Human core duplicon gene families: game changers or game players?

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Abstract

Illuminating the role of specific gene duplications within the human lineage can provide insights into human-specific adaptations. The so-called human core duplicon gene families have received particular attention in this respect, due to special features, such as expansion along single chromosomes, newly acquired protein domains and signatures of positive selection. Here, we summarize the data available for 10 such families and include some new analyses. A picture emerges that suggests broad functions for these protein families, possibly through modification of core cellular pathways. Still, more dedicated studies are required to elucidate the function of core-duplicons gene families and how they have shaped adaptations and evolution of humans.

Key words: duplication; duplicons; gene family; human; adaptation; copy number variation

Introduction

The human genome harbors a number of rapidly evolving gene families that have been subjected to a combination of structural reorganization and bursts of segmental duplications between one to several hundred kilobases. Approximately 400 blocks of the human genome have been identified as having undergone multiple duplications during hominoid evolution. Overall, segmental duplications comprise approximately 5% of the human genome [1–3]. A detailed analysis of these segmentally duplicated regions has shown that subsets are formed around ‘core’ or ‘seed’ duplicons that are shared between all copies of the respective gene family [4–6]. Figure 1 shows the duplication structures of the Morpheus (NPIP) gene family as an example, which will be discussed in further detail below.

We focus here on 10 core duplicon gene families, which share a number of other features. (i) Their duplicates are generally confined to a single chromosome, partly in tandem but also dispersed along the chromosome. (ii) They have variable copy numbers in human populations and include some of the most variable human CNV genes (e.g. SPATA31, Morpheus (NPIP) and LRRC37A) [8–11]. (iii) Almost all of these genes show ubiquitous or at least broad patterns of expression, while their ancestral progenitor genes often exhibit tissue-specific expression, mostly in the testis [4]. Intriguingly, at least half of these core duplicon gene families (including Morpheus (NPIP), SPATA31, NBPF11, RGPD, GOLGA, PMS2P and TRIM51) evolved under positive selection (Table 1), making them among the fastest evolving genes in humans [12–17]. Hence, both the human lineage-specific expansion and the patterns of positive selection suggest that these gene families have played a direct role in the phenotypic evolution of humans.

Since the initial report of human core duplicons [4], most of the genes belonging to duplicons were evolutionarily and structurally characterized. However, only three (NBPF, TBC1D3 and SPATA31) were studied functionally in more detail. Here, we provide an overview on our current knowledge on the evolution and function of gene families that are parts of the human core duplicons. We describe these gene families according to their order along the human chromosomes. The general overview is provided in Figure 2.

Chromosome 1: Olduvai protein domain (NBPF gene) family

Evolution and comparative genomics

The initial name ‘Neuroblastoma Breakpoint gene Family’ (NBPF) was given because the first identified member of the family was found to be deleted in an individual with neuroblas-
Figure 1. The Morpheus (NPIP) gene family as an example for human core duplicons. Figure adapted from [4, 7]. The individual members of the Morpheus core duplicons are ordered according to location on chromosome 16 (left). The mosaic structure of the complex duplication blocks is depicted on the right. The core duplicon part, which is shared by all duplication blocks, is marked by the red broken lines. Numbers next to the fragments refer to the start and end positions on the chromosome (in kb), and arrows indicate the relative orientation. Different colors refer to distinct duplication blocks, which are predicted based on reciprocal comparisons of each human subunit and its flanking sequence to outgroup mammalian genomes [4].

Table 1. Signatures of positive selection in human core duplicons

| Chr. | Name | Alternative name(s) | Ancestral gene (mouse) | Signatures of positive selection | Selection test | Literature |
|------|------|---------------------|------------------------|--------------------------------|----------------|------------|
| 1    | Olduvai protein domain family | Neuroblastoma breakpoint gene family, NBPF | Pde4dip | Yes | PAML, dN/dS, The likelihood ratio test, Ka/Ks, Nei-Gojobori | [13,16] |
| 2    | RGPD | RANBP2-like gene family | Ranbp2 | Yes | PAML, dN/dS, The likelihood ratio test, Ka/Ks, Nei-Gojobori | [13,15] |
| 5    | SMA-GUSBP | SMA | Gusbp2 | None described | PAML, dN/dS, The likelihood ratio test; PAML, dN/dS, The likelihood ratio test | [12] |
| 7    | PMS2P | PMS2 gene family | Pms2 | Yes | PAML, dN/dS, The likelihood ratio test; PAML, dN/dS, The likelihood ratio test | [13] |
| 9    | SPATA31 | FAM75A | Spata31 | Yes | PAML, dN/dS, The likelihood ratio test; PAML, dN/dS, The likelihood ratio test | [17] |
| 11   | TRIM51 | SPRYDS | no homolog | Yes | PAML, dN/dS, The likelihood ratio test; PAML, dN/dS, The likelihood ratio test | [12,13] |
| 15   | GOLGA8 | GOLGA, golgin | Golga2 | Yes | PAML, dN/dS, The likelihood ratio test, Ka/Ks, Nei-Gojobori | [13,14] |
| 16   | Morpheus | NPIP | no homolog | Yes | PAML, dN/dS, The likelihood ratio test, Ka/Ks, Nei-Gojobori | |
| 17   | TBC1D3 | - | Usp6nl | None described | None described | None described | |
| 17   | LRRC37 | - | Lrrc37a1 | None described | None described | None described | |

toma [19]. NBPF gene family members include variable numbers of tandemly repeated DUF1220 domains within their coding sequences. Since the name DUF1220 was initially a working designation assigned by the Pfam database curators, Sikela and van Roy [20] have proposed to rename the domain Olduvai. The different NBPF core duplicon genes are distributed along chromosome 1 in 16 copies, of which 6 are in tandem and 10 are dispersed [21]. The macaque genome has three copies of NBPF genes, while mice and other mammals have no clear orthologs. A possible ancestral gene is PDE4DIP, which includes a single Olduvai domain [22]. The Olduvai domain copy number has particularly expanded in humans. It increased from a single domain in mouse to 30–35 copies in new and old world monkeys and up to 300 domains in humans [22]. Based on sequence similarity, the domain structure of Olduvai can be divided into six primary subtypes including CON 1, 2 and 3 and HLS 1, 2. 
Figure 2. Overview of human core duplicon gene families. The figure depicts the segmentally duplicated copies of core duplicon gene families from human, macaque and mouse and includes other mammals. Functional properties of Olduvai, SPATA31 and TBC1D3, which have been studied in detail, and possible/predicted functions of other core duplicon gene families are included. CNV (median:variance) was extracted from a previous study [10]. * indicates CNV estimate based on number of Olduvai domains. # indicates CNV information for TRIM51 genes was extracted from a previous study [17], and & indicates CNV for SPATA31 genes was extracted from a previous study [18].

and 3 [16, 22, 23]. The comparative analysis of Olduvai-domain-containing NBPF genes in primates has shown that NBPF genes evolve under strong positive selection [13, 16].

Expression and subcellular localization
NBPF genes are ubiquitously expressed in all human tissues and exhibit elevated expression in the testis. The promoter region of NBPF1 genes is derived from the unrelated gene EVI5 [22, 24]. Over-expressed, myc-tagged NPBF1 protein in human breast carcinoma cells (MCF7) was shown to be primarily localized to the cytoplasm [23].

Function
Despite its broad expression, the functional analysis of this gene family has focused on brain- and/or neuron-specific functions. This was triggered by the observation that the 1q21.1 chromosome region in humans, which is associated with brain disorders such as micro- or macrocephaly, autism and schizophrenia, includes a number of the NPBF1 genes [25].
**Human core duplicon gene families | 405**

Further, a correlation was found between Olduavi copy number and brain size in humans. This correlation was most prominent in affected patients, but copy number was also associated with gray-matter volume in healthy controls [26]. Over-expression of Olduavi sequences in neural stem cells promotes proliferation [27–29]. Further studies also suggested a correlation between Olduavi copy number and schizophrenia risk and severity [30] as well as with IQ and total mathematical aptitude scores [31], although the breadth of this latter study is limited. While these results suggest a particularly interesting function of NBPF genes in human brain evolution with implications for the etiology of brain diseases [21], more studies are required to support this notion. Notably, copy number variations (CNVs) in humans. families are of increased interest due to their special expansion brain size or the correlation is incidental because these gene families in different genomes, we found that all these gene families number of currently annotated gene copies for the various families are rapidly evolving. Different exons of RGPD genes were shown to evolve under positive selection [15]. The macaque genome, as well as the mouse and other mammalian genomes, does not contain duplicates, suggesting that expansion occurred within the great apes after the separation from old world monkeys.

**Expression and subcellular localization**

RGPD genes are ubiquitously expressed in human tissue with elevated expression in the testis [15]. Over-expression of GFP-fused RGPD5-7 revealed its localization to the cytoplasm around the nuclear envelope [15, 37].

**Function**

The RANBP2 protein encoded by the progenitor gene is primarily localized within the periphery of the nuclear envelope and is thought to be required for cargo import and export [37]. Hence, the RGPD gene family members may be modifiers of this function. Interestingly, RANBP2 was also shown to be involved in resistance against Simian Immunodeficiency Virus [38]. It is thus possible that the expansion of RGPD genes is the result of an arms race between virus evolution and host resistance acquisition. The Ranbp2 knockout in mice is homozygous lethal.

**Chromosome 5: SMA (GUSBP) gene family**

**Evolution and comparative genomics**

The repetitive nature of the spinal muscular atrophy (SMA) genes was first described [39] in the context of searching for candidate genes for SMA. However, SMA is caused by mutations in the duplicated copies of the SMN1 and SMN2 genes, which are located at chromosome 5q13.3 (reviewed in detail in [40]). SMA core duplicon copies are located in close proximity both upstream and downstream (within approximately 50 kb) of the SMN2 gene. Therefore, to avoid confusion with the disease-causing genes, we will use the designation SMA-GUSBP to represent the SMA gene family. SMA-GUSBP genes are organized in 2 tandem and 10 dispersed copies along human chromosome 5; an additional copy is located on chromosome 6, and this is most likely the ancestral copy. In the common ancestor of chimpanzees and humans, theERV1/LTR12C retroviral element integrated upstream of SMA-GUSBP. In macaque, the GUSBP and ERV1/LTR12C elements are found in different chromosomal locations (Supplementary Fig. 1). The SMA-GUSBP gene encodes a beta-glucuronidase-like domain (Supplementary Fig. 2). No homologs of the SMA-GUSBP genes have been observed outside the great apes to date, i.e. it expanded specifically in the human lineage [10]. Therefore, SMA-GUSBP genes are the youngest expanded core duplicon family in humans.

|                          | NBPF / Olduavi | RGPD | SMA-GUSBP | PMS2P | SPATA31 | TRIM51 | SPRYD5 | GOLGA | MORPHEUS | TBC1D3 | LRRC37 |
|--------------------------|---------------|------|-----------|-------|---------|--------|--------|-------|-----------|--------|--------|
| Brain mass (mg)          | 0.90**        | 0.91** | 0.90**    | 0.38* | 0.72**  | 0.87** | 0.68** | 0.66** | 0.82**    | 0.83** |       |
| Brain volume (mm³)       | 0.90**        | 0.91** | 0.90**    | 0.38* | 0.72**  | 0.87** | 0.68** | 0.66** | 0.83**    | 0.83** |       |
| Neocortex volume (mm³)  | 0.92**        | 0.90** | 0.92**    | 0.37* | 0.72**  | 0.86** | 0.68** | 0.65** | 0.81**    | 0.83** |       |
| Cerebellum volume (mm³)  | 0.83**        | 0.91** | 0.81**    | 0.36* | 0.72**  | 0.85** | 0.64** | 0.64** | 0.81**    | 0.77** |       |
| Body mass (g)            | 0.23**        | 0.57** | 0.24**    | 0.22**| 0.38*   | 0.43*  | 0.28** | 0.35** | 0.44**    | 0.27** |       |

*P < 0.05. **P < 0.001. ***P > 0.05.

### Correlation with brain size

As discussed above, there is a strong emphasis in the literature that NBPF/Olduavi copy numbers are correlated with increasing brain size in primates and humans. However, given that the pattern of gene family expansion also holds for the other core duplicon gene families discussed here, we have re-assessed whether the same correlation is more broadly apparent. Using the brain volume measures previously provided [29] and the number of currently annotated gene copies for the various families in different genomes, we found that all these gene families show a significant correlation. In contrast, there is only a partial correlation with body mass (Table 2). Hence, one can either conclude that all human core duplicon gene families influence brain size or the correlation is incidental because these gene families are of increased interest due to their special expansion in humans.

### Chromosome 2: RANBP2 (RGPD) gene family

**Evolution and comparative genomics**

RGPD genes (RanBP2-like, GRIP domain-containing Proteins) are derived from the RANBP2 gene. RANBP2 (NUP388) is a Ran-binding protein that was shown to interact with the nuclear pore complex. The RGPD gene family has expanded to eight dispersed copies on human chromosome 2 through segmental duplication [15]. Similar to other core duplicon gene families, RGPD genes

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Table 2. Linear regression analysis of human core duplicon gene families with brain volumes and body mass across primates

| Gene                        | Beta Coefficient (P-value) | Beta Coefficient (P-value) | Beta Coefficient (P-value) | Beta Coefficient (P-value) | Beta Coefficient (P-value) | Beta Coefficient (P-value) | Beta Coefficient (P-value) |
|-----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| NBPF / Olduavi              | 0.90**                     | 0.91**                     | 0.90**                     | 0.38*                      | 0.72**                     | 0.87**                     | 0.68**                     |
| RGPD                        | 0.90**                     | 0.91**                     | 0.90**                     | 0.38*                      | 0.72**                     | 0.87**                     | 0.68**                     |
| SMA-GUSBP                   | 0.92**                     | 0.90**                     | 0.92**                     | 0.37*                      | 0.72**                     | 0.86**                     | 0.68**                     |
| PMS2P                       | 0.83**                     | 0.91**                     | 0.81**                     | 0.36*                      | 0.72**                     | 0.85**                     | 0.64**                     |
| SPATA31                     | 0.23**                     | 0.57**                     | 0.24**                     | 0.22**                     | 0.38*                      | 0.43*                      | 0.28**                     |
Expression and subcellular localization

The human SMA-GUSBP mRNA transcripts include different splicing isoforms that extend more than 70 kb. The genes are broadly expressed, and the highest expression (15–20 fold) has been detected in the testis, thymus, brain and cerebellum (Supplementary Fig. 3A-B). Transiently over-expressed, C-terminally FLAG-tagged SMA-GUSBP proteins localize primarily in the vesicles of HeLa cells (Supplementary Fig. 3C).

Function

Although SMA-GUSBP genes were initially thought to be associated with SMA disease, there is no current evidence to support this, i.e. the close proximity of SMA-GUSBP genes to the SMN2 gene may not imply a functional connection. No direct functional analysis of SMA-GUSBP genes has been conducted so far.

Chromosome 7: PMS2P gene family

Evolution and comparative genomics

The PMS2P gene family is derived from the PMS2 gene, which encodes a homolog of the mutL, mismatch repair gene from bacteria [41]. PMS2P genes duplicated to eight dispersed copies (PMS2P1–5, 7, 9 and 11) from the C-terminal region of the PMS2 gene located on human chromosome 7 [42]. The current marmoset and macaque genome assemblies do not include an intact PMS2P gene. However, the Orangutan genome includes three complete PMS2P copies. This suggests an expansion of PMS2P genes occurred within great apes. More work will be required to show whether they were lost in some primate genomes, or whether this is still an annotation problem. The PMS2P gene region is highly repetitive and contains multiple transposable elements (SINEs and LINEs), which make its annotation problematic.

Expression and subcellular localization

Similar to other core duplicons, PMS2P genes are expressed ubiquitously and have enhanced expression in the testis (as annotated in the NCBI description). No further data is available on the subcellular localization of these proteins.

Function

No functional analysis has been performed for PMS2P genes to date.

Chromosome 9: SPATA31 gene family

Evolution and comparative genomics

SPATA31 (formerly known as FAM75A) genes expanded from a single copy in mouse to two copies in macaque and at least nine copies on human chromosome 9 by segmental duplication. Seven of these duplicated SPATA31 gene segments are distributed on the long arm, and at least two are in tandem on the short arm. Two copies on the long arm are considered pseudogenes due to premature stop codons [18]. During the process of duplication within the primate lineage, the 5′-region of SPATA31 genes acquired an additional exon and additional protein domains, in particular a cryptochrome domain [18]. Similar to other core duplcon gene families, the SPATA31 promoter region became highly restructured before or during the duplication events. This restructing includes the integration of a transposable element (LINE/L1, PA10-12) after the split between simians and prosimians [18].

Expression and subcellular localization

SPATA31 gene expression evolved from testis-specific expression in mice and macaques to ubiquitous expression in humans, but it still exhibits its highest expression in the testis [18]. Endogenous SPATA31 protein shows a dynamic localization between the cytoplasm and nucleus depending on fixation conditions and exposure to light [18]. In cell culture, SPATA31 protein re-localizes from the nucleolus to the nucleus upon UV exposure [18].

Function

SPATA31’s UV-exposure response, as well as its acquired protein domains, suggests a function in DNA damage repair. Functional analysis of cells with reduced SPATA31 copy number showed increased sensitivity to UV exposure [18]. Furthermore, over-expression of SPATA31A1 in epidermal cells leads to premature senescence [43]. Interestingly, long-lived individuals (>96 years old) have significantly fewer copies of SPATA31 genes on average compared to a control group. This observation suggests that the adaptive evolution of the SPATA31 gene family is an example of antagonistic pleiotropy; it provides a fitness benefit during the reproductive phase of life (better protection against UV-light damage), but it negatively influences overall life span possibly by causing more repair-induced mutations [43]. Knockout of the progenitor gene in mice leads to spermatogenesis defects and infertility [44], which is in line with its testis-specific expression in mice.

Chromosome 11: TRIM51 (SPRYD5) gene family

Evolution and comparative genomics

A first description of the evolution of TRIM51 genes is included in a general study of TRIM genes by Han et al. [17], who showed that TRIM51 genes are recently duplicated, hominoid-specific TRIM genes. Some of the TRIM51 genes (C1,C2) were found to have CNV in human individuals and to evolve under positive selection [17]. The human genome assembly includes seven full-length, duplicated copies of TRIM51 (SPRYD5) genes, at least five fragmented duplication blocks that are expanded mainly within the centromeric region of chromosome 11 and an additional copy on chromosome 2 (TRIM51JP). Comparisons of the available assembled genomes (rheMac8, ponAbe3 and hg38) in the UCSC genome browser and Synteny in Ensembl indicate that TRIM51 genes initially evolved by segmental duplication from TRIM51EP. There is a single full-length copy in the macaque genome, which shows high similarity to human TRIM51EP. However, more detailed work is required to resolve this.

Expression and subcellular localization

Low level TRIM51 expression was detected in the developing brain and testis (https://www.ebi.ac.uk/gxa/home). Although classified as TRIM genes, members of the TRIM51 gene family lack several important motifs and domains that are otherwise common to TRIM proteins (e.g. RING and B-Box 2) [45]. TRIM51 proteins contain a coiled-coil domain and a SPRY domain. To date, no reports have shown the subcellular localization of TRIM51 proteins.
Function
In general, TRIM- or SPRYD-domain-containing genes are involved in functions related to innate immune response [17,46]. However, there have been no studies investigating the function of TRIM51 proteins as an expanded gene family in humans because they are not classified with other TRIM- or SPRYD-containing genes [45]. But a possible involvement in immune response mechanisms could evidently explain their adaptive evolution.

Chromosome 15: GOLGA gene family
Evolution and comparative genomics
GOLGA (GOLGIN) genes encode long coiled-coil proteins associated with the Golgi apparatus. They form a large gene family distributed across different chromosomes in humans. Several of the GOLGA genes are ancient duplicates with orthologous copies in the mouse (GOLGA1, GOLGA2 on chr9, GOLGA3 on chr12, GOLGA4 on chr3, GOLGA5 on chr14, GOLGA7 on chr8 and GOLGA7B on chr10). However, there are also two subfamilies—GOLGA6 and GOLGA8—that share similarity to each other. GOLGA8 has human-specific core duplicons that are expanded along chromosome 15 by segmental duplications and are partially in tandem. The current human assembly contains 12 annotated duplicated GOLGA6 subfamily members, whereas the GOLGA8 subfamily includes 15 duplicated copies. They show the closest similarity to GM130 (GOLGA2), which is located on human chromosome 9 [47]. The macaque genome contains approximately 11 GOLGA6-like and at least 8 fragmented GOLGA8-like duplicates. The N-terminal portions of GOLGA8 genes show high variation in both macaque and human. The duplication architecture for GOLGA6 and GOLGA8 copies is complex and not yet well resolved.

Expression and subcellular localization
Both GOLGA6 and GOLGA8 are ubiquitously expressed at low levels in human tissue, and they are most highly expressed in the testis. There is no direct evidence for the subcellular localization of GOLGA6 and GOLGA8 proteins; however, based on similarity to GM130, they are predicted to localize to the Golgi apparatus, Golgi stack membrane and cytoplasm [47].

Function
The roles of the individual variants of the GOLGA proteins are not clear [47], but they may function in membrane trafficking or Golgi structure. Loss of individual GOLGA genes in mice or humans is not lethal, possibly due to functional redundancy between different copies. Palindromic GOLGA8 core duplicons promote recurrent chromosome 15q13.3 microdeletions that are associated with intellectual disability, schizophrenia, autism and epilepsy [48,49] but there are currently no data that would suggest a causative role of GOLGA8 losses for the disease effects.

Chromosome 16: Morpheus (NPIP) gene family
Evolution and comparative genomics
The ‘Morpheus’ gene family, also named the nuclear pore interacting protein (NPIP) family, is one of the best studied human core duplicon gene families. It is derived from a name-giving ‘low-copy repeat sequence on chromosome 16’, LCR16a, that is approximately 20 kb long and expanded in the great ape-human lineage along chromosome 16 through segmental duplications [7,14,50]. It can be subdivided into two distinct subfamilies, NPIPA and NPIPb, which mostly differ with respect to exon 5 and the structure of amino acid repeats in the C-terminal [7]. In contrast to other core duplicon gene families, it has not been possible to identify paralogs outside of primates, i.e. it appears to be a newly evolved or rapidly evolving gene. In fact, the Morpheus gene family was shown to be one of the most rapidly evolving gene families during hominoid evolution [14].

Expression and subcellular localization
Morphes genes are expressed in various tissues and are most highly expressed in the testis and thymus [7]. The 5’-exons show extensive variation in splicing [7]. Due to this alternative splicing and differences in the C-terminal repeat region, Morpheus proteins vary in size between 40 and 95 kDa. Over-expression of different types of NPIPB and NPIPA genes reveals different subcellular localizations within both the nucleus and cytoplasm [7].

Function
Although Morpheus proteins were initially suggested to interact with the nuclear pore complex [14], there has not yet been evidence to support this assumption. They were shown to be overexpressed in the retina of patients with macular degeneration [51], but the functional significance of this is unclear. Other observations indicate an involvement in innate immunity, especially with respect to viruses. Morpheus proteins were suggested to be involved in human immunodeficiency virus resistance [52,53], were shown to interact with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and were shown to restore the interferon-beta response in SARS-CoV cells [54]. Both Morpheus gene types (NPIPA and NPIPb) are also upregulated upon polyinosinic:polycytidylic acid (poly I:C) treatment (viral mimic), and auto-antibodies against NPIPB protein in humans have been detected [7]. It is thus possible that Morpheus genes could cause autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, myasthenia gravis and Wegener’s granulomatosis [55,56]. Notably, newly evolved genes in mammals can generally create complications with respect to generating autoimmune responses [57].

Chromosome 17: TBC1D3 gene family
Evolution and comparative genomics
The TBC1D3 gene family is characterized by the TBC domain, which plays a major role in endocytosis and intracellular trafficking in other proteins. TBC1D3 genes are derived from USP6NL (alias RNTRE) by segmental duplication [58]. Comparative genomic analysis suggests that TBC1D3 genes emerged before the split of new world monkeys since the macaque genome (rheMac8) includes at least five copies of TBC1D3-like genes. TBC1D3 genes are duplicated along human chromosome 17 in 12 copies including some processed pseudogenes [59,60]. TBC1D3 genes show extensive CNV between different populations (10 copies in Europeans and up to 50 copies in African populations) [10].

Expression and subcellular localization
TBC1D3 genes are broadly expressed in many tissues and are most highly expressed in the testis [59,60]. Different isoforms are expressed in different tissues [60]. In HeLa cells, ectopic expres-
sion of TBC1D3 genes led to alterations of the actin cytoskeleton of HeLa cells. Over-expressed TBC1D3 protein localized in the cytoplasm, in lipid rafts and on the plasma membrane [58, 61, 62].

Function

TBC1D3 was first described as an oncogene [63] and was also identified as PRC17 during the analysis of cells derived from prostate and breast cancer patients [64]. A predicted GAP activity of the TBC domain is equivocal. While a weak GAP activity was documented in one study [64], this finding could not be confirmed by others; however, TBC1D3 is still thought to be involved in macropinocytosis [58]. TBC1D3 dysregulates the epidermal growth factor receptor signal transduction pathway and enhances cell proliferation [61]. Further studies showed that TBC1D3 protein is ubiquitinated and palmitoylated, and degradation of TBC1D3 protein is regulated by Cul7 [62, 65]. TBC1D3 genes were also shown to be involved in Insulin/IGF signaling [66]. Over-expression of TBC1D3 leads to an increase in cell proliferation in basal regions of the developing mouse cortex, as well as disruptions to adherens junctions and formation of column-like structures [67]. Similar results were also obtained in cultured human brain slices, where it was shown that TBC1D3 is critical for the generation of outer radial glial cells [67]. Finally, it was shown that TBC1D3 affects the migration of human breast cancer cells by regulating TNFα/NF-κB signaling [68].

Chromosome 17: LRRC37 gene family

Evolution and comparative genomics

The LRRC37 (leucine-rich repeat containing 37A) gene family has expanded on human chromosome 17 [4] from a single ancestral copy in other mammals [69, 70]. In humans, this family’s gene structure is highly fragmented, and only 8 of 18 copies are complete. Two of these eight complete LRRC37 genes can be classified as the LRRC37B type. The number of the duplication segments is variable within the primate lineage; there are 4, 7, 10 and 18 copies in marmoset, macaque, orangutan and human, respectively [70]. Similar to the SPATA31 genes, the N-terminal region (especially exon 1) of LRRC37A has acquired novel structures and promoters in the primate lineage [69].

Expression and subcellular localization

LRRC37 is broadly expressed in primates, partly due to the acquisition of promoter elements from unrelated genes; however, it is still most highly expressed in the testis [69, 70]. Over-expressed LRRC37A1 protein is primarily localized to the plasma membrane. Pulse-chase experiments show that it is first localized to the Golgi and then transported to the plasma membrane where it co-localizes with Ezrin [70].

Function

The LRRC37 proteins contain six leucine-rich repeat motifs (LRR), which consist of repeating 20–30 amino acid stretches. Well-known LRR domain-containing proteins include those of the innate immune system, especially in mammals and plants. For example, Toll-like receptors are single-membrane-spanning proteins, and their extracellular domains are composed of LRRs, which recognize pathogen-associated molecular patterns such as LPS, single-stranded RNA and flagellin. LRR-containing proteins may also be involved in neuron-specific functions, such as axonal guidance and neuronal migration [71, 72]. However, it is not known whether LRRC37 genes play a role in any of these functions. On the other hand, the LRRC37 gene family in humans is located at the boundary of a common inversion polymorphism of approximately 970 kb at 17q21.31 [69, 73, 74]. This has been shown to be a significant risk factor locus for the tangle diseases, including progressive supranuclear palsy [75], corticobasal degeneration [76, 77], Parkinson’s disease [78, 79] and Alzheimer’s disease [80], and it is associated with microdeletion syndromes [81–83]. LRRC37B, a member of the LRRC37 gene family is also a breakpoint for NF1 microdeletion syndrome [84].

Discussion

The evolutionary patterns of human core duplcon gene families raise a number of challenging questions. First, what is the role of the cores in the duplication process? Second, why are the non-tandem segmental duplications mostly confined to single chromosomes? Third, why are the human core duplcon genes usually derived from genes that are highly expressed in the testis? Fourth and arguably most importantly, what has the role of human core duplcon gene families been in human evolution? The data available for a number of the gene families suggest that they may not have simple single functions but instead pleiotropic effects. While it seems natural that most studies have focused on inferred specific functions, which are often related to possible disease mechanisms, we advocate for investigators to keep a broad picture in mind. For example, a number of studies have focused on possible brain expansion effects for DUF1220/Olduavi repeats in the lineage toward humans, but we show that such correlations can be drawn for all of the core duplcon gene families (Table 1). Our own work with SPATA31 had initially focused on the repair of UV-induced DNA damage because of the newly acquired protein domains. However, the incidental observation that fibroblast cells with manipulated functional copy numbers of SPATA31 exhibited altered senescence led us to study a possible connection to aging.

The most direct connections of core duplcon gene families lie in their involvement in causing chromosomal aberrations and microdeletions. But this could be due to their general repeat structure, which makes them prone to recombinational unequal cross-over mechanisms that would also affect other genes in the respective regions. Hence, the involvement in such diseases may not necessarily serve as a direct pointer toward their protein functions.

All the core duplcon gene families include expansions of protein domains, of which many are known to be involved in basic cellular functions. Hence, it seems likely that they can molecularly interact with the target genes of their progenitor proteins and thus possibly modify or regulate their core functions. Future studies should focus more on this possibility.

The duplication process included the integration of repetitive transposable elements, LTRs (e.g.ERV1) or unrelated promoters (DND1 and BPTF for LRRC37A genes or EVIS for NBPFF1 genes). This integration broadened the expression to more tissues or caused ubiquitous expression. The highest expression usually remained in the testis, although the functional consequences of this expression have not been studied much to date. For example, dedicated studies should be designed to evaluate the effect of CNV of core duplcon genes on fertility phenotypes in humans.

Further, core duplcon genes commonly exist in two versions of gene structure; for example, SPATA31A versus SPATA31C, NPIPA versus NPIPB, LRRC37A versus LRRC37B, GOLGA6 versus GOLGA8 and TBC1D3 (1st cluster, A–D) versus (2nd cluster, E–H).
This points to diversification of effects during the duplication process, a concept that will also require more dedicated molecular studies.

Finally, it remains to be shown whether the expansion of core duplicon gene families is a specific phenomenon in the human lineage and whether they acted as ‘game changers’ with respect to human-specific adaptations. It has been possible to readily detect duplicon gene families in humans because of the abundant high-quality data and comparative genome sequencing efforts in the primate phylogeny. However, there are now also examples of lineage-specific expansions in other clades, such as rodents [85] and elephants [86]. Still, the specific duplicates in the human lineage could evidently have contributed to human-specific phenotypes and adaptations. After all, the signatures of positive selection found around human core duplicon gene families suggest an active evolutionary role. However, these signatures would likely also arise if these genes were mere modifiers of other major changes in core pathways, i.e. if they were ‘game players’. Hence, deeper studies will be required to solve the questions raised above.

Key Points
- Core duplicon gene families constitute a specific subset of gene duplicates in the human genome.
- They are derived from testis-expressed genes, have acquired new promoters and have specifically expanded in the evolutionary lineage toward humans.
- They express proteins with domains that suggest that they could be modifiers of general cellular pathways.
- Patterns of positive selection within the genes suggest that they were important for shaping the specific adaptations of humans.

Biographical notes
The authors work at the Max-Planck Institute for Evolutionary Biology on patterns of genome evolution in mammals with a specific interest in newly evolved genes. D.T. is member of the editorial board of BFG.

Acknowledgements
This work was supported by Türkiye Bilimsel ve Teknolojik Araştırma Kurumu (TUBITAK-1001 project 112T421 to C.B.) and Max-Planck Institutional Funds (to D.T.).

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