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Complexity of primate gene regulation revealed in β-type globin expression and distance, report Wayne State researchers in PNAS

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Phylogenetic comparisons suggest that the locus control region (LCR)—the area that regulates transcription—interacts with primate β-type globin genes to mediate different developmental expression patterns in different branches of the evolutionary tree. The primates more distantly related to humans, prosimians (like the African Bush Babies) and New World monkeys (flat-nose monkeys with prehensile tails), express embryonically the γ globin gene neighboring ε. In contrast, catarrhines (Old World monkeys and apes, including humans) express these genes primarily during fetal development.

The globin genes, labeled ε, γ, ψη, δ, β, fall into a cluster in this order located just downstream of the LCR. A short distance between ε and γ allows the LCR to drive embryonic expression in both genes, whereas a longer distance impedes embryonic activation of the downstream gene.

A report in the February 14 issue of the *Proceedings of the National Academy of Sciences* uses phylogenetic reconstructions to show that in prosimians, the LCR acts to fully turn on a single γ gene along with ε during embryonic life and then repressors act to shut both genes off at the beginning of fetal life at which time the LCR acts to fully turn on the δ and β genes. In simian primates, with their duplicated γ genes, two distinct patterns are seen: in New World monkeys, the γ gene closest to the LCR is predominantly embryonically expressed, whereas in catarrhines, it is predominantly fetally expressed. Furthermore, in New World monkeys, the γ gene furthest from the LCR is the major fetally expressed gene, whereas in catarrhines, it is the γ gene closest to the LCR that assumes this pattern. These differences can be attributed to the varying distances of these genes from the LCR: in New World monkeys, the first γ gene is approximately 6-7 kb from ε, whereas in catarrhines, it is 13-14kb.

The article is authored by Robert Johnson, Ph.D., professor of biochemistry and molecular biology at Wayne State University, and was contributed by Morris Goodman, Ph.D.,

distinguished professor, who is a member of the National Academy of Sciences. The full article, "Phylogenetic Comparisons Suggest That Distance from the Locus Control Region Guides Developmental Expression of Primate β-type Globin Genes," can be viewed online at: http://www.pnas.org/. Co-authors are: Tom Prychitko, Deborah Gumucio, Derek Wildman and Monica Uddin.

"Our approach is to examine the hemoglobin changes in primate species closely related to humans, in which the switching program is subtly different. By examining promoter regions from genes that turn on at different points in embryogenesis, we are able to pinpoint promoter changes that mediate the timing of the developmental switch," Dr. Johnson said.

During embryonic life, ζ and α genes switch on to encode α-type chains and the ε gene switches on to encode β-type chains. At about the sixth to eighth week of prenatal life—approximately the beginning of the fetal period—the ζ and ε chains switch off. In higher primates, the α genes remain on, but as the ε gene switches off, the two γ genes switch on. By contrast, there is only one γ gene in tarsiers (the small nocturnal arboreal primates with large round eyes and a long tail), but the γ gene is duplicated in simians.

Past collaborations among Drs. Johnson, Goodman and their colleagues have revealed that ε, the gene at the beginning of the globin cluster, had all the regulatory sequences that would characterize an embryonically expressed gene. The downstream β gene had all the regulatory sequences for a post-embryonically expressed gene. These results have been confirmed in Australian marsupial mammals, where the ε gene remains embryonic for about a day as the embryo migrates to the pouch, rapidly becomes fetal and then postfetal. After the one day migration, the ε hemoglobin gene is turned off and the β gene is turned on. Regulatory sequences in the proximity of each of the two genes play key roles in the switching, although the mechanism was not well understood until this publication that reports the importance of the LCR, whose relative distance can greatly enhance expression of each functional gene at the appropriate developmental stage.

These results reveal more than the complexity of factors regulating developmental expression patterns in primate β-type globin genes. They also provide treatment clues for hemoglobinopathies like sickle cell anemia and thalassemia. "We want to put our finger on those cis-regulatory elements that are part of the ancient machinery of hemoglobin switching and those cis-regulatory elements that are part of the recent machinery that causes these γ genes not to be expressed in embryonic life but rather fetal life. If we could understand the elements that control the expression of the γ gene, then we could play around with how to manipulate these elements

so that we can get the γ gene expressed after birth for patients with hemoglobinopathies," Dr. Goodman said.

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With more than 1,000 students, the Wayne State University School of Medicine is the nation's third largest medical school. Together with its clinical partners, the Wayne State University Physician Group, the Detroit Medical Center and other area health care providers, the school is a leader in medical research and patient care with emphases on cancer, women's and children's health, neurosciences, population studies and urban health.