Reply to Comments by Previc: Endocrine Differences Between Humans and Great Apes—Did Environmental Factors Provide Genetic Opportunities?

We are very glad to read of Dr. Previc's enthusiasm for our recent findings on thyroid hormone differences between humans and great apes (Gagneux et al., 2001). We are responding herewith to some of the interesting issues that he has raised.

Our paper presented human-ape comparative results on plasma thyroid hormone levels and levels of transthyretin (TTR) in plasma and cerebrospinal fluid (CSF). Given the crucial role of thyroid hormone in brain development, we suggested that developmental studies of humans and great ape thyroid hormone levels are warranted, especially for the CSF/brain side of the blood brain barrier. We did not hypothesize about how such hormonal differences originally came about. Extrapolating from current-day human-ape differences to the series of events that brought about these changes sometime during our evolutionary past is fraught with difficulty. However, we are glad if our results provide potential support to other existing hypotheses. Increased consumption of animal foods and frequent strenuous exercise may indeed have played a crucial role in resetting dopaminergic levels in hominoids, as proposed by Dr. Previc's extensively researched paper on this subject (Previc, 1999). However, it is also evident that present-day humans can achieve above-average cognitive capacities in the absence of meat-rich diets or increased physical activity levels. As far as we know, there is no evidence that strictly vegetarian modern humans who are mostly sedentary have diminished levels of cognitive ability. There also appears to be no evidence that dietary tyrosine is rate-limiting in thyroid hormone synthesis in modern humans, or that strict vegetarian diets are a risk factor for hypothyroidism. Thus, if dietary tyrosine and/or strenuous exercise played a major role in the evolution of human cognition by altering dopamine and/or thyroid hormone metabolism, we suggest that any resulting biological changes have since become genetically fixed in the human lineage, and are no longer dependent on environmental factors. The exception, of course, is the amount of iodine in the diet. However, the actual levels of iodine in meat are dependent on the kind of animals eaten, and their own dietary ecology.

There is now general agreement that we should leave the artificial dichotomy of "genes vs. environment." The role of environmental effects due to diet in hominid evolution, especially those acting via maternal effects, is clearly an important area to investigate. However, we doubt that such effects would occur in a genetic vacuum, as these could easily lead to selection of favorable mutations, allowing their carriers to make full use of novel dietary resources. Previc (1999) cites our statement that most genetic differences so far documented between humans and great apes are not linked to biochemical differences. However, we also previously pointed out that the available data set of such differences is quite small (Gagneux and Varki, 2001). Furthermore, in at least one instance, our laboratory documented a defined biochemical difference between humans and great apes, which affects virtually every cell surface in the body of humans (Muchmore et al., 1998; Chou et al., 1998; Varki, 2002). We recently showed that this difference is clearly linked to a specific genetic event, namely a replacement of one human genomic *Alu* sequence by another, causing the loss of an exon in the human CMP sialic acid hydroxylase gene uniquely in the hominid line (Hayakawa et al., 2001). The significance of this biochemical change is being investigated (Varki, 2002). Furthermore, recent human-specific gene duplications such as those documented for chromosome 22 (Bailey et al., 2001) point to more dynamic genomic changes in recent human evolution. It is safe to assume that a multitude of gene products interact with the environment and with each other during brain development. However, it cannot be easily predicted which elements of such genetic networks are responsible for dramatically changing the resulting development, and whether or not these are due to minor or major mutation(s). Looking for differences in dynamically changing parts of our genome increases the likelihood of identifying potential genomic triggers for any observed endocrine differences.

We were unaware of the earlier suggested differences in size of adrenal vs. thyroid glands between

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humans and great apes. While such morphological comparisons are interesting, they need to be followed up by measurements of the actual levels of hormones, if we are to understand their role in human development. The paper cited by Dr. Previc on the effect of low thyroid levels on human skin and fingernails is strictly speculative and actually incorrect with respect to chimpanzee behavior. In spite of their strong nails, chimpanzees can indeed clench their fists and are capable of wielding sticks with great strength (Gagneux, personal observation; Karl Amman, personal communication).

Finally, we point out that the studies cited by Dr. Previc on thyroid hormone and cognitive capacities in humans do not include measurements made on the brain side of the blood-brain barrier. We wish to reemphasize our suggestion that thyroid hormone levels in the brains of developing humans and chimpanzees need to be studied, in order to assess the potential role of these hormones in determining differences in neural development and function.

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LITERATURE CITED

Bailey JA, Yavor AM, Viggiano L, Misceo D, Horvath JE, Archidiacono N, Schwartz S, Rocchi M, Eichler EE. 2001. Human-specific duplication and mosaic transcripts: the recent paralogous structure of chromosome 22. Am J Hum Genet 70:83–100.

Chou H-H, Takematsu H, Diaz S, Iber J, Nickerson E, Wright K, Muchmore EA, Nelson DL, Warren ST, Varki A. 1998. A mutation in human CMP-sialic acid hydroxylase occurred after the *Homo-Pan* divergence. Proc Natl Acad Sci USA 95: 11751–11756.

Gagneux P, Varki A. 2001. Genetic differences between humans and great apes. Mol Phylogenet Evol 18:2–13.

Gagneux P, Amess B, Diaz S, Moore S, Patel T, Dillmann W, Parekh R, Varki A. 2001. Proteomic comparison of human and great ape blood plasma reveals conserved glycosylation and differences in thyroid hormone metabolism. Am J Phys Anthropol 115:99–109.

Hayakawa T, Satta Y, Gagneux P, Varki A, Takahata N. 2001. Evidence for an Alu conversion event mediating the human-specific inactivation of the CM acetylneuraminic acid hydroxylase gene. Proc Natl Acad Sci USA 98:11399–11404.

Muchmore EA, Diaz S, Varki A. 1998. A structural difference between the cell surfaces of humans and the great apes. Am J Phys Anthropol 107:187–198.

Previc FH. 1999. Dopamine and the origins of human intelligence Brain Cogn 41:299–350.

Varki A. 2002. Loss of N-glycolylneuraminic acid in humans: mechanisms, consequences and implications for hominid evolution. Yrbk Phys Anthropol 44:54–69.