315 **METHODS**

316

317 **Phenotype definitions**

318 We studied individual-level genotypic and phenotypic data of 52,000 participants
319 from the Estonian Biobank (EstBB) and 500,000 participants from UK Biobank
320 (UKBB). Both are population-based cohorts, providing a rich variety of phenotypic
321 and health-related information collected for each participant. All participants have
322 signed a consent form to allow follow-up linkage of their electronic health records
323 (EHR), thereby providing a longitudinal collection of phenotypic information. EstBB
324 allows access to the records of the national Health Insurance Fund Treatment Bills
325 (since 2004), Tartu University Hospital (since 2008), and North Estonia Medical

326 Center (since 2005). For every participant there is information on diagnoses in ICD-
327 10 coding and drug dispensing data, including drug ATC codes, prescription status
328 and purchase date (if available). We extracted information on penicillin allergy by
329 searching the records of the participants for Z88.0 ICD10 code indicating patient-
330 reported allergy status due to penicillin. Information on phenotypic features like age
331 and gender were obtained from the biobank recruitment records. Since Z88.0 code
332 seemed underreported in Estonia, we also used self-reported data on side-effects
333 from penicillin for 1,015 (961 unrelated) participants who reported hypersensitivity
334 due to J01C* ATC drug group (Beta-Lactam Antibacterials, Penicillins) in their
335 questionnaire when joining EstBB.

336

337 We also extracted likely penicillin allergies in the EstBB from the free text fields of
338 the EHRs using a rule-based approach; the text had to contain any of the possible
339 forms of the words 'allergy' or 'allergic' in Estonian as well as a potential variation of
340 a penicillin name. As drug names are often misspelled, abbreviated or written using
341 the English or Latin spelling instead of the standard Estonian one, we used a regular
342 expression to capture as many variations of each penicillin name as possible. In
343 addition, we applied rules regarding the distance between the words 'allergy' and the
344 drug name as well as other words nearby to exclude negations of penicillin allergies
345 in the definition.

346

347 To analyze the effect of self-reported allergy status on the number on penicillin
348 prescriptions in EstBB we performed a Poisson regression among 37,825 unrelated
349 individuals with J01C* prescriptions considering age, gender and 10 principal
350 components (PC) as covariates. Units were interpreted as follows: 1-

351 $\exp(\beta) * 100\% = 1 - \exp(-0.18) * 100\% = 16\%$. The Poisson model was considered
352 appropriate as there was no large overdispersion.

353

354 **Overview of genetic data**

355 The details on genotyping, quality control and imputation are fully described
356 elsewhere for both EstBB^{48,49} and UKBB⁵⁰. In brief, of the included EstBB
357 participants 33,277 have been genotyped using the Global Screening Array v1
358 (GSA), 8,137 on the HumanOmniExpress beadchip (OMNI), 2,641 on the
359 HumanCNV370-Duo BeadChips (370) and 7,832 on the Infinium CoreExome-24
360 BeadChips from Illumina (CE). Furthermore, 2,056 individuals' whole genomes have
361 been sequenced at the Genomics Platform of the Broad Institute. Sequenced reads
362 were aligned against the GRCh37/hg19 version of the human genome reference
363 using BWA-MEM1 v0.7.7. The genotype data was phased using Eagle2 (v. 2.3)⁵¹
364 and imputed using BEAGLE (v. 4.1)^{52,53}, software implementing a joint Estonian and
365 Finnish reference panel (described in⁵⁴). If one individual was genotyped with more
366 than one microarray, duplicates were removed by prioritizing as follows: Whole
367 genome > GSA > OMNI > 370 > CE. The total dataset comprises 32,608 unrelated
368 participants that is based on the inclusion of individuals with PiHat < 0.2. When
369 excluding relatives for a GWAS, we favored individuals who had self-reported ADRs
370 due to drugs.

371 In UKBB, genotype data are available for 488,377 participants of which 49,950 are
372 genotyped using the Applied Biosystems™ UK BiLEVE Axiom™ and the remaining
373 438,427 individuals were genotyped using the Applied Biosystems™ UK Biobank
374 Axiom™ Array by Affymetrix. The genotype data was phased using SHAPEIT3⁵⁵,

375 and imputation was conducted using IMPUTE4⁵³ using a combined version of the
376 Haplotype Reference Consortium (HRC) panel⁵⁶ and the UK10K panel⁵⁷.
377 We excluded individuals who have withdrawn their consent, have been labelled by
378 UKBB to have poor heterozygosity or missingness, who have putative sex
379 chromosome aneuploidy and who have >10 relatives in the dataset. We further
380 removed all individuals with mismatching genetic and self-reported sex and ethnicity.
381 GWAS was executed on unrelated individuals with confirmed white British ancestry.
382 Only one individual from each pair of second- or higher-degree relatives (KING's
383 kinship coefficient > 0.0884) were included, by favoring the carriers of Z88.0 ICD10
384 code. After following these steps, we ended up with 377,545 unrelated individuals.
385

386 **Genome-wide study and meta-analysis**

387 In the Estonian biobank, we conducted the penicillin GWAS among 31,760 unrelated
388 individuals (PiHat < 0.2) of whom 961 were cases with self-reported allergy from
389 J01C beta-lactam drugs and 30,799 undiagnosed controls. The controls were
390 selected from a set of individuals with no self-reported ADRs or with ICD10
391 diagnoses covered in a list of 79 ICD10 codes (described in⁵⁸) with a possible drug-
392 induced nature or diagnoses described as "due to drugs". The GWAS was run with
393 the EPACTS software⁵⁹ using an additive genetic logistic model. To minimize the
394 effects of population admixture and stratification, the analyses only included samples
395 with European ancestry based on PC analysis (PCA) and were adjusted for the first
396 ten PCs of the genotype matrix, as well as for age, sex and array.
397

398 In the UKBB, GWAS on penicillin allergy (Z88.0) was performed among 15,690
399 cases and 342,116 controls. Similarly as for EstBB, the controls were selected from

400 a set of individuals with no ICD10 diagnoses covered in a list of 79 ICD10 codes
401 (described in ⁵⁸). GWAS of imputed genotype data was performed with the BOLT-
402 LMM software tool ⁶⁰ using a linear mixed model and considering the
403 aforementioned covariates (10 PCs, age, sex). LD scores appropriate for the
404 analysis of European-ancestry was used for calibration of the BOLT-LMM statistic
405 reference.

406 We performed meta-analysis of 19,051,157 markers (MAF>0.1%) based on effect
407 sizes and their standard errors using METAL ⁶¹. Results were visualized with R
408 software (3.3.2) ⁶².

409

410 **Post-GWAS annotation**

411

412 FUMA (Functional mapping and annotation of genetic associations) ¹² is an
413 integrative web-based platform using information from multiple biological resources,
414 including e.g. information on eQTLs, chromatin interaction mappings, and LD
415 structure to annotate GWASes. We applied FUMA to identify lead SNPs and
416 genomic risk loci for results of the meta-analysis, using the European LD reference
417 panel from 1000G⁶³. Further eQTL associations were identified based on data from
418 the the eQTLGen consortium, which is a meta-analysis of 37 datasets with blood
419 gene expression data pertaining to 31,684 individuals ¹³.

420

421 HaploReg ¹⁴ was used for exploring annotations, chromatin states, conservation, and
422 regulatory motif alterations. To estimate the relative deleteriousness of the identified
423 SNPs we use the Combined Annotation Dependent Depletion (CADD) framework ¹⁶.

424

425 **HLA-typing**

426

427 HLA-typing of the EstBB genotype data was performed at the Broad Institute using
428 the SNP2HLA tool ⁶⁴, which imputes HLA alleles from SNP genotype data.
429 Single Nucleotide Variants (SNVs), small INsertions and DEletions (INDELs) and
430 classical HLA variants were called using whole genome sequences of 2,244 study
431 participants from the Estonian Biobank sequenced at 26.1x. We performed high-
432 resolution (G-group) HLA calling of three class-I HLA genes (HLA-A, -B and -C) and
433 three class-II HLA genes (HLA-DRB1, -DQA1 and -DQB1) using the HLA*PRG
434 algorithm ⁶⁵. SNVs and INDELs were called using GATK version 3.6 according to the
435 best practices for variant discovery ⁶⁶. Classical HLA alleles, HLA amino acid
436 residues and untyped SNPs were then imputed using SNP2HLA and the reference
437 panel constructed using the 2,244 whole-genome sequenced Estonian samples. The
438 imputation was done for genotype data generated on the GSA, and after quality
439 control the four-digit HLA alleles of 22,554 individuals were used for analysis.

440

441 In UKBB we used four-digit imputed HLA data released by UKBB ⁵⁰. The imputation
442 process, performed using HLA*IMP:02 ⁶⁷, is described more fully elsewhere ^{50,68}. We
443 applied posterior thresholding (at a threshold of 0.8) to the imputed data to create a
444 marker representing the presence/absence of each HLA allele.

445

446 To compare obtained frequencies of HLA alleles with reported frequencies in
447 European, Asian and African populations we used the database of Allele
448 Frequencies of worldwide populations (<http://www.allelefreqencies.net/default.asp>).
449 We queried the frequencies of four-digit alleles choosing the following regions:

450 Europe, North-East Asia, South-Asia, South-East Asia, Western Asia, North Africa
451 and Sub-Saharan Africa. Frequency comparisons were visualized with R software
452 (3.3.2) ⁶²using ggplot2 package.

453

454 We performed separate additive logistic regression analysis with the called HLA
455 alleles using R *glm* function in EstBB including age, sex and 10 PCs as covariates.
456 In UKBB we performed association analysis of each four-digit allele with the Z88.0
457 subcode using logistic regression function *glm* in R, adjusting for sex, age, age²,
458 recruitment center, genotyping array, and the first 15 principal components (and
459 excluding related [up to 2rd degree or closer] individuals and those of reported non-
460 white ancestry). Meta-analysis of 162 HLA alleles was performed with the GWAMA
461 software tool ⁶⁹. A Bonferroni-corrected P-value threshold of 3.09×10^{-4} was applied
462 based on the number of tested alleles: $0.05/162$. Meta-analyzed results passing this
463 threshold were considered significant.

464

465 **HLA-B*55:01 replication**

466 Replication analysis of the HLA-B*55:01 allele was tested on 87,996 cases and
467 1,031,087 controls of European ancestry (close relatives removed) from the
468 23andMe research cohort. The self-reported phenotype of penicillin allergy was
469 defined as an allergy test or allergic symptoms required for cases, with controls
470 having no allergy. All individuals included in the analyses provided informed consent
471 and participated in the research online, under a protocol approved by the external
472 AAHRPP-accredited IRB, Ethical & Independent Review Services (E&I Review). A
473 logistic regression assuming an additive model for allelic effects was used with
474 adjusting for age, sex, indicator variables to represent the genotyping platforms and

475 the first five genotype principal components. In the 23andMe replication study, the
476 HLA imputation was performed by using HIBAG⁷⁰ with the default settings. We
477 imputed allelic dosage for HLA-A, B, C, DPB1, DQA1, DQB1 and DRB1 loci at four-
478 digit resolution⁷¹.

479 Meta-analysis of the HLA-B*55:01 association in four cohorts was performed with the
480 GWAMA software tool⁶⁹ and results were visualized with R software (3.3.2)⁶².

481

482 **Phenome-wide study and HLA-B*55:01 allele association with lymphocyte** 483 **levels**

484

485 To analyze other traits that are associated with the tag variant of the HLA-B*55:01
486 allele in the UK Biobank and GWAS Catalog summary statistics, we used the Open
487 Targets Genetics platform²⁰. To study the association between the HLA-B*55:01
488 allele and lymphocyte levels in EstBB, we extracted the information on measured
489 lymphocyte levels (number of cells per nanoliter) from the free text fields of the
490 medical history of 4,567 unrelated individuals with genotype data. After removing
491 outliers based on the values of any data points which lie beyond the extremes of the
492 whiskers (values > 3.58 and < 0.26), a linear regression was performed using R
493 software and with age and sex as covariates.

494

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525

526 **Author Contributions**

527

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529 supervised and generated genotype data or HLA typing data. D.S. and S.L.
530 generated allergy data from free-text. K.K., J.B., M.L., T.J., J.C.C., J.F, W.W., A.A.,
531 performed the data analysis. K.K., J.B., M.V.H. C.M.L., R.M., L.M., J.C.C. and J.F.
532 conducted data interpretation. K.K. prepared the figures and tables. K.K, J.B., L.M.
533 and J.F. drafted the manuscript. K.K., J.B., M.V.H. C.M.L., M.L., R.M., L.M., J.C.C.,
534 W.W., A.A. and J.F. reviewed and edited the manuscript. All authors contributed to
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547

548 **Competing Interests statement**

549 C.M.L. has collaborated with Novo Nordisk and Bayer in research, and in
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551 W.W., A.A., and members of the 23andMe Research Team are employed by and
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553

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805 **Figure Legends**

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807 **Figure 1. Manhattan plot (A) and HLA locus (B) of the genome-wide association study**
808 **of allergy status to penicillin.**

809 The X-axes indicate chromosomal positions and Y-axes $-\log_{10}$ of the P-values **(A)** Each dot
810 represents a single nucleotide polymorphism (SNP). The dotted line indicates the genome-
811 wide significance ($P\text{-value} < 5.0 \times 10^{-8}$) P-value threshold. **(B)** SNPs are colored according to
812 their linkage disequilibrium (LD; based on the 1000 Genome phase3 EUR reference panel)
813 with the lead SNP. The SNP marked with a purple diamond is the top lead SNP
814 rs114892859 identified depending on LD structure.

815

816 **Figure 2. HLA-B*55:01 allele association with penicillin allergy-** The odds ratios (dots)
817 and 95% confidence intervals (CI, horizontal lines) for HLA allele associated with penicillin
818 allergy. The plot is annotated with P-values and case-control numbers. Color coding blue
819 and black indicates the results for discovery cohorts Estonian UK biobank and replication
820 results of the HLA*B-55:01 allele in 23andMe research cohort (green) and Vanderbilt
821 University's biobank BioVU (purple). Results of the meta-analysis of all four cohorts is
822 indicated with a diamond (red).

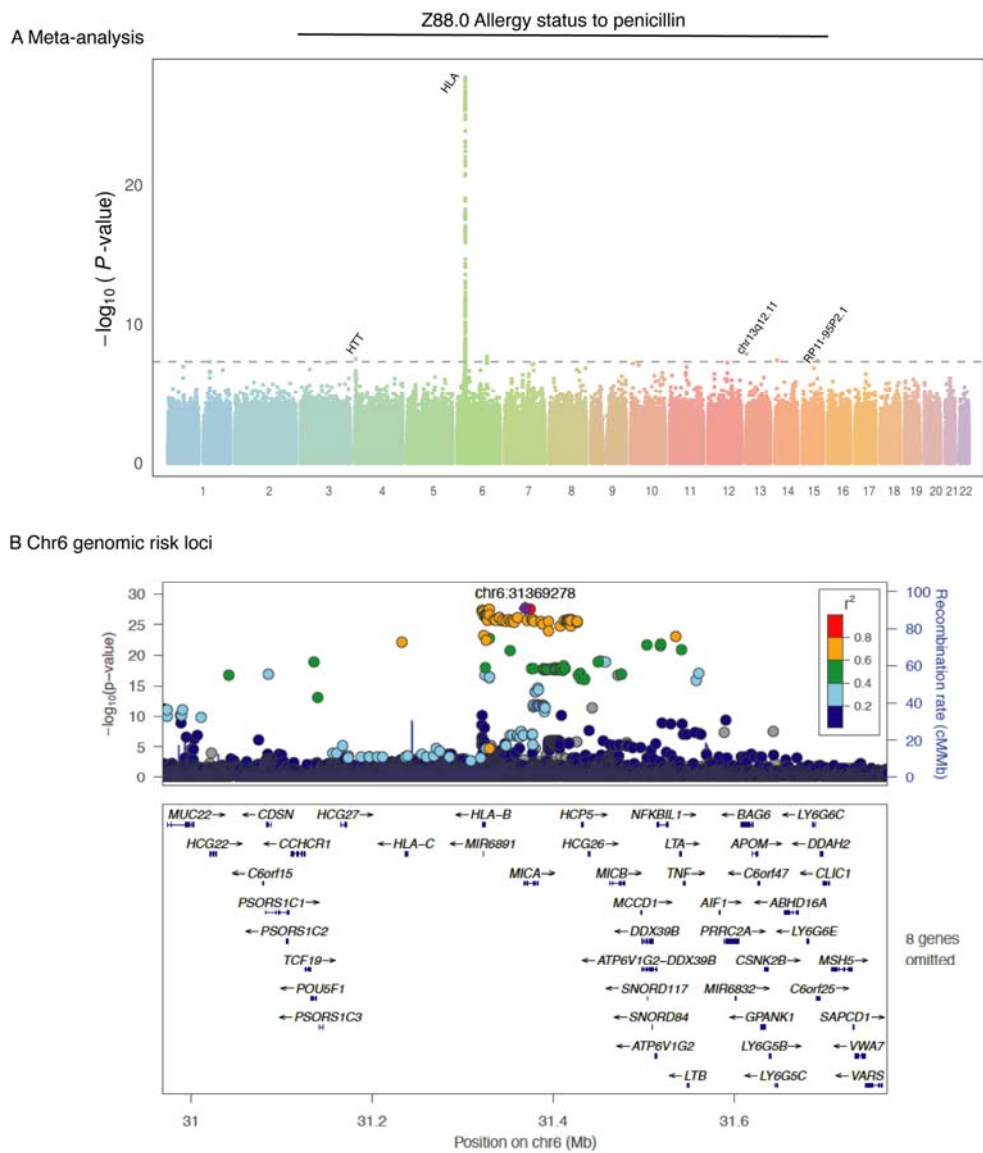
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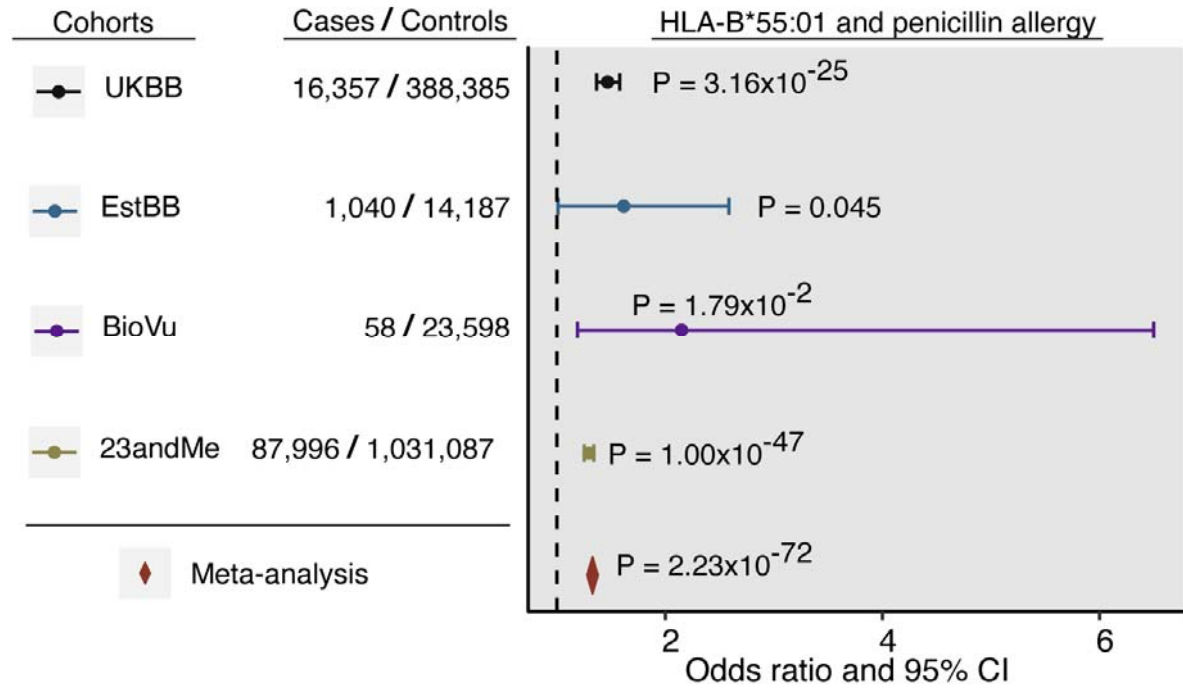
824 **Tables and Figures**

825

826 **Figure 1**

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