Human *Gonadotropin* genes: genetic variation and comparison to our sister-species, common chimpanzee

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The gonadotropin hormone β-subunit (*GtHB*) family is represented in human by seven duplicated Luteinizing Hormone Beta (*LHB*) /Chorionic Gonadotropin Beta (*CGB*) genes located at 19q13.32 and two single-copy genes – Follicle-stimulating hormone beta (*FSHB*) at 11p13-p14 and *TSHB* at 1p13.2. *GtHB* genes have an essential role in human reproduction and all but placenta-specific *CGB*-s are expressed by anterior pituitary. We have addressed by resequencing the fine-scale variation and recombinational landscape in *LHB/CGB* and *FSHB* genomic regions. Despite the evolutionary and functional relatedness, the *GtHB* family members exhibit contrasting diversity patterns. In the *LHB*/*CGB* region, characterized by high sequence homology between the duplicated genes, meiotic gene conversion has had an important role in spreading polymorphisms among duplicon copies. The diversity level of *LHB/CGB* cluster is one of the highest reported for human genes. In contrast, a single-copy *FSHB* located in a gene-poor genomic region is characterized by low diversity, no non-synonymous mutations and excess of SNPs with intermediate allele frequencies. Diversity data supported the functional conservation of *FSHB* and the influence of natural selection. We identified (1) only two worldwide 'yin-yang' *FSHB* variants; (2) low divergence and only three amino acid differences in great apes relative to human *FSHB*; (3) a *FSHB* promoter SNP located within a conserved region acting as Progesterone Responsive Element in ovine *Fshb* and significantly associated with serum FSH level in men.
To further explore the evolutionary dynamics of primate-specific *LHB/CGB* genomic region, we constructed a shotgun library and sequenced the entire *LHB/CGB* cluster in the common chimpanzee. We found structural variation resulting in discordant number of *CGB* genes (6 in human, 5 in chimpanzee) in sister-species. The most parsimonious solution to explain the interspecies structural differences was the scenario of species-specific parallel duplications. There are strong footprints of intraspecies gene conversion shaping the *LHB/CGB* gene cluster in primates. The substitution divergence (1.8-2.59%) exceeded two-three fold the estimates for single-copy loci and the fraction of transversional mutations was increased compared to the unique sequences (43% versus ~30%). Despite the high sequence identity among *LHB/CGB* genes, there are signs of functional differentiation among the gene copies.

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