THE INFLUENCE OF GENES, miRNAs AND RETROELEMENTS ON PSYCHOLOGICAL WELL-BEING

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Abstract. The heritability of human psychological well-being ranges from 36 to 48%. GWAS conducted between 2016 and 2019 identified 364 SNPs significant for well-being. A significant association with psychological well-being has been shown for the *APOE, OXTR, OXT, NMUR2, CNR1, CRHR1*, and *CYP19A1* genes. The greatest influence on psychological well-being is exerted by allelic variants of the *MAYA, 5-HTT, COMT* genes, and the *CTRA* gene group (conservative transcriptional response to adversity). Brain functioning is influenced by the peculiarities of VNTR distribution in the regulatory regions of the *5-HTT, SLC6A3, AVPR1A, FUS, OXT, PARK7, POMC, TACR3, TRPV1* and *TRPV3* genes. These features are due to the individual distribution of SVA (SINE-VNTR-Alu) retroelements, which belong to transposons that are drivers of epigenetic regulation. Features of activation of retroelements located in the regulatory regions of genes may affect the individual level of well-being. This is evidenced by the association with psychological well-being of *DRD4, MAOA, SLC6A3, 5-HTT* genes alleles, determined by the length of VNTR in their regulatory regions. Evidence of retroelements role in well-being regulation is that retroelements are sources of protein-coding genes and microRNAs involved in brain functioning. The Arc gene, derived from retroelements, is characterized by transport into neuronal dendrites with translation regulation. We analyzed the MDTE DB database on transposon-derived microRNAs and scientific literature. According to the results, 12 miRNAs, derived from transposons, are associated with major depressive disorder. The data obtained indicate the influence of transposons on psychological well-being, which is assessed by the absence of depression.

Keywords: genes, depression, long non-coding RNAs, microRNAs, heritability, psychological well-being, transposons.

List of Abbreviations

ERV – endogenous retrovirus
HERV – human endogenous retrovirus
LINE – long interspersed elements
LTR – long terminal repeats
lncRNA – long noncoding RNA
MDD – major depressive disorder
MDTE DB – microRNAs derived from transposable elements database
miR – microRNA
PWB - psychological well-being
REs – retroelement
SINE – short interspersed elements
SVA – SINE-VNTR-Alu
TE – transposable elements
TSS – transcriptional start site
UTR – untranslated region

Introduction

Psychological well-being (PWB) refers to positive cognitive and emotional assessments of a person's life, as well as their experience of self-realization and social relationships (Liu *et al.*, 2017). According to Martin Seligman's theory, PWB is not just the absence of negative emotions, but also the presence of positive emotions, engagement, relationships, meaning and cchievement, which in the abbreviation means PERMA (Seligman, 2012). The term "happiness" is also used as a synonym for PWB (van de Weijer *et al.*, 2022). Subjective PWB includes cognitive assessment of life satisfaction and emotional state (Jorm & Ryan, 2014). Therefore, to determine subjective PWB, self-assessment of life satisfaction is measured on a discrete scale from 0 to 10 (Bretoni & Corazzini, 2018). In addition, negative criteria such as depression and anxiety can be used to evaluate PWB (Bradley & Gamsu, 1994). Certain domains of life satisfaction have the greatest impact on PWB and health. This is evidenced, in particular, by a study conducted in 2022 on 13,752 people over the age of 50. Such domains include family satisfaction and non-

work activities, followed by financial satisfaction (Nakamura *et al.*, 2022).

In 2005, in a study of 5,668 twins from the Netherlands, the heritability of life satisfaction was 38% regardless of gender (Stubbe *et al.*, 2005). In 2010, a comparative study of 349 monozygotic and 321 dizygotic twin pairs showed 72% heritability of PWB (Keyes *et al.*, 2010). In 2015, a meta-analysis of 13 scientific papers on 30,000 twins (12 – 88 years old) from 7 countries found that genetic factors are responsible for 40% of the differences in subjective PWB indicators (Nes & Roysamb, 2015). A meta-analysis conducted in the same year on 55974 twin pairs showed the heritability of PWB in 36% (Bartels, 2015). In 2022, the results of a longitudinal 10-year study of 1,669 adult Australian twins of European origin showed the heritability of PWB total COMPAS-W at 48% (Park *et al.*, 2022).

The scales of subjective well-being diagnostics are used to evaluate PWB. Back in 1985, Diener *et al.* reported on the developed Satisfaction With Life Scale – SWLS (Diener *et al.*, 1985). In 1988, Watson *et al.* we have developed the Positive and Negative Affect Schedule - PANAS (Watson *et al.*, 1988). In 2013, Pontin *et al.* created the modified BBC subjective well-being scale (Pontin *et al.*, 2013). In 2016, Kjell *et al.* published the harmony in life scale complements the satisfaction with life scale: expanding the conceptualization of the Cognitive Component of Subjective Well-Being (Kjell *et al.*, 2016).

The influence of genes on psychological well-being

In 2013, a comprehensive analysis of GTA genome traits was conducted, with an assessment of the relationship between identical SNPs and PWB. 11,500 residents of Denmark and Sweden were studied, as a result, the additive effect of polymorphisms explaining the variance of subjective well–being was 5-10% (Rietveld *et al.*, 2013). Based on GWAS conducted in 2016 on 298,420 healthy people, associations with PWB of the following genetic variants were found: 3 SNPs (rs3756290 (*RAPGEF6* gene, encodes Rap guanine nucleotide exchange factor 6), rs2075677 (*CSE1L* – human homologue of the yeast chromosome segregation gene), rs4958581 (*NMUR2* – neuromidin U receptor 2) (Okbay *et al.*, 2016). In 2018, GWAS was performed on 354,462 individuals – 49 different SNPs were identified (Turley *et al.*, 2018), and the results of GWAS in 2019 on 2,370,390 healthy volunteers showed 304 significant SNPs (this increased the predictive ability to assess the effect of genes on PWB by 57%) associated with PWB (Baselmans *et al.*, 2019). The issue of whether hedonism and eudaimonia are two different forms of PWB is also a matter of debate (Baselmans & Bartels, 2018). In 2018, a GWAS of eudaemonic PWB (108,000 people) and hedonic PWB (222,000 people) revealed 2 independent loci for eudaemonic PWB (rs79520962; rs7618327) and 6 for hedonic PWB (rs34841991; rs261909; rs746839; rs4239724; rs6732220; rs146213057) (Baselmans & Bartels, 2018).

In 2014, Dfarhud *et al.* showed that the genes *MAOA* (encodes monoamine oxidase-A) and *5-HTT* (polymorphic element of the serotonin transporter) have the greatest influence on the development of PWB, which indicated the relationship between *5-HTTLPR* and life satisfaction as a cognitive measure of happiness (Dfarhud *et al.*, 2014). In 2016, an analysis of DNA samples from 48 (average age 60.88 years) American residents (25 women, 23 men) showed that carriers of the Met158 allele in the *COMT* gene have lower levels of PWB at a young age compared to the elderly (Turan *et al.*, 2016). In 2017, a study of 445 healthy adults revealed that individuals with rs4680 polymorphism in the *COMT* gene have better PWB, fewer symptoms of depression, and an increased tendency to gratitude and forgiveness. The *COMT* gene is localized at 22q11 and encodes a protein involved in the degradation of the catecholamines dopamine and norepinephrine. In individuals with the Val/Val genotype, an increase in the activity of the COMT protein is determined by 40% (Liu *et al.*, 2017).

The search for associations of candidate genes showed a reliable association with psy-

chological well-being of SNP rs429358 and rs7412 in the *APOE4* gene (Martin *et al.*, 2014), rs2254298 and rs53576 in the *OXTR* gene (encodes the oxytocin receptor) (Lucht *et al.*, 2009), rs4813625 in the *OXT* gene (oxytocin) (Love *et al.*, 2012), rs4680 in the *COMT* gene (catechol-O-methyltransferase) (Jimenez *et al.*, 2017; Liu *et al.*, 2017), rs4958581 in the *NMUR2* gene (neuromidin U receptor 2) (Lachmann *et al.*, 2020), rs806377 in the *CNR1* gene (cannabinoid receptor 1) (Matsunaga *et al.*, 2014), rs878886 in the *CRHR1* gene (corticoliberin receptor) (Sleijpen *et al.*, 2017), rs700518 in the *CYP19A1* gene (cytochrome P450) (Yang *et al.*, 2017).

Research in the field of human social genomics has revealed preserved transcriptional response to adversity (*CTRA*), which is characterized by increased expression of pro-inflammatory genes (*IL1B, IL8, PTGS2, TNF*), as well as reduced expression of genes involved in the interferon-I response (*IFI, ISG, MX, OAS*) and antibody synthesis (*IGJ*) (Fredrickson *et al.*, 2015). In 2013, blood samples from 80 healthy North Carolinians (60% women) were analyzed. In people with high levels of hedonic PWB, increased expression of proinflammatory *CTRA* genes and decreased expression of those involved in the synthesis of IFN and antibodies were determined (Fredrickson *et al.*, 2013). A 2015 a study of 122 healthy adults found a significant inverse relationship between the expression of *CTRA* indicator genes and the total measure of eudaimonic PWB (Fredrickson *et al.*, 2015). In the same year, DNA samples from 108 elderly people from America were studied. *CTRA* gene expression was increased during loneliness and suppressed during eudaimonic PWB (Cole *et al.*, 2015). In 2020, the results of a PWB study of 152 healthy adults from Korea (average age 44.64 years, 50% women) using the MHC-SF (Mental Health Continuum short form), PWB (Ryff Scales of Psychological Well-being), SWB (subjective well-being) scale were published. The expression of *CTRA* genes decreased significantly in eudaimonia in accordance with the MHC-SF and PWB scores (Lee S.H. *et al.*, 2020).

Influence of VNTR of individual genes on psychological well-being

The effect of gene-environment interactions is important in the realization of genetic predisposition for PWB. Such interactions are mediated by epigenetic factors (which include DNA methylation, histone modifications, and non-coding RNA effects) that cause changes in the expression of specific genes. Transposable elements (TEs) are used as direct sensors transmitting information of environmental changes to the epigenetic regulation of genes. They are classified into those that moving using a cut-and-paste mechanism (DNA transposons) and copy-and-paste mechanism (retroelements – REs) (Mustafin & Khusnutdinova, 2019). In addition, TEs have a cis-regulatory effect, since they are located near or as part of protein-coding genes, forming binding sites for transcription factors (Mustafin, 2019). One of the manifestations of this phenomenon is the distribution of VNTRs in the regulatory regions of many genes, including those involved in the development and functioning of the brain. VNTRs are part of the non-autonomous retroelements SVAs (SINE-VNTR-Alus). The distribution of SVAs in the human genome is not random – they are located mainly in loci with a high GC content, mainly around gene regions. More than 60% of all SVAs are located inside genes or within 10,000 bp upstream of them (Savage *et al.*, 2013).

There are a number of *in vivo* and *in vitro* studies showing the ability of SVAs to regulate the expression of genes involved in brain functioning: the *PARK7* gene (encodes the protein deglycase DJ-1) (Savage, *et al.* 2013), *FUS* (encodes an RNA-binding protein) (Savage , *et al.* 2014), various neuropeptide genes (for example, the *AVPR1A* - arginine vasopressin 1a receptor is regulated by two VNTRs, called RS1 and RS3; the *POMC* - pro-opiomelanocortin is regulated by elements nPE1 and nPE2; the *TACR3* - tachykinin receptor 3 is regulated by SVA B; *OXT* – oxytocin – by SVA B; *TRPV1* and *TRPV3* (transient receptor pptential vation channel subfamily 5 member 1 and 3) – by SVA D (Gianfrancesco *et al.*, 2017). In the second intron of the *5-HTT* gene there is a VNTR, con-

sisting of 9–12 repeats 17 bp long. At a distance of 208 bp. upstream from the TSS (transcriptional start site) of this gene, VNTR has been identified, polymorphic variants of which are associated with anxiety in 4–5% of the world's population (Helis *et al.*, 1997). In the 3' UTR (untranslated region) of the dopamine transporter gene (*SLC6A3*) there is a VNTR, consisting of 7-11 repeats, the number of which affects the level of gene expression. With a repeat number of 10, gene transcription is significantly higher compared to 7 or 9 (Fuke *et al.*, 2001).

Human PWB is associated with VTNR features near or within specific genes that regulate brain function. The distribution of VNTRs in the genome plays a role in transcriptional regulation. For example, the activity of the *MAOA* gene promoter depends on the number of repeats in two VNTRs, consisting of 30 bp. and located at 1000 bp. upstream from the TSS and from 10 bp. at a distance of 1500 bp. The latter is rich in CpG, the methylation of which has a greater effect on the expression of the *MAOA* gene (Philibert *et al.*, 2011). In 2018, a study of 298 young German residents found a strong three-way relationship between the S allele (due to a shorter VNTR in the regulatory region) of the *5-HTT* (*5-HTTLPR* variant) gene and low levels of PWB in subjects who were exposed to stress in childhood (Gartner *et al.*, 2018). With regard to PWB, the distribution features of VNTR in the *5-HTT* gene and in the genes of the dopamine receptor *DRD4* and dopamine transporters *SLC6A3* have been well studied, polymorphic variants of which are regarded as biallelic short and long alleles, while for *MAOA* – as biallelic risk and wild alleles. Features of their distribution turned out to be associated with PWB (van de Weijer *et al.*, 2022).

In 2011, an analysis of DNA samples from 2574 American residents showed a significant association of functional polymorphism of the *5-HTT* gene with subjective PWB (De Neve, 2011). A 2012 study of 2,545 people showed a relationship between functional polymorphisms in the *5-HTT* gene and life satisfaction. Individuals with a transcriptionally more efficient variant of this genotype were found to have greater life satisfaction (De Neve *et al.*, 2012). In 2013, in 34 men and 58 women in Japan, results were obtained confirming the association of the polymorphic L-allele (a longer VNTR within the gene - Long allele) of the *5-HTT* gene with PWB (Matsunaga *et al.*, 2013). In 2018, a study of 298 German residents revealed an association of low levels of PWB with the short S allele (Short-allele) in young people and with the L allele in older people (Gartner *et al.*, 2018). In 2019, it was shown that in individuals with the S allele of the *5-HTT* gene, a higher level of PWB is determined by social support from friends (environmental factors) (Sheffer-Matan *et al.*, 2019). In 2013, in a study of 345 Caucasians (152 men and 193 women), a significant association of PWB with the *MAOA-L* allele was determined (Chen *et al.*, 2013). In 2018, a study of 867 men from Russia revealed an association of uVNTR-3R of the *MAOA* gene with low levels of PWB (Gureev *et al.*, 2018).

The role of transposable elements in brain function

One of the components of PWB is the state of memory and learning ability, for which the hippocampus is responsible, the expression of genes of which in humans differs significantly from monkeys (about 2500 genes compared to chimpanzees). It was found that these species-specific differences are due to the influence of RE-derived enhancers, mainly evolutionarily young ones, such as endogenous retroviruses (ERVs) and SVAs (Patoori *et al.*, 2022). In the dentate gyrus of the hippocampus there is a neurogenesis zone, the neuronal stem cells of which are characterized by significant activity with many insertions in their DNA that change cell phenotypes and contribute to their functional significance. Genome sequencing of individual hippocampal neurons revealed an average of 13.7 LINE-1 insertions per cell (Upton *et al.*, 2015). During differentiation, neuronal stem cells containing specific LINE-1 insertions in areas of genes important for neurogenesis create clones of cells located in strictly defined areas of the brain and performing characteristic functions (Evrony *et al.*, 2015). At the same time, the activation of REs in certain areas of the brain changes depending on environmen-

tal influences, performing adaptive functions (Lapp & Hunter, 2016), which reflects the general property of TEs (Mustafin & Khusnutdinova, 2019).

REs are characterized by similar activation mechanisms to brain genes. For example, the 5'UTR of the *NeuroD1* gene (transcription factor that controls neurogenesis genes) contains sequences similar to the LINE-1 retroelement, indicating a similar expression pattern during differentiation of neurons in the hippocampus (Thomas & Muotri, 2012). An experiment on mice showed a nervous system activation-dependent increase in LINE-1 activity and insertions. At the same time, the expression of LINE-1 in the hippocampus of adult individuals ensured the formation of long-term memory (Bachiller *et al.*, 2017). Another similar study in mice examined the role of LINE-1 in context-sensitive memory reconsolidation. The results revealed an increase in the expression of ORF1 and ORF2 mRNA in the medial prefrontal cortex during the memory of fear 24 hours and 14 days after exposure to fear (Zhang *et al.*, 2021). REs have an extremely high potential for being co-opted by host genomes to control the expression of their own genes. Thus, a 2017 analysis of the *cis*-regulatory activity of 69 subfamilies of REs using luciferase reporter assays showed the functioning of 95.6% of the tested REs as transcriptional activators or repressors. At the same time, ERVs and SVAs are included in evolutionarily new cis-regulatory elements, while REs are found in only 16% of elements conserved between species (Trizzino *et al.*, 2017).

VNTRs are part of non-autonomous retroelements specific to great apes: SVAs, LAVAs (LINE1-Alu-VNTR-Alu), PVAs (PTGR2-VNTR-Alu), FVAs (FRAM-VNTR-Alu). The organization of VNTRs within these REs is non-random - there are arrays of conservative repeat units (RU - repeat units) at the 5' and 3' ends of human, chimpanzee and orangutan SVAs and gibbon LAVAs. All 4 non-autonomous elements (SVA, LAVA, PVA, FVA) are mobilized by the LINE1 REs using an *in trans* mechanism. The expansion and decrease in size of these elements at the DNA level is mediated by a mechanism controlled by microhomology (Lupan *et al.*, 2015). Since VNTRs are able to move within the genome using enzymes of autonomous REs, the distribution and characteristics of VNTRs may depend on the individual activity of REs in the human genome.

Analysis of the distribution of SVA in the human genome showed their regulatory role in the expression of many genes (located within and within 10,000 bp upstream of genes) involved in the functioning of the brain genes (Vasieva *et al.*, 2016). The findings reflect the role of REs in regulating the functioning of the human brain. Evidence of this is the work of the authors who determined the predominance in the hippocampus (in the zone of neurogenesis) of an adult in comparison with other tissues of transpositions of LINE-1, Alu and SVA, which are programmed insertions that contribute to changes in the expression of genes for the functioning of neurons (Coufal *et al.*, 2009; Bailie *et al.*, 2011; Kurnosov *et al.*, 2015; Sultana *et al.*, 2017).

The key role of REs in the functioning of the brain is evidenced by the origin of the *Arc* gene in evolution from the LTR-containing RE Ty3/gypsy (Zhang *et al.*, 2015). The Arc protein product forms virus-like protein capsids that transfer RNA between neurons via intercellular communication mediated by specialized extracellular vesicles (Pastuzyn *et al.*, 2018). The Arc protein plays an important role in the formation of long-term memory by interacting with specific effector molecules in dendritic spines and nuclear domains, regulating synaptic strength. This effect is mediated by the connection of Arc with components of the clartry-mediated endocytosis machinery, endophilin-3 and dynamin-2 (promoting postsynaptic internalization of AMPAR glutamate receptors and recruitment of endosomes), direct interaction of Arc with presenlin, which cleaves the amyloid precursor protein (Nikolaienko *et al.*, 2018).

The relationship of transposable elements with epigenetic factors in the development of psychological well-being

Levels of depression and anxiety are used to assess PWB (Bradley & Gamsu, 1994). There

are common genes for major depressive disorder (MDD) and PWB (Gatt *et al.*, 2015). A GWAS of DNA samples from 298,420 healthy individuals with PWB and 161,460 patients with depression showed the presence of common SNPs for these phenotypes (Okbay *et al.*, 2016). Therefore, it can be assumed that there are also common epigenetic changes in the development of MDD and PWB. Their research is promising due to the possibility of using non-coding RNAs for the treatment of MDD. The intermediaries between epigenetic regulation and environmental influences are TEs, the impact of which with the help of microRNAs can be effective way to treat MDD and correct PWB. It should be noted that TEs are the most important sources of microRNA genes in evolution (Wei *et al.*, 2016), therefore, transposable elements contain sequences complementary to microRNAs, which makes it possible to use TEs as targets for effective targeted therapy. Analysis of the microRNAs derived from TEs database (MDTE DB) (Wei *et al.*, 2016) showed an association of some of these miRNAs with the development of depressive disorders.

MDD is associated with miR-1202, which originated from LINE-1. This primate-specific microRNA is expressed at a high level in the human brain with elevated levels in patients with depression. MiR-1202 inhibits the mRNA of the metabotropic glutamate receptor *DRD4* gene, affecting the response to antidepressants (Lopez *et al.*, 2014). MiR-192, which originated from LINE-2, is also associated with MDD. In the dorsolateral prefrontal cortex, miR-192 expression is significantly higher in MDD patients compared to healthy controls. *In vitro* studies have shown the role of this microRNA in synaptic plasticity and neurogenesis by regulating Fbln2/TGF-β signaling (Yoshino *et al.*, 2021). miR-320b originated from the hAT-Charlie DNA transposon, characterized by enhanced expression in MDD (Fiori *et al.*, 2021). The target of miR-320b is the mRNA of the *FOXM1* (Forkhead box protein M1) gene, which encodes a transcription factor that plays a role in the development of the cell cycle (Jingyang *et al.*, 2021).

LINE-1 is the evolutionary origin of miR-320d, which is upregulated in MDD (Liu *et al.*, 2014). The targets of miR-320d are the mRNAs of the matrix metalloproteinase genes *MMP-2, MMP-9* and neuronal cadherin *CDH2* (Qin *et al.*, 2017). LINE-2 gave rise to miR-325, a low level of which is associated with depression, as well as with transcription of the neuropeptide *CART* gene (Aschrafi *et al.*, 2016). MiR326 originated from the DNA transposon hAT-Tip100. This microRNA regulates the expression of neuropeptide *UCN1* gene in neurons of the midbrain. Low miR326 levels are detected in MDD and suicidal thoughts (Aschrafi *et al.*, 2016). From SINE/MIR derived miR-335, which regulates the expression of the metabotropic glutamate receptor gene *GRM4*. Low levels of miR-335 are associated with MDD (Li *et al.*, 2015). MiR-3664 evolved from the Tcmax-Tiger DNA transposon. MiR-3664 expression is associated with the rs7117514 allele variant of the *SHANK2* gene involved in the development of depression (Ciuculete *et al.*, 2020).

From LINE-1 came miR-450a, which is found to be at high levels in MDD. The target of this microRNA is mRNA of the epidermal growth factor gene *EGFR* (Kaadt *et al.*, 2021). LINE-1 gave rise to miR-511, the increased expression of which is characteristic of depression. The target of miR-511 is the 3'UTR of the *GFRA1-L* gene (GDNF (glial cell line-derived neurotrophic factor) family receptor alpha) (Maheu *et al.*, 2015). MiR-5695 derived from ERV1. Expression of this miRNA correlates with suicidal ideation in depression treatment. The targets of miR-5695 are the mRNAs of many genes involved in the regulation of cell proliferation, such as *SYCE2* (Synaptonemal Complex Central Element Protein 2), *ZNF136* (zinc finger protein 136), *ZNF44*, *ZNF564*, *YJU2B* (YJU2 splicing factor homolog B) (Belzeaux *et al.*, 2019). From ERVL derived miR-646, which reduces the expression of the alpha-2A adrenergic receptor gene *α2AAR*, suppressing the development of postpartum depression (Duan *et al.*, 2021). The table 1 shows our systematic data on the role of microRNAs derived from TEs in the development of MDD, which in the future can become the basis for the

Table 1

Association of transposon-derived microRNAs with major depressive disorder (MDD)

MiRNA	Transposon-source	Type of expression changes in MDD (aurtor) (↑ - increase, ↓ - decrease)	Mechanism of influence of miRNA on the development of MDD
miR-1202	LINE-1	↑ (Lopez *et al.*, 2014)	inhibits mRNA of the *GRM4* gene (Lopez *et al.*, 2014)
miR-192	LINE-2	↑ (Yoshino *et al.*, 2021)	regulates Fbln2/TGF-β signaling (Yoshino *et al.*, 2021)
miR-320b	hAT-Charlie	↑ (Fiori *et al.*, 2021)	suppress the expression of the *FOXM1* gene (Jingyang *et al.*, 2021)
miR-320d	LINE-1	↑ (Liu *et al.*, 2014)	regulates *MMP-2, MMP-9, CDH2* genes (Qin *et al.*, 2017)
miR-325	LINE-2	↑ (Aschrafi *et al.*, 2016)	inhibits CART neuropeptide production (Aschrafi *et al.*, 2016)
miR-326	hAT-Tip100	↓ (Aschrafi *et al.*, 2016)	regulates the expression of UCN1 neuropeptide (Aschrafi *et al.*, 2016)
miR-335	SINE/MIR	↓ (Li *et al.*, 2015)	inhibits the *GRM4* gene (Li *et al.*, 2015)
miR-3664	TcMar-Tigger	↑ (Ciuculete *et al.*, 2020)	regulates the expression of the *SHANK2* gene (Ciuculete *et al.*, 2020)
miR-450a	LINE-1	↑ (Kaadt *et al.*, 2021)	suppresses mRNA of the *EGFR* gene (Kaadt *et al.*, 2021)
miR-511	LINE-1	↑ (Maheu *et al.*, 2015)	inhibits the *GFRA1-L* gene (Maheu *et al.*, 2015)
miR-5695	ERV1	↑ (Belzeaux *et al.*, 2019)	regulates the expression of *SYCE2, ZNF44, ZNF564, YJU2B* genes (Belzeaux *et al.*, 2019)
miR-646	ERVL	↓ (Duan *et al.*, 2021)	inhibits the *α2AAR* gene (Duan *et al.*, 2021)

development of targeted therapy for this pathology and for improving PWB.

Long non-coding RNAs (lncRNAs) also play an important role in the regulation of brain functioning and neurogenesis (Upton *et al.*, 2015), which reflect the participation of TEs in these processes. In particular, the lncRNA RMST is required for neurogenesis and is expressed during neuronal differentiation. RMST promotes interaction of SOX2 with the promoter region of neurogenic transcription factors (Ng *et al.*, 2013). For the transition of neuronal stem cells from one stage to another, the regulatory action of specific lncRNAs Six3os, Dlx1as, Pnky is necessary (Pereira Fernandes *et al.*, 2018). LncRNAs GOMAFU, MALAT1, NEAT1, TUG1 involved in embryonic neurogenesis are characterized by increased expression in the subventricular zone during aging (Barry *et al.*, 2015). In the human neurogenesis zone, in the dentate gyrus of the hippocampus, the expression of lncRNA2393 is determined, which is involved in the regulation of neuron differentiation (Deng *et al.*, 2017).

In the human neurogenesis zone, a high level of retroelement transpositions is determined (Kurnosov *et al.*, 2015; Upton *et al.*, 2015). This is due to the formation of lncRNAs genes in evolution from TEs. This is evidenced by data on the content of 83% of lncRNA domains with more than one TEs fragment. At least 41% of the functional lncRNA domains originate directly from TEs, which form many repeats resembling protein domains (Johnson & Guigo, 2014). It has also been proven that in humans, more than 10% of lncRNAs transcripts are initiated from LTR-containing REs. At the same time, lncRNAs are directly formed from HERVE genes (Kapusta & Feschotte, 2014). LTR-containing REs turned out to be the sources of thousands of different lncRNA genes in evolution (Hadjiargyrou & Delihas, 2013).

Transcripts of some HERVs (Lu *et al.*, 2014) and LINE-1s (Honson & Macafrlan, 2018) function directly as lncRNAs. Similar to the *Arc* gene derived from REs (Pastuzyn *et al.*, 2018), specific lncRNAs are transported to the dendrites of neurons, where they control the translation of proteins in synapses. For example, lncRNA BC1 suppresses the participation of the small ribosomal subunit in the formation of the 48S preinitiator complex (Wang *et al.*, 2002).

Changes in the expression of specific lncRNAs in MDD have been identified in several studies in peripheral blood samples. A decrease in lncRNAs *TCONS_L2_00001212*, NONHSAT102891, ENST00000566208, NONHSAG045500, NONHSAT034045, TCONS_00019174, ENST00000 517573, NONHSAT142707 (Cui *et al.*, 2016), LINC00998 (Ye *et al.*, 2017), *AP000350.5*, *MIF-AS1*, *RP11-51J9.5* (An *et al.*, 2019a), RMRP (Seki *et al.*, 2019) levels was detected. An increase in the expression of lncRNAs LINC01108 (Ye *et al.*, 2017), Y5, MER11C, PCAT1, PCAT29, XIST (Seki *et al.*, 2019), XIST, RP11-706O15.3, RP11-706O15.5, RP11-415F23.2, RP11-1250I15.1, CTC-523E23.11, RP11-706O15.7, AL122127.25, TNRC6C-AS1, RP4-575N6.4 (An *et al.*, 2019a), NEAT1, DLGAP-AS1 (An *et al.*, 2019b) was detected. The following associations of polymorphic variants of lncRNA have been identified with major depressive disorder: rs12526133 LINC01108 (Ye *et al.*, 2017), rs12129573 LINC01360 (Liu *et al.*, 2020b), rs1333045 и rs1333048 ANRIL (Namvar *et al.*, 2020), rs1899663 HOTAIR (Sayad *et al.*, 2020). In addition, reduced levels of lncRNA LINC004J3 were identified in brain samples of deceased people who suffered from MDD during their lifetime (Issler *et al.*, 2020). It should be noted that in addition to the role in the evolutionary origin of lncRNAs as sources of their genes, TEs insertions form promoters, polyadenylation sites, and splicing sites for these genes (Johnson & Guigo, 2014). Therefore, the regulation of TEs activity is promising for controlling the expression of lncRNAs involved in the development of MD, which in the future may become the basis for the correction of PWB. In addition, lncRNAs can bind to the RISC system and be processed to form microRNAs (Guo *et al.*, 2014).

Conclusion

The influence of heredity in the development of psychological well-being is estimated at an average of 42%. Genetic studies have shown the association of a number of genes with psychological well-being, which include *APOEε4* (rs429358 и rs7412), *OXTR* (rs2254298 и rs53576), *OXT* (rs4813625), *COMT* (rs4680), *NMUR2* (rs4958581), *CNR1* (rs806377), *CRHR1* (rs878886), *CYP19A1* (rs700518), *CTRA* genes. Psychological well-being is affected by allelic variants of the *DRD4*, *5-HTT*, *MAO-A*, *SLC6A3* genes associated with VNTR features in their regulatory regions. The reasons for VNTR variations in these genes are individual inherited features of the distribution of SVAs retroelements, which play an important role in regulating the expression of genes that specifically function in the human brain. Other transposons have the same properties, including LINE-1, SINE, Alu, HERV retroelements. This demonstrates the impact of transposons on psychological well-being. Retroelements also have a regulatory effect on the brain through epigenetic regulation, since they are sources of long non-coding RNAs and microRNAs. Since psychological well-being is also assessed by negative criteria, such as depression, a search was conducted for transposon-derived microRNAs associated with major depressive disorder. As a result, 12 such microRNAs were found: miR-1202, -192, -320b, -320d, -325, -326, -335, -3664, -450a, -511, -5695, -646, which indicate the role of transposons in epigenetic regulation of psychological well-being, since microRNAs derived from transposons are involved in epigenetic regulatory networks with the participation of transposons due to the presence of complementary nucleotide sequences between them.

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