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Cognitive Functions: Human vs. Animal – 4:1 Advantage |-FAM72–SRGAP2-|

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Abstract With the advent of computational genomics, an intensive search is underway for unique biomarkers for *Homo sapiens* that could be used to differentiate taxa within the Hominoidea, in particular to distinguish *Homo* from the apes (*Pan*, *Gorilla, Pongo,* and *Hylobates*) and species or subspecies within the genus *Homo* (*H. sapiens, H. heidelbergensis, H. neanderthalensis, H. erectus*, and the Denisovans). Here, we suggest that the |-FAM72–SRGAP2-| (family with sequence similarity 72/SLIT-ROBO Rho GTPase activating protein 2) gene pair is a unique molecular biomarker for the genus *Homo* that could also help to place *Australopithecus* at its most appropriate place within the phylogenetic tree and may explain the distinctive higher brain cognitive functions of humans.

Keywords Ape · Brain · Evolution · *Homo* · Neuron · Phylogenetic tree · Synapse · Taxonomy

Introduction

The evolutionary relationships between modern *Homo sapiens* and other hominin species are controversial. Many scientists believe that *H. sapiens* evolved from populations of *H. heidelbergensis* in Africa (~150 and 200 ka) and later (~40–50 ka) migrated out of Africa, replacing all populations of *H. neanderthalensis* in Europe and *H. heidelbergensis* elsewhere. Others, however, believe that archaic populations evolved into *H. sapiens* in each region of the world, and therefore consider *H. neanderthalensis* to be a subspecies of *H. sapiens*. This multiregional hypothesis permits the evolution of regional characteristics that distinguish populations in different regions, while still allowing universally favorable traits to spread across regions by gene flow. Supporters of this idea believe that interbreeding between *H. neanderthalensis* and *H. sapiens* was more widespread than is traditionally accepted by the opposing "Out of Africa" perspective and that *H. neanderthalensis* made important genetic contributions to living *H. sapiens*. The recent complete sequencing of the *H. neanderthalensis* genome indicates that the levels of interbreeding between *H. neanderthalensis* and *H. sapiens* were in fact greater than previously thought, and therefore the question of whether or not *H. sapiens* and *H. neanderthalensis* were different species becomes philosophical (Becoming human: *Homo sapiens* 2016; Encyclopedia Britannica: *Homo sapiens* 2016; Encyclopedia of Life: *Homo sapiens* - Modern Human 2016; Institute of human origins: Human Origins 2016; Smithsonian National Museum of Natural History: What does it mean to be human 2016).

For this review, all the chromosome (chr) datasets were downloaded from the public database of the National Center for Biotechnology Information (NCBI). We relied on the taxonomy offered by NCBI and reconstructed the simplified taxonomic tree from publically available databases. Additionally, we retrieved the genomes of species within the taxonomy from assemblies offered by NCBI and all data retrieval occurred automatically by evaluating database-information

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available on NCBI-servers as described previously (Kutzner et al. 2015).

A Simplified Phylogenetic Tree of the Hominoidea

Evolutionary and molecular anthropologists are trying to explain the gap between humans (genus *Homo*) and the remainder of the Hominoidea by focusing their studies on whole genomes to understand the evolution of uniquely human traits in a phylogenetic context (Fig. 1). Rapid progress in biotechnology has led to the development of "omics" research (e.g., genomics, proteomics, metabolomics) in healthcare science to help understand the causes and mechanisms of complex human diseases (Sun and Hu 2016; Suravajhala et al. 2016; Yugi et al. 2016).

Human Genomics

Whole genome studies allow for the exploration of genomic commonalities and differences between the human and ape subfamilies. Meanwhile, despite high-throughput next generation sequencing (NGS) efforts associated with the 1000 Genomes Project C et al. (2012)–Genomes Project C et al. 2015, and The International Genome Sample Resource [IGSR]) (1000 Genomes Project 2016), comprehensive data are lacking, and the high costs of genome sequencing forced researchers to cease further investigations. Sequencing costs limit the accuracy of genome reconstruction by limiting genome depth (x-fold of genome coverage) (Sims et al. 2014). Although the final 1000 Genomes data set comprises 2504 present-day human individuals from 26 populations around the world, only low coverage (2-6x) whole-genome sequencing (WGS) data, and mainly exome sequence data, are available for all individuals, while data for only 24 individuals were subjected to high coverage sequencing for validation purposes (Genomes Project C et al. 2012, 2015; Sankararaman et al. 2014; Sudmant et al. 2015).

To close the genomic gap and identify differences between taxa such as *Pan* and *Homo,* continuing solid and well-grounded research-based substantiated genome data analyses are urgently needed. Current state-of-the-art NGS technology, combined with steady improvements in big data computing whole genome analysis, could provide the background for (i) coordinated present-day human genome studies across the globe under the auspices of IGSR to ensure that existing population diversity gaps are filled, and (ii) genome comparisons across the entire phylogenetic tree to gain further insight into the relationships among the Hominidae (Fig. 1).

Only with full access to entire representative genomes of modern human population diversity across the globe will we be able to detect variations within present-day humans, which in turn would then allow us to make more reasonable statements with regards to archaic human taxa such as Neanderthals or Denisovans (Meyer et al. 2016; Sudmant et al. 2015).

Considering the many genomic variations detected in the 1000 Genomes Project data, including larger deletions, a recent study compared the mitochondrial genome of one individual from the Sima de los Huesos (SH) to only one Neanderthal (Altai), one Denisovan, and one present-day modern human (MButi) from Africa. This study is limited by problems in terms of genome quantity ("extremely small amounts of data available") and quality (degradation and contamination with modern human and/or microbial DNA) (Meyer et al. 2016). Thus, conclusions drawn from such studies require due diligence.

Biomarkers for the Genus Homo

The use of omics "big data" analysis may aid in the search for possible biomarkers distinguishing the genus *Homo* and may

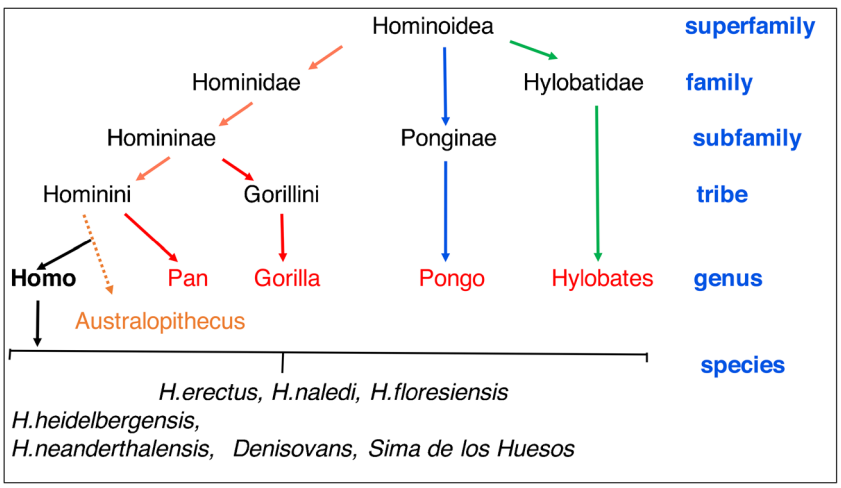

Fig. 1 A simplified phylogenetic tree explaining the development of modern humans based on current evolutionary theories. Thus far, *Australopithecus* is considered to be one of the common ancestors of the genus *Homo,* although clear-cut sequencing (e.g., |-FAM72–SRGAP2-| evidence for the correct categorization of *Australopithecus* as a subspecies of *Homo,* as a separate genus within the Hominini, or even as a subspecies of *Pan* is lacking (Wikipedia: Australopithecus 2016)

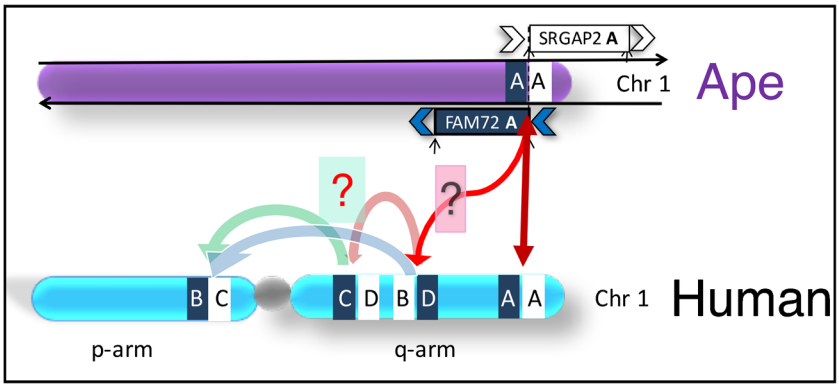

Fig. 2 The FAM72 (A–D) and SRGAP (A–D) gene pairs in apes and human. While four |-FAM72–SRGAP2-| gene pairs are found in *Homo* (including e.g., Neanderthals and Denisovans), only one gene pair is present in the apes. The mechanism underlying the human |-FAM72–SRGAP2-| gene pair duplication and amplification (*arrows* indicate the different options in the schematic) remains to be elucidated. When comparing the master gene |-FAM72–SRGAP2-| on chr 1 in apes and chr 1 in human, non-preserved areas are observed in the middle of preserved areas. It is still not known how |-FAM72A–SRGAP2A-| was transferred and amplified to the other gene pairs |-FAM72D–SRGAP2B-|, |-FAM72C–SRGAP2D-| and |-FAM72B–SRGAP2C-| in *Homo* during evolution, while no species have been observed with two or three |-FAM72–SRGAP2-| gene pairs (Kutzner et al. 2015). For clarity, official gene symbols are used instead of gene names in Italics style and protein names in Roman style

help to further unravel the significant commonalities and differences between modern humans and the apes.

The human brain, with its higher cognitive functions, distinguishes humans from all other hominoid species. Therefore, the human brain may serve as a special source of possible genomic biomarkers to clearly differentiate humans among hominoids. A recently described unique gene pair, FAM72 (controls neuronal stem-cell proliferation/development (Benayoun et al. 2014))–SRGAP2 (neuronal development, differentiation, synaptic, and cerebral plasticity (Charrier et al. 2012; Rincic et al. 2016)), could explain the distinctive nature of human higher brain development, brain plasticity, and cognitive functions (Dennis et al. 2012; Kutzner et al. 2015). Therefore, this gene pair is a potential *H. sapiens* biomarker (Fig. 2).

Evolutionary Perspective

From an evolutionary perspective, the single |-FAM72–SRGAP2-| gene pair defines the notochord-containing vertebrates, whereas the four paralogous |-FAM72–SRGAP2-| gene pair couples seem to be a distinctive feature of *H. sapiens* only among the Hominidae, a finding that is perhaps associated with higher (e.g., explicit) cognitive capabilities, language activity, and consciousness (Geschwind and Konopka 2012; Geschwind and Rakic 2013; Kutzner et al. 2015). It might be possible to consider the |-FAM72–SRGAP2-| gene pair as one master gene. While the cell activates FAM72 in neuronal progenitor cells (and keeps SRGAP2 switched off), it turns SRGAP2 on (and FAM72 off) during differentiation and neuron maturation. However, it remains an enigma why no species contains two or three |-FAM72–SRGAP2-| gene pairs; the other great apes (chimpanzees and gorillas) also contain only one such gene pair.

Current theories cannot adequately explain this gap between humans and the other great apes (Dennis et al. 2012; Dewey 2011; Geschwind and Konopka 2012; Geschwind and Rakic 2013; Wolfe 2000). It also remains a point of special interest whether any species can be identified within the genus *Homo* that carries or carried two or three |-FAM72–SRGAP2-| gene pairs. With *Australopithecus* considered as one of the common ancestors of the genus *Homo*, *A. africanus* probably evolved into *A. sediba*, which some scientists think may have evolved into *H. habilis*, *H. erectus,* and eventually modern humans, *H. sapiens* (Fig. 1) (Bruxelles et al. 2014; Granger et al. 2015; Kivell 2015; Zihlman et al. 1978). Other species in question include *H. naledi* (Berger et al. 2015; Dirks et al. 2015; Harcourt-Smith et al. 2015; Stringer 2015) and *H. floresiensis* (Brown and Maeda 2009; Daegling et al. 2014; Jungers et al. 2009; Orr et al. 2013). Thus far, clear-cut proven genomic sequencing evidence does not exist.

Conclusion

Qualitative assessments and impartial communications regarding the strength of genomics data across related species are essential for the long-term management of predictive uncertainty and for the successful application of human genomics in systematics. The master gene |-FAM72–SRGAP2-| constitutes a potential human biomarker defining *H. sapiens* with higher brain cognitive functions, and its malfunction could lead to pathological conditions (Guo et al. 2008; Heese 2013; Kutzner et al. 2015; Nehar et al. 2009; Pramanik et al. 2015).

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Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflicts of interest.

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