THE ROLE OF TRANSPOSABLE ELEMENTS IN THE ASSOCIATION OF POLYMORPHIC VARIANTS WITH MULTIFACTORIAL DISEASES

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Abstract. Molecular genetic studies make it possible to determine associations of multifactorial diseases (MFDs) with many specific SNPs, which influence on MFDs etiopathogenesis is often difficult to explain. This is due to the one-sided focus of strategies in the search for mechanisms of these SNPs influence, which are mainly limited to determining the role of protein-coding genes, near or within which these polymorphisms are located. This article provides data on the mechanisms of SNP influence on MFDs etiopathogenesis due to changes in the transposable elements, which leads to their activation, dysfunction or susceptibility to exogenous viral infections. As a result, the relationship of transposable elements with specific proteins, non-coding RNA and epigenetic factors changes, which is a predisposing factor for MFDs development. Indeed, most disease-associated SNPs are located in intronic and regulatory regions of genes, and in intergenic regions. Transposable elements of the human genome are also localized in these places. Therefore, the association of specific SNPs with certain MFDs is due to the different activities of specific transposable elements. Determining the influence of SNPs on transposable elements is promising in bioinformatics studies with the construction of maps of the distribution of these elements in the genome within genes and in intergenic regions with the identification of changes in their structure under the influence of polymorphisms. Using neurodegenerative diseases as an example, it has been shown that pathological functioning and activation of retroelements due to SNPs in the regions of their location in the human genome leads to these MFDs development.

Keywords: associations, multifactorial diseases, single nucleotide polymorphisms, retroelements, transposable elements, targeted therapy.

List of Abbreviations

GWAS – genome-wide association study
lncRNAs – long noncoding RNAs
MFD – multifactorial diseases
ncRNAs – noncoding RNAs
SNP – single nucleotide polymorphism
TE – transposable element

Introduction

All hereditary human diseases can be divided into three large groups: chromosomal syndromes (caused by genomic and chromosomal mutations), monogenic diseases (caused by pathogenic gene mutations) and multifactorial diseases (MFDs) (formed as a result of genetic predisposition due to changes in many genes (mainly single nucleotide polymorphisms - SNP) under the influence of environmental factors). Most hereditary diseases are MFDs, and studies such as genome-wide association studies (GWAS) are conducted to determine the role of specific genetic changes in their development. According to the results obtained, the distribution of SNPs associated with different MDs across the human genome varies greatly. However, most of these SNPs are located outside the coding regions, that is, between genes, in introns and regulatory regions (Yong *et al*., 2020). In this regard, the influence of the main part of SNPs on the development of MFDs is difficult, since even when located in promoters, they do not always disrupt gene expression, and when localized in introns, they are often not the cause of the formation of an alternative splicing variant of the mature transcript. However, the detection of a reliable association with MFDs indicates the existence of mechanisms for the influence of these SNPs on the disease's development (Yong *et al*., 2020). Such mechanisms may be due to changes in the nucleotide sequences of transposable elements (TEs) of the human genome, which are located mainly in non-coding regions and introns and occupy almost half of all DNA sequences. As a result of the disruption of TEs functioning, there is an effect on the expression of protein-coding genes in various ways, including through interaction with non-coding RNAs (ncRNAs) (Fig. 1). Of the 3 billion bp of the haploid human genome, TEs account for 1.4 billion bp. (Nurk *et al*.,

2022). Moreover, TE-derived ncRNA sequences (including microRNA and long non-coding RNA (lncRNA) genes) (Park *et al*., 2022) occupy a large part of the human genome. In addition to 19,969 annotated protein-coding genes, 7,565 small non-coding RNA genes (mainly miRNAs) and 20,424 lncRNA genes are known (Nurk *et al*., 2022). Therefore, as early as 2011, the identification of specific oligonucleotides corresponding to human TEs made it possible to determine that more than 2/3 of the human genome consists of TEs sequences and repeats derived from them (de Koning *et al*., 2011). These sequences are distributed in non-coding, intronic and regulatory regions, where most SNPs associated with multifactorial diseases are localized (Yong *et al*., 2020).

The effect of polymorphism-induced TEs on the development of MFDs may be related not only to the effect on ncRNAs, but also to the direct involvement of TEs in the epigenetic regulation of the human genome (Mustafin & Khusnutdinova, 2018). Changes in nucleotide sequences of TEs can have a global impact on the functioning of the body, leading to the development of systemic pathology in MFDs (Fig. 2). This is due to the fact that TEs serve as cis-regulatory elements (promoters, enhancers, and silencers of protein-coding genes (Lawson *et al*., 2023)), splicing modifiers (Drongits *et al*., 2019), insulators (regulatory elements of chromatin organization) (Park *et al*., 2022), and binding sites for transcription factors in regulatory regions of genes (Ito *et al*., 2017). In addition, pathological activation of TEs leads to their direct somatic transpositions with disruption of the functions of the genes near or within which they are inserted. The role of such transpositions in the development of such MFDs as neurodegenerative and mental illnesses (Abrusan, 2012), as well as sporadic cancer (in which activated TEs also cause recombinations and genomic instability) has been shown (Chenais, 2022)). In addition to the described mechanisms of influence of pathologically activated TEs in the development of multifactorial diseases, the effect may be associated with the induction of immune responses, especially in autoimmune diseases (Mustafin, 2022) and aging-associated diseases. This is associated with the role of progressive derepression of TEs in the development of physiological aging (Gorbunova *et al*., 2021), in which transposon expression products induce interferon production and inflammatory processes in organs and tissues (de Cecco *et al*., 2019). In addition, the mutual regulation of various TEs by influencing the ncRNAs that evolved from them (Park *et al*., 2022) in the mechanisms of RNA-directed DNA mathylation (Watcharanurak & Mutirangura) may affect immune responses. This is related to the origin of the V(D)J recombination system of the immune system of humans and other mammals in evolution through the domestication of RAG DNA-transposon genes (Lescale & Deriano, 2016). Transpositions to genes involved in immune system function lead to efficient production of a wide variety of antibodies (Lapp & Hunter, 2016).

An example of the influence of a polymorphism located in the TE gene on the development of the disease is a change in the functioning of the ORF1p LINE1 translation product, which is capable of forming cytoplasmic aggregates and is similar to RNA-binding proteins involved in neurodegeneration. Changes in specific amino acids in the ORF1p protein affect the efficiency of retrotransposition and the dynamics of protein aggregation. Proteins that play a key role in the development of ALS are co-localized with ORFp-LINE1 RNP particles in cytoplasmic RNA granules. Accordingly, ALS-associated polymorphisms in the intergenic and intronic regions where REs are localized may have a similar effect, enhancing the ability of REs expression products to form TDP-43 aggregates (Pereira et *al*., 2018). Another example is the multiple sclerosis-associated polymorphism rs1414273, located in intron 1 of the *CD58* gene, which is reflected in the disruption of processing of the miR-348ac microRNA encoded in this intron, which occurred during evolution from the Made1 transposon. The rs1414273 polymorphism is located at the base of the miR-348ac stem-loop and is in strong linkage disequilibrium with a haplotype associated with multiple sclerosis. As a re-

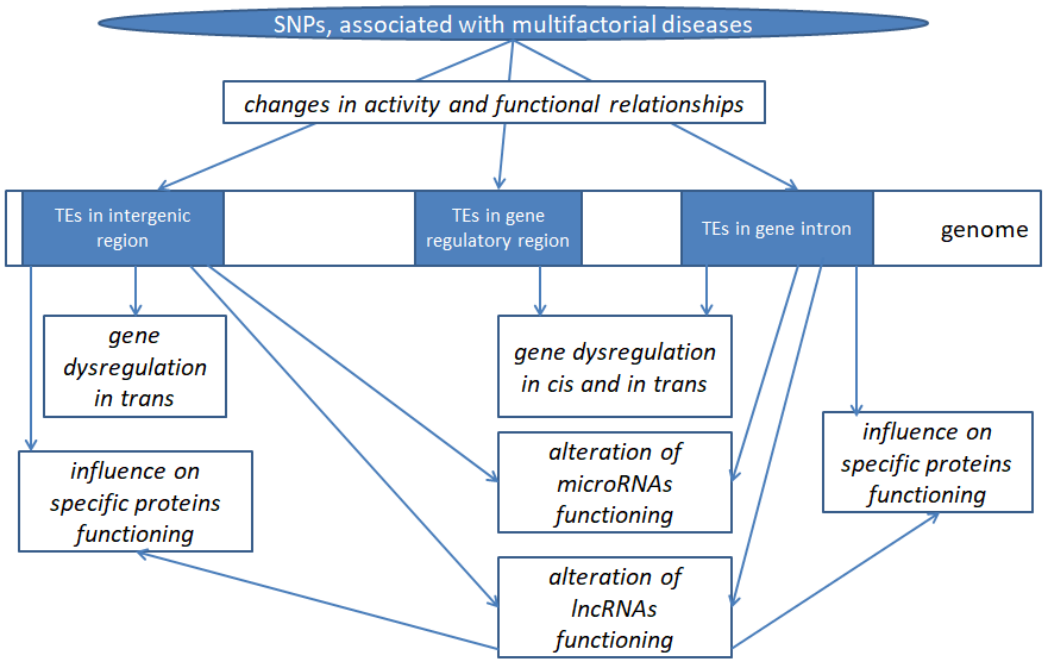

Fig. 1. Scheme of the influence of transposable elements (TEs) on gene expression under the influence of SNPs associated with multifactorial diseases located in intergenic, regulatory and intronic regions

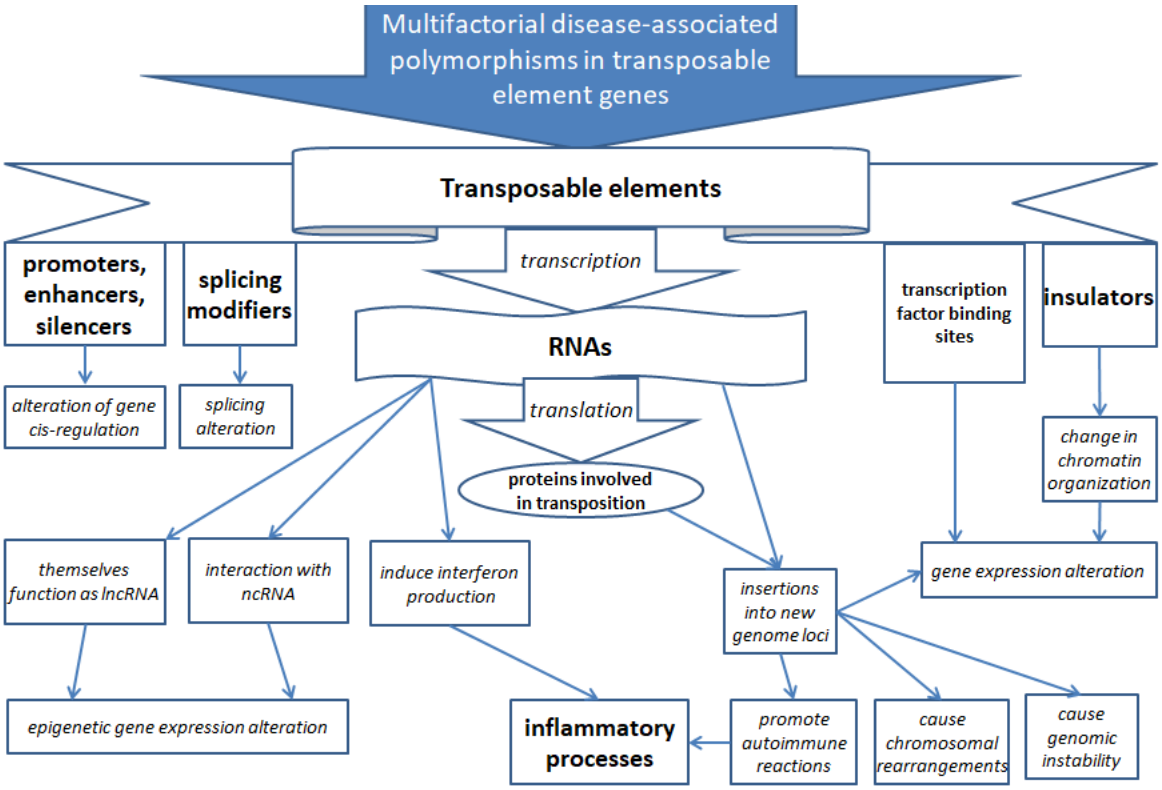

Fig. 2. Global regulatory effects of transposable element changes under the influence of polymorphisms associated with multifactorial diseases

sult, this SNP affects the recognition of the primary hairpin microRNA by the enzyme Drosha and its cofactor DGCR8 (Hecker et *al*., 2015).

It is also necessary to take into account individual (Kojima *et al*., 2023) and population (Shin *et al*., 2013, Rishishwar *et al*., 2015, Rishishwar

et al., 2018) features of the distribution of TEs in human genomes, which can influence the development of MFDs due to the different influence of SNPs associated with these diseases (Yong et al., 2020) located in the loci of TEs location (Nurk *et al*., 2022). It is necessary to analyze in more detail the mechanisms of influence of changes in TEs activity as a result of the impact of polymorphisms on them in MFDs on changes in epigenetic regulation of genes.

The relationship between transposable elements and epigenetic factors in the development of multifactorial diseases

Analysis of the origin of ncRNAs from TEs revealed that in the human genome at least 404 microRNAs originated from TEs, and 75% of all lncRNA transcripts contain exonized TEs (Park *et al*., 2022). Moreover, it was found that TEs regulate human development directly through their transcripts, which themselves function as lncRNAs. This phenomenon was found in LINE1 retroelements (Honson & Macfarlan, 2018) and LTR-containing retroelements (Lu *et al*., 2014). TEs also play an important role in regulating the function of most lncRNAs, as they are located not only in their exons but also in their introns and promoter regions (Johnson & Guigo, 2014). Therefore, changes in TEs activity under the influence of MFDs-associated polymorphisms may influence disease development by disrupting interactions with their derived ncRNAs. As a result, this is reflected in epigenetic regulation, since lncRNAs affect histone modification and DNA methylation in relation to gene expression (Johnson & Guigo, 2014), and microRNAs exert post-transcriptional silencing due to complementary binding to mRNA, and also act as guides for methylation of specific genes in the mechanism of RNA-directed DNA methylation (Watcharanurak & Mutirangura).

Pathological activation of TEs in multifactorial diseases may influence the expression of their derived miRNAs in several ways. Firstly, activated TEs act as “sponges” for miRNAs by complementary binding to nucleotide sequences due to their evolutionary relationship. This blocks the effect of RNA interference on the mRNA of the target genes of these microRNAs (Cornec & Poirier, 2023). The translation products of TEs act as competitive endogenous RNAs. The name refers to the fact that these RNA molecules compete for binding to the same mRNA targets that miRNAs target. Genes containing target sites for both miRNAs and LINE1 transcripts were found to be overexpressed, supporting the role of LINE1s as sources of competitive endogenous RNAs (Esposito *et al.*, 2022). Secondly, some miRNAs are formed directly from TEs genes, which are the basis for pre-miRNA hairpin structures. Such miRNAs lead to spatiotemporal dynamic expression networks, for the analysis of which the Brain miRTExplorer web application was created (Playfoot & Adams, 2022). Therefore, pathological activation of TEs leads to the formation of various microRNAs from their transcripts, which affect the regulatory networks of other microRNAs in the body. Third, TEs have a regulatory effect on microRNAs by forming small interfering RNAs (siRNAs) from their transcripts. Moreover, siRNAs are competitive molecules for binding to mRNA targets for microRNAs, neutralizing their impact on gene expression. This effect is associated with the host cell defense systems against activated TEs in their genomes and triggers the degradation of TE transcripts by ribonucleases to miRNAs. The latter exert post-transcriptional inhibition of mRNA genes due to partial complementarity (McCue *et al*., 2013).

Fourthly, one of the ways in which microRNAs interact with TEs in regulating gene activity is also the suppression of their expression when microRNAs bind to specific DNA structures formed due to TEs embedded in these regions. In the human genome, Z-form DNA is produced by endogenous retroviruses that provide functional genes with alternative promoters (Lee *et al*., 2022). In addition, the phenomenon of RNA-directed DNA methylation (RdDM) has been described in humans, due to which microRNAs (Playfoot *et al*., 2022) and miRNAs (McCue *et al*., 2013) formed from TEs transcripts can affect the expression of TEs through complementary interactions of sequences in the genome structure (Chalertpet *et*

al., 2019). The fact that MFDs-associated polymorphisms located in TEs loci affect the expression of TEs-derived microRNAs is confirmed by articles published in the scientific literature. They describe associations with atherosclerosis (Mustafin, 2024a), Alzheimer's disease (Mustafin & Khusnutdinova, 2024), osteoarthritis (Mustafin, 2024b), malignant neoplasms (Mustafin, 2022a) and autoimmune diseases (Mustafin, 2022b). It should be noted that the risk of the listed MFDs, including autoimmune diseases (Zheng et al., 2023), increases with age. This is due to the inducing effect of aging mechanisms in deregulation with hyperactivation of TEs (De Cecco *et al.*, 2019; Gorbunova *et al*., 2021) in the development of these diseases. Predisposition factors are detectable SNPs associated with MFDs and located mainly in intergenic, regulatory and intronic regions (Yong *et al*., 2020), where most TEs are localized (Nurk *et al*., 2022). Viruses that can activate TEs expression and the pathology of molecular mechanisms involved in the development of MFDs also have an inducing effect. The most striking example of such effects are neurodegenerative diseases.

Molecular mechanisms of viral induction of transposable elements MFDs dysregulation in neurodegenerative diseases

Like most other MFDs, neurodegenerative diseases are also associated with age, including Alzheimer's disease (occurring in 5% of people regardless of age and in 22.5% of those aged 85 and older) (Niu *et al*., 2017). Parkinson's disease is found in 0.85% of the general population (Ding *et al*., 2022) and in 1.7% of people aged 80–84 years (Klokkaris & Migdalska-Richards 2024). The prevalence of amyotrophic lateral sclerosis is 4.42 per 100,000 population and increases with age (Xu *et al*., 2020). The incidence of frontotemporal degeneration in Europe averages 2.36 per 100,000, with a significant increase with age. The peak incidence is at age 71 (13.09 per 100,000 for men and 7.88 per 100,000 for women) (Logroscino *et al*., 2023). The pathogenesis of Alzheimer's disease consists of extracellular deposition of fibrils consisting of β-amyloid peptides in the form of senile plaques and intracellular accumulation of hyperphosphorylated tau protein in the form of neurofibrillary tangles (Ando *et al*., 2022). The pathogenesis of Parkinson's disease is caused by the degeneration of dopaminergic neurons of the brain substantia nigra under influence of the accumulation of alpha-synuclein in these cells, which forms aggregates in the form of Lewy bodies (Leblanc & Vorberg, 2022). All patients with amyotrophic lateral sclerosis are characterized by the accumulation of protein aggregates of the TDP-43 protein in neurons of the central nervous system, leading to progressive neurodegeneration. Clinically, the disease is characterized by progressive death of upper and lower motor neurons with widespread atrophy of skeletal muscles (Bennett *et al*., 2019). Proteinopathy of the FUS protein is also specific for amyotrophic lateral sclerosis (Shelkovikova *et al*., 2019). Frontotemporal degeneration develops due to the accumulation and misfolding of three proteins TDP-43 (DNA-binding protein TAR 43), FUS (fused in sarvoma protein) and microtubule-associated protein Tau, with the formation of pathological intracellular aggregates from them. (Rahmani *et al*., 2022).

According to a number of molecular genetic studies and GWAS, similar to other MFDs (Yong *et al*., 2020), neurodegenerative diseases are also associated with numerous SNPs, most of which are located in intergenic, intronic and regulatory regions where TEs are localized. This characteristic has been identified for Alzheimer's disease (GNS *et al*., 2021), Parkinson's disease (Kim *et al.,* 2024), amyotrophic lateral sclerosis (van Rheenen *et al*., 2021), and frontotemporal degeneration (Pottier et *al*., 2024). Therefore, polymorphisms associated with these diseases may cause changes in the expression and function of TEs, which are capable of interacting with beta-amyloid, tau protein (Grundman *et al.*, 2021), alpha-synuclein (Gordevicius *et al*., 2023) and TDP-43 (Liu *et al.*, 2023). In addition to aging and polymorphisms in TEs genes, inducing factors may also include viruses, which, like TEs expression products, are capable of interacting with beta-amyloid, tau protein, alpha-synuclein, and TDP-43, causing their aggregation. At the same time, the

listed proteins are characterized by antiviral activity, inhibiting specific viruses. The most typical data interactions with herpes viruses. For example, under the influence of HHV-6, there is an increase in the expression of β-amyloid and tau (with an increased percentage of its phosphorylated forms) in human microglial cells (Bortolotti *et al*., 2019). In HSV-1-infected hippocampal neurons, tau has been shown to act as an danger-associated molecular pattern (Powell-Doherty *et al*., 2020). The role of herpes viruses in the pathogenesis of Parkinson's disease has been determined (Leblanc & Vorberg, 2022).

The inducing role of HIV and influenza viruses in relation to antiviral proteins involved in the pathogenesis of neurodegenerative diseases has been revealed. Despite adequate antiretroviral therapy, HIV-infected individuals can constantly produce the HIV-Tat protein (transactivator of transcription), which promotes phosphorylation of tau through a cascade of cellular processes leading to the formation of neurofibrillary tangles characteristic of Alzheimer's disease (Hategan *et al*., 2019). HIV-Tat also interacts with beta-amyloid, causing the formation of double-twisted fibrils with subsequent formation of thick unstructured strands and aggregates of homogeneous amyloid fibrils in the brain of HIV-infected people (Hategan *et al*., 2017). HIV promotes the accumulation of alpha-synuclein in neurons, which explains the development of cognitive and motor disorders in HIV-infected patients, among whom the frequency of SNCA/alpha-synuclein staining is higher than in healthy people of the same age (Santerre *et al*., 2021). Direct antiviral activity of the TDP-43 protein against HIV (Cabrera-Rodriguez *et al*., 2023) and influenza A virus has been identified (Dupont *et al*., 2024). The ability of beta-amyloid to inhibit the influenza A virus has also been determined (White *et al*., 2014).

The same viruses that are characterized by association with neurodegenerative diseases and the ability to induce the production and aggregation of antiviral proteins beta-amyloid, tau, alpha-synuclein and TDP-43 protein are also activators of TEs expression. This ability has been identified for HIV (Dopkins *et al*., 2024), influenza A virus (Wang *et al*., 2021), herpes viruses (Bello-Morales *et al*., 2021). Accordingly, it can be assumed that under the influence of specific viral infections caused by herpes viruses, HIV, and influenza viruses, there is an increase in the production of antiviral proteins involved in the pathogenesis of neurodegenerative diseases, as well as an increase in the expression of TEs. In people with a hereditary predisposition (due to the presence of polymorphisms in the intergenic and intronic regions where the TEs genes are located), such induction by viruses can cause the progression of the pathology, since the expression products of activated TEs, like viruses, also interact with beta-amyloid, tau, alpha-synuclein and the TDP-43 protein, causing their aggregation. Normally, these proteins are inhibitors of TEs expression (Grundman *et al*., 2021; Ramirez *et al*., 2022; Guo *et al.*, 2018; Gordevicius *et al*., 2023; Tam *et al*., 2019), which is associated with their antiviral activity (Bortolotti *et al*., 2019; Cabrera-Rodriguez *et al*., 2023; Dupont *et al*., 2024; Hategan *et al*., 2017; Hategan *et al*., 2019; Powell-Doherty *et al*., 2020; Santerre *et al*., 2021; White *et al*., 2014). However, under the influence of pathologically activated TEs, the resulting aggregates of these proteins (Gordevicius *et al*., 2023; Grundman *et al*., 2021; Guo *et al.*, 2018; Ramirez *et al*., 2022; Tam *et al*., 2019) are not capable of this and contribute to the derepression of TEs. As a result, a “vicious circle” develops, in which the progression of the pathology is associated with the fact that accumulated aggregates of beta-amyloid, tau, alpha-synuclein and TDP-43 protein cause derepression of TEs, and the products of TEs expression stimulate the production of these antiviral proteins and aggregation (Grundman *et al*., 2021; Ramirez *et al*., 2022; Guo *et al.*, 2018; Gordevicius *et al*., 2023; Tam *et al*., 2019). An additional inducing mechanism is aging, which is associated with neurodegenerative diseases (Niu *et al*., 2017; Klokkaris *et al*., 2024; Xu *et al*., 2020; Logroscino *et al*., 2023), which is associated with pathological activation of TEs during aging (De Cecco *et al*., 2019).

It can be assumed that the presented mechanisms of development of neurodegenerative diseases are an example of the influence of polymorphisms associated with MFDs on the development of pathology when induced by such factors as aging and viral infections. Research in this direction is promising due to the possibility of using methods to inhibit the pathological activity of TEs and the use of specific antiviral drugs in the treatment of MFDs. Thus, in multiple sclerosis, in the etiopathogenesis of which the role of herpes viruses (Khalesi *et al*., 2023) and TEs (HERVs) (van Horssen *et al*., 2016) and their mutual potentiation (Cossu *et al*., 2023; Perez-Perez *et al*., 2022) has been proven, the method of inhibiting HERV using the monoclonal antibody temelimab, directed against Env HERV-W, has shown its effectiveness (Derfuss *et al*., 2015; Porchet *et al*., 2019). Chromatin remodeling drugs – remodelin (an inhibitor of the enzyme N-acetyltransferase 10) (Balmus *et al*., 2018), antiretroviral therapy (Li & Pandya, 2022), antibodies against the HERV-K Env protein (Steiner *et al*., 2022) and antiviral drugs that inhibit prion-like protein spread by targeting HERV proteins have also been proposed for the treatment of amyotrophic lateral sclerosis (Liu *et al*., 2023) Since the regular activation of TEs occurs during physiological development, since TEs are the basis for epigenetic regulation of ontogenesis (Mustafin & Khusnutdinova, 2018), it is most appropriate to inhibit only those TEs whose pathological activation is involved in the development of MFDs. In this regard, targeted therapy is possible using TEs-derived microRNAs as tools, which are fully complementary to them and are capable of specifically inhibiting their expression. Previously published data on changes in the expression of such microRNAs in atherosclerosis (Mustafin, 2024a), Alzheimer's disease (Mustafin & Khusnutdinova, 2024), osteoarthritis (Mustafin, 2024b), malignancies (Mustafin, 2022a) and autoimmune diseases (Mustafin, 2022b) can form the basis for such an approach.

Conclusion

Multifactorial diseases are characterized by hereditary predisposition (which is reflected in associations of specific polymorphisms with these diseases, with population characteristics) and manifestation under the influence of environmental factors (including viruses) and aging. The key players in the interactions of these factors are TEs, which make up at least half of all nucleotide sequences in the human genome. The role of TEs in these processes is due to the fact that MFDs-associated polymorphisms are located mainly in TEs genes, affecting their activation and functioning. TEs are characterized by global regulatory influence on the expression of various genes both through in cis and in trans influences and through interactions with epigenetic factors, since many lncRNAs and microRNAs are derived from TEs. Accordingly, polymorphisms in TEs genes are reflected in changes in the expression of genes involved in MFDs pathogenesis. Additional factors are population features of TEs distribution in genomes, which is reflected in population features of SNP associations with multifactorial diseases. Aging and viruses are factors activating transposable elements. This may explain the association of a significant proportion of MFDs with aging, as well as the inducing effect of viruses on the development of MFDs. Using neurodegenerative diseases as an example, the key role of TEs in the mechanisms of development of this group of MFDs has been demonstrated: under the inducing influence of aging and viruses, TEs are activated, which cause the aggregation of antiviral proteins and stimulate the expression of their genes. As a result, a «vicious circle» is formed, the impact on which by inhibitors of transposable elements can become an effective method of pathogenetic treatment. Similar mechanisms may underlie other MFDs, as they have been shown to be induced by aging and viral infections, and literature review has shown a role for TEs and their derived microRNAs. Therefore, a promising method for studying MFDs is to create bioinformatic maps of genome analysis data on the exact distribution of TEs genes in the human genome relative to protein-coding genes and ncRNAs genes. The use of such bioinformatic maps will help to identify the localization of disease-associated polymorphisms in the genes of specific TEs and predict their impact on epigenetic regulation (as this may affect the interaction with ncRNAs or the formation of ncRNAs from TEs transcripts).

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