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Jumping Genes-"*The Other Half of the Human Genome*" and the Missing Heritability Conundrum of Human Genetic Disorders

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Authors' contributions

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Review Article

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ABSTRACT

Almost 45% of the human genome is composed of transposons with about 4 million copies. The retrotransposons constitute 42% of the human genome with active families (Long Interspersed Nuclear Element, SINE-R, VNTR, and *Alu*) allied with insertional mutagenesis and diseases. There are >500,000 L1 copies which represent ~17% with less than 100 active copies and are inserted in the human genome; >1 million *Alu* copies referred to as "a parasite's parasite" and ~3,000 SVA (SINE-R, VNTR, and *Alu*) copies. Some Human Endogenous Retroviruses are still active in humans. Nonactive DNA transposons embody 3% of the human genome. TEs are known to engender genomic instability and reorganize gene expression system in germline as well as the somatic cells. The amended retrotransposon expression or function appears to be associated with stress, alcohol, neurodegeneration and aging. This review highlights recent findings on the role of jumping genes in human genetic disorders like cancer, autoimmune and neurological diseases.

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1. INTRODUCTION

Transposons play a vital role in evolution and 45% of our genome encompasses transposable elements [1] (Fig. 1). Human transposons can be categorized as RNA transposons (retrotransposons) and DNA transposons. Retrotransposons which move by the process of retrotransposition (copy-and-paste mechanism) can be further subdivided into LTR (Long Terminal Repeat) (e.g; HERVs (Human Endogenous Retroviruses) and non-LTR transposable elements (e.g; LINEs (Long Interspersed Elements), SINEs (Short Interspersed Elements), *Alus* (*Arthrobacter luteus*) and SVAs) while the DNA transposons mobilize by a cut-and-paste mechanism. The LINE-1 (L1), *Alu* and SVA which are explicitly active non-LTR retrotransposons, reciprocally make up about one third of the human genome (Fig. 2a) [2,3] and there are more than 60 reported cases of *de novo* insertions responsible for human genetic disorders [4-8]. For 80 to 100 latently active L1 in any individual, 101 *de novo* disease-causing germline retrotransposon insertions have been differentiated [6]. *De novo* insertions of L1 and SVA elements emerge respectively at the rate of roughly 1 in 108 births and 1 in 916 births [9], [10]. Approximately, 65 syndrome-based mutations in humans have been accredited to L1-mediated retrotransposition proceedings [11]. The most active *Alu* elements, account for 1 *de novo* germline insertion per 20 births [12]. L1 elements solitary encode which specially identify L1 mRNA molecules and the L1 machinery is co-opt by *Alu* and SVA elements. Endogenous retroviruses (ERVs) and ERV-like sequences comprise 8% of the human genome at 700,000 different loci [13]. About 40,000 HERV elements with truncated and solitary long terminal repeats have been identified. Almost 22 families of human ERVs are identified with one equipped of forming entire virus. ERVs may penetrate the genome via infection or through replication of accessible elements and shuffle DNA, add new promoters and new genes but also lead to various disease formations [14]. Diverse families of human endogenous retroviruses (HERVs) are present including HERV-E (30 to 50 copies per genome), HERV-R (1 copy per genome), HERV-H (50-100 with a provirus structure, thousands with a transposon structure), HERV-I (2-25 copies per genome), HERV-P (10-20 copies per genome), and HERV-K (20-50 copies per genome). Some ERVs may still be active in humans' enzymes which are obligatory for retrotransposition [15], although the vast majority is nonfunctional. The expression of ERV sequences has been allied with a number of human diseases, such as multifactorial etiology or dysregulated immune functions, multiple sclerosis, Type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, schizophrenia, cancer, cell tumours, melanoma and hematological disorders germ [13,16] but that expression as cause or effect of these diseases is not elucidated yet [16].

Brain often displays a surprising level of somatic mosaicism as compared to the rest of the body. Somatic mosaicism means the presence of two or more populations of cells with different genotypes in one individual who has developed from a single fertilized egg [17]. Somatic retrotransposition is linked to neurobiological genes. Severe mosaicism as chromosomal malformations can be a cancer sign; considerable mosaicism in a single gene across tissue types can be pinpointing to genetic diseases like the polyQ (polyglutamine) diseases; and moderate mosaicism is normal and to be expected [18,19]. Some transpositionally active LINE-1 retrotransposons contribute to brain mosaicism predominantly within the hippocampus, which produces neurons throughout [2]. LINE-1 retrotransposons are active and itinerant during neurogenesis in humans [20-22]. The recognition of somatic mobilization of active retrotransposons like LINEs, *Alus'* and SVA in varied human brain regions [3] advocates' role of active mobilization of transposons in normal brain development and budding substantiation implies alliance of unregulated transposon activation with neuropathology. The neuronal mosaicism due to L1 activity is apparent all over embryo development and in the adult brain [23], which is causative of genomic neuronal diversity athwart neurons of same individual leading to the phenomenon of the "one human, multiple genomes" [24]. That neuronal somatic mosaicism caused by retrotransposons [25] has broad repercussions in vast subject of neuroscience [2], [21,26]. The activation of transposons in human brain has been experiential in macular degeneration [27], FXTAS-Fragile-X associated tremor/ataxia syndrome [28], aging [29],

neurodegenerative diseases [30], alcoholism [31], ALS [32], Rett syndrome [33], Prion diseases [34,35], neurogenesis [20,21,33] and PTSD- post- traumatic stress disorder [36]. The macular degeneration and FXTAS may be attributable to activation of SINEs and LTR-retrotransposon [27,28]. According to Li et al. [30], TDP-43 broadly targets TE-derived transcripts of SINE, LINE, LTR and some DNA transposable elements. The compromise of TDP-43 protein function leads to over-expressed TEs causing genome instability and accumulation of TE-derived RNAs or proteins causes activation of DNA-damage stress response or toxic effects. This toxicity may contribute to TDP-43-mediated neurodegenerative disorders. Higher levels of L1 correlate with the occurrence of brain disorders, including Rett syndrome, major depression and Louis-Bar syndrome. Bundo et al. [37] while examining the brain tissue of deceased schizophrenia patients, found a 1.1-fold enhancement in L1, than in healthy controls. Baillie et al. [2] reported a somatic retrotransposition event in the intron of a histone deacetylase *Hdac1*- a known regulator of L1 expression within the human genome, suggesting how a single transposition event might alter the capacity of a given cell to regulate further insertions [38]. Retrotransposition may create target-site duplications (TSD)-microsatellites within the genome at the insertion points and trinucleotide repeats are indicative of a number of ailments, essentially of the central nervous system. The "polyQ disorders" known as "polyQ" because "Q" is the symbol for the amino acid, glutamine, which is coded by the sequence "CAG are due to CAG repeat expansion within coding regions of certain genes, resulting in protein product with an expanded glutamine tract. The polyQ Disorders have reported somatic mosaicism within the mutated genes, such that different extremes of expansion are seen in different organ systems and include: spinal and bulbar muscular atrophy (SBMA), Huntington's disease (HD), dentato rubral pallido luysian atrophy (DRPLA),and spinocerebellar ataxias (SCA) type 1, 2, 3, 7, and 17. The polyQ tracts may also form cytotoxic neuronal intranuclear inclusions (NII) [39]. For the CAG repeat disorders, the brain exhibits comparatively greater expansion than other tissues, with the notable exception of SBMA with greater variability in cardiac and skeletal muscle, skin, and prostate [40].

According to Kazazian et al. [4], Hemophilia A was due to *de novo* TE insertion which was one of the first studies to reveal that a TE insertion in human genome cause disease wherein an examination of 240 unrelated hemophilia A male patients showed that autonomous L1 mutagenic insertions into exon 14 of the *Factor VIII* gene caused this disease in two persons. The insertions of 3.8 and 2.3 kilobases contained 3' portions of the L1 sequence, along with the poly (A) tract, which create TSDs (Target Site Duplications) of at least 12 and 13 nucleotides of the factor VIII gene and their 3'-trailer sequences following ORF-2 are almost indistinguishable from the consensus sequence of L1 cDNAs leading to confirmation of this disease by insertional mutation [4]. Similarly, 21 patients of

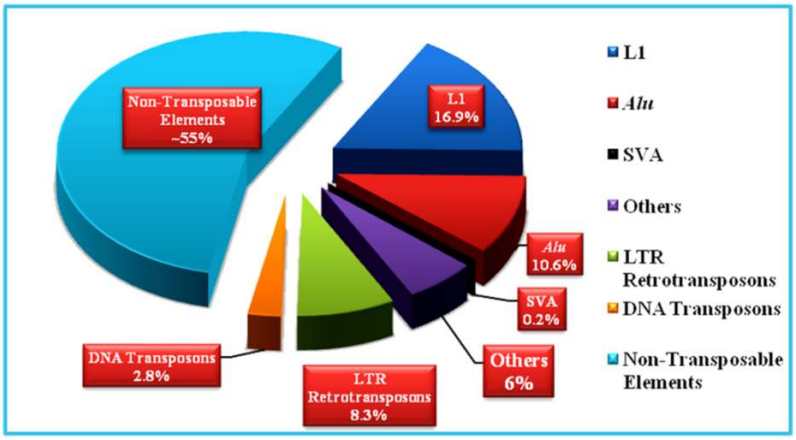

Fig. 1. The transposable element content of the human genome

About 45% of the human genome is composed of transposable elements, the vast majority of which are non-LTR retrotransposons (L1, Alu and SVA elements)

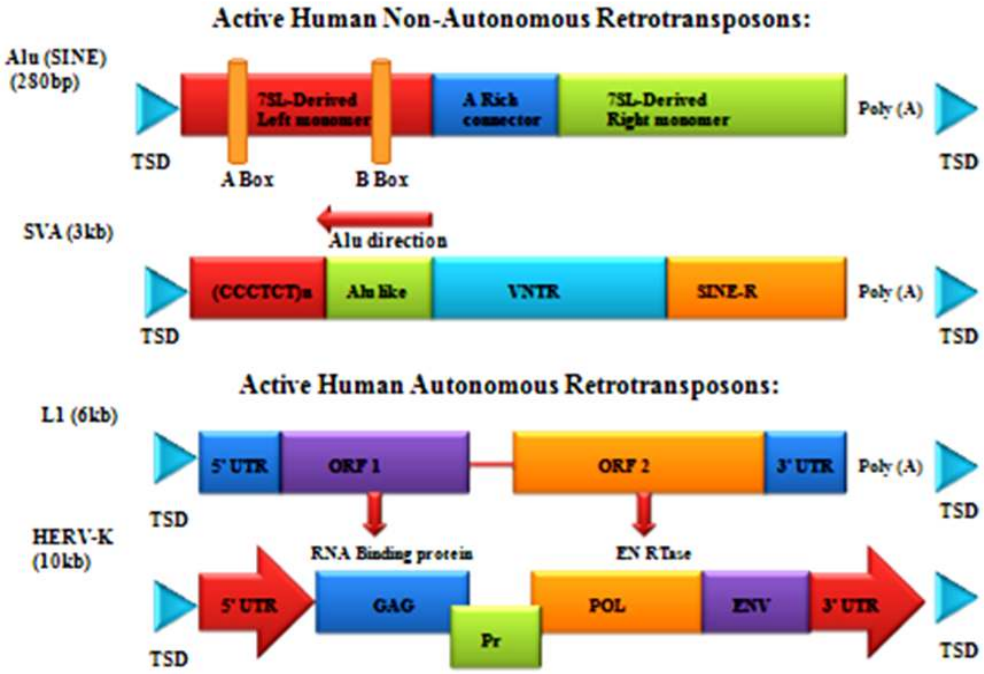

Fig. 2. Structure of active human retrotransposons

Autonomous elements encode the factors for their own mobilization. L1 ORF1 encodes RNA binding protein and ORF2 encodes a protein with endonuclease & reverse transcriptase roles. Human ERVs contain GAG, POL, and ENV genes. ERVs are flanked by LTRs (triangles) of 300–1,200 nucleotides. Alu and SVA are nonautonomous, relying on the L1-encoded retrotransposition machinery

Jewish ancestry suffering from retinitis pigmentosa was reported with having *Alu* insertion into an exon of the *MAK* (male germ-cell-associated kinase) gene [41] and Duchenne muscular dystrophy in a Japanese boy was identified due to L1-mediated orphan 3' transduction into the *dystrophin* gene [25].

Epigenetic and post-transcriptional suppression obstruct somatic cell retro transposition [38,42], excluding early embryo development [43] and some malignancies [38,43]. On the compromise of DNA methylation-mediated suppression system, HERVs and LTRs can cause detrimental and/or self-protecting effects. CSF1R oncogene activation by a MaLR LTR in Hodgkin's lymphoma and RCC-specific novel HERV-E antigen expression was reported. Methylation of HERV-W sequences was lost in the tumor DNA, symptomatic of interrelated DNA methylation and HERV-W expression in tumor milieu [44]. Human tumors having novel L1 retrotransposition events furthermore, displayed global patterns of hypomethylation, affording a correlative linkage between epigenetic changes and augmented L1 retrotransposition in tumors. Hypomethylation of L1 5′ UTR has been experiential in malignant and cancer tissue, and is associated with amplification in L1 mRNA and/or ORF1p expression [45].

The role of transposable elements in some of the human diseases is discussed briefly below.

1.1 Cancer

It is being hypothesized that the transposition of HERVs and other TEs in somatic cells, may insert in tumour suppressor genes which could lay foundation of neoplastic transformation. According to Tost J. [46], several cancers mark comprehensive DNA hypomethylation and local hypermethylation of CpG islands of tumour suppressor genes. Attributable to global DNA hypomethylation, the TEs transpose and may insert in or near the promoter region of tumour suppressor genes thus impeding their function and initiates neoplastic transformation on account of alteration in the cell cycle, blocking apoptosis or blocking DNA repair [46] followed by CpG island hypermethylation of promoters of genes inhibiting cell invasion and dissemination [47]. LTR of a MaLR human endogenous retrovirus leads to aberrant activation of a proto-oncogene, thereby causing lymphoma [34]. Hypomethylation of the HERV-K locus results in

increased HERV-K (22q11.23) expression in prostate and ovarian cancers [48,49] while hypomethylation of CpG dinucleotides within the promoter region results in HERV-W expression in ovarian cancer [50] and HERV-H (Xp22.3) expression in colon, gastric, and pancreatic cancers [51]. Hypomethylation of the U3 region of several HERV-W loci may lead to HERV-W activation in testicular cancer [52]. The HERV-K provirus family causes several cancers, because its members have open reading frames (ORFs) for all their viral genes. An endogenous retroviral envelope protein 'syncytin' has a role in placental trophoblast cell fusion, breast cancer-endothelial cell and endometrial carcinoma cell fusions [53]. LINE-1 transposons involve the *myc gene* in breast carcinoma and L1 insertion into the *adenomatous polyposis coli* (*APC*) gene in a colorectal tumor [53,54].

The identification of numerous non-germline *de novo* insertions in various kinds of cancers like lung cancer [55,56], brain cancer [57], glioblastoma [58,59], ovarian cancer [58,59], colorectal cancer [54,56,57], prostrate cancer [57], multiple myeloma [57], hepatocarcinoma, breast cancer [56], and acute myeloid leukemia [56] was performed with high-throughput sequencing. Primary melanomas and testicular germ-cell cancers are extensively studied with evidence of HERVs in their tumorigenesis. HERV-K (HML-2) transforms melanocytes to melanomas while HERV-K ENV and GAG proteins preferentially express in primary melanoma cells and melanoma cell lines except benign melanocytic tumors. HERV-K also express in lymphoid metastases originating from primary tumors [60,61]. Testicular germ cell cancers caused by HERVs wherein Testicular germ cell tumors (GCT) arise from a dysfunction in spermatogenesis and HERV-K (HTL- 2) produce viral-like particles [62] with HERV-K transcripts and proteins in GCT cells [63]. Further in GCT patients, a specific immune response against HERV-K proteins is found [64]. HERV-K (HTL-2) Rec and Np9 proteins interact with PLZF and avoid accurate functioning of PLZF in the host and obstruct sperm cell maturation [65], while in normal cell, PLZF interrelates with proto-oncogene *c-myc*, inhibits its transcription, and proceeds as a spermatogenial stem cell regulator. By Rec and Np9 inhibition of PLZF, *c-myc* expression elevates and spermatogenial stem cells become unbalanced [66] while Np9 causes genetic instability in germ cells due to intervention with the Numb/Notch pathway [66,67] confirming their roles in tumorigenesis.

1.2 Autoimmune Diseases

Three mechanisms molecular mimicry, superantigen production, and LTR-mediated alterations of gene expression have been proposed for HERV-related pathology of autoimmune diseases.

1.2.1 Rheumatoid arthritis

Expression of multiple ERVs was detected in RA patients and that of HERV-K10 in juvenile RA. In juvenile rheumatoid arthritis patients HERV-K10 expression was up-regulated possibly because of Super-Antigen Stimulation in auto-reactive T cells causing autoimmunity [68,69]. The GAG and ENV proteins of HERV-K10 share the peptide sequences with the rheumatoid factor epitopes on IgG1Fc, entailing molecular mimicry [70]. HERV-K10, HERV-W (MSRV) and ERV-9 showed expression in normal and diseased synovium [68]. Friemanis et al. [70] using Quantitative RT-PCR and ELISA showed higher levels of HERV-K10 GAG activity in RA patients than controls. The prevalence of HERV-K113 exhibit increased levels in patients with SLE and RA [71] suggesting a role of HERVs in disease pathogenesis. According to Nelson et al. [72] there is noteworthy alliance of sequence homology between HERV-K10 and rheumatic arthritis. Reynier et al. [73] noticed higher levels of HERV-K10 in plasma of RA patients with NASBA and Ejtehadi et al. [74] observed Enhanced expression of HERV-K10 in RA with Multiplex RT-PCR.

1.2.2 Systemic lupus erythematosus

HERV-K ENV protein causes autoimmunity via molecular mimicry and immunomodulation. In this disorder the determinant shared by the host and the HERV-K ENV protein induces immune response and tissue destruction [71]. Banki et al. [75] using the Western blot and ELISA showed increased HRES-1 peptide binding activity in sera of patients than controls while Perl et al. [76] showed autoantibodies to HRES-1 in this disease. The HRES-1 (Human T-cell lymphotropic virus-related Endogenous Sequence) locus at the 1q42 chromosomal region controls SLE development and expressions [77]. Deas et al. [78] illustrated that the cells exposed to HIAP-1 may be guarded from apoptosis. Talal et al. [79,80] exhibited presence of antibodies to p24 GAG of HIV-1 in nonexistence of HIV-1 infection and anti-Sm antibodies can cross-react with p24 GAG.

Hypomethylation of HERV-E and HERV-K was observed in SLE patients [81,82].

1.2.3 Sjögren's syndrome

The cells exposed to salivary tissue from patients with Sjögren's syndrome showed presence of HIAP-1 [83]. Considerably higher levels of antibodies to HTLV-1 [84] and Anti-p30 GAG antibodies (HERV-E ENV protein) were perceived in sera of several diseases [85].

1.2.4 Insulin dependent diabetes mellitus

Immunemediated (Type 1) diabetes is a multigenetic and autoimmune disease [86]. HERV-K18 which encodes for a T-cell superantigen (SAg) is involved in the etiology of type 1 diabetes. T-cells with T-cell receptor Vβ7 chains reactive to the SAg and HERV-K18 mRNA were enriched in the pancreas, spleen [87,88] and in circulation [89] at the onset of the disease. HERV-K18 transcription and SAg function in cells (induced by proinflammatory stimuli) trigger progression of disease to insulitis or from insulitis to overt diabetes [90,91]. HERV-K (C4) is a novel marker of Type 1 diabetes and individuals with Type 1 diabetes have appreciably lower HERV-K (C4) copies [92]. According to Conrad B. [93], HERV-K ENV encodes a super-antigen responsible for the etiology of insulin-dependent *Diabetes mellitus*.

1.2.5 Psoriasis

The retroviruses were suggested to have a role in psoriasis [94] and retroviral like proteins were found in urine, skin and lymphocytes of psoriasis patients [95].Expression of HERV-W, HERV-K, and HERV-E and a newly identified ERV-9/HERV-W variant in psoriasis development was reported by Moles J. P. et al. [96].

1.2.6 Multiple sclerosis

HERV-W family has a physiological role in multiple sclerosis as a cofactor and predictor of disease progression [97]. Multiple Sclerosis Associated Retroviral element have been correlated with the evolution and prognosis of Multiple sclerosis, wherein HERV-W ENV gene codes for an envelope protein called syncytin-1 [98], which distinct from its positive role in placenta morphogenesis, operates as a potent immuno-pathogeneic molecule that prompts a pro-inflammatory and autoimmune cascade. There is a strong linkage between the MS-associated retroviral element (MSRV)-type HERV-W and MS wherein the ENV RNA and protein expression considerably increases in the blood and brain cells, HERV-H/F family HERV-Fc1 expression in T lymphocytes and the plasma HERV-Fc1 RNA level also boosts in patients with MS. HERV-K18 (chromosome 1) was initiated to be a risk factor of MS and other human autoimmune disorders [99-103]. The Immune tolerance of HERV-W Env (Syncytin-1), GAG and other HERV-W proteins would avert the production of an immune response against HERV-W/MSRV antigens that initiate MS owing to altered or ectopic expression [104].

1.3 Neurological Diseases

1.3.1 Schizophrenia

Schizophrenia and brain-related genes likely house higher-than-average transposable elements, causing relative instability, enhanced insertion and recombination rates. The negligible TE insertions lead to mutations in schizophrenia-related genes [37], while the enhanced rates of “successful” TE insertions are still active in the human genome. The neurons taken from schizophrenic patients postmortem showed higher numbers of L1 retrotransposons than glial cells within the same brains, liver tissue from same patient in comparison to control brain and liver tissues i.e.; individual neurons from schizophrenics showed higher levels of L1-induced somatic mosaicism and the L1 insertions tended to preference synaptic, cytoskeletal and cell adhesion genes of central nervous system-related genes in schizophrenics. Bundo et al. [37] reported an increase in copy number of LINE1 in postmortem tissues and induced pluripotent stem cells (iPSC) from schizophrenic patients diagnosed with 22q11-deletion syndrome. The most cases of 22q11 deletion syndrome likely stem from *Alu*-mediated recombination, not from L1 insertion [68]. According to Bundo et al. [37] hyperactive retrotransposition of L1 in neurons elicited by milieu and/or genetic factors may add to the vulnerability and pathophysiology of schizophrenia. Gottipati et al. [39] suggests that the gene-associated forms of schizophrenia and autism may be because of a variety of recombinatory and transposition events arising from gene destabilization such as occur during transcription. Muotri et al. [21], reported substantially increased L1 retrotransposition in neural progenitors during early stages of differentiation. In the late 1950’s and early 1960’s, a study on the blood samples from pregnant women showed that antibody to HSV- 2 correlated with offspring development of

schizophrenia [105]. It in conjunction with the proof of HERV protein expression in the brains of patients, demonstrates that attacking pathogens may have the prospective to transactivate HERV sequences causing elevated disease sternness [106,107]. Rees et al. [108], reported that, in contrast to copy number variant deletions at the genetic locus, *22q11*, which increase schizophrenia risk, duplications in the same region appear to be linked with greater protection against the condition. Bundo et al. [37] study has highlighted the potential importance of genetic instability in schizophrenia's etiology. However, while some gene mutations may arise due to retrotransposon insertion, this is probably only one of a number of destabilizing events that target schizophrenia-risk genes. Karlsson et al. [109] established that RNA transcripts homologous to HERV-W family members are upregulated to different levels in the frontal cortex obtained from post-mortem schizophrenic patients than RNA in the plasma of patients with recent-onset schizophrenia [110].

Yolken et al. [111] reported the up regulation of HERV-W and HERV-K transcription and Frank et al. [112] reported over-expression of HERV-K in the cortex of post-mortem brains of SCZ and BD versus Healthy Controls. Weis et al. [113] reported reduced expression of HERV-W GAG in neurons and astroglial cells in SCZ, BP and MDD versus Healthy Controls while Lin et al. [114] reported more frequent HERV-K115 insertion in patients with younger onset of schizophrenia than those with later onset. According to Dickerson et al. [115] two-polymorphism haplotype in the envelope region of HERV K-18, located in the CD48 SLAM- signaling lymphocyte activating gene on chr1, is highly associated with type 2 diabetes in a population of 229 individuals with SCZ versus 136 Healthy Controls. Perron et al. [116] reported significantly higher antigenemia of HERV-W ENV and GAG proteins in individuals with SCZ versus Healthy Controls; and significant correlation of antigenemia with C-reactive protein (CRP).

Yao et al. [117] reported higher prevalence of HERV-W GAG transcripts in SCZ versus HC and higher rate transcription of intronic elements on the noncoding strand of PTD015 (11q13.5) in the patients during the transition from susceptibility to manifestation of symptoms. Huang et al. [118] showed higher prevalence of HERV-W ENV transcripts in SCZ versus HC and over-expression of HERV-W upregulate BDNF, NTRK2, DRD3 and increase CREB protein. Further, significant increase in HERV-W ENV transcription in BD and in SZ versus Healthy Controls was reported and the corresponding DNA copy number was paradoxically lower in the genome of patients with BD or SZ than in Healthy Controls [119,120]. Abrusan [121] reported the effect of somatic retrotransposition on brain metabolism and biosynthesis of 250 metabolites, together with dopamine, serotonin and glutamate in Schizophrenia and Parkinson's disorders.

1.3.2 Autism

Autism-related genes house large TE content. The DNA fragments which house numerous TEs attract extra TEs over evolution. The genes with TE in intronic regions usually have all types of transposable elements therein, suggesting that coding regions may have a hard time accommodating TE insertion ultimately selecting against it and that introns attract TE insertion. The more TEs, the more TEs they attract over the epochs and the greater the TE content, the more unstable that region is overall. Some of the largest genes in the human genome known for high rates of mutation, several of them also high-risk autism genes like *CNTNAP2* and *DMD*, which house thousands of intronic transposable elements. These results suggest a relationship between transposable element content and autism-risk genes and have implications for the stability of those genomic regions" [122]. In a similar study [11,123] reported higher percentages of transcripts from subfamilies of LTR retroelements in cases of autism in contrast to controls and HERV-H over-expression in ASD versus Healthy Controls and HERV-W down-expression in ASD versus Healthy Controls.

1.3.3 Attention Deficit Hyperactivity Disorder (ADHD)

Attention deficit hyperactivity Disorder (ADHD) is a neurodevelopmental disorder occurring because of complex interaction of environmental, biological and genetic factors. The expression of retroviral mRNAs from the three HERV families (HERV-H, K and W) was evaluated in peripheral blood mononuclear cells (PBMCs) from ADHD patients. The expression levels of HERV-H were notably elevated in ADHD patients in comparative to healthy controls suggesting a role of HERVs in the neurodevelopment diseases, while HERV-K and W showed no difference in expression [123].

1.3.4 Bipolar disorder

Yolken et al. [111] reported the up regulation of HERV-W and HERV-K transcription in the cortex of postmortem brains of SCZ and BD versus Healthy Controls [112]. According to Perron et al. [116] there is drastically higher HERV-W ENV transcription in BD and in SZ versus Healthy Controls. The analogous DNA copy number was ironically lesser in the genome of patients with BD or SZ than in Healthy Controls. Weis et al. [113] reported reduced expression of HERV-W GAG in neurons and astroglial cells in SCZ, BD and MDD versus Healthy Controls in post-mortem brain tissue.

1.3.5 Major depression

Weis et al. [113] reported reduced expression of HERV-W GAG in neurons and astroglial cells in SCZ, BD and MDD versus Healthy Controls in post-mortem brain tissue.

1.3.6 Post-traumatic stress disorder

Rusiecki et al. [124] reported DNA methylation evaluated via pyrosequencing in pre- and post deployment serum that the LINEs were hypermethylated in controls post- versus predeployment, hypomethylated in cases versus controls post deployment. *Alus'* were hypermethylated for cases versus controls pre deployment. According to Ponomarev et al. [36], genome-wide gene expression profile in amygdale leads to identification of a module of stress regulated highly co-expressed transcripts with no annotations mapping to genomic locations corresponding to LINE-1.

1.3.7 Alcohol dependence

Post-mortem brain from central and basolateral nucleus of amygdala, plus the superior frontal cortex illustrated co-expressed SINE and LTR up-regulated in the central and basolateral amygdala and superior frontal cortex of the alcoholic brain; and regions similar to upregulated probes corresponding to a currently "active" LINE-1 family, L1HS show increased hypomethylation in alcoholics [22]. The stress and/or chronic alcohol may lead to TE transcriptional activation. Chronic alcohol abuse resulted in DNA hypomethylation and transcriptional activation of LTR-containing transposons LINE-1 TE [31].

1.3.8 Ataxia telangiectasia

Ataxia telangiectasia is an autosomal recessive disorder leading to progressive neurological degeneration, immune deficiency, lymphoreticular malignancies, chromosomal instability, growth retardation, gonadal dysgenesis, telangiectases and premature aging of skin and hair with a frequency of 1:40,000–100,000 live births worldwide. In this neurodegenerative disorder, enhanced retro transposition activity in L1 cells with lack of ATM and enhanced copy number of L1HS in Ataxia telangiectasia patients versus Healthy Controls was reported in L1RP–EGFP post-mortem tissue of human brain [125].

1.3.8.1 Infantile encephalopathy

In post-mortem brain tissue [126] point mutation in intron of SLC7A2 in a primate-specific retrotransposon sequence and related enhancement of neuronal apoptosis in vitro KO for this transcript were reported.

1.3.8.2 Frontotemporal Lobar Degeneration (FTLD)

The cross linking immunoprecipitation sequencing data, RNA immuno-precipitation sequencing data, CLIP-seq and mRNA-seq datasets of human and mouse, Li et al. [29,30] reported that TDP-43 broadly targets TE-derived transcripts, including many SINEs, LINEs, LTR retroelements plus some DNA elements and the association between TDP-43 and TE-derived RNA targets lessens in FTLD patients relative to healthy subjects and over-expression of TE derived transcripts in each of two different mouse models with TDP- 43 dysfunction in this neurodegenerative disorder.

1.3.8.3 Di George syndrome

DiGeorge syndrome is the most recurrent contiguous-human gene deletion syndrome having an incidence of 1 in 4,000 live births [127]. In this mental retardation, *Alu*-mediated chromosomal rearrangements leading to micro deletions on 22q11 were reported [97].

1.3.8.4 Motor neuron disease

Motor neuron disease which is a clinical syndrome is mainly caused by the mutation of superoxide dismutase 1 (SOD1) gene. This gene is modulated by the HERV W ENV protein synctin in the placenta wherein its expression is elevated [109]. The elevated expression of HERV-W ENV and GAG genes have been detected and proposed in this pathogenesis [36].

Table 1. Some other human disorders where transposons cause insertional mutagenesis and recombination in genes

Transposons involved	Copy number	Gene	Disorders reported in humans	Element	References
SINES	1 million	NF1	Neurofibromatosis type1	*Alu Ya5*	[128-130]
Alu		*FGFR2*	Apert Syndrome	*Alu Ya5*	[128-129]
		BCHE	Acholinesterasemia	*Alu Yb8*	[131]
		Factor IX	Hemophilia B	*Alu Ya5, Yb8*	[128-129]
		Factor VIII	Hemophilia A X-linked Severe Bleeding Disorder	*Alu Yb8, Yb9*	[128-129]
		CASR	Familial Hypocalciuric Hypercalemia and hyperparathyroidism	*Alu Ya4*	[128-129]
		ADD1	Huntington Disease	*Alu*	[132]
		GK	Glycerol Kinase Deficiency	*Yc1*	[128-129]
		CTDP1	CCFDN Syndrome	*YF4*	[133]
		Fas	Autoimmune Lympho Proliferative Syndrome	*Sb1*	[128-129]
		CLCN5	Dent's Disease	*Ya6, Ya5*	[128-129]
		BTK	X-Linked Agammaglobulinemia	*Y, Y*	[128-129]
		IL2RG	X-linked severe combined immunodeficiency disease	*Ya5*	[128-129]
		CD40LG	Hyper IgM syndrome	*Yb8*	[128-129]
		ATP7A	Menkes Disease	*Ya5a2*	[128-129]
		CRB1	Retinitis Pigmentosa	*Y*	[128-129]
		ZFHX1B	Mowat-Wilson Syndrome	*Ya5*	[128-129]
		BCHE	Cholinesterase Deficiency	*Yb8*	[128-129]
		MLVI2	Associated with leukemia	*Ya5*	[128-129]
		APC	Hereditary Desmoid Disease	*Yb8*	[128-129]
		P5N1	Chronic Hemolytic Anemia	*Ya5*	[128-129]
		EYA1	Branchio-oto-renal Syndrome	*Y*	[128-129]
		LPL	Lipoprotein Lipase Deficiency	*Yb9*	[128-129]
		POMT1	Walker Warburg Syndrome	*Ya5*	[128-129]
		TNFRSF6	Autoimmune Lymphoproliferative Syndrome	*Yb8*	[128-129]
		C1NH	Complement Deficiency	*Yc1*	[128-129]
		AIP	Acute Intermittent Porphyria	*Ya5*	[128-129]
		BRCA1	Breast Cancer	*Ya5*	[128-129]
		GNPTAB	Mucolipidosis	*Y*	[134]
		BRCA2	Breast Cancer	*Ya5, Yc1, Y*	[135]
		PMM2	Congenital Disorder of Glycosylation Type I	*Yb8*	[136]
		CHD7	Charge Syndrome		[137]

Transposons involved	Copy number	Gene	Disorders reported in humans	Element	References
		ZEB2	Muckle–Wells Syndrome		[138]
LINES	500000	Factor VIII	Hemophilia A	*L1*	[138]
L1		APC	FAP	*L1*	[139]
		Dystrophin	Muscular Dystrophy	*L1*	[140]
		Globin (HBB)	Beta Thalassemia	*L1*	[138]
		RP2	X-linked Retinitis Pigmentosis	*L1*	[138]
		DMD	X-linked Duchenne Muscular Dystrophy	*L1*	[138][141]
		Fukutin	Cyctic Fibrosis	*L1*	[142]
		Factor IX	Hemophilia B	*L1*	[138]
		CHM	Choroideremia	*L1*	[138]
		CYBB	Chronic Granulomatous Disease	*L1*	[138]
		RPS6KA3	Coffin–Lowry syndrome	*L1*	[138]
		APC	Colon Cancer	*L1*	[138]
		FKTN	Fukuyama-type Congenital Muscular Dystrophy	*L1*	[138]
		PDHX	Pyruvate Dehydrogenase Complex Deficiency	*L1*	[143]
SVA	~3,000	Fukutin-FKTN	Fukuyama-type Congenital Muscular Dystrophy		[138]
		BTK	X-linked Agammaglobulinemia		[140][138]
		LDLRAP	Autosomal Recessive Hypercholesterolemia		[138]
		SPTA	Hereditary Elliptocytosis and Hereditary Pyropoikilocytosis		[138]
HERVs	200000	AZFa (Azoospermia Factor A)	Male Infertility	*HERV15*	[144-145]

Hsmar2 DNA transposons is related with hotspots for homologous recombination connected with human genetic disorders like Charcot–Marie–Tooth, Prader-Willi/Angelman, and Williams syndromes [17,146,147].

The other human diseases which are caused by various categories of transposons through insertional mutagenesis of retrotransposons and recombination in genes are listed in the Table 1.

2. CONCLUSION AND RECOMMENDATIONS

To conclude the transposon insertions can lead to various human genetic disorders and signify that there's a great deal to a genome than genes. Incidentally, medical therapeutics comprehending the core progressions of transposons producing human diseases could facilitate their forestalling and alleviation, like in multiple sclerosis a novel salutary approach involves targeting of the MSRV-ENV (Human Endogenous Retroviral protein) with a copious humanized monoclonal antibody [5,148]. Again HERVs signatures linked with definite cancers, along with epigenetic signatures are promising bio-indicators which are being deciphered and data based as a means for assessing, cancer risk, premature cancer detection, treatment scrutinization and prediction in the future. This can be applicable to other human syndromes involving HERVs and epimutation signatures [129,130,18]. The somatic retrotransposition high frequency elucidates why such as homozygote twins may possibly have cacophonous conducts and/or syndrome effects, and can explicate the omitted heritability dilemma for several ailments including the psychiatric and neurological disorders. Markedly, the “JUNK” of yesterday is stepping into the glare of publicity and is proving as “Just Unrevealed New-fangled Know-how” of tomorrow hidden in our genomes which may be involved in some phenotypic variations and human-specific traits as well and holds the promise in personalized medicine.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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