Potential impact of primate-specific SVA retrotransposons during the evolution of human cognitive function

Olga Vasieva,[1] Sultan Cetiner,[1] Abigail Savage,[2] Gerald G. Schumann,[3] Vivien J. Bubb,[2] John P. Quinn[2]

[1]Institute of Integrative Biology, University of Liverpool, UK; [2]Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, UK; [3]Division of Medical Biotechnology, Paul-Ehrlich-Institut, Langen, Germany

Abstract

The SVA family of hominid-specific non-LTR retrotransposon comprises the youngest group of transposable elements in the human genome. The propagation of the most ancient SVA subfamily took place about 13.5 million years ago, and the youngest SVA subfamily appeared in the human genome after the human/chimpanzee divergence. Functional analysis of genes associated with SVA insertions demonstrated their link to multiple ontological categories, with one of the major categories being attributed to brain function. Further analysis of this subset demonstrated that SVA elements expanded their presence in the human genome at different stages of hominoid evolution and were associated with progressively evolving behavioral features that indicate a potential impact of SVA propagation on the cognitive ability of a modern human. Our analysis suggests a potential role of SVAs in the evolution of human central nervous system and especially in the emergence of functional trends relevant to social and parental behavior. Co-evolution of behavioral features and reproductive functions are suggested by our analysis and discussed.

Introduction

Genetic studies have been successful at determining the changes that alter pathways involved in evolution. Transposable elements (TEs), despite long being thought of as *junk* DNA, have impacted the human genome during its evolution through a variety of mechanisms causing structural varia-tions including insertional mutagenesis, generation of deletions at the insertion site, 3' or 5' transduction events, non-allelic homologous recombination and exonisation.[1-4] More than 10,000 TE insertions occurred in the human genome since human-chimpanzee divergence which were suggested to have implications on human evolution and especially its reproductive, cognitive and immune functions that diverged strongly during a relative short time period.[4,5] The large number of such TEs in the genome makes an analysis of their specific contribution to evolution very difficult, and previous studies highlighted the potential role of mainly self-propagating (L1, ERV/ETR) and Alu elements.[4] We have focused on the functions of genes in proximity to the integration sites of the less studied hominoid-specific composite retrotransposons termed SINE-VNTR-Alu (SVA) elements.[6] SVA elements represent the youngest non-LTR retrotransposon family in humans and the human genome harbors approximately 2700 SVAs.[7-9] We and others have demonstrated that SVA elements have properties of transcriptional regulators of gene expression both *in vivo* and *in vitro*,[8,10,11] and that a significant number of SVA elements are located within 10kb of the major transcriptional start site of many genes.[8] Therefore, SVA insertions established in the hominoid lineage could be responsible for altering the transcriptome in a developmental, tissue-specific or stimulus inducible manner, as was already suggested earlier for Alu elements and demonstrated for LTR sequences of endogenous retroviruses.[4]

SVA elements are categorized into subfamilies A to F and F1,[11] and their age was estimated at 13.56 million years (Myrs) for the oldest subfamily (A) and 3.18 Myrs for the youngest subfamily (F). Subfamily D is by far the largest and encompasses 44% of all SVAs in the human genome. The subfamily termed F1 represents the smallest group covering only 3% of all SVA elements. Subfamilies E, F and F1 are human-specific and correspond to the period since the human chimpanzee divergence that occurred ~6 million years ago.[5] The implications of SVA insertions for the evolution of other hominoid lineages is quite obvious, because, for instance, the family of gibbon-specific LAVA retrotransposons, derived from an SVA A element, has been implicated in the molecular mechanism underpinning genome plasticity of the gibbon lineage.[12] We have previously examined in detail the SVA insertions found upstream of the genes PARK7 and FUS, which are genes implicated in neurodegeneration, and demonstrated that the SVAs associated with these genes have tran-scriptional regulatory properties both *in vivo* and *in vitro*.[7] In this communication, we wanted to further explore the potential of members of the different SVA subfamilies (A-F1) to modulate specific genes involved in CNS function. Here, we demonstrate that SVA insertion and subfamily appearance in evolution correlate with the acquisition of certain behavioral traits.

Materials and Methods

Generation of the list of genes associated with SVA insertions

Genomic coordinates of all SVA *loci* in the human genome (Hg19 reference genome sequence) were extracted from the UCSC genome browser (http://genome.ucsc.edu/index.html). This included many SVA sequences that were fragmented in the Repeat Masker track; therefore, this list was manually annotated to generate a list of coordinates of complete SVA sequences

resulting in a total of 2676 elements encompassing all seven SVA subfamilies.[8] The coordinates of all known genes and their transcripts were extracted from the UCSC genome browser, and Galaxy software (http://galaxyproject.org/) was used to generate coordinates of the 10-kb genomic regions flanking all known transcripts. Finally, the SVA *loci* were intersected with the three lists of genomic coordinates (all known genes, 10kb upstream and 10kb downstream of known genes). Duplicates were removed from each list individually. For functional enrichment analysis, the defined SVA coordinates have been used to produce a shorter list of the Genome Reference Consortium Human Build 38 (*GRCh38*) genes directly mapped via BIomart Martview service (www.biomart.org/biomart/martview/).

Ingenuity pathway analysis

Ingenuity Pathway Analysis (IPA) software (Ingenuity Systems, Inc.) was used to investigate biological functions associated with the data sets generated from genes associated with an SVA insertion.[13] The IPA database is composed of comprehensive information on genes and pathway ontologies. The database contains approximately 200 canonical pathways as well as 27 higher-order disease and function categories for *Core* functional enrichment analysis. Right-tailed Fishers Exact statistical tests was used to calculate whether the likelihood of associations between a set of focus genes and a category was due to a random chance. The tool enabled production of graphical networks that illustrated mapped genes and their functional connections.

Meta-analysis of gene expression

Genevestigator software was used to perform a meta-analysis of gene expression in different tissues.[14] For each gene/tissue an average level of expression is determined via automated cross-analysis of normalized published Affymetrix microarray data, filtered for statistically significant values and stored in the *Genevestigator* database. The highest and lowest detected average expression levels define a 100-unit scale that is used for presentation of each gene/tissue related average expression value.

Results

Relevance of SVA-associated genes to neural system and cognitive function

The top ranked categories identified by IPA for the data set generated from genes

associated with an SVA insertion were *Cardiovascular disease* and *Glucose tolerance*. However the next highest ranked were *Guidance of axons* and *Synaptic processes* (P=1E-5 and P=6E-5 correspondingly). The genes classified to the latter categories were associated with a number of canonical pathways (such as *Synaptic Long Term Potentiation* or *Axonal Guidance Signaling*) with no specific enrichment in any of those top-ranked pathways (Supplementary Material). To better reveal functional trends for potential SVA impact on human cognitive function, we focused only on genes relevant to CNS categories (Table 1 and Supplementary Material) and these were re-analyzed by IPA (Supplementary Material). The top-ranked significantly enriched categories (-log(P-value)>12) were of morphology and development of forebrain/telencephalon and multiple categories relevant to axon growth and synaptic processes. From the mapped behavioral categories, *Learning* and *Social Behavior* were the generally most enriched (-log(P-value)>4.6) categories and *Nest building behavior*, *Nursing*, *Sexual behavior, Sexual receptivity of female organism*, *Grooming*, *Emotional behavior*, *Aggressive behavior*, *Vocalization* and *Walking* were the most significantly enriched categories in the SVA B and/or SVA D associated sets of genes. *Social Behavior* was the only significantly enriched category attributed to the gene sets associated with the youngest SVA subfamilies F and F1. Many categories across the sets were mapped by one or two genes. All the defined behavioral categories were presented against the timeline of occurrence of insertions of the different SVA subtypes in the human genome as

shown on Figure 1.

A number of behavioral categories show an evolutionary corresponding pattern of connection to SVA insertions. The walking-category-associated group of genes ([AGTPBP1 (ATP/GTP binding protein 1)], [CACNB4 (Calcium channel, voltage-dependent, B4 subunit)], [FXN (Frataxin), SCN8A (Sodium channel, voltage gated, type VIII alpha subunit)], [ATG7 (Autophagy related 7 homolog)] contain SVA D or F insertions while the functions of climbing activity-associated genes [KCNJ6 (Potassium inwardly-rectifying channel, J6)] and [HTT (Huntingtin)] are associated with earlier SVA A and B insertions (Supplementary Material). We may speculate that alteration of the functionality of these genes overall could have had an impact on changing from climbing to the walking moving mode over the period of hominoid evolution. Consistent with that the decline in Nest building activity was also speculated to have an enhancing impact on evolution of walking survival skills, and we see this category associated with two SVA B and D types. In that respect a modulation of a limited number of genes in a specific pathway could have a major effect on the overall pathway. Behavioral characteristics encoded by genes containing younger SVA elements are generally of a more executive nature, for instance [CREB1 (cAMP responsive element binding protein 1)] associated with an SVA E insertion, is involved in both vertical and spatial learning and place preference, while [PSEN1 (Presenilin-1)] is associated with an SVA F element and plays a role in social order recognition, memory and social behavior. In this respect, it attracts our

Figure 1. Behavioral categories attributed to genes associated with SVA insertions at different periods during evolution.

attention that 3 genes with functions relevant to maternity care: *Mother preference* associated gene - [OMP (Olfactory marker protein)] and metabolic functions associated with *Nursing* and *Feeding* categories ([ACOT11 (Acyl-CoA thioesterase)], [MKL1 (Megakaryoblastic leukemia (translocation))]), are also associated with the recent SVA F (Supplementary Material). Interestingly, the number of functions associated with regulation of mating and parental behavior is also affected by SVA D insertions. Among those genes involved are genes encoding regulators of hormonal biosynthesis and response ([CYP19A1 (Aromatase)], [ESR1 (Oestrogen receptor 1)]), metabolism ([LEPR (Leptin receptor)], [ATP8A2 (Phospholipid transporting ATPase 8A2)], [FTO (Alpha-ketoglutarate-dependent dioxygenase)]), synaptic function ([SHANK2 (SH3 And Multiple Ankyrin Repeat Domains 2)], [GPHN (Gephyrin)]), and immune response ([IL1RN (IL1 receptor antagonist)], [OCLN (Occludin)]). Several genes found to be associated with SVA insertions are involved in multiple ontological categories, *e.g.* the genes HTT associated with SVA B, or [BRCA1 (Breast cancer type 1 susceptibility protein)], associated with SVA F, could have been especially significant at particular evolutionary stages whilst having largely pleiotropic effects (Figure 2). It is indicative that genes with different SVA insertions functionally crosstalk. BRCA1, for instance, is not only linked to DNA repair processes but is also involved in interactions with a number of transcription factors, such as ER1, which itself has an SVA insertion (Figure 2). As an extreme example of crosstalk between different SVA subtypes are many cases of distinct subtype insertions in a single gene (Table 1 and Supplementary Material).

Meta-analysis of anatomical relevance of SVA-associated behavioral gene expression

Forebrain and hindbrain were confirmed to be the sites of high expression of the majority of the genes attributed to behavioral phenotypes. High expression levels of the majority of genes associated with all 7 SVA subtypes were also found outside of the CNS which indicates a pleotropic multi-tissue effect of the genes with behavioral phenotypes and suggests their coordinated evolution. Potential positive selection of SVA-associated genes could be attributed, among other factors, to their direct effect on an organism's reproduction. Nearly 80% of all genes associated with members of the SVA A and B subtypes were highly expressed in placental chorion

(Supplementary Material). Similarly, all genes were expressed in testis at above average levels. A number of the behavioral SVA-associated genes exhibited their highest expression levels in oocytes: [TIMD4 (T-cell immunoglobulin and mucin domain containing 4)], [OXT (Oxytocin/Neurophysin I)], [KALRN (Kalirin)], [cyp7B1(Cytochrome 7B1)] and already mentioned genes MKL1 and ATG7, which are enriched for SVA F and SVA F1 insertions. Some genes whose expression is known to cause a strong *neural* phenotype, such as [GABBR2 (GABA B receptor 2)] (SVA A) and CREB1 (SVA E), are also highly expressed in oocytes. Interestingly, germ cells are characterized by increased mobilization of endogenous retrotransposons in general,[15] and attribution of SVAs to genes expressed in these germ cells might therefore be relevant for the SVA mobilization and propagation in this cell type. Analysis of attribution of the gene set with neuronal and behavioral functions in phenotypic reproductive categories (IPA analysis, Supplementary Material) also highlighted their link to spermatogenesis (in particular, sperm motility [(ADCY10 (Adenylate cyclase 10)]), atrophy of testis and seminiferous tubules (HTT)), infertility in both genders ([STAR (Steroidogenic acute regulatory protein)], [ABCA1 (ATP-binding cassette A1)], [MKKS (McKusick-Kaufman syndrome)], [NPEPPS

(Puromycin-sensitive aminopeptidase)]), maturation ([LFNG (O-Fucosylpeptide-3-Beta-N-acetylglycosyl transferase)]) and fertilisation ([CLIC4 (Chloride intracellular channel 4)]) of oocytes. Several genes, such as [CYP19A1 (Cytochrome 19A1)], [ABL2 (Non-receptor tyrosine kinase)], [SHANK1 (SH3-and-multiple-ankyrin repeat-domains protein 1)] and already mentioned ESR1, CREB1 and NPEPPS also have an association in the IPA knowledgebase with the following behavioral aspects of reproduction: sexual receptivity of female organism, mating behavior, intromission, mounting and pup retrieval.

Discussion

Retrotransposons have been suggested to be major drivers of genome evolution, both through structural variations such as insertional mutagenesis and modulation of the transcriptome.[4,16] SVAs can also induce alternative splicing and exon skipping which can result in the generation of alternative transcripts of a gene as documented by disease causing insertions.[17-19] Thus SVA insertions may generate new interactions between what would otherwise be distinct pathways.[8,20] In this communication, we suggest a more global involvement of genes associated with SVA insertions in
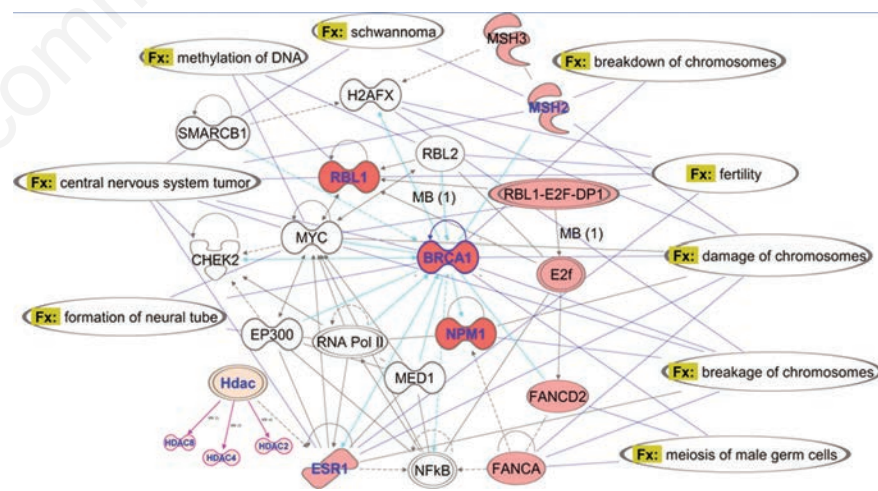

Figure 2. Functional networks reconstructed from SVA-associated genes and classified in neuronal and behavioral categories. Fx-labels correspond to gene-attributed functions and diseases. Solid lines - experimentally validated functional interactions, dashed lines - protein binding. The color intensities of blocks correspond to types of intragenic SVA insertions increasing in the order: B, D, F. Blue lettering indicates the genes associated with neuronal and behavioral categories. ACOT11(Acyl-CoA thioesterase 11), [CDK5RAP2 (CDK5 regulatory subunit associated protein 2)], [DIXDC1(DIX domain containing 1)], [E2F (Elongation factor 2)], ESR1 (Estrogen receptor1), [FANCA (Fanconi anemia protein A)], [FANCD2 (Fanconi anemia protein D2)], [HdaC (Histone deacetylase)], MSH2(MutS homolog 2)], [NPM1 (Nucleophosmin)], [POLA1(Polymerase (DNA directed), alpha 1, catalytic subunit)], [RBL1 (Retinoblastoma-like 1)], VPS35 (Vacuolar protein sorting 35 homolog).

Table 1. Genes associated with SVA insertions and classified to 4 categories relevant to neural system function.

	SVA_A	SVA_B	SVA_C	SVA_D	SVA_E	SVA_F	SVA_F1
Behavior							
	GABBR2 KCN16, PLCB4	CLCN3, HDAC4, HTT, MAPK1, RCAM, NRXN1, OXT, SEC24D, TACR3, TIMD4, UBR1, USF1	ABCA1, ABHD12, ATF2, FGF12, LRRK2, MKKS, NPEPPS, SLC16A2	ABL2, AGTPBP1, ATP7A, ATP8A2, CACNB4, CNTNAP2, CYP19A1, ESR1, F2RL1, FTO, FXN, GABRA2, GABRG3, GFRA2, GNAQ, GPHN, IL1RN, LEPR, LRPAP1, MOS, MTOR, NFATC3, NIPBL, NRXN1, OCLN, PARK7, PBX3, PRKG1, SCN8A, SHANK2, SYTL4, TRPV1, UBR1, VAMP7, VEZT	CREB1, OPHN1, UBR1	APLP2, KALRN, LEF1, MYH10, OMP, PARK2, PDE11A, PSEN1	ACOT11, ATG7, CYP7B1, MKL1
Nervous system development and function							
	ADCY10 AKAP9, CASP6, GABBR2, KCN16, PHB, PLCB4, SMO, TRA, ULK4, UNC13B	ARHGAP5, CLCN3, CNTN4, DCLK1, DST, FBXL20, GRID1, HDAC2, HDAC4, HTT, MAPK1, MYO5A, NCOR1, NR1H2, NRCAM, NRXN1, OXT, PARD3, PDS5B, PRPH2, RPGRIP1L, SMAD2, TACR3, TRPM6, UBR1, UBR2, UTRN	ALPL, APBB2, ATP2, HEY2, HYOU1, LAMA2, LRRK2, MKKS, PARG, PTPN9, RORA, SILI, STAR	ABL2, ADAM19, AGTPBP1, AHI1, ALOX5, ANK2, ARHGAP35, ASPA, ATP7A, ATP8A2, ATRX, ATXN2, BRAF, C2CD3, CACNB4, CAMK1D, CNTNAP2, CRB1, CYP19A1, DDIT3, DIXDC1, EIF2B3, EIF4G3, ELMO1, ERBB2IP, ESR1, F2RL1, FAIM2, FER, FGD4, FTO, FXN, GFRA2, GNAQ, GPHN, IL1RAPL1, L1RN, JARID2, KIF15, LEPR, LI1RB3, LPAR4, LRP4, LRPAP1, MOS, MTOR, MYH9, NCOR1, NFATC3, NIPBL, NRXN1, NRXN2, OCLN, PARK7, PBX3, PCMT1, PDGFRA, PDS5B, PEX5, POR, PRKG1, PTPN9, RBL1, RGS11, RPGRIP1L, SCN8A, SHANK2, SILI, SLC17A5, SNTB2, SPTBN1, SYNE2, SYTL4, TACC2, TENM4, TRPV1, TRPV3, UBE4B, UBR1, ULK1, ULK4, UTRN, VAMP7, VEZT, YWHAE	ADIPOQ, ANXA2, ATP2C1, CASP8, CLIC4, CREB1, DST, LFNG, OPHN1, UBR1, VAV2	APAF1, APLP2, BRCA1, CLIC4, EIF2B4, ERBB3, FSTL1, KALRN, LEF1, LRP2, LRRC4C, MYH10, NPM1, OMP, PARK2, PDE11A, PPARD, PSEN1, RBL1, ROBO2, TENM4, ZEB1	ATG7, CDK5RAP2, CYP7B1, HTR1E, PTPN9, SV2C
Neurological disease							
	AARS2, ARL13B, BBS9, CASP6, CLN6, DYX1C1, FAF1, GABBR2, KCN16, MKS1, PHB, PLCB4, REEP1, RTTN, SMO, TAF1, TRA, ULK4, UNC13B	ACS14, CACNA2D4, CCM2, CLCN3, DST, FAF1, GRID1, HDAC4, HDAC8, HLA-DRB1, HTT, IGBP1, IGBP1, NR1H2, NRCAM, NRXN1, OXT, PARD3, PARP1, PDS5B, PRPH2, PTPRD, RPGRIP1L, SMAD2, TACR3, TRPM6, UBR1, YARS, ZDHHC15	ABCA1, ABHD12, APBB2, ARNT,ATF2, CFLAR, DNAJC1, DYSF, FGF12, HYOU1, KDM6A, LAMA2, LOC440040, LPIN1, LRRK2, MFN2, MKKS, PARG, PIGL, PNKD, PTPN9, RAB7A, RORA, SILL, SLC16A2, SLC25A12, STAR, TFAP2B, VAMP1, WDR62	ADAM19, ADORA3, AHI1, AIP, ALOX5, ANKRD11, ARHGAP35, ASPA, ATP7A, ATRX, ATXN2, BBS5, BRAF, BRWD3, C9, CACNB4, CAMTA1, CASK, CFB, CNTNAP2, CPA6, CRB1, CYP19A1, DDIT3, EIF2B3, ELMO1, ESR1, F2RL1, FGD4, FUS, FXN, GABRA, GABRG3, GFRA2, GLRA3, GNAQ,GOLPH3, GPR98, IL1RAP1, IL1RN, LEPR, LRP4, LRPAP1, MSH2, MTOR, MYH9, NRXN1, OCLN, OTOGL, PARK7, PCMT1, PDE4D, PDGFRA, PDS5B, PEX5, PH78PIGV, PNPT1POR, PTPN9, PUS1, RAB7A, RBL1, RMND1, RPGRIP1L, SCN8A, SILI, SNTB2, SPRN, SPTBN1, SYTL4, TAF1, TAOK1, TENM4, TRIOBP, TRPV1, UBE4B, UBR1, ULK4, VAMP7, VPS35, XK, YWHAE, ZDHHC9	ADIPOQ, ANXA2, ATP2C1, BRAT1, CASP8, CREB1, DST, HMBOX1, HUWE1, MYO1B, NBAS, OPHN1, PDE9A, PDXDC2P, RNFI35, SNX2, UBR1, VAV2	ALDH7A1, APAF1, APLP2, BRCA1, CECR2, CTSS, EIF2B4, ERBB3, IFT140, KDM6A, LRP2, MS4A1, NEU1, ORC6, PARK2, PCSK5, PPARD, PSEN1, RANBP2, SERAC1, SLC30A10, SPTLC1, TMC1, VAPB, VPS35	ACOT11, ATG7, CDK5, RAP2, CYP7B1, POLA1, PTPN9, RAD54L, SLMAP, SV2C
Psychological disease							
	GABBR2, ULK4	CACNA2D4, HLA-DRB1, HTT, NRXN1, OXT, PTPRD	ABCA1, APBB2, ARNT, CFLAR, DNAJC1, DYSF, FGF12, LOC440040, LRRK2, MFN2, PNKD, STAR, VAMP1	ADORA3, ALOX5, ANKRD11, ASPA, BRAF, C9, CACNB4, CFB, CRB1, CYP19A1, DDIT3, EIF2B3, ELMO1, ESR1, GABRA2, GABRG3, GOLPH3, IL1RN, LRP4, LRPAP1, MSH2, MTOR, MYH9, NRXN1, PARK7, PCMT1, PDE4D, PEX5, SCN8A,SYTL4, TENM4, TRPV3, UBE4B, UBR1,ULK4, VAMP7, VPS35	ANXA2, CASP8, CREB1, HUWE1, MYO1B, PDE9A, UBR1	APLP2, BRCA1, CTSS, PARK2, PSEN1, SLC30A10 SPTLC1, VPS35	ACOT11,RAD54L, SLMAP

CNS-relevant pathways. Our data has established that more primitive behavioral characteristics (as climbing, for example) are prominent for the genes associated with the older SVA subtypes A and B and later insertions are more related to younger trends, such as walking. Overall, results revealed a striking correlation between the timing of SVA insertions (Figure 1) and functional significance of these associated genes at particular stages of hominoid evolution.[21] This may not be surprising but could be consistent with the lineage variation of the phylogenic tree for primates (Figure 1). It attracts our attention, particularly, that a number of behavioral characteristics relevant to maternity care such as *Nursing*, *Feeding*, *Nest Building*, *Mother Preference*, were populated by SVA-associated genes during the last 6 Myrs of hominoid evolution (Figure 1). Provided these structural changes are functionally significant, they can correspond to a consistent neotenisation of hominoids and development of a family-based social structure.[21] Another example is *Nest Building Behavior* that is associated with SVA types B and D and is known to decline with evolution of hominoids due to a switch to ground-sleeping.[22] This decline was speculated to be also an enhancer of walking survival skills, innovation, procedural memories and gender specification. The associated insertions can suggestively play a suppressive or deleterious role in this behavioral trend. Some of the SVA insertions could also have a gender-specific influence on cognitive functions. The *BRCA1* gene, for instance, which is associated with an SVA F insertion and is one of the hubs in SVA integrated functional network (Figure 2), was shown to be in a cross talk with the estrogen receptor ESR1.[23,24] *BRCA1* is also known to have a strong role in the control of brain size,[25,26] especially in regions responsible for learning, memory, muscle control and balance. Interestingly, structurally related PGR (progesterone-dependent transcription factor) binding sites were shown to be enriched in ancient mammalian TEs linked to evolution of pregnancy,[27] and LTR and Alu elements were also shown to be strongly associated with genes relevant to reproduction.[4]

Moderate expression of the majority of behavioral-SVA-associated genes in male germ cells (in contrast to less than 10% though strongly, expressed in oocyte) could make this cell type a particular source of *trans*-mobilized SVA elements which are inheritable and passed on to following generations. This hypothesis would be supported by a strong expression of L1 retrotransposons in this niche which are known to provide the protein machinery required for SVA trans-mobilization.[28]

Behavioral trends caused by SVA insertions in genes expressed in brain could be thus linked to a higher rate of an inheritable SVA *trans*-mobilization. Thus, being subjected to positive or negative selection at particular stages of hominoid evolution, those behavioral trends could be associated with waves of heritable SVA propagation in the genome. The mechanisms of acceleration and inhibition of propagation of SVAs may be common for all TE, and the wavy nature of this process have been mentioned earlier.[4] Genes associated with both neuronal and reproductive phenotypes as well as with TE *trans*-mobilization properties could be in the first line of the TE-driven evolutionary changes. Interestingly, genes involved in CNS and reproductive functions and DNA repair are associated with different autonomous and non-autonomous TE elements,[4] that potentially make a cumulative evolutionary impact.

Conclusions

Our systems analysis suggests an impact of SVA retrotransposition on evolution and performance of human cognitive functions. Data revealed that insertions of members of the older SVA subtypes A-C occurred in genes involved in more primitive characteristics whereas younger SVA D-F1 insertions were present in genes linked to more sophisticated human-specific traits. The presence of SVAs in multiple genes within a network may allow for a concerted response to an environmental stimulus modulated by factors targeting SVA regulatory sequences. Potential positive feedbacks in SVA-associated functional networks and crosstalk between cognitive and reproductive functions would lead to waves of SVA trans-mobilization in the course of hominoid evolution. Considering that genetic polymorphisms in the human population are associated with SVA insertions and that the youngest SVA insertions are documented in human brain and germ line tissues, it can be suggested that SVAs have a modulatory impact on recent human behavioral trends and susceptibilities to psychiatric disorders.

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