RHEUMATOLOGY

Rheumatology 2017;56:i67–i77
doi:10.1093/rheumatology/kew399
Advance Access publication 5 December 2016

The SLE review series: working for a better standard of care

The effect of ethnicity and genetic ancestry on the epidemiology, clinical features and outcome of systemic lupus erythematosus

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Abstract

In this in-depth review, we examine the worldwide epidemiology of SLE and summarize current knowledge on the influence of race/ethnicity on clinical manifestations, disease activity, damage accumulation and outcome in SLE. Susceptibility to SLE has a strong genetic component, and trans-ancestral genetic studies have revealed a substantial commonality of shared genetic risk variants across different genetic ancestries that predispose to the development of SLE. The highest increased risk of developing SLE is observed in black individuals (incidence 5- to 9-fold increased, prevalence 2- to 3-fold increased), with an increased risk also observed in South Asians, East Asians and other non-white groups, compared with white individuals. Black, East Asian, South Asian and Hispanic individuals with SLE tend to develop more severe disease with a greater number of manifestations and accumulate damage from lupus more rapidly. Increased genetic risk burden in these populations, associated with increased autoantibody reactivity in non-white individuals with SLE, may explain the more severe lupus phenotype. Even after taking into account socio-economic factors, race/ethnicity remains a key determinant of poor outcome, such as end-stage renal failure and mortality, in SLE. Community measures to expedite diagnosis through increased awareness in at-risk racial/ethnic populations and ethnically personalized treatment algorithms may help in future to improve long-term outcomes in SLE.

Key words: systemic lupus erythematosus, lupus nephritis, ethnicity, ethnic groups, ancestry, genetics, epidemiology, incidence, prevalence, autoantibodies

Rheumatology key messages

- SLE occurs more frequently in African, Caribbean, Asian and Hispanic individuals compared with white Europeans.
- African, Asian and Hispanic individuals with SLE are at risk of more severe and more destructive disease.
- African ancestry is associated with worse outcome in SLE, including end-stage renal failure and mortality.

Introduction

Over recent years, our understanding of SLE has advanced at the level of its epidemiology, genetic susceptibility and depth of understanding of molecular mechanisms underlying its pathogenesis. These advances have been achieved through national and international collaboration between SLE researchers and clinicians, in conjunction with the harnessing of post-genome era technology. Early studies on the influence of ethnicity on the incidence and prevalence of SLE are thoroughly described in a key review by Danchenko *et al*. [1], and a subsequent analysis of SLE epidemiological studies including the effect of ethnicity on clinical manifestations was last comprehensively conducted by Borchers *et al*. [2]. The present review concentrates on highlighting and contrasting additional information from subsequent studies.

Worldwide epidemiology of SLE

Reliable studies of the incidence and prevalence of SLE remain few and far between, owing to problems of cohorts

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Submitted 25 July 2016; revised version accepted 3 October 2016

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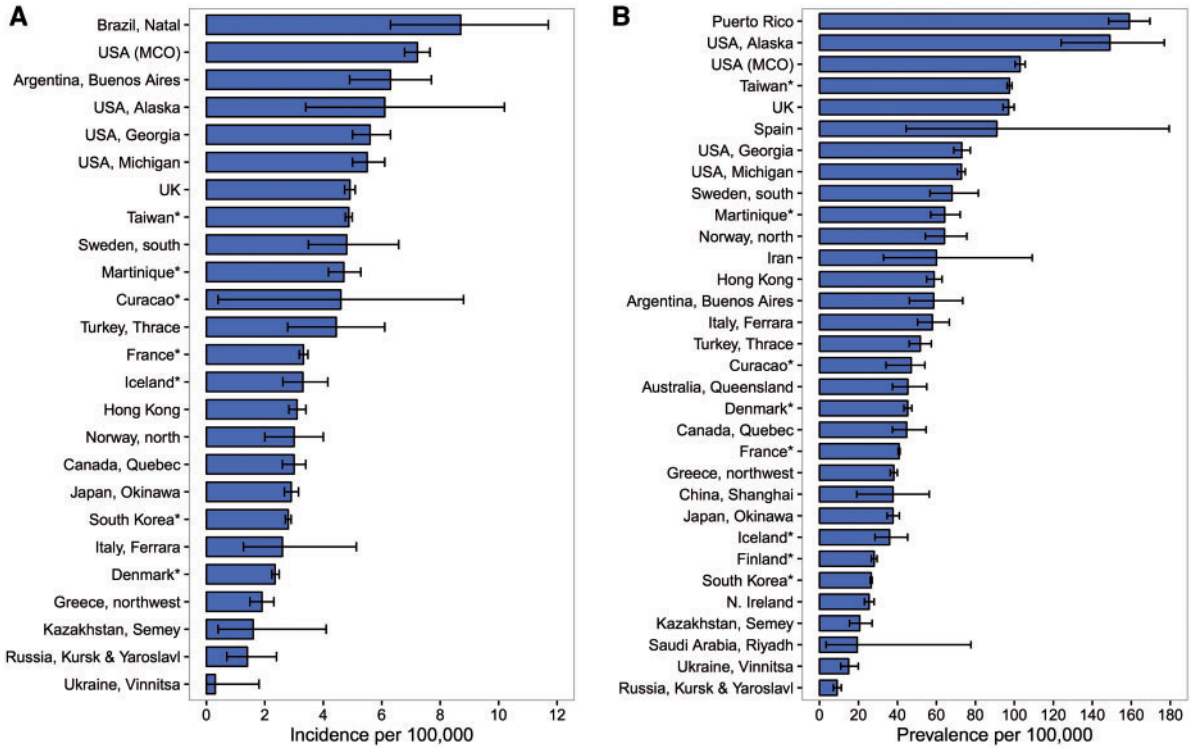
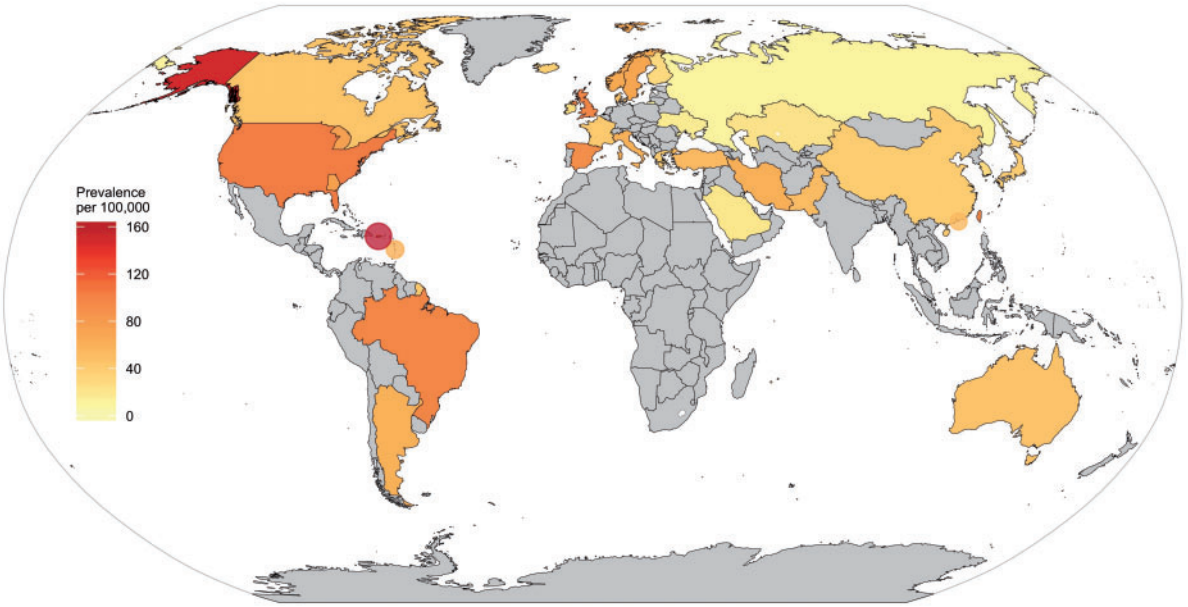
Fig. 1 Epidemiological studies of SLE in different countries



Incidence (**A**) and prevalence (**B**) of SLE in epidemiological studies across the world. Where multiple studies are available for a country or region, the largest and/or most recent data are represented. Error bars show 95% CIs for incidence and prevalence. Where CIs were not published, they were calculated based on case number and incidence/prevalence. Asterisks indicate countries/administrative regions with nationwide data.

being incomplete or drawn from populations that are not closed or for which the boundaries are unclear. In many countries, a lack of high-quality census data has prohibited many cohort studies from reporting accurate incidence and prevalence figures, even where consistent patient registries have been built up over a number of years. In countries with more extensive public health systems, accurate SLE patient registries have in the past provided important information on incidence and prevalence, including studies from Denmark, Finland, Norway, Sweden and the UK [3–7]. More recent studies have benefited from improved definitions of SLE diagnosis based first on the 1997 ACR classification criteria for SLE, and the more recent 2012 SLICC revision of the ACR criteria. However, few studies have used the capture–recapture technique to improve validity. Two recent large and comprehensive studies from Michigan and Georgia cohorts in the USA [8, 9] showed remarkable consistency and reported the incidence of SLE as 5.5 and 5.6 per 100 000, respectively, and the prevalence of SLE as 72.8 and 73.0 per 100 000, based on data from 2002–4. Comparison of studies across the world shows a wide range of prevalence from 25–28 per 100 000 in Northern Ireland, Finland and Denmark [3, 7, 10] to 149 per 100 000 in Alaska [11] and 159 per 100 000 in Puerto Rico [12]. These studies are summarized in Figs 1 and 2. Direct comparisons between countries are problematic, because of a clear increase in both the incidence and prevalence of SLE over time, as shown in Fig. 3. A recent large UK study reported a relatively stable overall incidence of 4.9 per 100 000 per year over the time period 1999–2012, whereas the prevalence of SLE increased steadily from 65.0 per 100 000 in 1999 to 97.0 per 100 000 in 2012 [13]. Comparison of studies across the world from the 1970s through to the present day (Fig. 2) illustrates that the prevalence of SLE has increased over time, with studies in the 1970s reaching a maximal prevalence of 40 per 100 000, whereas several large studies performed since 2000 have reported point prevalence of 100 per 100 000 or more [12–15]. The incidence of SLE has not increased over time to the same extent, but there are still a significant number of recent studies from the UK, USA and Taiwan with incidence rates ranging from 4.8 to 7.2 per 100 000, a level not seen in early studies. This increase in prevalence is a feature of a number of studies and presumably reflects improved diagnosis over time as well as improved survival rates, alongside the lifelong chronicity of the illness. Although the SLICC modification of the ACR classification criteria for SLE has not yet been used by any of the currently reported epidemiological studies, it is likely to increase the diagnostic rate for SLE further [16].

Fig. 2 Choropleth map showing prevalence of SLE around the world



Countries lacking prevalence data are shown in grey. Coloured circles highlight prevalence data from Puerto Rico, Martinique and Hong Kong.

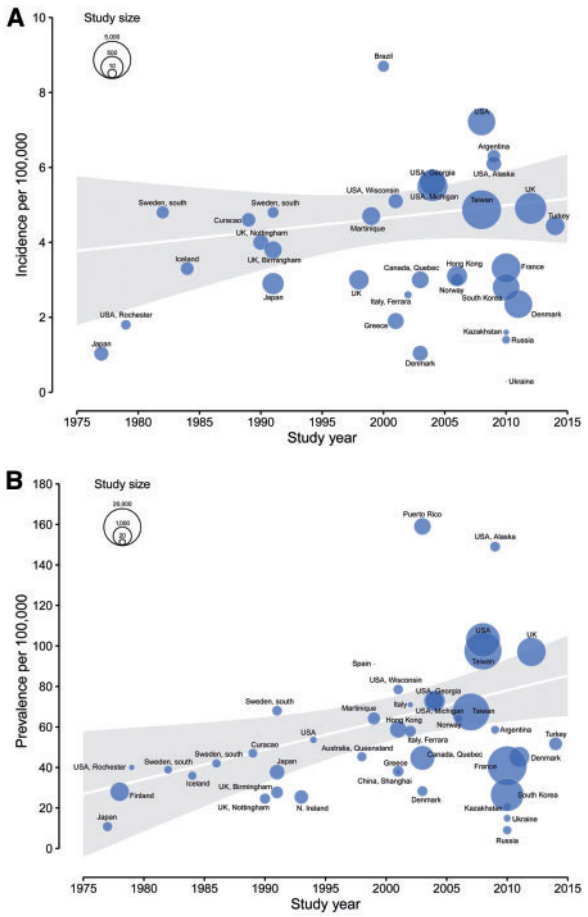
Defining race, ethnicity and ancestry in clinical studies

Although race and ethnicity are terms that are commonly used in medical studies, their definition is complex. The concept of race originally arose to group individuals by biological differences such as skin colour, with associated social and cultural differences. However, the term ran into difficulties when describing increasingly mixed populations, such as in the USA. A later concept of ethnicity emphasized cultural, social and religious qualities, as opposed to genetic ancestry. However, both race and ethnicity are fluid, and perceived racial or ethnic groups change over time. Genetic studies often use the term ancestry, by which individuals are categorized according to the origins of their ancestors. Ancestry is usually defined geographically (e.g. East Asian, sub-Saharan African, northern European), and self-reported ancestry tends to correlate reasonably well with genetically determined ancestry. However, ancestry is a multidimensional continuum with endless possible subrefinements (e.g. Norwegian *vs* Scandinavian) [17]. In practice, all three terms of race, ethnicity and ancestry are interlinked. US government guidelines for reporting race and ethnicity include five minimal categories of race (American Indian/Alaska Native, Asian, Black/African American, Hawaiian/Pacific Islander and white), whereas Hispanic/Latino individuals are categorized separately under ethnicity, referring to people of Mexican, South or Central American or other Spanish culture, regardless of race [18]. Amerindian is a broad ancestral term that refers to indigenous people of the Americas, including Central or South America. Genetic analyses reveal that Hispanic individuals display ancestral genetic diversity, with Hispanics from Texas showing a significant proportion of Amerindian ancestral genes, whereas African and white European ancestral genes are more common in Hispanics from Puerto Rico [19, 20]. The Mestizo, studied under the ethnic grouping Hispanic, are individuals of combined European and Amerindian (usually indigenous Mexican/central American) ancestry. Asian is an ambiguous term, because in the UK it usually refers to individuals from India, Pakistan, Bangladesh or neighbouring regions, whereas in the USA it usually refers to individuals of Chinese, Korean or Japanese origin. Hence, in this article we distinguish between South Asian and East Asian, although these terms are generally not used in the source studies.

Effect of race and ethnicity on incidence and prevalence of SLE

A consistent finding across epidemiological studies is that SLE is significantly more common in black individuals and specific races and ethnicities compared with white individuals. This finding has been repeatedly confirmed in numerous studies across the USA through to the present day [8, 9, 21–23]. Similar findings were reported in UK studies based in Birmingham and Nottingham [4, 24], which showed a 5- to 9-fold increase in incidence and 5- to 10-fold increase in prevalence of SLE in Afro-Caribbeans, as well as a 1.2- to 6-fold increase in incidence and 2- to 2.4-fold increase in prevalence in South Asian individuals compared with white individuals. Further

FIG. 3 Bubble chart summarizing studies of incidence and prevalence of SLE over time



Linear regression models (white line) were calculated in R, with region within 95% CI shaded grey.

attempts to define ethnic groups at risk of SLE are complicated by the lack of racial and genetic homogeneity for certain ethnicities. SLE in Hispanic individuals has been studied extensively in the Lupus in Minorities: Nature *vs* Nurture cohort studies [20]. In Canada, a 2-fold increase in incidence and prevalence of SLE was observed in native American Indian individuals compared with whites [25], and a later study observed that American Indian and Alaska Native individuals demonstrated an incidence of 7.4 per 100 000 and prevalence of 178 per 100 000 of SLE, which are some of the highest rates recorded and comparable to African Americans [11]. Although substantial information is available about SLE in individuals of African ancestry living in the Americas and Europe, there are currently no accurate studies of the incidence or prevalence of SLE in Africa, the Middle East or South Asia. A recent UK study, which is one of few to subdivide South Asian ethnicity into subgroups, found that Indian ethnicity is associated with higher incidence (9.9 per 100 000) and prevalence of SLE (193 per 100 000), although not as high as in Afro-Caribbeans (incidence 31.5 and prevalence 518 per 100 000). The incidence (10.0 per 100 000) of SLE was higher in UK Pakistanis, although the prevalence was not increased (143 per 100 000) [13]. The incidence and prevalence of SLE in UK Bangladeshi individuals was apparently not increased compared with whites. However, a problem with this study is the high percentage of individuals with unknown or unclassified ethnicity. Subgroup analysis of the Michigan Lupus registry suggests that the incidence of SLE in individuals of Arab or Chaldean origin was 2.1-fold increased compared with white individuals [26].

Early studies anecdotally suggested a low prevalence of SLE in Africa. Although there remains a lack of high-quality epidemiology studies from African countries, data on migrants show that the incidence and prevalence of SLE is high in Africans, Caribbeans and South Asians who have migrated to the UK [4, 27]. Recent evidence suggests that SLE and LN are a significant health burden in Africa [28, 29]. An interesting study showed that rates of SLE autoantibody positivity were similar in a cohort of healthy Gullah individuals (African Americans from the Sea Islands of South Carolina of low genetic admixture) compared with a genetically similar population of women from Sierra Leone [30].

No studies directly comparing diverse populations have reported statistically significant variance from the gender bias towards female individuals being affected by SLE. In studies across multiple populations, the percentage of females affected ranged from 88.3 to 96.2%, giving a female-to-male sex ratio centred around 9:1, ranging from 7.5:1 in Curaçao to 23:1 in Oman and 25:1 in Hispanic individuals in a USA cohort [31–33].

Genetics, ancestry and SLE

SLE is known to have a strong genetic link, with a heritability of ~66%. The twin concordance rate for SLE is 24% in monozygotic twins compared with 2% in dizygotic twins [34]. SLE has a sibling recurrence risk ratio (λ_s) of 29, compared with 5.3 in RA [35]. Since the advent of genome-wide association studies (GWAS), at least 52 genetic loci with strong evidence of association with susceptibility to SLE have been confirmed [36–41]. Although cohort size is a major factor, which has increased the power of these studies to find genetic associations, the veracity of these large-scale studies is also underpinned by radical improvements in computer science in data storage, quality control, statistical and analytical techniques. The region of the genome with by far the strongest association with susceptibility to SLE is the MHC, located on chromosome 6. Prior to GWAS-scale studies, the 8.1 ancestral haplotype has long been known to be associated with endocrine, gastrointestinal, haematological/immunological autoimmune diseases and sarcoidosis through to multiple connective tissue diseases, including SLE. This MHC haplotype extends to include *HLA-A1*01:01*, *B*08:01*, *C4AQ0*, *C4B1*, *DRB1*03:01*, *DQA1*05:01*, *DQB1*02:01* (A1::DQ2 in older nomenclature), encompassing two significant class III genetic variants, complement *C4A* null as

well as the *TNF-308A* allele. Major confounding factors affecting MHC genetic association studies are long-range linkage disequilibrium and duplications of regions leading to copy number variation and pseudogenes. Only the largest, most recent genetic studies using techniques including trans-ancestral mapping have sufficient power to dissect which genes within the MHC are responsible for disease susceptibility rather than finding associations with the whole MHC block. The highest HLA association with SLE has been observed for *HLA-DRB1*03:01*, with a weaker effect observed for *HLA-DRB1*15:01* [42]. However, although this study including multiple cohorts from different countries, including the USA, the individuals included were predominantly of European ancestry. Trans-ancestral mapping of UK, Spanish and Filipino SLE patients showed differential MHC signals according to ancestry [43]. Independent association of *HLA-DRB1*08:01* was seen in Spanish individuals with SLE but not in other groups, in addition to known association with *HLA-DRB1*03:01* and *HLA-DRB1*15:01*. Single nucleotide polymorphisms (SNPs) with the best odds ratio in Spanish SLE clustered around the DNA repair gene *MSH5*. The top SNP in Filipino SLE, rs9271366, located between *HLA-DRB1* and *HLA-DQA1*, may represent association with *HLA-DRB1*15:02*. The risk haplotype with the top three independent MHC SNPs was also more common in Filipino SLE, consistent with the increased prevalence of SLE in the East Asian population. The association of *HLA-DRB1*03:01* with SLE is stronger in anti-Ro and anti-La antibody-positive SLE, suggesting that this HLA haplotype promotes break of tolerance to Ro and La autoantigens, independently of its association with SLE [44]. Interestingly, a study of black women with SLE could not confirm association of SLE with *HLA-DRB1*03:01* and *HLA-DRB1*15:01* in this population, although of the four independently associated SNPs, two are located in the MHC class II region, consistent with other studies in Europeans and East Asians [38, 42]. A relatively small study suggested that *HLA-DRB1*15:03* and *HLA-DRB1*08* were more frequent in African American and Hispanic individuals with SLE, respectively [45]. These dissimilarities are in keeping with the heterogeneity of the extended MHC locus and will require larger studies to dissect differences between ancestries fully in terms of MHC region-mediated susceptibility to SLE. In comparison, in RA five key amino acid residues in HLA-DRβ1, HLA-B and HLA-DPβ1 are able to explain almost completely the genetic susceptibility to RA conferred by the HLA region [46]. Trans-ancestral studies in RA show that these amino acids confer shared effects in Asian individuals [47]. Similar in-depth trans-ancestral analyses of the MHC, including HLA amino acid variation in SLE, are currently lacking. Genes encoding complement C4 and TNF-α are also located within the MHC region. A study of northern European (UK) and southern European (Spanish) SLE populations showed that C4 copy number variation was not an independent risk factor for SLE susceptibility in either population [48]. A meta-analysis suggested that the *TNF* promoter $-$308A/G polymorphism may increase risk of SLE in European populations, but not in Asian populations [49].

Outside of the MHC, recent GWAS have superseded older candidate gene studies and have shown $>$40 genes associated with SLE in European populations reaching genome-wide significance ($P < 5 \times 10^{-8}$) [36]. Comparison with GWAS in Han Chinese individuals initially suggested some differences in gene associations [38], with associations found in *RASGRP3*, *ETS1* and *WDFY4*/*LRRC18*, which had not been previously identified in Europeans, and association with *IKZF1* and *SLC15A4*, for which early European data were only suggestive of association. These differences are largely attributable to altered risk variant frequency, with apparently East Asian specific variants being more common in East Asians than in Europeans and vice versa. However, as GWAS become larger and larger, some risk variants that are rarer in certain populations are likely to be revealed as part of a commonality of genetic susceptibility across multiple ancestries, and this has proved to be the case for all the above genes except *RASGRP3*, which remains the only gene associated with Chinese SLE not to be replicated in Europeans at the time of writing [36]. A fresh meta-analysis of European and Chinese GWAS data [41] confirmed substantial commonality in shared risk variants between the two populations. This is similar to trans-ancestral GWAS in RA, which showed that $>$80% of the heritability attributed to 101 RA risk loci was shared between Europeans and Asians [50]. Overall, risk variant frequencies were higher in Chinese individuals than in Europeans, in keeping with the higher prevalence of SLE in Chinese individuals, suggesting a greater SLE genetic risk burden in East Asia. GWAS in Amerindian SLE identified association with *IRF5*, *ITGAM*, *STAT4*, *TNIP1*, *NCF2* and *IRAK1*, all of which were previously identified in European SLE GWAS [36]. However, it was striking that the association with *IRF5* (interferon response factor-5) was stronger than the HLA association in this cohort. This study also identified rs4917385 in proximity of *USMG5* with expression quantitative trait loci (eQTL) evidence that this SNP affects *USMG5* expression as an Amerindian-specific susceptibility locus. A candidate gene study in African American individuals suggested *MECP2*, *MBL2* and *PXK* as European-only-associated SLE susceptibility genes [51]. Results of an ongoing GWAS in individuals with SLE of African ancestry are not yet available but will further inform our understanding of ancestral differences in genetic susceptibility to SLE once available. Trans-ancestral fine mapping studies of individuals' genes are rare but informative. They illustrate that although the most strongly associated SNPs vary with ancestry, common risk haplotypes can be identified across different ancestries; for example, for *TNFSF4* (which encodes OX40L, an activatory ligand for the OX40 receptor on T lymphocytes) [52] and the *IL2/IL21* locus [53]. Functional genetic studies have also begun to elucidate the immunological mechanisms of SLE susceptibility variants in ancestrally diverse populations [54, 55].

A crucial component of modern genetic studies is the use of ancestry-informative markers, which measure genetic admixture in order to account more accurately for the effect of ancestry when studying genetic susceptibility to SLE. Ancestry-informative markers are necessary to exclude genetic variants whose apparent association with SLE is merely attributable to a confounding association with ancestral grouping. Ancestry-informative markers can be also used to probe for interaction between specific genes and ancestry in the development of SLE in different ancestral groups. Using this method, Amerindian admixture was modestly correlated with increased numbers of risk alleles in a study of 16 confirmed genetic susceptibility loci [56].

Racial differences in gene expression have been reported, with high expression of *TLR9* and DNA methyltransferase *DNMT3A* observed in African American SLE compared with other ethnicities, associated with higher serum concentrations of TNF and IL-6 [57, 58].

Effect of ethnicity on clinical features and disease activity

Many studies have examined whether ethnicity affects the clinical phenotype in SLE. However, these studies are complicated by the exceptional heterogeneity of disease manifestations in SLE: both diversity of organ involvement and heterogeneity between individuals. Differences in reporting methods for clinical features as well as accurate recording of cumulative occurrence of manifestations add to the complexity of comparing studies. Previous reviews have compared clinical features across studies in different countries [2, 20]. Rates of ACR criteria manifestations were uniformly lower in the study by Cervera *et al.* [59] of 1000 predominantly white Europeans compared with the GLADEL study by Pons-Estel *et al*. [61] and the Lupus in Minorities: Nature *vs* Nurture cohort by Alarcón *et al*. [31]. Rates of clinical manifestations in a study of Hong Kong Chinese fell in between these studies [60]. These differences are perhaps more likely to be attributable to methodology than real differences between ethnicities. Studies that specifically aim to compare different races/ethnicities over the same time period and similar geographical areas are more likely to be accurate and representative. Thus, it is generally accepted that individuals of African or Caribbean ancestry are more frequently affected by discoid rash (20–34%) compared with white Europeans (11–12%) [31, 61, 62], whereas photosensitivity may be more common in Europeans (81%) and individuals from Puerto Rico (90%) who have some European admixture compared with African Americans or Hispanics in Texas (both 56%) [20, 31, 63]. In UK studies, Afro-Caribbean individuals with SLE tended to develop renal disease earlier in the course of their illness and develop renal disease more frequently [64, 65]. Similar findings are reported in non-Europeans in France and in African Americans in the USA, Canada and Latin America [25, 61, 63, 66–68]. High levels of renal involvement are found in South Africa [69], Martinique [70], in Arab populations in Tunisia and Saudia Arabia [71, 72], and in Asian populations, including Chinese, Malaysians, Filipinos and Indians [60, 73–76]. A systematic review of glomerulonephritis in Africa identified LN as one of the most common causes of secondary glomerular disease [28]. Individuals of African ancestry and Hispanics from Texas show more severe renal involvement with greater rates of progression to end-stage renal disease [66, 67], although Hispanic SLE patients from Texas developed more severe disease than those in Puerto Rico [77]. Renal disease is also more frequent in Mestizo populations (mainly from Guatemala, Mexico and Peru) with SLE [61]. Rates of neuropsychiatric SLE varied widely from cohort to cohort in older studies, with a range of 14–91%, rendering direct comparisons between studies problematic. However, the SLICC inception cohort has reported several studies in this area, looking at individual neuropsychiatric SLE manifestations. In this cohort, seizure occurrence was 2.0-fold increased in African and 1.6-fold increased in Hispanic inidviduals with SLE compared with white individuals using multivariate analysis, with a tendency for seizures to be lower in frequency in Asian individuals with SLE [78]. Mood disorders were lower in Asian individuals with SLE, confirmed in South Korean patients [79]; however, there was no effect of ethnicity/race on the prevalence of lupus headache [80]. However, the SLICC cohort made no distinction between South and East Asia. Ethnicity/race has not been shown to predispose to thrombotic events [81, 82].

Some studies have suggested that non-European individuals with SLE show a higher frequency of positivity for specific autoantibodies, such as anti-Sm [83]. Using a bead-based autoantibody assay, African American and Hispanic SLE patients showed positivity for a greater number of autoantibodies concomitantly; 53% of African American and 34% of Hispanic individuals with SLE demonstrated four or more autoantibody specificities compared with 19% of European individuals with SLE [84]. Anti-chromatin, anti-Sm, anti-RNP, anti-dsDNA positivity was higher in African American SLE and to a lesser extent Hispanic SLE compared with European SLE in this study. Other studies have confirmed the higher rate of anti-Sm and anti-RNP positivity in non-European ancestry SLE [20, 85, 86], but not all studies have confirmed this [61]. In contrast, anti-Ro and anti-La positivity tends to be similar across ethnicities.

Impact of ethnicity on disease activity, damage accumulation and mortality

Consistent with these trends that ethnicity/race influences rates of skin, renal, neuropsychiatric and immunological manifestations, ethnicity impacts disease activity as a whole, with non-white individuals showing higher SLEDAI scores compared with whites both at baseline and over time [45, 87, 88]. Beyond the observation that clinical manifestations may be both more common and of greater severity in black and Hispanic individuals and, to a varying degree, Asian individuals, ethnicity has a knock-

on effect on damage accumulation and outcome over time. Doubling of creatinine and progression to end-stage renal failure (ESRF) are more common in African American and Hispanic individuals with LN [89], and presentation with ESRF or rapid progression to ESRF in newly diagnosed SLE patients is significantly more common in African Americans [90]. Large studies observing >12000 LN patients in the US ESRF registry have shown that African American SLE patients who reach ESRF have higher mortality rates than non-African populations, although one study suggested that this effect might be related to median income [91] and a second study showed higher levels of cardiovascular events in the African American group [92]. Current data suggest that different ethnicities show similar allograft failure rates following renal transplantation for LN [93]. In the SLICC cohort, African American individuals with SLE showed the highest rates of progression of SLICC/ACR damage index, followed by Hispanic individuals, with the rate of progression in Asian individuals with SLE being lower than for white individuals [94]. Other key factors predictive of damage accrual are age and disease activity, including the number of flares and corticosteroid use [94, 95]. Black and Hispanic individuals with SLE also respond more slowly to treatment and show slower reductions in disease activity over time compared with white patients [96]. Increased rates of damage accumulation in African ancestry SLE is of major concern, because it has been consistently shown that the damage score at baseline and damage accrual rates are a major predictor of mortality in SLE and, consistent with this, mortality is higher in African individuals with SLE [97–99]. A meta-analysis of mortality rates in SLE showed comparable rates between Asian studies in China and Taiwan compared with Europe and North America [100].

Interestingly, there is some evidence of differential response to therapy according to ethnic group, although few studies have examined this issue systematically. African and Hispanic SLE patients showed greater response to rituximab compared with other groups [101]. Black and mixed-race individuals with SLE showed poorer response to i.v. CYC [102, 103]. Future randomized controlled trials that include genotype data on study participants will be better placed to dissect these issues by measuring genetic admixture instead of self-reported race/ethnicity, especially in the case of mixed-race individuals, who may be incorrectly categorized.

Socio-economic factors

In many countries where private health care predominates, including the USA, poorer access to health care is self-evidently linked to worse outcome and morbidity. Thus, a number of studies have attempted to distinguish the effect of ethnicity from socio-economic factors, such as employment status, annual income, education level and social support network. General consensus from these studies is that although socio-economic factors play a definite role in worse outcome, especially in individuals with SLE who have renal disease [91], ethnicity still acts as an independent risk factor for increased prevalence and severity of disease and worse outcome [45, 65, 67, 104]. This effect of ethnicity above and beyond socio-economic factors also remains true in the UK, where health care is primarily funded publically [105]. This evidence supports the notion that genetically determined ancestry and, possibly, environmental factors related to ethnicity are involved in biological processes that increase SLE prevalence and disease severity.

Comparison with other autoimmune diseases

These effects of race/ethnicity, which have been strongly observed for SLE as described above, are specific to SLE. Although the incidence and prevalence of RA show variation in different countries, there is a lack of evidence for a significant effect of race/ethnicity in RA [106]. Likewise, the systemic vasculitides, which themselves can be difficult to classify, vary in incidence and prevalence in different countries [107], although specific types of vasculitis show well-known regional distributions; for example, Behçet's disease in Turkey and the Silk Road [108], and Takayasu's disease in the Far East. It is worth noting that multiple sclerosis shows inversion in terms of race/ethnicity in comparison with SLE, because multiple sclerosis is substantially more common in white individuals compared with black or South Asian populations, consistent with the geographical distribution of white populations [109, 110].

Conclusions

The overall message from an extensive body of literature is consistent; ancestry, race and ethnicity together have a major effect on the way in which SLE manifests. Black, Asian and Hispanic individuals with SLE tend to develop more severe disease, exhibit a greater number of manifestations and accumulate damage from lupus more rapidly. Even after taking into account socio-economic factors, race/ethnicity remains a key determinant of poor outcome, such as ESRF and mortality, in SLE. Ongoing genetic studies suggest an increased genetic risk burden in these populations associated with increased autoantibody reactivity in non-European SLE, which may partly explain the more severe lupus phenotype. Subgroup analyses from randomized controlled trials have shown that different ethnic groups respond differentially to therapeutic interventions. Community measures to improve early diagnosis through increased awareness in at-risk racial/ethnic communities, together with more ethnically personalized treatment algorithms, may be required in future to reduce the severity of SLE in high-risk populations and thus improve long-term outcome.

Acknowledgements

M.J.L. is the recipient of an Arthritis Research UK Clinician Scientist Fellowship (19631).

Funding: This work was supported by Arthritis Research UK.

Disclosure statement: The authors have declared no conflicts of interest.

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