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Ethnic differences in CD1E, but not CD1A, gene polymorphisms between Sub-Saharan Africans, West Asians and Europeans

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ABSTRACT

The five closely linked CD1A-E genes encode the human CD1 family of proteins. Few studies of the allele frequencies of these genes in African populations have been published so far. This study aimed to genotype CD1A and CD1E variants and to compare their frequencies in Sub-Saharan Africans from Gabon and Ivory Coast, and Non-Africans from Syria and France.

A restriction analysis of DNA fragments generated by PCR was performed to detect CD1A and CD1E alleles in 105 subjects from Gabon, 169 subjects from Ivory Coast, 107 subjects from Syria and 181 subjects from France.

The frequencies of the CD1E*02 allele were high among Sub-Saharan Africans (87%) and low in West Asians (44%) and Europeans (36%), whereas the contrary was obtained for the CD1E*01 allele (7%, 55% and 64% respectively). Frequencies of CD1A alleles were similar between all groups, the CD1A*02 allele was most prevalent (91%).

The high frequency of the CD1E*02 allele in Sub-Saharan Africans suggest that future work should investigate the relationship between CD1 polymorphism and infectious diseases.

1. Introduction

CD1 glycoproteins are a small family of molecules that present lipid and glycolipid antigens to T cells. Humans have five different CD1 isoforms called CD1a, b, c, d, and e which share a highly conserved alpha heavy chain homologous to the β-microglobulin-binding domain of major histocompatibility complex class I antigens [1]. Of these, CD1a-d molecules assemble in the endoplasmic reticulum and travel to the cell surface through the secretory pathway, whereas the CD1e molecule is transported by the endosomal pathway and facilitates the presentation of antigens by all other CD1 antigen-presenting molecules [2,3].

Five closely linked genes, CD1A-E, located on chromosome 1 (1q22-23), encode the human CD1 family of proteins [4]. CD1 genes have been detected in all mammalian species analysed to date, but not all CD1 isoforms are expressed in all species. For example, mice and rats do not express the CD1*a*, *b*, *c*, and *e* genes and have a duplicated CD1*d* gene, whereas guinea pigs express multiple variants of CD1*b* and *c* genes, and rabbits and sheep have lost the CD1*c* gene [5].

Among humans, allelic polymorphisms have been observed in all five CD1 genes in exon 2 and exon 3. The polymorphisms of CD1B (T174TC) and CD1C (C99T) are silent and the polymorphisms of CD1D (A136T), CD1D (C136T) and CD1D (C98T) are rare [6]. There are two linked mutations in the CD1A gene, T38C (I13T) and G153C (W51C), generating two alleles [4]. CD1E is the most polymorphic CD1 gene with six reported alleles [4,7,8]. The polymorphic nucleotides of the CD1E gene are located in exons 2 and 3, encoding the α1 and α2 domains, respectively [4,7,8].

Little on the allele frequencies of the CD1 genes in African populations has been published so far [6,9].

The objectives of this study were to: (i) genotype variants of the most highly represented polymorphic CD1 genes in the human population, CD1A and CD1E, in subjects from Gabon, Ivory Coast, Syria, and France; and (ii) compare the allelic frequencies of CD1 variants between Sub-Saharan African (SSA), West Asian and European groups.

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2. Materials and methods

DNA samples were derived from unrelated, healthy adult individuals from different ethnic backgrounds: 274 SSA subjects of which 105 were from Gabon and 169 from Ivory-Coast, 107 West Asian subjects from Syria, and 181 European subjects from France. All samples were collected from individuals living in each country by members of the author's laboratories. DNA was extracted from all blood samples by the phenol/chloroform procedure. Informed consent was obtained from all participants.

A restriction analysis (using *HphI* (codon 13) and *HaeIII* (codon 51) restriction enzymes) of DNA fragments generated by PCR was carried out to detect of the two mutations in exon 2 of the CD1A gene [4,8].

The CD1E alleles were genotyped using a PCR-RFLP (restriction fragment length polymorphism) assay in which one of the primers had an introduced mismatch to create an *Rsa I* restriction site [8]. Two restriction sites (for *Hpa II* and *RsaI*) were used to detect mutations in Exon 2; and three restriction sites (for *MaeI*, *HpaII* and *DdeI*) were used to determine mutations in exon 3 [8].

All CD1 variants studied were analyzed against expected Hardy-Weinberg values in each population by Fisher's Exact test. Fisher's Exact test was also used to compare CD1A and CD1E allelic frequencies in populations from Sub-Saharan Africa, West Asia and Europe. All Black subjects were grouped as SSA (not in Africans because the majority of North Africans are white people) while White subjects were grouped as Non-Africans.

3. Results

CD1 genotypes and allelic frequencies in the four populations are shown in Tables 1 and 2.

The CD1A genotype distributions concerning both CD1A*01 and CD1A*02 were similar for all populations studied. Statistically, the CD1A genotype distribution was not different between SSA and Non-SSA (P = 1, Table 1). Both CD1A*01 and CD1A*02 alleles were in Hardy-Weinberg equilibrium in populations from Gabon, Ivory-Coast, Syria and France (P = 0.9, Table 1). The CD1A*02 allele was more prevalent than the CD1A*01 allele in all populations studied (0.92 *vs.* 0.08).

The CD1E genotype distributions for both CD1E*01 and CD1E*02 were different between SSA and Non-Africans (P < 0.001, Table 1). The CD1E*02 allele was the most prevalent in SSA (0.87) while the CD1E*01 allele was the most prevalent in Non-Africans (0.61). We found four CD1E alleles (CD1E*01, CD1E*02, CD1E*05, and CD1E*06) in Gabonese subjects, whereas we only found two alleles (CD1E*01 and CD1E*02) in French subjects (Table 1). The CD1E*05 allele was absent in French subjects, but present in Gabonese subjects at rate of 0.06 (equal frequency that the CD1E*01 allele) and in subjects from Ivory-Coast (0.05) and Syria (0.01). Both CD1E*01 and CD1E*02 alleles were in Hardy-Weinberg equilibrium in the four populations studied (P > 0.7; Table 1).

The CD1E*02 allele was significantly more prevalent in SSA (Gabon and Ivory-Coast) than in Non-Africans (Syria and France) (P < 0.001; Table 2). In contrast, the CD1E*01 allele was significantly more prevalent among Non-Africans than in SSA (P < 0.001; Table 2). We observed a high prevalence of the CD1E*02 allele in SSA, but a low prevalence in Non-SSA, with the opposite pattern for the prevalence of the CD1E*01 allele (P < 0.001; Table 2).

Other populations from Europe and West Asia where CD1A and CD1E variants were analysed were reported for comparison with our results for CD1A and CD1E alleles (Table 2). Fisher's tests revealed the same results that we observed in our studied populations: ethnic differences in the distribution of CD1E, but not CD1A, between SSA and Non-Africans (P < 0.001; Table 2).

4. Discussion

To our knowledge, our study was the first to report CD1 gene polymorphisms in multiple SSA populations. Ethnic differences in CD1E but not CD1A gene polymorphisms between SSA and Non-Africans were observed.

The CD1A polymorphism profile was similar in all our studied populations and in other investigated populations [10–14]. The CD1A*02 allele, which was prevalent in all populations, was not associated with defects in surface expression on transfected cells and dendritic cells [15]. There are conflicting results concerning associations of CD1A alleles with Guillain-Barré syndrome [11,12,16]. A microbial infection, tuberculosis, has recently been found to be associated with a CD1A allele in a Vietnamese cohort, but the CD1E alleles were not studied [17]. This contrasts with an earlier study showing no association with tuberculosis was found between CD1A and CD1E alleles [10], again showing contradictory results for associations between CD1A variants and disease.

The number of CD1E variants is higher among Gabonese subjects than French subjects, raising the possibility of impaired lipid and glycolipid antigen presentation, because CD1e molecules aid in antigen

Table 1
CD1A and CD1E genotypes, and results of statistical tests comparing subjects from Gabon, Ivory Coast, Syria, and France.

CD1 genotypes	Subjects from Gabon (1)	Subjects from Ivory-Coast (2)	Subjects from Syria (3)	Subjects from France (4)	Sub-Saharan subjects (1 + 2)	Non-African subjects (3 + 4)
	N = 105	N = 169	N = 107	N = 181	N = 274	N = 288
CD1 A*01/A*01	2 (1.9%)	2 (1.2%)	2 (1.9%)	2 (1.1%)	4 (1.4%)	4 (1.4%)
CD1 A*01/A*02	15 (14.3%)	23 (13.6%)	15 (14.0%)	24 (13.3%)	38 (13.9%)	39 (13.5%)
CD1 A*02/A*02	88 (83.8%)	144 (85.2%)	90 (84.1%)	155 (85.6%)	232 (84.7%)	245 (85.1%)
Fisher's Exact Test for	P = 0.89	P = 0.91	P = 0.89	P = 0.91	P = 1	
CD1A	With H-W expected values	With H-W expected values	With H-W expected values	With H-W expected values	Between CD1 genotype distribution in Sub-Saharans and Non-Africans	
CD1 E*01/E*01	1 (1%)	0 (0%)	34 (31.8%)	75 (41.4%)	1 (0.4%)	109 (37.8%)
CD1 E*01/E*02	9 (8.6%)	27 (16%)	49 (45.8%)	83 (45.9%)	36 (13.1%)	132 (45.8%)
CD1 E*01/E*05	1 (1%)	1 (0.6%)	1 (0.9%)	0 (0%)	2 (0.7%)	1 (0.4%)
CD1 E*02/E*02	82 (77.9%)	126 (74.5%)	23 (21.5%)	23 (12.7%)	208 (75.9%)	46 (16%)
CD1 E*02/E*05	11 (10.5%)	15 (8.9%)	0 (0%)	0 (0%)	26 (9.5%)	0 (0%)
CD1 E*02/E*06	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Fisher's Exact Test for	P = 0.73	P = 0.76	P = 0.89	P = 1	P < 0.001	
CD1E	With H-W expected values	With H-W expected values	With H-W expected values	With H-W expected values	Between CD1 genotype distribution in Sub-Saharans and Non-Africans	

Note: H-W = Hardy-Weinberg.

Table 2
Comparison of CD1A and CD1E allelic frequencies between Sub-Saharan Africans, and Non-Africans.

Populations [References]		CD1A Allelic frequencies		CD1E Allelic frequencies	
		CD1A*01	CD1A*02	CD1E*01	CD1E*02
Gabon		19/210 (9.1%)	191/210 (90.9%)	12/210 (5.7%)	185/210 (88.1%)
Ivory-Coast		27/338 (8.0%)	311/338 (92.0%)	28/338 (8.3%)	294/338 (87.0%)
Syria		19/214 (8.9%)	195/214 (91.1%)	118/214 (55.1%)	95/214 (44.4%)
France		28/362 (7.7%)	334/362 (92.3%)	233/362 (64.4%)	129/362 (35.6%)
Iran [13]		69/622 (11.1%)	553/622 (88.9%)	374/622 (60.1%)	248/622 (39.9%)
Netherlands [11]		27/424 (6.4%)	397/424 (93.6%)	282/424 (66.5%)	142/424 (33.5%)
UK [9]		34/684 (5%)	650/684 (95%)	458/684 (67%)	226/684 (33%)
Italy [10 + 12]		51/464 (11%)	413/464 (89%)	286/464 (61.6%)	178/464 (38.4%)
Sub-Saharan Africans (Gabon, and Ivory-Coast)		46 (8.4%)	502 (91.6%)	40 (7.3%)	479 (87.4%)
Non-Africans (Syria, and France)	Frequencies	47 (8.2%)	529 (91.8%)	351 (61.0%)	224 (39.0%)
	Fisher's test	P = 0.9140; OR = 1.0313 95% CI: [0.6588; 1.6138]		P < 0.001; OR = 0.0535 95% CI: [0.0362; 0.0774]	
Europeans (France, Netherlands, UK, and Italy)	Frequencies	140 (7.2%)	1794 (92.8%)	1259 (65.1%)	675 (34.9%)
	Fisher's test	P = 0.3590; OR = 1.1741 95% CI: [0.8104; 1.6759]		P < 0.001; OR = 0.0448 95% CI: [0.0312; 0.0629]	
West Asians (Syria, and Iran)	Frequencies	88 (10.5%)	748 (89.5%)	492 (58.9%)	343 (41.1%)
	Fisher's test	P = 0.1948; OR = 0.7790 95% CI: [0.5234; 1.1472]		P < 0.001; OR = 0.0583 95% CI: [0.04; 0.0833]	
All Non-Africans (Europeans, and West Asians)	Frequencies	228 (8.2%)	2542 (91.8%)	1751 (63.2%)	1018 (36.8%)
	Fisher's test	P = 0.8655; OR = 1.0216 95% CI: [0.717; 1.4303]		P < 0.001; OR = 0.0680 95% CI: [0.0475; 0.0951]	

Note: Fisher's test was used to compare Sub-Saharans with each group of populations (Non-Africans, Europeans, West Asians, and All Non-Africans).

loading. In contrast to CD1a-d proteins that directly present lipid and glycolipid antigens, CD1e molecules modulate all CD1-restricted responses, influencing lipid antigen availability, as well as the generation and persistence of CD1-lipid complexes [3]. For example, the CD1E*04 allele that was absent in our study is assembled inefficiently with the CD1b molecule and the complex is poorly transported to late endosomal compartments [18].

The CD1E*05 allele in SSA subjects appeared to be as polymorphic as the CD1E*01 allele, showing that it should be considered in further studies in African populations. The CD1*05 allele was discovered in black individuals [8] and is absent in French population, but a Syrian subject presented this allele suggesting West Asian populations may present a CD1E pattern intermediate between SSA and Europeans. This hypothesis is supported by frequencies observed in a Central Asian population from Bangladesh where the CD1E*02 allele frequency was 49% [16], an intermediate value between 87.4% (SSA) and 34.9% (Europeans).

Our study shows that the CD1E*02 allele is more prevalent in SSA than in Non-Africans. The prevalence of this allele shows opposite patterns in SSA (Gabon and Ivory-Coast) and Europeans (France) or West Asians (Syria). The higher prevalence of the CD1E*02 allele in SSA, where the burden of infectious diseases remains high, suggests that this allele may be involved in immunity against infectious diseases. A recent study has shown an association between the prevalence of the CD1E*02 allele and resistance to mild malaria [9]. Another study has shown that the CD1E*02 allele is associated with an enhanced immune response in African American individuals with prostate cancer [19].

5. Conclusion

Our study has shown that the frequencies of the CD1E*02 allele are high among SSA and low in West Asians and Europeans, whereas the contrary was obtained for the CD1E*01 allele. In contrast, the frequencies of the CD1A alleles are similar for all populations, with a high prevalence of the CD1A*02 allele (91%). The ethnic differences observed for the CD1E alleles in subjects from Sub-Saharan Africa suggest the potential importance of these variants in the context of infectious diseases.

6. Footnotes

The authors do not have any commercial or other association that might pose a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humimm.2018.12.008.

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