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Review Article

What Makes Humans Human?
A review of important genetic differences between chimpanzees and humans

Danielle Taylor Cormier[a], Autumn Brooke Berry[a], Matthew Rhodes[a] and Jeffrey Michael Copeland[a]

What makes humans human? Genomic comparisons of humans and chimpanzees provide a new tool for addressing this interesting question. Genetic comparisons show remarkable similarity between chimpanzees and humans; indeed, the human and chimp genome are 96% similar, with only a 1% difference in nucleotide substitutions and a 3% difference in chromosomal insertions and deletions. But even modest differences in genomes can have profound biological effects. In this review, we tackle this formidable topic by summarizing the effects of transposon mobility, gene duplications, and uniquely human genes in conferring important phenotypic changes from chimpanzee to human.

Keywords: Human; Chimpanzee; SRGAP2; miR-941; Mobile Elements

Introduction

One way of identifying physiological and morphological attributes unique to humans has been to compare humans to their closest biological relatives, the chimpanzees (*Pan troglodytes* and *Pan paniscus)*, which diverged genetically approximately 5-7 million years ago (Wood & Harrison, 2011). Since 2005, when the first draft of the chimpanzee genome sequence was released, comparative genomic research has made substantial progress in answering the fundamental question: what makes humans human? Though the human and chimpanzee genome are 96% identical, there are clear phenotypic and behavioral differences between these two creatures (Sequencing & Consortium, 2005; Varki & Altheide, 2005). For example, chimpanzees have relatively equalized strength between their legs and the arms, while humans have longer, more powerful legs (Sockol, Raichlen, & Pontzer, 2007). Posture and bipedal gait have been attributed to the evolution of these features of human limb structure (Sockol et al., 2007). The size and composition of the frontal cortex in the brain also differ between humans and chimps. The human frontal cortex is larger and has a greater amount of white matter with axonal fibers enwrapped in myelin sheaths (Schoenemann, Sheehan, & Glotzer, 2005). This additional amount of white matter allows humans to develop increased neural interconnections which might account for important human cognitive abilities such as forethought, memory and complex speech (Varki & Altheide, 2005).

The anatomical and physiological differences between humans and chimps, both the obvious and the subtle, are somehow connected to only a 4% change in genetic sequence. In this review, we summarize some of the significant differences that have been found in recent genetic comparisons of humans and chimpanzees. This is quite a formidable topic, so we will highlight a few of the unique human genes that confer novel neurological function. We will also describe important large-scale genomic differences and differences in transposon activity that also have been shown to distinguish key traits between these genetically related species.

Cytological Changes

The first genetic comparisons between humans and chimps began over (Warburton, Firschein, Miller, & Warburton, 1973) four decades ago with chromosome banding studies. These first karyotypes revealed a difference in chromosome number between humans and chimps. The human set of chromosomes is reduced by one; human chromosome 2 is the result of a fusion of the chromosomes 2a and 2b found in apes (Yunis, Sawyer, & Dunham, 1980). Relative to the chimp genome, the human genome boasts other significant cytogenetic alterations including 9 chromosomal inversions and 1 translocation. Comparative genome hybridizations on microarrays have been useful for detecting small-scale insertions and deletions that are different between the two genomes (Frazer et al., 2003; Locke et al., 2003).

Within the past decade, genome sequencing projects have provided details regarding base pair changes to the genome; namely, single nucleotide polymorphisms accounting for a 1.2% difference and insertions and deletions accounting for 3% of the dissimilarities (Sequencing & Consortium, 2005; Ventura et al., 2012). Interestingly, many changes in the genome are the result of small duplications. In the human genome, 515 regions harbor duplications, particularly on chromosomes 5 and 15, not found in the chimpanzee genome (Cheng et al., 2005). In the comparative study, chimpanzees have an additional 112 Mb sequence not found in the human genome.

Mobile DNA Elements

Mobile DNA elements (or transposable elements) account for approximately 45% of both the human and chimpanzee genomes, and given their sheer abundance and diversity, they are important in considering the biological differences between the two species (Mills et al., 2006; Prüfer et al., 2012b). These mobile elements are especially interesting because they are able to disrupt gene function and potentially cause disease or drive gene expression (Cordaux & Batzer, 2009). Transposable elements can be categorized by the mechanism of mobilization. DNA transposons (or class II) move throughout the genome by a simple "cut and paste" mechanism

a. Department of Biology, Eastern Mennonite University, Harrisonburg, VA, 22802
Correspondence: jeffrey.copeland@emu.edu

and are capable of moving directly to a separate genomic area (Burns & Boeke, 2012). No longer active specifically in humans or chimps, class II transposons comprise about 3% of the human and about 4% of chimp genome (Cordaux & Batzer, 2009; Lander et al., 2001). Class I elements, or retrotransposons, mobilize through a RNA intermediate to create a derivate copy of themselves elsewhere in the genome. Since the original retrotransposon is left behind, class I elements use a "copy and paste" system of movement (Lee, Han, Meyer, Kim, & Batzer, 2008).

The SINE (Short Interspersed Transposable Element) and LINE (Long Interspersed Transposable Element) retrotransposons are the two most abundant classes of transposons in the human and chimpanzee genomes, and both are still active (Lander et al., 2001; Sequencing & Consortium, 2005). Within the SINE class of retrotransposons, the *Alu* type is most abundant and is primate-specific (Xing, Witherspoon, Ray, Batzer, & Jorde, 2007). *Alu* elements are roughly 300 nucleotides in length and are present at 1.09 million copies in the human genome (Lander et al., 2001). The LINE-1 (L1) transposon, a type of LINE transposon, comprises approximately 17% of the human genome, making it the most prevalent mobile element regarding occupied space (Cordaux & Batzer, 2009; Lander et al., 2001). L1 elements are larger (6000 bp) and encode two functional genes, ORF1 and ORF2. Upon transcription of the L1 element, the gene products of ORF1 and ORF2 bind to the L1 RNA and facilitate re-integration at a different genomic locus (Burns & Boeke, 2012; Feng, Moran, Kazazian, & Boeke, 1996). The presence of ORF1 and ORF2 permit autonomous transposition, unlike the *Alu* elements which rely on other transposons for mobility (Burns & Boeke, 2012; Dewannieux, Esnault, & Heidmann, 2003). SVA (SINE/VNTR/*Alu*) elements are the most recent transposon to appear in the primate lineages and are a composite of these three retrotransposon elements (Mills et al., 2006; Stewart et al., 2011). The SVA group ranges in size from 700 to 4000 bp (Burns & Boeke, 2012). There are about 3,000 SVA copies within the human genome, but like *Alu* elements SVA elements require the presence of LINE elements, like L1, for mobility (Cordaux & Batzer, 2009). While other transposable elements exist in both the human and the chimpanzee genomes, like the ERV class of LTR retrotransposons, the *Alu*, L1, and SVA comprise the bulk of mobile elements found.

All three types of retrotransposons, *Alu*, L1, and SVA, are still active in both chimps and humans; in fact, it has been deduced that 600 million people have unique insertions from transposon activity (Cordaux, Hedges, Herke, & Batzer, 2006; Iskow et al., 2010). Importantly, the relative amounts of each have shifted since the last shared ancestor. In humans, the *Alu* elements have tripled in comparative abundance, while in chimpanzees the frequency of L1 elements has increased (Hormozdiari et al., 2013; Mills et al., 2006; Prüfer et al., 2012a). Interestingly, movement of L1 and *Alu* elements has had profound impact in the structural variation seen in the genomes. Of the 252 inversions (DNA sequence reversal) found different between the two genomes, 44% are caused by L1 and *Alu* elements (Lee et al., 2008). In addition, the L1 elements are responsible for the 73 human-specific deletions, representing 450 kb (Han et al., 2008).

The genomic position of the transposons and the changes in the genome structure they cause can have important consequences. A significant number have landed in the transcriptional control elements of developmental genes and thus have the potential for altering gene expression (Cordaux & Batzer, 2009; Lowe, Bejerano, & Haussler, 2007; Lowe & Haussler, 2012). Indeed, the MER 41 class of retrotransposons are predominantly found in genes responding to IFN-γ, a pro-inflammatory cytokine of the innate immune system, acting as necessary regulatory elements for gene transcription (Chuong, Elde, & Feschotte, 2016). The reelin signaling pathway provides another example. The reelin pathway is essential in neuronal migration and adhesion in the developing cerebral cortex, and importantly, a L1 retrotransposon rests in the control elements of four of the reelin signaling pathway genes in all mammals (Lowe et al., 2007). While much work needs to be still done to show the role of transposable elements as one mean of driving speciation, it is clear that the presence of transposable elements can alter gene expression in species- or tissue-specific ways (Garcia-Perez, Widmann, & Adams, 2016).

Genes Unique to *Homo sapiens*

In addition to gross chromosomal changes and a characteristic profile of transposons, humans do possess some unique genes. Gene duplication has been identified as an essential source for the phenotypic alterations and adaptive evolution that produce unique genes (Samonte & Eichler, 2002). Once a gene has been duplicated, the new version is not under any selective pressure and may accumulate nucleotide variations and acquire a novel cellular function. In a genome comparison between six primate species, for example, it was found that 663 and 562 genes were accumulating base pair substitutions at an accelerated rate in the human and chimpanzee lineage, respectively, suggesting selective evolutionary pressure (Scally et al., 2012). Both the human and chimpanzee genomes have witnessed an abundance of gene duplications over the past 10 million years, and genes involved in human neurodevelopmental processes have been duplicated disproportionally (Dennis et al., 2012). There have been over 60 gene duplications identified as candidates for producing some of the phenotypic differences between humans and chimpanzees (Varki & Altheide, 2005).

It is very difficult to pinpoint the exact number of novel human genes, in part because it is difficult to define what constitutes a unique gene. How many nucleotides need to change from the precursor before a gene qualifies as unique? In looking for genes no longer under negative selection, one attempt to uncover uniquely human genes identified 202 possible candidates (Pollard et al., 2006). Using a hybridization technique between the genomes of the hominid species, Fortna et al. report 134 genes unique to humans, many of which are implicated in brain function (Fortna et al., 2004). In another study comparing the genomes between six primates,

SRGAP2 – the self-antagonizing gene duplication

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some of the phenotypic differences between humans and chimpanzees (Varki & Altheide, 2005).

The *SRGAP2* (Slit-Robo Rho GTPase-activating protein 2) gene illustrates the role of gene duplication in the speciation of humans and chimps. Gene duplication occurs during DNA replication or through the movement of retrotransposons, both of which could result in the eventual formation of genes with entirely new functions. The *SRGAP2* gene, also known as *SRGAP2A* in humans, is involved and highly expressed during the development of the cortical regions of the brain (Wong et al., 2001). *SRGAP2* consists of an N-terminal F-Bar domain, a Fx domain, a central Rho-GAP domain and a C-terminal tail SH3 domain (Sporny et al., 2017). Dennis et al. (2012) demonstrate that the ancestral *SRGAP2* gene, present only in one copy in chimpanzees, duplicated multiple times in humans over the last 3.4 million years to create the truncated *SRGAP2B, 2C,* and *2D* homologs (Figure 1). Both the duplicated *SRGAP2B* and *SRGAP2C* are nearly identical to each other, and their expression results in truncated proteins lacking the Rho-GAP and SH3 domains. The *SRGAP2D* protein is even smaller and is predicted to only encode 23 amino acids (Charrier et al., 2012). It is the creation of these truncated *SRGAP2* homologs that allow for the development of novel gene function and cell behavior.

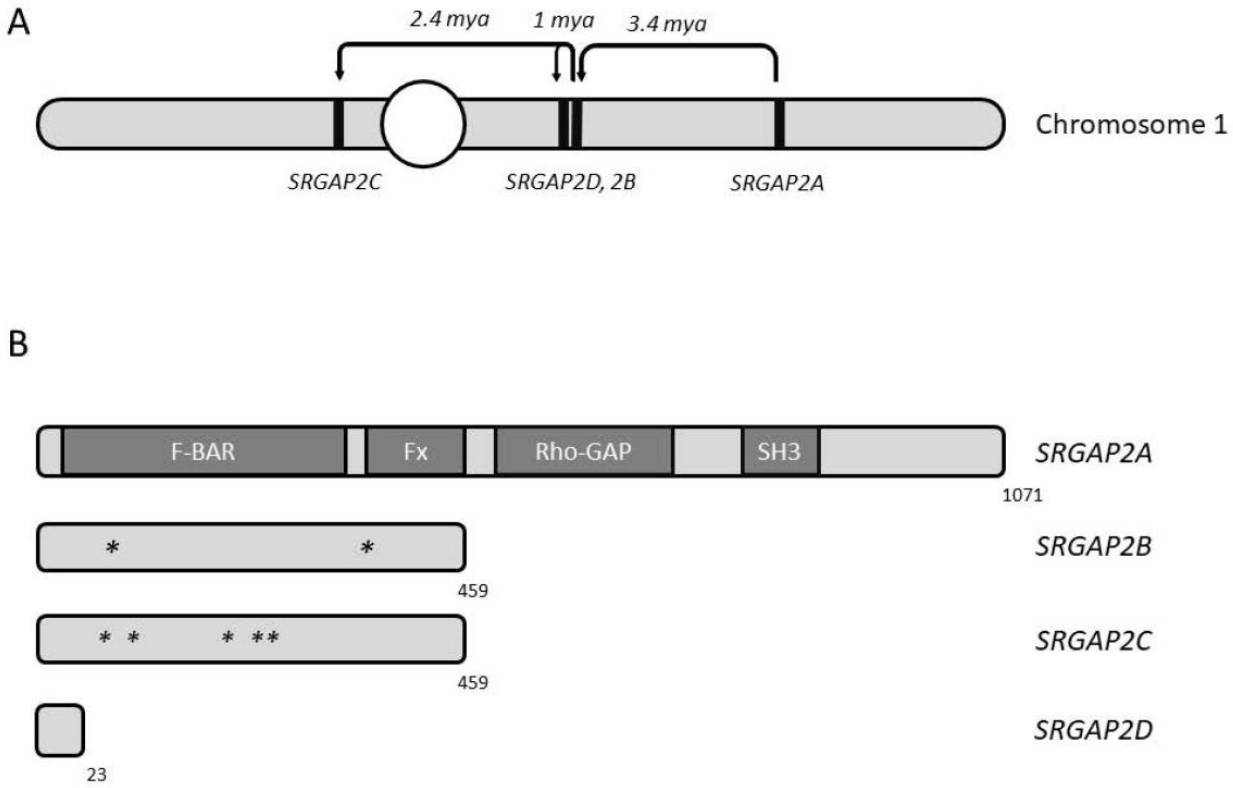

Figure 1. *SRGAP2A* duplicated three times to create genes found only in humans. A. The ancestral *SRGAP2A* gene duplicated in humans 3.4 mya from chromosomal position 1q32.1 to chromosome 1q21.1, creating *SRGAP2B. SRGAP2B* itself duplicated 2.4 mya to chromosome 1p12 (*SRGAP2C*) and again 1 mya to 1q21.1 (*SRGAP2D*). B. The comparative alignment of the human homologs illustrates that the truncated *SRGAP2B* and *SRGAP2C* lack the Rho-GAP and SH3 domain and contain additional amino acid substitutions (*) in the F-BAR domain. The *SRGAP2D* gene contains an early stop codon and encodes a truncated protein in length.

SRGAP2 is up-regulated at the end of cortical neuron migration and has been implicated in regulating neurite initiation, migration, and branching. The F-Bar domain of *SRGAP2A* facilitates the deformation of the cell membrane, eventually inhibits neuronal migration and enhances neurite branching (Guerrier et al., 2009). The Rho-Gap domain binds to Rac-1 and stimulates its GTPase activity. Rac1 is involved in neuronal migration, and stimulating its GTPase function could prohibit this activity (Kawauchi, Chihama, Nabeshima, & Hoshino, 2003). The SH3 domain has been shown to bind the N-Wasp and Robo1 proteins, though the biological relevance of these interactions has yet to be elucidated (Guerrier et al., 2009; Linkermann et al., 2009; Wong et al., 2001). Fossati et al. (2016) revealed that the *SRGAP2C* protein binds to and antagonizes the function of *SRGAP2A*, resulting in effects similar to a *SRGAP2A* deficiency. By inhibiting *SRGAP2A* and subsequently delaying cortical neuron maturation, the *SRGAP2* homologs may increase dendritic density and neck elongation. Furthermore, this prolonged growth may enhance synaptic connectivity allowing for

cortical pyramidal neurons to obtain and assimilate a higher degree of synaptic signals, which has been correlated with a greater capacity for intelligence (Charrier et al., 2012; Fossati et al., 2016; Hu et al., 2012).

microRNAs

Alterations in gene expression patterns is likely a key contributor to the phenotypic differences between *Homo sapiens* and *Pan* species. MicroRNA (miRNA) molecules are 20-24 nucleotides in length and facilitate the degradation or translation inhibition of their sequence complementary partners (Bartel, 2004). Genes expressed in the developing human prefrontal cortex are enriched for miRNA target sites, which suggests that miRNA molecules may play a critical role in brain development and be a factor contributing to the neurological differences between humans and chimpanzees (Chen & Qin, 2015; Hu et al., 2012; Somel et al., 2011). *miR-941* is one particularly intriguing example.

miR-941 is a miRNA molecule unique to humans and is highly expressed in the human brain. Interestingly, *miR-941* is not a fixed entity; in fact, many copy number variants and multiple single nucleotide polymorphisms exist in different human populations (Duan, Mi, Zhang, & Dolan, 2009; Hu et al., 2012). *miR-941* has been shown to affect important signaling pathways, as *miR-941* targets SMO and GLI1 of the hedgehog pathway, and IRS1, PPARGC1A, and FOXO1 of the insulin-signaling pathway (Hu et al., 2012). Both the hedgehog and insulin pathways have a pleiotropic effect but importantly act on neuronal identity, stem cell maintenance, and longevity (Alic et al., 2014; Ingham, Nakano, & Seger, 2011). Additionally, *miR-941* has been shown to target cysteine-string protein-α (CSPα) and RAB3A both of which are involved in neurotransmitter release in neurons. Deletions in the genomic region containing the *miR-941* gene result in cognitive and speech impairments as well as developmental delays. This implies that *miR-941* may be involved in such processes during development (Hu et al., 2012).

Conclusion

The genomes of chimps and humans are remarkably similar; indeed, comparisons reveal only a 4% sequence difference. In this review, we explored some of the genetics that underlies the gross anatomical, cognitive, and behavioral differences between these two species. Transposons are ubiquitous in both genomes, but some of them, due to their position, are capable of altering gene expression, as shown with the example of the reelin signaling pathway. The different patterns of transposon activity in chimps and humans may be one key to understanding the genetic variation between the two species. Unique genes found only in humans, such as *SRGAP2* and *miR-941*, are important in cognition and neuronal migration. Genetic comparisons of these two primates demonstrate that even modest changes in DNA sequence can impart significant differences in brain development and all of the higher level cognitive functions that depend on the resulting neuronal connections.

On a genetic level, to be human is to possess a fused chromosome, a handful of unique genes, a pattern of jumping transposons, and some interesting single nucleotide mutations. The genetic changes from chimpanzee to human seem modest until you begin to trace the wave of effects that result from each mutation, deletion, or duplication. There are also important differences in gene regulation that separate humans from chimpanzees and this is an active and promising area of future research. Even when all of the genomic comparisons are done, clearly there will still be plenty of room for wondering about the nature of humans.

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