Human leukocyte antigen associations with renal function among ethnic minorities in the United Kingdom

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1 Title page

1.1 Title

Human leukocyte antigen associations with renal function among ethnic minorities in the United Kingdom

1.2 Short title

HLA and renal function in UK BAME communities

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1.6 Keywords

Kidney Failure, Chronic; Renal Insufficiency; Glomerular Filtration Rate; HLA Antigens; Genome-Wide Association Study; Polymorphism, Single Nucleotide; Imputation

2 Abstract

2.1 Background

Human leukocyte antigens (HLA) have been independently associated with increased or decreased renal function. However, previous studies report contradictory findings with little consensus on the exact nature or impact of this observation. There has been a lack of research into how HLA affects renal function in Black, Asian and Minority Ethnic (BAME) people in the UK, despite the fact that BAME people are disproportionately affected by renal dysfunction.

2.2 Methods

This study included over 27,000 subjects of six different ethnicities (>12,100 Irish, >5,400 Indian, >4,000 Black Caribbean, >3,000 Black African, >1,600 Pakistani, and >1,400 Chinese) aged 39-73 when they were recruited by UK Biobank between 2006 and 2010. Subjects' high-resolution HLA genotypes were imputed using HLA*IMP:02 software. Regression analysis was used to compare a total of 110 imputed HLA alleles with two different measures of estimated glomerular filtration rate (eGFR), one based on serum creatinine and one based on serum cystatin. Secondary analysis of CKD stage 2 subjects (compared to healthy controls) was also performed.

2.3 Results

Eleven imputed HLA alleles were associated with eGFR ($P < 0.001$). Six of these associations were based on creatinine in Black African subjects: HLA-B*53:01 ($\beta = -2.628$, $P = 8.38 \times 10^{-6}$); C*04:01 ($\beta = -1.667$, $P = 4.80 \times 10^{-4}$); DPA1*02:01 ($\beta = -1.569$, $P = 3.25 \times 10^{-4}$); and DPA1*02:02 ($\beta = -1.716$, $P = 4.49 \times 10^{-4}$) were linked to decreased renal function, while DRB1*03:01 ($\beta = 3.200$, $P = 7.13 \times 10^{-5}$) and DPA1*01:03 ($\beta = 2.276$, $P = 4.13 \times 10^{-7}$) were linked to increased renal function. Two of these alleles (HLA-B*53:01 and C*04:01) are commonly inherited together. In Irish subjects, HLA-DRB1*04:01 ($\beta = 1.075$, $P = 3.01 \times 10^{-4}$) and a lack of DRB4 genes ($\beta = 0.6193$, $P = 8.62 \times 10^{-4}$) were linked to increased eGFR (based on cystatin); in Indian subjects, HLA-DRB1*03:01 ($\beta = -1.72$, $P = 8.69 \times 10^{-5}$), DQB1*02:01 ($\beta = -1.755$, $P = 4.11 \times 10^{-5}$), and a reduced frequency of DRB3 genes ($\beta = -1.033$, $P = 4.88 \times 10^{-4}$) were associated with decreased eGFR (based on cystatin). No significant associations were found between HLA and renal function in any of the other three ethnic groups.

2.4 Conclusion

Eleven HLA alleles appear to be associated with kidney function in people of BAME backgrounds in the UK. This could have important applications for the diagnosis and treatment of renal disease and could help reduce health inequalities in the UK.

3 Main text

3.1 Introduction

Chronic kidney disease (CKD) is 17th in the worldwide list of diseases which cause the most “years of lost life”, according to the Global Burden of Disease 2015 study; it was 21st in 2005 and 25th in 1990¹. The same study reported that CKD caused 1.2 million deaths in 2015, an increase of 32% compared to 2005. In developed countries, treatment for end-stage renal disease (ESRD) typically accounts for around 2-3% of the overall healthcare budget². In England, CKD affects over 1.8 million people and over 40,000 people are on some form of renal replacement therapy (RRT, usually either dialysis or kidney transplantation)³.

Renal dysfunction is a problem that disproportionately affects Black, Asian and Minority Ethnic (BAME) people in the UK. Although BAME people represent only 11% of the UK population⁴, they accounted for 24% of patients dependent on renal replacement therapy in 2017⁵. BAME people are more likely to develop CKD than white people⁶, and those who have CKD experience faster decline in renal function than white people⁷. Understanding the genetic causes of renal dysfunction in BAME people in the UK could play an important role in reducing these health inequalities.

Heritability of CKD is thought to be between 30-75%⁸. The Human Leukocyte Antigen (HLA) system, encoded within the major histocompatibility complex, has been reported to be associated with renal function⁹. This may be because unique HLA alleles confer different levels of protection from different diseases associated with ¹⁰kidney dysfunction. Almost 100 HLA alleles and haplotypes have been linked to increased or decreased risk of renal failure¹¹. However, conflicting associations have been reported, for example HLA-A*11 was linked to increased ESRD in a study of Azerbaijani subjects¹² but protective against ESRD in a study of Turkish subjects¹³. This and other conflicting findings may be in part due to population stratification, as well as differing patterns of linkage disequilibrium (which lead to different combinations of genes among different ethnicities), and environmental effects.

This study uses a cohort of over 27,000 subjects aged 39-73 who were recruited in the UK but do not identify as ethnically “British”. The study aims to discover high-resolution HLA alleles which are associated with either increased or decreased renal function. Most previous studies used case-control methodology with a smaller number of subjects, usually all of a single ethnicity or nationality. Here we present the findings of a retrospective cohort study using subjects of six different ethnicities who are mostly healthy.

3.2 Methods

3.2.1 Quality control and identification of study population

This study used data from UK Biobank (UKB) to test for associations between HLA and renal function in over 27,000 subjects from six different self-reported ethnic groups (Irish, Indian, Black Caribbean, Black African, Pakistani, and Chinese). UKB holds data on 502,616 subjects who were aged 39-73 when they were recruited in the UK between 2006-2010. 409,692 subjects (81.5%) reported their ethnic background as “British” and genetic principal component analysis performed by UKB concurred; these subjects were analysed separately and the results reported elsewhere. The remaining 92,924 subjects (those who did not report their ethnic background to be “British”, and those who self-identified as “British” but UKB’s principal component analysis suggested were not British) were considered for this study.

714 individuals were removed during quality control. Of these: 129 had ambiguous genetic sex (a confounder in the calculation of subjects’ kidney function); 420 were related to other subjects in the cohort (kinship coefficient ≥ 0.044 ; the individual with the most complete set of genetic data was included); 132 were removed at UKB’s recommendation due to “missing genetic data”; and 33 withdrew their consent to be included in the study. There were 92,210 subjects remaining after quality control.

As previous studies have suggested that HLA associations with renal function vary depending on ethnicity, subjects were analysed only within their ethnic groups. There were 23 different groups depending on subjects’ answers to the question, “What is your ethnic background?” Only groups of 1,000 or more subjects were analysed in this study in order to reduce type I and type II errors. A minimum cohort size of 1000 unrelated individuals provides 94% power to detect a genetic effect size of 3%, assuming a 5% minor allele frequency (minimum used in our analysis) and additive model. We used a significance threshold of $P < 7.4 \times 10^{-5}$ (correction for multiple testing). Furthermore, ethnic backgrounds which were unknown, mixed, or categorised as something “other” than the options provided (for example “any other white background”) were excluded from the analysis due to possible heterogeneity. Finally, the subjects who self-reported as “British” but whom UKB deemed not to be British were also excluded. This left a total of six ethnic backgrounds to be analysed: Irish (N=13,071); Indian (N=5,919); Black Caribbean (N=4,488); Black African (N=3,386); Pakistani (N=1,822); and Chinese (N=1,563). Table 1 shows the 23 ethnic groups, the number of subjects in each group, and whether the group was included in the analysis (along with reasons for exclusion if applicable).

Table 1

3.2.2 HLA typing

Subjects were HLA typed by UKB using single nucleotide polymorphism imputation. HLA*IMP:02 software¹⁴ was used to impute the following HLA loci: HLA-A, B, C (Class I) and DPA1, DPB1, DQA1, DQB1, DRB1, DRB3, DRB4, DRB5 (Class II) at a level equivalent to high-resolution typing using eight reference datasets. 362 high-resolution HLA genotypes were imputed, though some were excluded due to their frequencies not being in Hardy-Weinberg equilibrium (HWE), $P < 0.00014$. Overall, 9 alleles were excluded from particular ethnic groups due to HWE analysis (1 Irish, 4 Indian, 1 Black Caribbean, 1 Black African, 2 Pakistani, and 0 Chinese). Only alleles with $>5\%$ frequency were considered for analysis. There were a total of 110 alleles with $>5\%$ frequency in at least one cohort (47 for Irish subjects, 58 Indian, 56 Black Caribbean, 57 Black African, 56 Pakistani, and 50 Chinese). Table 2 shows the alleles which had $>5\%$ frequency in each ethnic group, as well as which alleles were excluded due to HWE analysis.

Table 2

3.2.3 Measuring renal function

Renal function was primarily measured using estimated glomerular filtration rate (eGFR), based on two biomarkers: creatinine and cystatin. High levels of these biomarkers in a subject's serum are a sign of decreased renal function, while low levels are a sign of increased renal function. Subjects with decreased renal function have lower eGFRs than those with normal or increased renal function. This study used the CKD-EPI method of calculating eGFR¹⁵, which adjusts for age, sex, and ethnicity. Two separate formulae were used: one based on creatinine, and one based on cystatin. 2,333 subjects were missing creatinine values (7.8%) and 2,322 were missing cystatin values (7.7%), and were excluded from the corresponding analyses. For both formulae, eGFR is measured in millilitres per minute and the unit of any eGFR value reported in this text is "mL/min/1.73m²". eGFR ≥ 120 mL/min/1.73m² is considered healthy, with lower eGFRs being indicative of decreasing renal function. eGFR < 60 is indicative of CKD stage 3, while eGFR < 15 mL/min/1.73m² is indicative of CKD stage 5 (ESRD, requiring RRT). A table summarising eGFRs by ethnicity can be seen in the Results section.

Subjects were also sorted into categories based on their eGFR and secondary "case-control" analysis was performed. Subjects with eGFR (based on cystatin) < 90 mL/min/1.73m² (a "mild" decrease in renal function, indicative of at least CKD stage 2 when combined with evidence of kidney damage¹⁶) were compared to subjects with eGFR ≥ 90 mL/min/1.73m² ("normal or increased" renal function).

3.2.4 Regression analysis

Linear regression analysis was used to test for associations between HLA alleles (the predictor variable) and eGFR (a continuous outcome variable). 188 subjects who had received RRT were excluded from this analysis, as their eGFR values may have suggested healthy renal function even though their native function was poor. The total number of subjects included in analysis of eGFR based on creatinine was: 12,140 Irish; 5,427 Indian; 4,068 Black Caribbean; 3,012 Black African; 1,649 Pakistani; and 1,432 Chinese (27,728 total). For analysis of eGFR based on cystatin, the number of subjects included was: 12,143 Irish; 5,428 Indian; 4,068 Black Caribbean; 3,017 Black African; 1,649 Pakistani; and 1,434 Chinese (27,739 total). Separate regression analyses were performed for each of the six ethnic groups and both eGFR formulae.

Logistic regression analysis was performed to test for HLA associations in subjects with eGFR (based on cystatin) $<90\text{mL/min/1.73m}^2$ versus controls with eGFR $\geq 90\text{mL/min/1.73m}^2$. After excluding subjects with missing eGFR and those who had received RRT, there were 12,752 cases and 14,987 controls (Irish: 5,964 cases and 6,179 controls; Indian: 3,199 cases and 2,229 controls; Black Caribbean: 1,406 cases and 2,662 controls; Black African: 951 cases and 2,066 controls; Pakistani: 905 cases and 744 controls; Chinese: 327 cases and 1,107 controls).

In all analyses, age and sex were included as covariates. Bonferroni correction thresholds were applied for each ethnic group based on the number of alleles analysed within that group. P values for significance ranged from $P < 0.00109$ (0.05/46, Irish subjects) to $P < 0.00089$ (0.05/56, Black African subjects and Black Caribbean subjects). All analysis was performed using Plink software¹⁷.

3.3 Results

3.3.1 eGFR values by ethnicity

Table 3 summarises the eGFR values calculated, stratified by ethnicity. All calculated eGFR values are included, although some subjects were excluded from analysis due to receiving RRT.

Table 3

3.3.2 Regression analysis

After correction for multiple testing, eleven associations were found between HLA and renal function in UK ethnic minority groups. Six of these relate to Black African subjects: HLA-B*53:01 (beta= -2.628 , $P=8.38 \times 10^{-6}$); C*04:01 (beta= -1.667 , $P=4.80 \times 10^{-4}$); DPA1*02:01

($\beta=-1.569$, $P=3.25 \times 10^{-4}$); and DPA1*02:02 ($\beta=-1.716$, $P=4.49 \times 10^{-4}$) were linked to decreased eGFR (based on creatinine) in Black Africans, while DRB1*03:01 ($\beta=3.200$, $P=7.13 \times 10^{-5}$) and DPA1*01:03 ($\beta=2.276$, $P=4.13 \times 10^{-7}$) were linked to increased eGFR (also based on creatinine). In Irish subjects, HLA-DRB1*04:01 ($\beta=1.075$, $P=3.01 \times 10^{-4}$) and a lack of DRB4 genes ($\beta=0.6193$, $P=8.62 \times 10^{-4}$) were associated with increased eGFR (based on cystatin). HLA-DRB1*04:01 was also associated with decreased risk of CKD (stage 2 or worse) in Irish subjects (odds ratio=0.836, $P=1.77 \times 10^{-4}$). In Indian subjects, HLA-DRB1*03:01 ($\beta=-1.72$, $P=8.69 \times 10^{-5}$), DQB1*02:01 ($\beta=-1.755$, $P=4.11 \times 10^{-5}$), and a lack of DRB3 genes ($\beta=-1.033$, $P=4.88 \times 10^{-4}$) were associated with decreased eGFR (based on cystatin). There were no significant associations found between HLA and eGFR for any of the other three ethnic groups (Black Caribbean, Pakistani, and Chinese). Table 4 shows all alleles significantly associated with eGFR. The table also shows the frequency of the allele within the ethnic group, the direction of the allele's association with kidney function (increase or decrease), which eGFR formula the allele was associated with (creatinine or cystatin), the beta value (the size and direction of the association with eGFR) and (if applicable) the odds ratio (size and direction of the association with CKD stage 2 or worse). Adjusted P values of the associations are also provided.

Table 4

3.4 Discussion

The findings suggest that there may be HLA alleles which are associated with kidney function in BAME groups in the UK, especially Black Africans. Some findings replicated associations which had previously been reported. HLA-DRB1*03 has been found to be protective against IgA nephropathy in European people¹⁸; this study found that DRB1*03:01 was linked to increased renal function in Black African subjects. On the other hand, the same gene has been reported to be linked to increased risk of kidney dysfunction in Taiwanese¹⁹, Saudi Arabian²⁰, Turkish¹³, and Brazilian²¹ subjects. This study also found that HLA-DRB1*03:01 is linked to decreased kidney function in Indian subjects. Similarly, HLA-DRB1*04:01 has been linked to increased renal function in a study of Mexican subjects²², but decreased renal function in two Chinese studies^{23,24} and one German study²⁵. This study found HLA-DRB1*04:01 to be associated with increased kidney function in Irish subjects. HLA-DRB1*03:01 and DRB1*04:01, therefore, appear to have complex interactions with kidney function which may differ depending on ethnicity. Furthermore, our observation that HLA-B*53:01 is linked to decreased kidney function in Black Africans replicated the findings of a study of Venezuelan subjects, for whom the allele was associated with increased ESRD²⁶. Finally, our finding that HLA-DQB1*02:01 was linked to decreased kidney function

in Indians replicated a study of Chinese subjects, for whom the gene was associated with increased renal failure²⁷.

Two of the alleles linked to decreased kidney function in Black African subjects (HLA-B*53:01 and C*04:01) form a common (9.2% frequency) haplotype in African Americans²⁸. This suggests that the genes may not be independently associated with renal function, but represent an associated haplotype. HLA-C*04:01 was analysed in every ethnic group except Chinese in this study but was only significant in the analysis of Black Africans. This may suggest that the gene itself does not contribute to decreased kidney function, but its apparent association is a result of its strong linkage disequilibrium with HLA-B*53:01. Alternatively, it may be associated with renal function in other ethnicities but this association may not have been detected due to lower frequency (and therefore reduced power) in non-Black cohorts. The other genes associated with renal function in Black African subjects do not appear to be part of well-documented haplotypes.

Six of the eleven significant associations relate to creatinine in Black African subjects. A possible reason for this may be that creatinine levels are partially dependent on muscle mass and are therefore affected by ethnicity¹⁵. This may particularly affect estimates of GFR for Black subjects, who have higher muscle mass than other ethnic groups on average²⁹. The CKD-EPI formula does adjust for ethnicity, but it is possible that this adjustment is not adequate, which could lead to false positive findings when analysing Black subjects.

The different populations showed different allele frequencies. 110 different alleles had >5% frequency in at least one ethnic group, but only 17 had >5% frequency in all six groups. As allele frequencies were so different among the different ethnic groups, it was essential to analyse ethnic groups separately in this study. The differing HLA frequencies across different populations may explain why renal dysfunction is more prevalent in some ethnic groups than others. However, Black African and Black Caribbean cohorts showed similar frequencies for many alleles, but none of the findings were replicated across the two groups. This is typical of association studies between HLA and renal function; findings are often not replicated even among apparently similar cohorts, possibly due to environmental differences or other genetic factors.

3.4.1 Implications

These findings suggest that, even within a broadly healthy population of people, HLA alleles may have an impact on renal function. Absolute effect sizes range from 0.62mL/min/1.73m² to 3.20mL/min/1.73m². One finding (HLA-DRB1*04:01 being linked to increased eGFR in Irish subjects) was replicated in the secondary analysis of clinical outcomes (the gene was linked to decreased risk of CKD stage 2 or worse); this suggests that small beta values are

not a contraindication of clinical relevance. HLA typing may, therefore, help predict which people are at increased or decreased risk of developing adverse clinical outcomes. HLA association typing is already used to help diagnose a number of diseases³⁰⁻³²; it may be possible to use the findings of this study to help identify patients at risk of developing renal dysfunction and provide them with accelerated clinical pathways. It may particularly be of importance in combination with other concomitant clinical conditions like diabetes and hypertension which have a direct impact on kidney function. Likewise, it may be possible to use this data to reassure potential kidney donors with very good and stable renal function about long-term renal function. However, the findings are limited and additional research is required before these changes could be enacted.

3.4.2 Strengths and weaknesses

A strength of this study is that the primary outcome measure, eGFR, is an accurate and precise way to measure kidney function. Renal function is a continuous spectrum, and eGFR reflects this. Previous studies, which often used binary categorisations such as “ESRD or healthy”, sacrificed precision by using these broad categories. The CKD-EPI method is particularly accurate when assessing renal function in healthy individuals³³, so was the most appropriate formula for this study. Another strength of this study may be the size of the study groups (ranging from >1,400 Chinese subjects to >12,000 Irish), which are larger than many previous studies which have attempted to find associations between HLA and renal function. However, most previous studies used a case-control methodology, rather than a retrospective cohort methodology, so it is difficult to directly compare sample sizes. The adjustment for multiple testing applied in this study was stringent, with low P values required for results to be declared significant. For this reason, significant results are less likely to include type I errors. Age and sex were adjusted as covariates, which further reduces the chance of type I errors.

A limitation of this study is the HLA typing method (imputation), which is not as accurate as direct genotyping³⁴. The reason that imputation was used is that it is more cost-effective than laboratory-based typing, which would have been prohibitively expensive. The imputation program used by UKB, HLA*IMP:02, was reported to be only 62% accurate when imputing African American subjects. The same study found another HLA imputation program, SNP2HLA, to be 92% accurate³⁴. However, only nine alleles were not in HWE for particular ethnic groups (while 2,163 were in HWE, 99.6%), demonstrating that the frequencies of alleles were consistent with expected frequencies. This contributed to an increased confidence in HLA assignment.

Although this study includes six different ethnic groups (whereas most of the existing literature focuses on only a single ethnicity), there were many ethnic groups excluded from the analysis. Repeating the testing with more ethnicities may lead to further discoveries, since it appears that HLA associations with renal function vary according to ethnic background. The study also used self-reported ethnicity, which may be less accurate than evaluations of ethnicity based on more thorough genetic analysis. The UKB dataset may also not be representative of the respective populations. This would limit the extent to which findings can be applied to the populations as wholes. Finally, although study groups were relatively large, the lack of significant findings suggests that larger samples may be required in order to reliably detect associations, particularly if the associations are small.

3.5 Conclusion

This study identified eleven HLA associations with eGFR in people from BAME backgrounds in the UK. Six of these relate to Black African, three to Indian and two to Irish populations. One finding was replicated in the secondary analysis of clinical outcomes. No associations were found for any of the other three ethnicities studied. All of the alleles studied were in HWE and were present in >5% of the relevant population. It is possible that there are further HLA associations with renal function but this study's cohort may not have been large enough to detect these; future analysis with larger study groups and a broader range of ethnicities may reveal additional associations.

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The authors declare no conflicts of interests.

Data cannot be shared as access is restricted to individuals named on the application to UK Biobank.

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6 Tables

Table 1: Subjects by self-reported ethnic background

Self-reported ethnic group	Self-reported ethnic background	N	Included in analysis
White	Prefer not to answer	567	No [†]
	British	32,662	No [‡]
	Irish	13,071	Yes
	Any other white background	16,252	No*
Mixed	Prefer not to answer	48	No**†
	White and Black Caribbean	619	No**†
	White and Black African	423	No**†
	White and Asian	831	No**†
	Any other mixed background	1,029	No*
Asian or Asian British	Prefer not to answer	42	No [†]
	Indian	5,919	Yes
	Pakistani	1,822	Yes
	Bangladeshi	236	No [†]
	Any other Asian background	1,809	No*
Black or Black British	Prefer not to answer	27	No [†]
	Caribbean	4,488	Yes
	African	3,386	Yes
	Any other Black background	123	No**†
Chinese		1,563	Yes
Prefer not to answer		1,651	No*
Do not know		216	No**†
Other ethnic group		4,537	No*
Data missing		889	No**†
Total		92,210	

*Excluded as ethnic group was mixed or “other” or missing

†Excluded as group size was less than 1,000

‡Excluded as these subjects self-reported their ethnic background as “British”, but UKB’s principal component analysis suggested they were not British

Table 2: HLA alleles by ethnicity with >5% frequency and HLA alleles excluded due to HWE analysis

HLA-	Irish	Indian	Black Caribbean	Black African	Pakistani	Chinese
A*01:01	23.1%	15.2%	-	-	15.9%	-
A*11:01	6.9%	13.4%	-	-	13.3%	24.0%
A*11:02	-	-	-	-	- †	-
A*02:01	25.9%	5.2%	10.6%	9.4%	5.8%	8.7%
A*02:02	-	-	-	5.1%	-	-
A*02:07	-	-	-	-	-	8.6%
A*23:01	-	-	11.3%	10.7%	-	-
A*24:02	6.3%	11.6%	-	-	11.4%	14.9%
A*26:01	-	5.5% †	-	-	7.1%	-
A*30:01	-	-	7.6%	8.1%	-	-

A*30:02	-	-	6.7%	8.1%	-	-
A*03:01	14.2%	6.4%	7.9%	7.1%	5.8%	-
A*33:03	-	9.3%	5.9%	6.0%	7.2%	11.1%
A*68:01	-	6.7%	-	-	7.4%	-
A*68:02	-	-	6.6%	7.1%	-	-
A*74:01	-	-	6.5%	6.1%	-	-
B*13:01	-	-	-	-	-	5.9%
B*15:02	-	-	-	-	-	6.3%
B*15:03	-	-	-	5.4%	-	-
B*35:01	-	-	6.6%	6.8%	-	-
B*35:03	-	5.6%	-	-	5.3%	-
B*40:01	-	-	-	-	-	13.7%
B*42:01	-	-	5.9%	6.4%	-	-
B*44:02	12.1%	-	-	-	-	-
B*44:03	5.6%	6.1%	-	-	-	-
B*46:01	-	-	-	-	-	13.4%
B*51:01	-	7.7%	-	-	9.1%	5.1%
B*52:01	-	7.2%	-	-	7.4%	-
B*53:01	-	-	13.0%	14.4%	-	-
B*57:01	-	5.2%	-	-	-	-
B*58:01	-	-	-	-	-	9.3%
B*07:02	17.8%	-	6.8%	6.2%	-	-
B*08:01	17.5%	6.4%	-	-	9.6%	-
C*01:02	-	-	-	-	-	20.1%
C*12:02	-	8.2%	-	-	7.9%	-
C*12:03	-	5.9%	-	-	6.9%	-
C*15:02	-	10.4%	-	-	10.3%	-
C*16:01	-	-	9.2%	9.5%	-	-
C*17:01	-	-	7.1%	8.1%	-	-
C*03:02	-	-	-	-	-	9.4%
C*03:04	5.4%	-	5.1%	5.1%	-	10.5%
C*04:01	6.6%	13.3%	22.4%	23.4%	12.5%	-
C*05:01	12.0%	-	-	-	-	-
C*06:02	9.3%	13.3%	6.9%	6.5%	13.6%	-
C*07:01	20.3%	9.4%	12.1%	11.5%	8.1%	-
C*07:02	18.9%	13.6%	6.7%	6.0%	14.2%	17.7%
C*08:01	-	-	-	-	-	10.6%
C*08:02	5.7%	-	-	-	-	-
DPA1*01:03	18.0%	33.9%	34.7%	28.0%	32.7%	32.2%
DPA1*02:01	14.3%	24.6%	32.6%	32.7%	24.7%	9.0%
DPA1*02:02	-	8.2%	18.7%	22.3%	6.8%	45.1%
DPA1*03:01	-	-	9.7%	11.7%	-	-
DPB1*01:01	-	-	33.5%	37.9% †	-	-
DPB1*13:01	-	6.2%	-	-	5.6%	5.6%
DPB1*17:01	-	-	6.3%	6.9%	-	-
DPB1*18:01	-	-	5.4%	-	-	-
DPB1*02:01	10.1%	18.4%	8.9%	7.9%	16.5%	15.3%
DPB1*02:02	-	-	-	-	-	6.3%
DPB1*26:01	-	5.1%	-	-	5.4%	-
DPB1*03:01	9.5%	-	-	-	-	-
DPB1*04:01	47.2%	36.0%	8.2%	-	38.1%	8.1%
DPB1*04:02	8.8%	7.4%	11.6%	12.4%	7.5%	-

DPB1*05:01	-	-	-	-	-	40.4%
DQA1*01:01	12.4%	18.0%	13.1%	13.4%	16.2%	11.4%
DQA1*01:02	23.4%	9.9%	30.4%	30.1%	9.2%	17.5%
DQA1*01:03	-	20.6%	-	-	18.5%	7.4%
DQA1*02:01	15.7%	15.0%	10.4%	8.9%	14.6%	-
DQA1*03:01	18.1%	9.5%	7.9%	7.4%	7.3%	28.1%
DQA1*04:01	-	-	11.6%	12.8%	-	-
DQA1*05:01	23.3%	21.6% †	17.8%	18.0%	30.0%	16.8%
DQA1*06:01	-	-	-	-	-	10.2%
DQB1*02:01	17.5%	12.2%	12.4%	12.9%	18.1%	7.1%
DQB1*02:02	9.6% †	8.4%	-	-	8.9%	-
DQB1*03:01	15.4%	13.0%	16.9%	16.9%	13.9% †	20.8%
DQB1*03:02	8.5%	7.9%	-	-	5.9%	6.3%
DQB1*03:03	5.1%	5.6%	-	-	5.5%	16.2%
DQB1*04:01	-	-	-	-	-	5.4%
DQB1*04:02	-	-	7.3%	8.0%	-	-
DQB1*05:01	10.9%	9.8%	14.3%	15.0%	8.9%	-
DQB1*05:02	-	-	-	-	-	10.2%
DQB1*05:03	-	8.6%	-	-	7.3%	-
DQB1*06:01	-	14.6%	- †	-	12.8%	10.9%
DQB1*06:02	18.8%	-	17.3%	16.1%	-	-
DQB1*06:03	-	6.8%	-	-	6.3%	-
DRB1*10:01	-	6.4%	-	-	5.3%	-
DRB1*01:01	7.1%	-	-	-	-	-
DRB1*01:02	-	-	5.1%	5.7%	-	-
DRB1*11:01	-	5.3%	7.7%	8.0%	5.6%	-
DRB1*12:02	-	-	-	-	-	10.6%
DRB1*13:01	-	6.5%	-	5.7%	6.0%	-
DRB1*13:02	-	-	6.5%	7.0%	-	-
DRB1*15:01	19.2%	9.8%	-	-	8.3%	8.8%
DRB1*15:02	-	10.1%	-	-	9.5%	-
DRB1*15:03	-	-	12.7%	13.1%	-	-
DRB1*03:01	17.5%	11.6%	6.4%	6.6%	17.7%	7.2%
DRB1*03:02	-	-	6.2%	7.3%	-	-
DRB1*04:01	9.8%	-	-	-	-	-
DRB1*04:05	-	-	-	-	-	6.0%
DRB1*07:01	15.7%	14.9%	8.9%	7.7%	14.6%	-
DRB1*08:03	-	-	-	-	-	6.2%
DRB1*08:04	-	- †	6.5%	7.0%	-	-
DRB1*09:01	-	-	-	-	-	15.6%
DRB3*01:01	19.5%	5.8%	13.4%	14.5%	5.1%	-
DRB3*02:02	9.3%	27.8% †	24.0%	24.6%	35.3%	20.3%
DRB3*03:01	-	-	9.4%	10.1%	-	11.6%
DRB3 - no gene	32.7%	41.2%	49.2%	47.9%	47.3%	40.4%
DRB4*01:01	9.1%	-	8.4%	8.0%	-	-
DRB4*01:03	23.2%	20.5%	-	-	19.1%	27.8%
DRB4 - no gene	33.7%	24.9%	16.2%	14.7%	22.5%	34.2%
DRB5*01:01	19.1%	8.8%	15.0%	13.8%	7.8%	12.0%
DRB5 - no gene	19.6%	11.7%	17.5%	16.7%	11.4%	14.3%
No. alleles included in analysis	46	55	56	56	55	50

- Allele had <5% frequency among this ethnic group so was excluded from analysis

† Allele was not in HWE in this ethnic group so was excluded from analysis

Table 3: summary of calculated eGFR values

Ethnicity	No. subjects with eGFR based on creatinine calculated	Average eGFR based on creatinine in mL/min/1.73m ² (SD)	No. subjects with eGFR based on cystatin calculated	Average eGFR based on cystatin in mL/min/1.73m ² (SD)
Irish	12,191	92.4 (13.3)	12,194	89.1 (16.2)
Indian	5,475	94.6 (14.4)	5,475	84.5 (18.4)
Black Caribbean	4,101	98.3 (17.7)	4,100	94.5 (16.7)
Black African	3,038	102.0 (18.1)	3,041	96.1 (16.8)
Pakistani	1,662	97.0 (17.6)	1,662	86.5 (17.7)
Chinese	1,435	98.2 (12.6)	1,437	98.9 (13.5)

Table 4: Alleles associated with renal function

HLA-	Freq	Effect on renal function	eGFR				CKD stage 2 or w	
			Based on	Beta (mL/min/1.73m ²)	P value	Adjusted P value	Odds ratio	P value
Black African subjects (P<8.9x10 ⁻⁴)								
B*53:01	14.4%	Decrease	Creatinine	-2.628	8.38x10 ⁻⁶	4.7x10 ⁻⁴	Not significant	
C*04:01	23.4%	Decrease	Creatinine	-1.667	4.80x10 ⁻⁴	0.027		
DRB1*03:01	6.6%	Increase	Creatinine	3.2	7.13x10 ⁻⁵	0.004		
DPA1*01:03	28.0%	Increase	Creatinine	2.276	4.13x10 ⁻⁷	2.3x10 ⁻⁵		
DPA1*02:01	32.7%	Decrease	Creatinine	-1.569	3.25x10 ⁻⁴	0.018		
DPA1*02:02	22.3%	Decrease	Creatinine	-1.716	4.49x10 ⁻⁴	0.025		
Irish subjects (P<1.1x10 ⁻³)								
DRB1*04:01	9.8%	Increase	Cystatin	1.075	3.01x10 ⁻⁴	0.014	0.836	1.77x10 ⁻⁴
DRB4 – no gene	33.7%	Increase	Cystatin	0.619	8.62x10 ⁻⁴	0.040	Not significant	
Indian subjects (P<9.1x10 ⁻⁴)								
DRB1*03:01	11.6%	Decrease	Cystatin	-1.72	8.69x10 ⁻⁵	0.005	Not significant	
DQB1*02:01	12.2%	Decrease	Cystatin	-1.755	4.11x10 ⁻⁵	0.002		
DRB3 – no gene	41.2%	Decrease	Cystatin	-1.033	4.88x10 ⁻⁴	0.027		