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**Perspective**

# North African genetic variation of cytochrome and sulfotransferase genes

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This review is focused on the genetic variation of sulfotransferases (SULTs) and cytochromes (CYPs) genes among different ethnic groups, mainly focusing in variation in North African populations. Polymorphisms of SULTs and CYPs proteins are associated with altered enzymatic activity and physical characteristics. Single nucleotide polymorphisms (SNP) in these genes have shown relevant ethnic differences among Sub-Saharan African and European groups that might contribute to understand the variability in drug metabolism and risk to certain cancers that has been described among these two groups. Taking into account that North African populations have been scarcely described for these genes, and considering the rich genetic past of this region with a noticeable Sub-Saharan African contribution to their original background, it is interesting a revision and description of some relevant polymorphisms (González-Pérez et al. 2010; Hen et al. 2012)

Sulfotransferases catalyze the conjugation of sulfate groups to endogenous and exogenous substrates containing aryl alcohol, alkyl alcohol, hydroxylamino, or amino groups. SULTs play an important role in the homeostasis of the body in two ways. First, they remove drugs and xenobiotic compounds by sulfoconjugating reaction via hepatobiliary and urinary systems. Secondly, they sulfoconjugate and deactivate endogenous active substances such as dopamine, estrogen or thyroid hormones (Cole et al. 2010). To date, five distinct gene families

of SULTs have been identified in mammals: SULT1, SULT2, SULT3, SULT4, and SULT5. The SULT1 family or phenolic SULT gene family has eight distinct members: A1, A2, A3, A4, B1, C2, C4 and E1 (Gamages et al. 2006). This review will focus only on three of these members: sulfotransferase 1A1 (SULT1A1), sulfotransferase 1A2 (SULT1A2) and sulfotransferase 1E1 (SULT1E1).

The sulfotransferase genes SULT1A1 and SULT1A2 are located close to each other on chromosome 16p11.2. SULT1A1 is highly expressed in liver, but is also expressed in platelets, adrenal gland, endometrium, colon and brain. SULT1A2 is expressed in liver, platelets, heart, brain and skin. The sequences of these two genes are 93% similar. Differences are most apparent in the 5' promoter and intron sequences (Gamages et al. 2006).

SULT1E1 maps to chromosome 4q13 and the protein codified by this gene has a high affinity for the sexual hormone estradiol and estrone, and a variety of synthetic estrogens such as diethylbestrol and tamoxifen (Gamages et al. 2006). SULT1E1 is expressed at high levels in liver during the first trimester of development, decrease shortly after birth. SULT1E1 is also expressed in estrogen-responsive tissues including breast, endometrium, prostate and testis (Charles et al. 2009).

Several alleles have been identified for these three SULTs, but three SNPs have shown relevant interethnic differences: SULT1A1*2 (rs 9282861), SULT1A2*2 (rs 1136703) and SULT1E1*2 (rs 3736599).

The common SNP (rs 9282861) reported for SULT1A1 has been associated with a variation in activity and thermal stability. SULT1A1*2 is a transition of G to A at the nucleotide 638 producing a substitution of histidine by arginine in the codon 213 (Arg213His). Compared to the wild-type allele (Arg213 allele), the SULT1A1*2 (His213) has less enzymatic activity and thermostability. SULT1A1 allele frequencies have been reported in different populations. In Europeans the most frequent allele (or the wild type) is allele *1 (Arg213) whereas allele *2 (His213) is less frequent (0.656 for allele *1 and 0.332 for allele *2, respectively). Related with this SNP, another genetic variant resulting on the combination of SNP rs9282861 and SNP rs1801030 produces a third allele (*3) with marked differences between Sub-Saharan African (allele *3 0.224) and European (allele *3 0.012) populations (Swati et al. 2006; Coughtrie 1999).

SULT1A2 has two relatively common variants, SULT1A2*2 and SULT1A2*3 (with rs10797300). The SULT1A2*2 differs in two amino acid residues (Ile7thr and Asn235THr) in comparison of SULT1A2*1 (the wild type). This exchange in codon 235 appears to be functionally important because Thr in that position reduces the affinity for the substrate. Variants *2 and *3 exhibit a lower enzyme activity levels than the wild-type (Hansruedi and Walter 2004; Shah et al. 2015). Ethnic variation in allele frequencies also exists for SULT1A2. In these case, Europeans and African-American populations have a high frequency of allele *1 (wild-type), being followed by allele*2 and finally allele *3 (Carlini et al. 2001).

Concerning SULT1E1 polymorphism, allele *2 is a result of a transition from guanine to adenine in the promoter at the position -64. This is the less common variant in most populations although Sub-Saharan African groups show relatively higher frequencies as compared with Europeans (0.306 in Yorubans, 0.07 in Tuscans, 0.117 in Iberians; data from 1000 Genomes. Project available at:
*http://www.ensembl.org/Homo_sapiens/Variation/Sample?db=core;r=4:69859603-69860603;v=rs3736599;vdb=variation;vf=103510171*). (Adjei et al. 2003)

Concerning association of these polymorphisms and different types of cancer, association between SULT1E1 gene and endometrial adenocarcinoma has given contradictory results (O'Mara et al. 2011). SULT1A1 Arg213His polymorphism has been associated with breast cancer in Asian women and postmenopausal women among all ethnic groups, although there are no exact effects to increase the risk of breast cancer in premenopausal women (Yiwei et al. 2010). This variant of SULT1A1 is associated to infant acute lymphoblastic leukemia and acute myeloid leukemia risk in males (Lopes et al. 2015). SULT1A1 Arg/Arg (*1/*1) genotype has been related with prostate cancer in Europeans whereas no association has been described between SULT1A1*2 and prostate cancer (Serdal et al. 2011). On the other hand, SULT1A1 *1/*1 genotype, higher in Asians, has been associated with increased bladder cancer risk (Wencheng and Min 2014).

Cytochromes (CYPs) are hemoproteins located in the cytoplasmic, mitochondrial and endoplasmic reticulum membrane. CYPs are hemoproteins because they have a heme group core associated with processes like ATP synthesis via electron transport. Cytochromes in the P4503A family are estimated to participate in the metabolism of 40 to 60% of all clinically administered drugs. Specifically, they catalyze the oxidative, peroxidative, and reductive

metabolism of many endogenous substrates and xenobiotics. The two CYPs revised here, CYP3A4 and CYP4A5, are part of a cluster of cytochrome P450 genes mapped on chromosome 7q21.1.

Cytochrome P450 3A4 (or CYP3A4) is highly expressed in the liver and small intestine of adults. This cytochrome catalyzes a big amount of oxidative reactions of substances like fatty acids. It acts, also, over 6o% of drugs. CYP3A4 seems to have an important role in the metabolism of cyclosporine A and some antibiotics like erythromycin. At the same time, it catalyzes the 6-beta-hidroxilation of some steroids such as testosterone, progesterone, and cortisol. CYP3A5 may be an important genetic contributor to interindividual and interethnic differences in CYP3A-dependent drug clearance and response.

The polymorphisms revised here are CYP3A4*1B (rs2740574) and CYP3A5*3 (rs776746). Allelic variants of these genes induce structural differences in the enzymes they encode, causing a >99% reduction in their catalytic activity (Garsa et al. 2005).

CYP3A4*1B polymorphism encodes a variant consisting of a transition of an A to G in the 5'-flanking region. (Kuehl et al. 2001; Yousef et al. 2012; Sanchez-Cuenca 2014). The most common nonfunctional variant of CYP3A5 is designated as CYP3A5*3. CYP3A5*3 changes A to G at the position 22,893, creating a cryptic splice site in intron 3, resulting in altered mRNA splicing. CYP3A5*1 has an A at this position. Its frequency varies widely across human populations. In Caucasians the most frequent allele is *3 (0.977 in an European sample from data from dbSNP Sort Genetic Variations, NCBI)

(*http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?searchType=adhoc_search&type=rs&rs=rs776 7 46*). Sub-Saharan African samples show low frequencies of this allele (0.060 In Nigerians).

Regarding the association of these polymorphisms with cancer, CYP3A4*1B has been associated with increased risk of prostate cancer among African populations. This association has not been observed in European and Asian groups. This polymorphism is not associated with breast cancer and leukemia. Other studies suggested that genotype CYP3A5 * 1 / * 3 may be involved in salt and water retention and the risk for hypertension sensitive to salt. Apparently, variants that affect the homeostasis of salt have a selective pressure that gives an environmental variation in correlation with latitude (Kuehl et al. 2001; Thompson et al. 2014; Garsa et al. 2005; Lamba et al. 2012).

Six different North African samples from Morocco (North East Atlas, Middle Atlas and High Atlas), Algeria, Tunisia and Libya have been genotyped for SULT1A1*2 and SULT1A1*3, SULT1A2*2 and SULT1A2*3, SULT1E1*2, CYP3A4*1B , CYP3A5*3 alleles. As a summary of the genetic variation in North Africa, these six groups have been compared with samples of European and African origin (because of the scarce data available, data from different studies has been taken to represent these two groups; (Swati et al. 2006; Carlini et al. 2001; and the 1000 genomes project *http://www.1000genomes.org*). The main objective was to detect possible Sub-Saharan African influences in the genetic background of North African groups for a set of SULT and CYP genes with biomedical interest that present striking interethnic differences between Caucasian and Sub-Saharan African groups.

A global approach to genetic diversity can be observed in the MDS (multidimensional scaling) that represents Reynolds genetic distances among these populations (Figure 1). As expected, the North African and the European samples are clearly separated from Africa (Sub-Saharan). The six North African samples do not cluster together; Northeast Atlas is the most differentiated. This Moroccan group is the one showing the highest genetic diversity (Figure 2). In fact, pairwise population differences point to Northeast Atlas as the group showing the highest number of significant population differences (9 out 15 after Bonferroni correction). High Atlas showed the same number of significant differences. In addition, a rough (because only 5 SNPs have been used) approximation to the genetic contribution of Sub-Saharan African variation into the genetic background of these samples has also been tested (Figure 3). Sub-Saharan African contribution ranged from 10% in Tunisia to 19% in Algeria and Northeast Atlas.

In conclusion, North African samples enlarge the genetic variation of SULT and CYP genes in Caucasian groups. Sub-Saharan African contribution and variants that have shown the highest frequencies in these groups as compared with other European and African samples could explain the genetic richness found in North African populations.

**Figure 1.** MDS of Reynolds genetic distances based on CYP3A4*1B, CYP3A5*3, SULT1A1*2, SULT1A2*2 and SULT1E1*2 SNPs (stress 0.067)

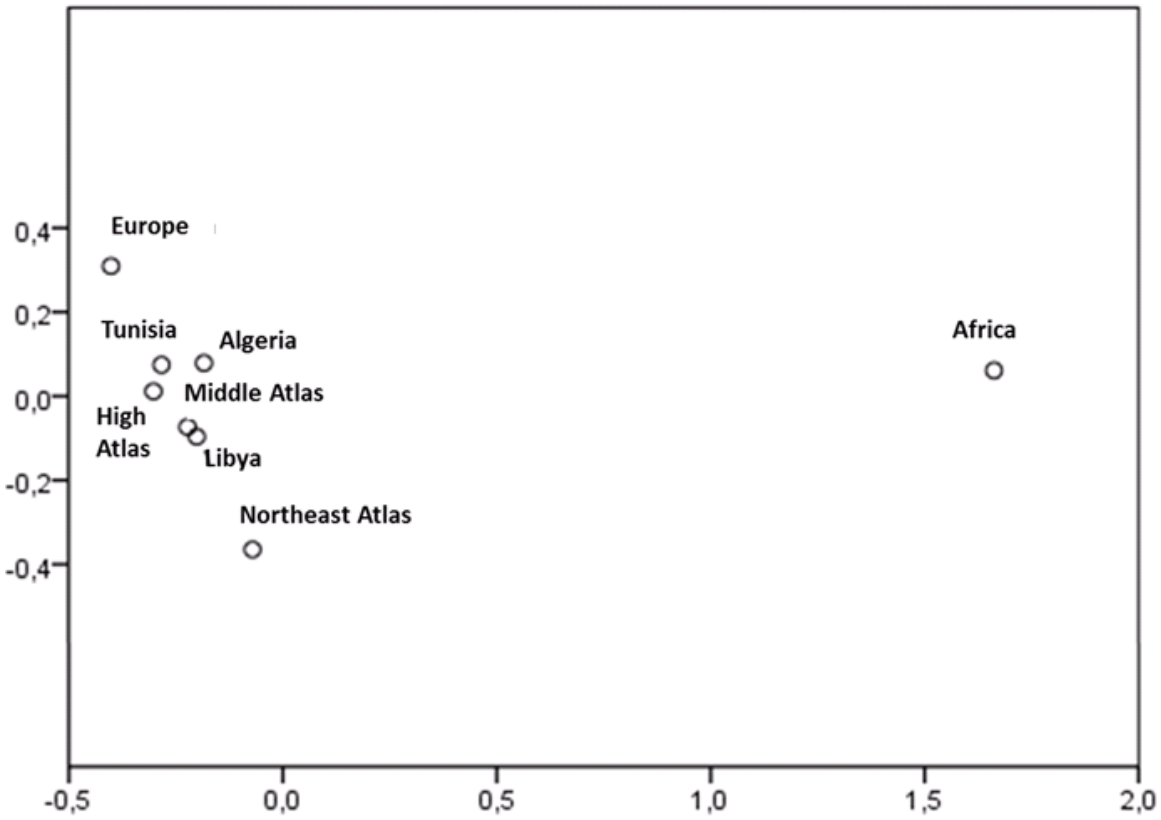
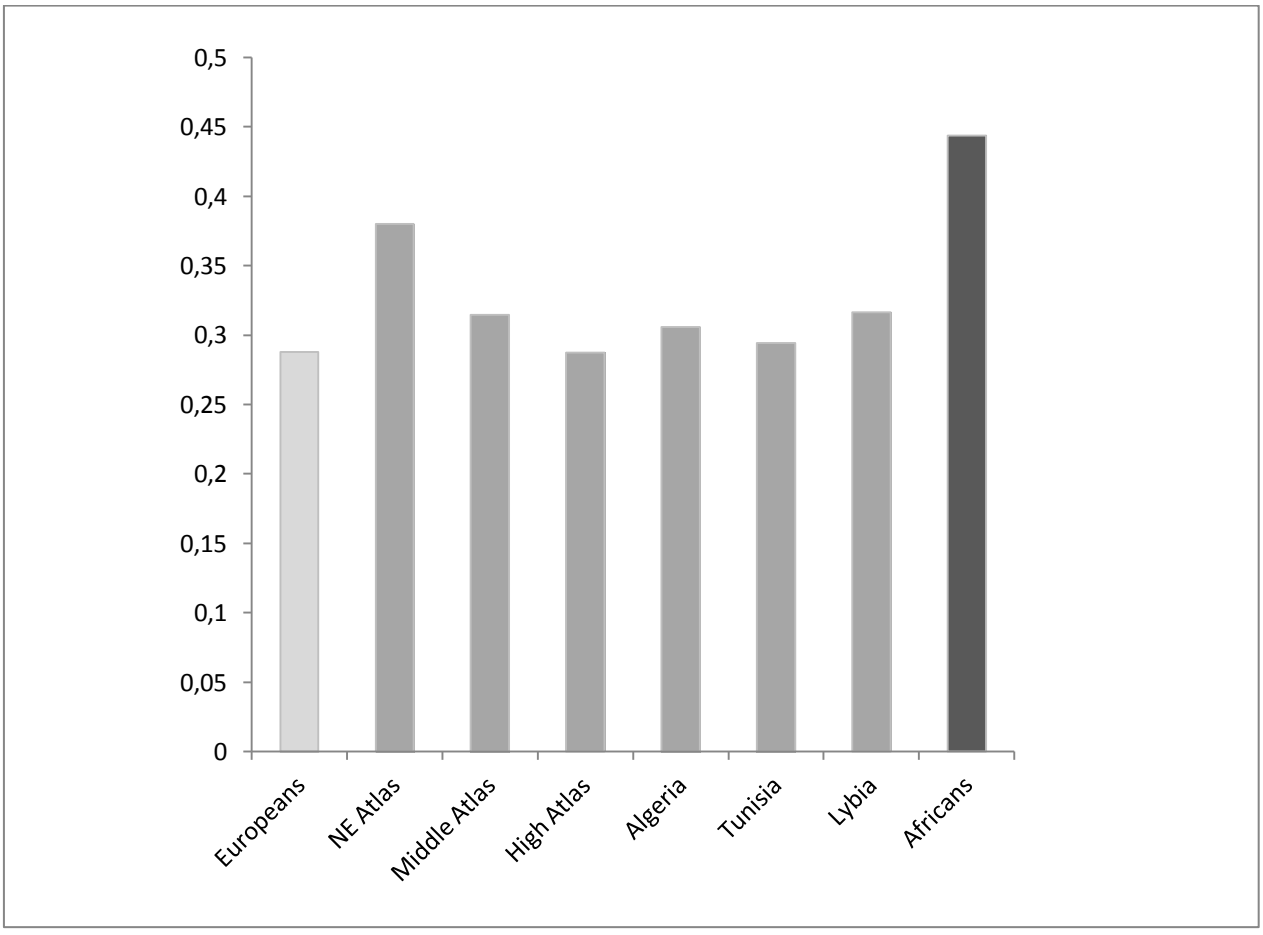
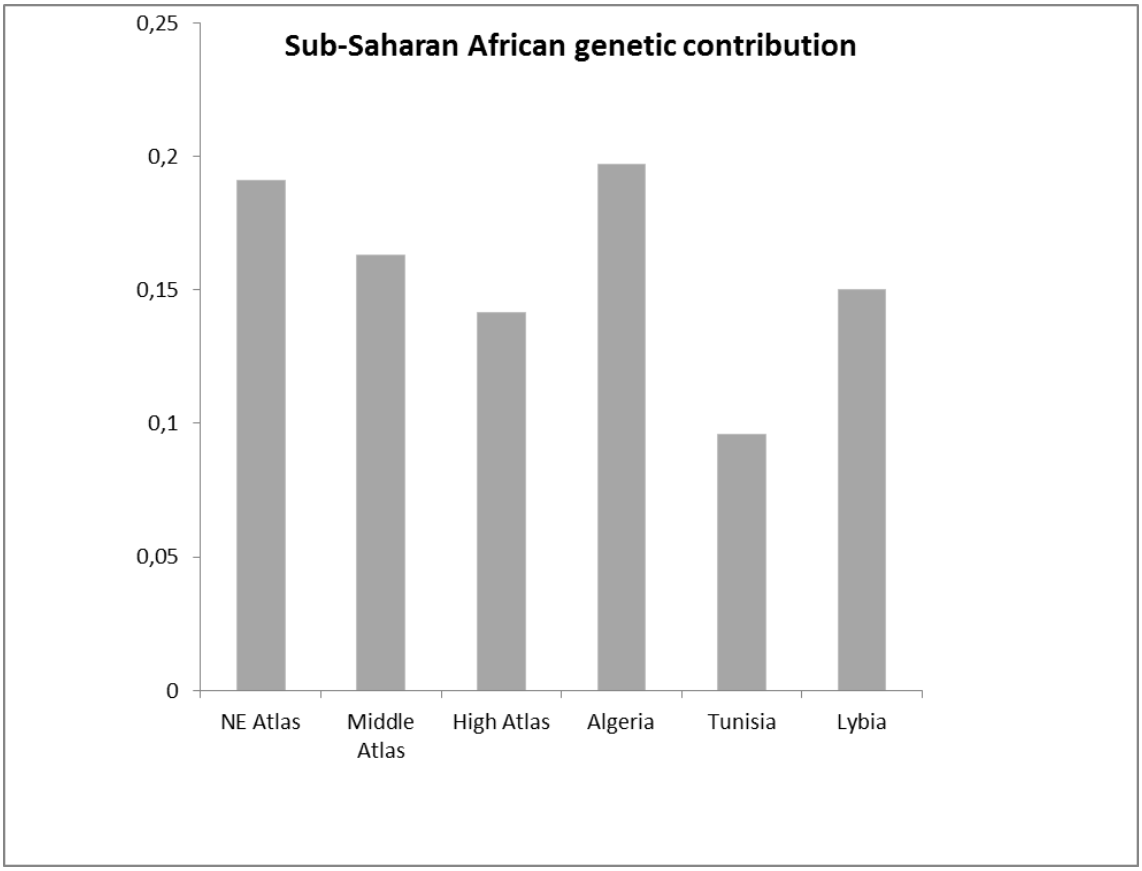


**Figure 2.** Mean Heterozygosity of CYP3A4*1B, CYP3A5*3, SULT1A1*2, SULT1A2*2 and SULT1E1*2 SNPs




| Mean Heterozygosity values | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0.288 | 0.380 | 0.315 | 0.287 | 0.306 | 0.294 | 0.317 | 0.444 |

**Figure 3.** Sub-Saharan African genetic contribution based on CYP3A4*1B, CYP3A5*3, SULT1A1*2, SULT1A2*2 and SULT1E1*2 SNPs



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