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# Resolution of a human chromosomal mystery: Evolutionary complexity revealed

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**The human complement of chromosomes differs from our closest primate relatives by virtue of a unique chromosome fusion event. In this issue of *Cell Genomics*, Yang et al. provide the first detailed analysis of the site of chromosome fusion and reconstruct the complex evolutionary relationships among the genomic elements within the human fusion site and their related sequences in our great ape relatives.**

Identifying the when, how, and why of the speciation event that separated human ancestors from our closest great ape relatives is a long-standing goal of researchers from various disciplines. Studies of the fossil record provide an approximate time frame and environmental context[1] but have not yet provided a detailed definition of either the biology of the last common ancestor or the features that distinguish the earliest members of our human lineage from the lineage that produced modern chimpanzees (*Pan troglodytes*) and bonobos (*Pan paniscus*). Comparative genomics is an orthogonal approach that provides many unique insights into the evolutionary divergence of human ancestors from our closest living nonhuman primate relatives.

In this issue, Yang et al.[2] present a comparative analysis of chromosome structure and content among humans, chimpanzees, bonobos, gorillas (*Gorilla gorilla*) and orangutans (genus *Pongo*) that provides novel insight into an intriguing aspect of great ape (including human) genomic evolution. Their results constitute a valuable description of one specific event in human genomic history that has intrigued and frustrated investigators for years. The chromosomes of our species can be unambiguously aligned against the chromosomes of our closest ape relatives. All human chromosomes, save one, exhibit a one-to-one correspondence between the chimpanzee and human orthologs.[3] However, human chromosome 2 occurs in *Pan* and all other great apes as two separate chromosomes. At some point after the divergence of human ancestors from the ancestors of the genus *Pan*, a chromosome fusion occurred to create human chromosome 2.[4] When this happened, what impact this had on evolutionary boundaries between diverging lineages, and what consequences it had for the origin of human phenotypic traits, has been obscure.[5,6]

Yang et al. used recently published, nearly telomere-to-telomere quality reference genomes[7] for five great ape species (chimpanzee, bonobo, gorilla, and both Bornean and Sumatran orangutans) to investigate the evolution of the fusion site present on human chromosome 2. They found unanticipated complexity in the evolutionary relationships among species for distinct regions within the 109 kilobase fusion site (Figure 1). To reconstruct the phylogenetic history, they divide the fusion site into three domains, each a segmental duplication (SD) that has close relationships with chromosomal segments in the nonhuman great apes. But those relationships are not consistent across the three SD elements. One of the three human SDs is most closely related to sequences now found in gorillas, while the second appears derived from a sequence present in chimpanzees, bonobos, and gorillas. The third human SD is most similar to a sequence found only in bonobos.

This complexity of relationships across regions within a single 109-kb human fusion site is a strong indication of incomplete lineage sorting (ILS). This is the population genetic process in which different segments within a polymorphic ancestral genome segregate independently into three or more descendant lineages. Among the descendant lineages, ILS produces one pattern of inter-species phylogenetic relationships for some genomic regions and a different pattern of relationships for other regions. Yang et al. provide convincing evidence that the origin of the human fusion site and the subsequent history of retention or loss of specific sequences across the human and ape lineages is best explained as the result of ILS starting from a polymorphic common ancestor. Furthermore, the three human SDs at the fusion site all seem to share common ancestors with nonhuman great ape sequences between 7.4 and 6 million years ago. This places the evolutionary divergence of the human copies of the SD segments at roughly the same time that other efforts to date the human-chimpanzee divergence also infer that divergence event.[8]

Thus, Yang et al. have resolved a long-standing question in human evolutionary genomics; i.e., what is the structure within the human chromosome 2 fusion site and what were the genomic mechanisms that produced that fusion? This is an outstanding example of the value of telomere-to-telomere quality assemblies for reconstructing the history and mechanisms of genome evolution. In addition, the authors pushed further and asked (1) what genes were affected by the evolutionary rearrangements in these regions and (2) whether those genes play any role in the origin of the unique human phenotype. Using CRISPR-Cas9 to delete relevant chromosomal segments from

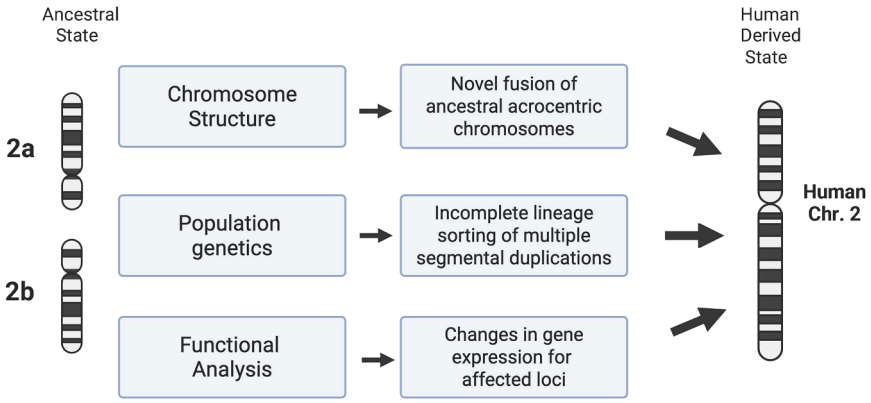


**Figure 1. Three aspects of the evolutionary process that generated human chromosome 2**

human iPSCs and then differentiating them into neural progenitor cells, they discovered that 277 genes display expression differences in the deleted lines compared to controls. Functional enrichment analysis indicates that many of these genes are associated with neural development and axonogenesis. While this is not definitive evidence, it is an intriguing suggestion that this fusion event itself may have played a role in the evolution of human neurodevelopment from the ancestral great ape state.

This work is an important advance for several reasons. First, it beautifully illustrates a key benefit of developing high quality reference assemblies for as many species as possible. Access to near-complete assemblies supports a wide range of research endeavors—comparative evolutionary genomics in this case—but also improved studies of animal models of human disease and expanded opportunities for comparative analysis of cell and developmental biology. This work also documents one example of complex chromosomal rearrangements driving genome evolution. Across nonhuman primates, and other groups as well, chromosomal differences frequently correlate with species boundaries. Whereas genomic changes in single-copy DNA have received extensive attention, detailed analysis at single base pair resolution of karyotype changes was not previously possible. Yang et al. illustrate how comparative analyses of difficult-to-sequence regions of genomes will likely identify mechanisms that underlie structural changes in chromosomes, allowing evaluation of their contributions to speciation. Chromosomal evolution is a substantial component of primate genetic evolution.[9,10] Finally, it is interesting that this fusion, which apparently occurred early in human evolution, possibly influenced gene expression during neurodevelopment. SDs and subtelomeric regions were indiscernible sequences without recent advances in sequencing and assembly methods. Yang et al. demonstrate that we can expect additional discoveries ahead through detailed analysis of such regions in various species groups. The approach pioneered here will likely pay dividends as our knowledge and understanding of genomic diversity expands.

## DECLARATION OF INTERESTS

The author declares no competing interests.

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