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Objective—Gender and ethnicity modulate the phenotypic expression of cardiovascular risk factors. In particular, men are at higher risk of developing cardiovascular diseases compared to women, whereas black populations of African origin display reduced mortality from coronary heart disease (CHD) as compared to both whites and South Asians. Because the male-specific region (MSY) of the human Y chromosome is an obvious candidate for gender-related differences in the development of cardiovascular diseases, we aimed to identify genetic variants of MSY influencing cardiovascular risk profile in different ethnic groups.

Methods and Results—We genotyped 4 polymorphisms of MSY (*Hind*III±, rs768983 of *TBL1Y*, rs3212292 of *USP9Y*, and rs9341273 of *UTY* genes) in 579 men of different ethnic groups (blacks, South Asians, and whites) from UK and in 301 whites in Italy. We found that the $TBL1Y_A$ $USP9Y_A$ haplotype, present only in blacks in whom it represents the most frequent allelic combinations (AA: n=125; all other combinations: n=45), was associated with lower levels of triglycerides (P=0.025) and higher levels of HDL-cholesterol (P=0.005) as compared to the other haplotypes.

Conclusion—The $TBL1Y_A$ $USP9Y_A$ haplotype of the Y chromosome, present only in black people of African origin, attributes a favorable lipoprotein pattern, likely to contribute to their reduced susceptibility to coronary heart disease. (***Arterioscler Thromb Vasc Biol*. 2008;28:1569-1574**)

Key Words: Y chromosome ■ cardiovascular risk ■ lipoprotein ■ ethnicity ■ male

Most health-related traits, such as cardiovascular risk factors, are complex traits influenced by the combined effects of unmodifiable and modifiable (environmental) factors. Among unmodifiable factors, gender and ethnicity play an important role in modulating the phenotypic expression of cardiovascular risk factors such as blood pressure and serum lipid levels. Men are at higher risk of developing cardiovascular diseases compared to age-matched premenopausal women.[1–2] On the other hand, there are important differences in the cardiovascular risk profile between ethnic groups. In particular, black populations of African origin living in the UK display reduced mortality from coronary heart disease[3–4] and have lower plasma triglycerides and high HDL-cholesterol levels than whites,[5] although a higher risk of coronary heart disease (CHD) is associated with raised plasma triglycerides and lower HDL-cholesterol levels in South Asians.[6] While there is debate about the appropriateness of a genetic approach to the study of racial or ethnic differences in phenotypic expressions,[7–10] the Y chromosome seems to be an obvious candidate for gender-related differences in the development of cardiovascular diseases.[11]

With the exception of 2 small recombining pseudoautosomal regions (PAR1 and PAR2), the male specific region of the Y chromosome (MSY), which comprises 95% of the length of the chromosome in humans, is functionally active and inherited in block from father to male offspring.[12] Although most genes in the MSY region are involved in male-specific function, such as sex determination and spermatogenesis, this region also contains genes probably involved in other cellular functions and possibly responsible for the sexual dimorphism of cardiovascular diseases. In fact, most of the genes of the male specific region of the Y chromosome (MSY) fall into 2 functional classes, with genes in the first group expressed in many organs throughout the body and genes in the second group expressed predominantly or exclusively in testes. Notably, all 12 ubiquitously expressed MSY genes reside in the X-degenerate regions, so the X- and Y-linked genes encode very similar but nonidentical

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protein isoforms.[12] Because of the haploid nature of the Y chromosome, it cannot be used in genome-wide scans for a linkage to cardiovascular phenotypes within the human genome. Therefore, classic fine mapping and positional analyses within the implicated regions are not possible. The candidate region approach is also not possible because of a lack of obvious candidate genes for cardiovascular and metabolic phenotypes. One of the most common strategies used in the studies of the Y chromosome is cladistic association analysis. This haplotype-based approach was successfully used in human studies investigating the influence of the Y chromosome on fertility-related phenotypes.[13]

In the last few years, population genetic studies explored the association between the biallelic *Hin*dIII(±) polymorphism of MSY and blood pressure[14–17] or serum lipid levels,[17–18] with contrasting findings, the more recent and largest studies reporting negative results.[16–17]

We focused our attention on 3 genes, *TBL1Y*, *USP9Y*, and *UTY*, located in the X degenerate region of MSY, spanning a region of about 5 Mb containing the *Hind*III polymorfic marker and not exclusively expressed in the testes. The aim of this study was to characterize allele frequencies of SNPs at these loci in different ethnic groups participating to the Wandsworth Heart & Stroke Study (WHSS) and to identify associations of SNPs or haplotypes with cardiovascular risk factors. Finally, these genetic markers of the Y chromosome were also analyzed in an independent sample of white Italian males.

Methods

Methods and populations of each survey have been described in detail elsewhere.[5,6,19] The studies were performed according to the Principles of the Declaration of Helsinki and were approved by the Ethics Committees of all the participating institutions. All study participants agreed to give blood samples for DNA analysis and biochemical measurements, by informed consent.

Population Sampling

Wandsworth Heart and Stroke Study

The study methodology as well as the general characteristics of the population sample are reported in great detail elsewhere.[5,6] In brief, men and women age 40 to 59 years were recruited from the lists of general practices in South London between March 1994 and July 1996. Ethnic group was recorded at the time of interview based on the answers to a combination of questions including place of birth, language, religion, history of migration, and parental country of birth. The final sample size was 1577, 794 of them were men. Of those, 579 (whites, 182; blacks, 174; South Asians, 223) for whom a DNA sample was available were genotyped for polymorphisms of male specific region of the Y chromosome (MSY). Participants from ethnic minority groups were all first generation immigrants. The general characteristics of those included in the analysis did not differ from those who were excluded because of lack of DNA samples.

Olivetti Heart Study

The Olivetti Heart Study (OHS) population was made of unselected white adult male individuals who were or had been part of the Olivetti factory work force in Campania, a region of Southern Italy.[19] The data were collected between January 2002 and May 2004 and derived from the examination of 997 participants. For the purpose of the present study, we genotyped one third of this population. Cases were randomly extracted by a random numbers generator software (Research Randomizer, www.randomizer.org). Of the 332 randomly extracted subjects, 301 had a complete data set and were used for the present analysis. This subsample was fully comparable to the whole 2002 to 2004 OHS population sample.

Anthropometric Measurements

In both studies, body weight and height were measured on a standard beam balance scale with an attached ruler. The body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). The waist circumference was measured at the umbilicus level and the hip circumference was measured at the widest circumference over the trochanters, at the nearest 0.1 cm with a flexible inextensible plastic tape, with the subject standing erect with the abdomen relaxed, arms at the sides, and feet together.

Blood Pressure Measurement

In both studies, blood pressure measurements were performed during the screening visit before blood sampling, with similar protocols. In the WHSS, blood pressure was measured using an automatic ultrasound sphygmomanometer (Arteriosonde, Roche Products) after the subject had been resting for at least 10 minutes in the supine position. In the OHS, blood pressure was measured with a random-zero sphygmomanometer (Gelman Hawksley Ltd) after the participant had been sitting upright for at least 10 minutes. In both studies, systolic and diastolic blood pressures were taken 3 times with 2-minute intervals between measurements, and the average of the last 2 readings was used for the analyses.

Biochemical Measurements

In both studies, blood samples for biochemical measurements and DNA extraction were obtained between 8 AM and 12 noon after an overnight fasting. Aliquots for lipid assay from the WHSS were shipped in dry ice to the University of Naples for biochemical analysis. Serum lipid levels were measured in both studies in the same laboratory at the University of Naples by automated methods (Cobas MiraRoche). The coefficient of variation between assays ranged from 1.70% for serum triglycerides to 1.97% for total cholesterol.

Genotyping

The DNA samples were genotyped by polymerase chain reaction (PCR)–restriction fragment length polymorphism (RFLP) (PCR-RFLP) for *Hin*dIII(±), according to Russo et al,[17] and for 3 SNPs located in *TBL1Y* (Transducin b-like 1Y protein), *USP9Y* (Ubiquitin-specific protease 9Y), and *UTY* (Ubiquitously transcribed Y chromosome tetratricopeptide repeat protein) genes spanning a region of about 5 Mb containing the *Hind*III polymorfic marker and expressed not exclusively in the testis.

In particular, rs768983 (A/G) located in the UTR region of *TBL1Y* gene; rs3212292 (L466H) located in the coding region of *USP9Y* gene; and rs9341273 (E34G) located in the coding region of *UTY* were selected from "GeneCard" (http://www.genecards.org/index.shtml) and NCBI-SNP (http://www.ncbi.nlm.nih.gov/SNP/) databases. The following sense and antisense primers were used: *TBL1Y* 5′-AACACACTCCTCTTCCTTCC–3′; 5′-TAACCGATAGTCCTTTTCAG-3′; *USP9Y* 5′-CAACTGATTCTTCCAATGAG-3′; 5′-TGTCATCCAGGTTTGCCAG-3′; *UTY* 5′-GAGAGTATCGCCAGCCAACC-3′; 5′-GGCGTCACAGTCTCAAGCAG-3′. These primers were selected with oligo 4.0-s (Primer Analysis Software version 4.0; Molecular Biology Insights Inc) in Y gene–specific regions to avoid nonspecific X gene copy amplification. Approximately 20 ng of DNA from each participant was added to a mix that contained 10 pmol of each primer, 1× PCR buffer (Gibco-Invitrogen), 0.2 mmol/L each of the 4 dNTPs (Gibco-Invitrogen),

1.5 mmol/L $MgCl_2$, and 0.5 U *Taq*DNA polymerase (Gibco-Invitrogen) to give a total reaction volume of 10 μL. The first denaturation step at 94°C for 3 minutes was followed by 35 cycles at 94°C for 30 seconds, 58°C (*TBL1Y* and *USP9Y*) or 64°C (*UTY*) for 30 seconds, and 72°C for 30 seconds, followed by a final extension time at 72°C for 10 minutes. The amplicons were then digested by the addition of 1 U of *Rsa*I (*TBL1Y*), *Nde*II (*USP9Y*), *Hin*fI (*UTY*) restriction endonucleases (Promega) in the presence of 1× appropriate buffer at 37°C for 2 hours. Digested products were resolved on a 2.5% agarose gel with ethidium bromide and visualized with Gel Doc BioRad apparatus. The digestions after amplification yielded 2 possible genotypes for each SNPs: *TBL1Y* allele A, 229 bp uncut product, or allele G, 2 products of 143 and 86 bp; *USP9Y* allele G, 131 bp uncut product, or allele T, 2 products of 89 and 42 bp; *UTY* allele C, 288 bp uncut product or allele T, 2 products of 207 and 92 bp. For each polymorphism, a 10% random sample was genotyped twice in a blinded fashion with concordant results.

Statistical Analysis

Data are presented as mean±SD. As the distribution of HDL-cholesterol and triglyceride levels deviated significantly from normality, they were normalized by log transformation; log-transformed values were used in the analysis, as appropriate. Differences in phenotypic variables between ethnic groups were assessed by multiple comparison test with Bonferroni correction. Differences in allele frequency between ethnic groups were determined by χ^2 statistics. Blood pressure comparisons both between and within ethnic groups were performed after the exclusion of participants under pharmacological antihypertensive treatment. Differences in phenotypic variables between quantitative genotypes within each ethnic group (WHSS whites, blacks, south Asians; OHS whites) were compared by analysis of covariance (ANCOVA), adjusting for covariates possibly affecting the variability of the phenotypes under study (age, BMI, alcohol intake expressed as grams/d).

On the basis of the exploratory genotype analysis, haplotype analysis was conducted by combining the most frequent alleles in blacks ($TBL1Y_A$ and $USP9Y_A$) and comparing this haplotype with all other possible allelic combinations.

For the assessment of possible genotype/phenotype associations within each ethnic group, each ethnic sample of the WHSS provided at least 80% power to detect at $P<0.05$ a 10/6 mm Hg difference for systolic and diastolic BP, respectively, a 0.23 mmol/L difference in serum triglyceride, and a 0.13 mmol/L difference in HDL cholesterol levels between genotypes. Statistical analyses were performed with the SPSS statistical software package (SPSS 11.0).

Results

The general characteristics of the WHSS populations are shown in Table 1. Significant interethnic differences in the levels of cardiovascular risk factors (Table 1) and in the allele frequencies (Table 2) were observed.

*Hind*III(±) polymorphism was not associated with cardiovascular phenotypes in both the WHSS white and in the Olivetti Heart Study (OHS) populations, as previously reported.[17] In blacks of African origin and in South Asian participants of the WHSS the allele frequency was significantly different from that observed in whites ($P<0.001$) (Table 2). However, in these 2 ethnic groups, no statistical association was observed between this marker and both blood pressure and serum lipids.

The locus for the *TBL1Y* A/G polymorphism (rs768983) was almost monomorphic in whites, only 1 participant of 182 bearing the A allele, and monomorphic in South Asians, whereas the A allele was the major allele in blacks of African origin (72.8%) (Table 2). The people of black African origin carrying the A allele had lower serum triglycerides ($P=0.033$) and higher HDL-cholesterol ($P=0.008$) levels (Table 3).

Table 1. Characteristics of the WHSS Participants

Variable (mean±SD)	Whites (n=182)	Blacks (n=174)	South Asians (n=223)
Age, y	50.3±5.5*†	52.0±5.7‡§	49.3±5.9
BMI, Kg/m^2	25.9±4.1‖¶	26.6±3.6‡§	24.6±3.6
WC, cm	92.3±10.8	91.0±9.6	90.4±10.1
SBP, mm Hg#	126.8±18.2*§	135.2±19.1‡†	130.2±19.4
DBP, mm Hg#	81.5±10.0*§‖§	88.1±10.0‡†	85.2±10.8
T-CHOL, mmol/L	6.19±1.15*§‖§	5.47±1.04‡†	5.77±1.02
HDL-CHOL, mmol/L	1.26±0.33*†‖§	1.34±0.34‡§	1.08±0.29
TG, mmol/L	1.47±0.86*§‖¶	0.98±0.50‡§	1.74±0.91
FBG, mmol/L	5.19±0.75*†‖§	5.70±2.02	5.87±1.99

BMI indicates body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; T-CHOL, total cholesterol; HDL-CHOL, high-density lipoprotein cholesterol; TG, triglycerides; FBG, fasting blood glucose.

P values are from 1-way ANOVA with Bonferroni correction for multiple comparisons.

*Whites vs Blacks; ‖Whites vs South Asians; ‡Blacks vs South Asians; #participants on pharmacological treatment for hypertension were excluded (whites: n=17; blacks: n=49; South Asians: n=34).

†$P<0.05$; ¶$P<0.01$; §$P<0.001$.

The A allele of the *USP9Y* A/T polymorphism (rs3212292) was the minor allele in both whites and South Asians, whereas it was the most frequent allele (79.1%) in black people of African origin (Table 2). No significant phenotypic expressions of cardiovascular risk factors were found in white and South Asian carriers of the *USP9Y* variant, whereas among the black people of African origin the carriers of the A allele had lower serum triglycerides ($P=0.029$) and higher HDL-cholesterol ($P=0.006$) levels (Table 3).

The locus of the *UTY* C/T polymorphism (rs9341273) was monomorphic in all ethnic groups (Table 2).

The $TBL1Y_A$ $USP9Y_A$ haplotype was present only in blacks, in whom it represents the most frequent allelic combinations (AA: n=125; all other combinations: n=45). The AA carriers at *TBL1Y* and *USP9Y* loci had lower levels of triglycerides ($P=0.025$) and higher levels of HDL-cholesterol ($P=0.005$) as compared to the other haplotypes (Table 3).

In the OHS the polymorphisms in *TBL1Y*, *USP9Y*, and *UTY* genes were genotyped in 301 males (age: 58.2±6.4 years; BMI: 27.4±3.4 Kg/m^2), randomly extracted from the 997 participants to the 2002 to 2004 follow-up.[19] The allelic distribution of *TBL1Y*, *USP9Y*, and *UTY* was similar to that observed in WHSS whites (*TBL1Y:* A=1%, G=99%; *USP9Y:* A=9.8%, T=90.2%; *UTY:* T=100%, C=0%). *TBL1Y* was almost monomorphic, only 3 participants of 301 bearing the A allele, and *UTY* monomorphic. Similarly to that observed in the white population of the WHSS, these variants were not associated with serum lipid levels nor with blood pressure.

Table 2. Allelic Frequencies of *HIND*III, *TBL1Y*, *USP9Y*, and *UTY* Polymorphisms in the WHSS Participants

	*HIND*III		*TBL1Y*		*USP9Y*		*UTY*	
	(+)	(−)	G	A	A	T	T	C
Whites, % (n)	28.6 (52)	71.4 (130)	99.4 (181)	0.6 (1)	4.9 (9)	95.1 (173)	100 (182)	...
Blacks, % (n)	81.6 (142)	18.4 (32)	27.2 (47)	72.8 (126)	79.1 (136)	20.9 (36)	100 (174)	...
S. Asians, % (n)	49.3 (110)	50.7 (113)	100 (220)	...	7.7 (17)	92.3 (206)	100 (223)	...

Discussion

People of African descent in the UK show a lower rate of coronary heart disease events than whites,[3] despite high prevalence of hypertension and diabetes.[5] Furthermore black men of African origin have significantly lower coronary heart disease rates than white men.[20–21] Among possible risk factors accounting for the lower rate of coronary events, the only well-documented differences are the higher HDL-cholesterol and lower triglycerides levels in blacks compared with whites. Although many environmental factors that may influence health outcomes among ethnic groups are known, it is unclear what proportion of overall influences on health is accounted for by genetic risk factors shared (or not) among populations.[9–10] One reason is the relatively low number of genetic association studies performed on population groups other than whites.[9,22] The lack of data hampered a systematic evaluation of possible differences in the effect of disease and associated gene variants across populations. The present study provides new insights. First, it is the first report on the association of genetic variants of the Y chromosome (others than the already investigated *Hind*III site polymorphism) with phenotypes of cardiovascular risk. Second, it is the first report that explored this association in different ethnic groups.

Several studies investigated the association of the *Hind*III site polymorphism with blood pressure and serum cholesterol levels in whites, with conflicting results.[14–18] This is the first report that explores the *Hind*III site polymorphism in populations other than whites. The frequency of the *Hind*III(+) allele was different among the 3 ethnic groups of the WHSS, being higher in blacks of African origin (81.6%) than in South Asians (49.3%) and in whites (28.6%). However, as previously reported by the largest studies on this marker in whites,[16–17] also in blacks and in South Asians no association was found with both blood pressure and lipid levels. The allele frequency for rs768983 (A/G), located in the UTR region of *TBL1Y* gene, was similar to that reported in the NCBI-SNP database for African and European populations (http://www.ncbi.nlm.nih.gov/SNP). This SNP is reported as TagSNP for African populations in the Seattle SNP database (http://pga.gs.washington.edu). To our knowledge, no frequency data for different ethnic groups are reported in the public SNPs database for rs3212292 (L466H), located in the coding region of *USP9Y* gene.

Data from a large Y chromosome collection (Y2) reported in the NCBI-SNP database (http://www.ncbi.nlm.nih.gov/SNP) showed that rs9341273 (E34G), located in the coding region of *UTY*, is almost monomorphic. Our data indeed confirmed this finding in all the ethnic groups under study.

A discussion of the mechanisms underlying the observed associations is beyond the objective and possibilities of the present study. Although the understanding of the Y chromosome has increased over the past decade, especially with the completion of the MSY sequence, there are only

Table 3. Cardiovascular Phenotypes in the Black Participants of WHSS, According to *Hind*III, *TBL1Y*, and *USP9Y* Genotypes and to *TBL1Y/USP9Y* Haplotypes

	*Hind*III			*TBL1Y*			*USP9Y*			*TBL1Y/USP9Y*		
	+ n=142	− n=32	*P*	A n=126	G n=47	*P*	A n=136	T n=36	*P*	AA n=125	GA/GT/AT n=45	*P*
SBP,* mm Hg	134.7±19.1	137.4±19.2	ns	134.4±18.6	137.2±20.6	ns	134.7±18.9	135.1±17.7	ns	134.4±18.6	136.0±19.1	ns
DBP,* mm Hg	87.9±10.4	88.9±7.9	ns	87.6±10.2	89.2±9.3	ns	87.8±10.3	88.2±7.5	ns	87.7±10.3	88.5±8.3	ns
T-CHOL, mmol/L	5.52±1.07	5.19±0.86	ns	5.51±1.08	5.37±0.93	ns	5.49±1.07	5.41±0.93	ns	5.51±1.08	5.38±0.93	ns
HDL-CHOL, mmol/L	1.34±0.32	1.34±0.40	ns	1.39±0.35	1.25±0.30	0.008	1.38±0.34	1.23±0.31	0.006	1.39±0.35	1.25±0.30	0.005
TG, mmol/L	0.96±0.48	1.07±0.58	ns	0.93±0.43	1.10±0.64	0.033	0.93±0.43	1.15±0.69	0.029	0.93±0.43	1.11±0.64	0.025
FBG, mmol/L	5.60±1.78	5.98±2.82	ns	5.72±2.03	5.65±2.05	ns	5.65±1.97	5.94±2.26	ns	5.73±2.04	5.68±2.06	ns

Mean±SD, adjusted for age, BMI, and alcohol intake; ns=not statistically significant.

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; T-CHOL, total cholesterol; HDL-CHOL, high-density lipoprotein cholesterol; TG, triglycerides; FBG, fasting blood glucose.

*Participants on pharmacological treatment for hypertension were excluded (n=49).

limited data available on the phenotypic characteristics of Y chromosome structural variants.[23] However, some working hypotheses are reported in a functional analysis of predictive models of the structure of proteins encoded by MSY genes.[24] According to these hypotheses, proteins encoded by *TBL1Y, USP9Y*, and *UTY* may have regulatory functions at the level of protein–protein interactions and protein turnover.[24]

In our study, the men of black African origin carrying the A alleles of both *TBL1Y* and *USP9Y* had a more favorable lipoprotein profile, characterized by lower levels of serum triglycerides and higher levels of HDL-cholesterol, thus indicating the existence of a "cardio-protective haplotype." In contrast, in white men, both from the UK and Italy, and in people of South Asian origin, the lipoprotein profiles were not affected by these genotypes. Although these findings are new, it is important to recognize that the present study does not fully meet all the criteria ideally required for a genetic association study.[25] In particular, because of the difficulty of gathering other well-characterized ethnic samples of African ancestry living in Europe, we only provided replication within 2 unrelated white populations in UK and Italy to confirm the lack of association within this ethnic group. Again, given the very low frequency of the A allele of *USP9Y* and the absence of the A allele of *TBL1Y* in whites and South Asians, the effects of these genotypes in these ethnic group must be interpreted with caution.

There may be different explanations for observing the significant associations only in men of African ancestry. One possibility is that the haplotype under study may not be the causal modulator of the observed differences in lipoprotein phenotypes and that some other causal polymorphisms are in strong linkage disequilibrium with *TBL1Y/USP9Y* haplotype only in men of African origin, but not in whites and South-Asians. In addition, the triglyceride and HDL-cholesterol levels in all individuals of African origin were generally low, compared with typical levels in whites.[3,5–6] Interestingly, the "cardio-protective" $TBL1Y_A$ $USP9Y_A$ haplotype is present exclusively in people of black African origin of the WHSS and is absent in both whites and South Asians, whereas blacks not bearing the AA haplotype show a worse lipid profile. This raises the question as to whether the A alleles of both genes are the original ancestral alleles. The data presented here suggest that G allele of *TBL1Y* and T allele of *USP9Y*, reported as the wild-type alleles in whites (http://www.ncbi.nlm.nih.gov/SNP) may be derived from the A alleles of both genes, which are the most frequent in black people of African origin. These A alleles might in fact be the ancestral ones, suggesting a possible founder effect, consistent with the hypothesized African origin of modern humans.[26]

In conclusion, the $TBL1Y_A$ $USP9Y_A$ haplotype of the Y chromosome, present only in black people of African origin, attributes a favorable lipoprotein pattern, likely to contribute to their reduced susceptibility to develop atherosclerosis and coronary heart disease in Africa, the Caribbean, and the UK.[27–28]

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Disclosures

None.

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