

Genes involved in vitamin D pathway and schizophrenia show signature of latitude-dependent adaptation

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Motivation

Genetic differences are present in humans at both individual and population level. Human genetic variations are studied for their evolutionary relevance and for their potential medical applications. In particular, high levels of population differentiation suggest the acting of a positive selection of advantageous alleles in one or more populations. This studies can help scientists in understanding ancient human population migrations as well as how selective forces act on the human being. Moreover, loci resulting from an adaptation to particular environmental factors can be of great interest when studying complex diseases. Adaptations to spatially varying selective pressures may be particularly important in human populations. Since the human species first arose in equatorial Africa, as humans spread out of equatorial Africa to regions at higher latitudes, many latitude-related phenomena likely became important selective forces. This scenario is likely to apply to a range of selective pressures, e.g. exposure to UV radiation, climate, diet, day-night cycle, etc.

Methods

To explore, at genome-wide level, possible genetic adaptations to latitude, in this work we defined a set of Latitude-Related Genes (LRGs) following a two step approach. We used genotype data at about 600000 SNP loci of 938 unrelated individuals from 51 populations of the Human Genome Diversity Panel. Firstly, we identified a set of SNPs with high levels of population differentiation. From this set we then extracted those SNPs showing high correlation of allelic frequencies with the geographical latitude. We finally obtained a set of 2239 SNPs corresponding to 1336 unique genes. We characterized this set of genes exploring both the tissue localization and the functional characterization. We then investigated for their enrichment in other sets of genes associated to physiological and pathological phenotypes.

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Results

Both functional characterization and expression localization of LRGs resulted in a strong enrichment in neural related processes. Among the four diseases tested (namely Parkinson's disease, Alzheimer's disease, multiple sclerosis and schizophrenia), we found a significant enrichment in genes related with schizophrenia for LRGs (Fisher's exact test, Bonferroni adjusted p-value $1.6E-5$). We thus investigated for a possible latitude dependent biological mechanisms linking latitude to neural development. A very important factor hypothesized to be latitude dependent and known to be related with neural development is the vitamin D. We found in the set of vitamin D related genes a significant enrichment by LRGs (p-value $3.5E-8$, Fisher's exact test). This result, for the first time at a genetic level, suggests an adaptation of vitamin D related genes driven by geographical latitude. We also found a significant overlap between schizophrenia and vitamin D related genes (p-value $1.4E-6$, Fisher's exact test) confirming the role of vitamin D in schizophrenia pathogenesis. Our results provide the first evidence, at a molecular level, of a previously hypothesized relationship among these phenomena. This result can also be useful for the identification of new candidate genes for this and other related pathology.

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