Co-adaptation of the vitamin D receptor (VDR) and color-determining genes to the latitude during humans' venture out of Africa

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CONTEXT: As modern humans ventured out of Africa, they received significantly less UVB radiation, and had to adjust their skin color for vitamin D generation. We hypothesized that as humans ventured out of Africa the VDR gene co-adapted with skin color (SC) genes to changing latitude and UVB exposure.

METHODS: To this end, we extracted DNA from 751 subjects from a range of geographical latitudes and skin colors, and determined 68 SNPs from SC genes (MC1R, TYR, TYRP1, OCA2, SLC45A2, SLC24A5, KITLG) and from the VDR gene.

COMPUTATION: A new method of identifying associations among SNPs was used called BlocBuster. It calculates a vector correlation that can attain multiple associations among SNPs and deal with underlying genetic heterogeneity. It detects haplotypes within small genomic regions and identifies multi-locus genetic states that frequently occur within individuals in a population.

RESULTS: 4/22 VDR gene SNPs, all in the 5' promoter region, are rare in Sub-Saharan Africa, but virtually fixed in all other populations, whereas coding region and 3' UTR SNPs have no such distinction power. Four SNPs of SLC24A5, SLC45A2, MC1R, all in the coding regions of SC genes, clustered in non-random associations with the VDR 5' promoter SNPs. The frequency of this cluster was 0.021 in Sub-Saharan Africa (latitude 0-8N), 0.276 in Egypt and Yemen (15-29N), 0.571 among Israeli Moslems and the Maghreb (31-33N), and 0.855 in Europeans (40-50N); the 8 SNPs in a 4-gene cluster correlated strongly with latitude, R^2 =0.873, p=3.7E-5.

CONCLUSIONS: A selective sweep favoring the VDR promoter haplotype happened almost as soon as *Homo sapiens* migrated out of Africa. When the VDR promoter haplotype combined with four SNPs in SC genes, a higher order cluster correlated strongly with latitude. Thus, the newly-described high frequency VDR promoter haplotype interacted with SC genes to produce fine-scale adaptation to northern latitudes and decreasing UVB irradiation along the route out of Africa.