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DISCUSSION

# In Search of Novel Diagnostic Biomarkers for Psychoneurological and Neurodegenerative Diseases: Translation Factors DENR and eIF2D

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**Abstract**—A rising global prevalence of psychoneurological and neurodegenerative disorders emphasizes the critical need for effective therapeutics and methods for early and highly sensitive diagnostics in order to ensure efficient and timely treatment of these disorders. Expanding the range of available biomarkers for better characterization of disease features and progression is a promising direction in modern diagnostics. The discovery of novel biomarkers depends on elucidating molecular mechanisms underlying disease development and pathogenesis. Numerous psychoneurological and neurodegenerative disorders are associated with the dysregulation of protein translation. The review summarizes information on the action mechanisms of translation factors DENR and eIF2D and evaluates their potential as diagnostic biomarkers for psychoneurological and neurodegenerative diseases.

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## INTRODUCTION

An increasing prevalence of psychoneurological and neurodegenerative disorders necessitates the development of effective treatment strategies and diagnostic systems for the early detection of these pathologies. For a long time, the primary diagnostic methods have been psychological tests and physical examinations, e.g., electroencephalography (EEG). However, these approaches lack accuracy and do not allow early disease diagnostics. Currently, the studies on the identification of biomarkers for psychoneurological and neurodegenerative diseases are coming to the fore. The search for biomarkers of neurological disorders requires elucidation of associated genetic mechanisms. Such studies pave the way for the development of early diagnostics methods, prediction of disease risk, monitoring of disease progression, and assessment of treatment efficacy in patients. Mutations, single-nucleotide polymorphisms (SNPs), and alterations in the transcriptome play a key role in the pathogenesis of nervous system disorders. Recent advancements in DNA and RNA sequencing technologies, such as the next-generation sequencing (NGS) and Nanopore technology, have made it possible to identify both rare and common genetic variations associated with neurological diseases [1]. Transcriptome analysis enables tracking of changes in gene expression in various neurological disorders. Furthermore, non-coding RNAs have been shown as critical factors in neurodegenerative processes. Other epigenetic mechanisms, such as DNA methylation and histone acetylation, also play an important role in the development of neurological diseases [1].

Currently, researchers actively search for biomarkers that can be used in the diagnostics of psychoneurological and neurodegenerative diseases. The heterogeneity of these disorders makes identification of universal biomarkers particularly challenging [2]. In addition to the diagnostic efficacy, the promising biomarkers should possess the following key properties: they should be suitable for early disease

diagnostics, serve as predictors of disease progression and treatment efficacy, and be cost-efficient to allow their clinical use. Hence, scientists continue their efforts in discovering candidate genes, metabolites, and proteins that can be used as biomarkers for various psychoneurological and neurodegenerative pathologies.

Dysregulation of translation processes plays an important role in the pathogenesis of neurological disorders [3]. In particular, mutations in genes encoding components of the translational apparatus and changes in the expression of these genes have been observed in the Charcot–Marie–Tooth disease, cerebellar ataxia, Parkinson's disease, and Huntington's disease [4-7]. For example, the translation initiation factor eIF4G1 is associated with the pathogenesis of the Parkinson's disease and a specific type of dementia, whereas dysregulation of the translational factor eIF2α was found in patients with amyotrophic lateral sclerosis (ALS) [8, 9].

This review discusses two translation factors, eIF2D and DENR, presumed to be involved in the non-canonical initiation of translation [10, 11]. According to the published studies, eIF2D and DENR play an important role in the functioning of the nervous system. Mutations in the corresponding genes or dysregulation of their expression lead to severe psychoneurological and neurodegenerative diseases. The data on the relationship between eIF2D and DENR and pathologies of the nervous system are summarized in Table 1. Despite the information indicating the association of these factors with a number of neurological diseases, their role in the pathogenesis of these disorders remains poorly understood.

This review examines neurological diseases associated with the DENR and eIF2D translation factors and proposes underlying molecular mechanisms. It systematizes and summarizes current information on the role of eIF2D and DENR in the pathogenesis of psychoneurological and neurodegenerative disorders, which may help to address the existing gap in knowledge in this research field. Also, a potential use of DENR and eIF2D in the diagnostics of psychoneurological and neurodegenerative diseases is discussed.

## THE STRUCTURE AND FUNCTIONS OF EIF2D AND DENR TRANSLATION FACTORS

eIF2D and DENR are components of the translational machinery. While eIF2D acts alone, DENR forms a heterodimer with MCTS1 (malignant T-cell amplified sequence 1) protein. This interaction is mediated by the N-terminal Zn-binding domain of DENR, which binds to the C-terminal domain of MCTS1 [25]. A remarkable feature of these proteins is a near-identical domain organization of eIF2D and the MCTS1-DENR dimer (Fig. 1). The N-terminal region of eIF2D contains the DUF1947 and PUA domains (which are also present in MCTS1) factor, while the C-terminal region harbors the SUI1 domain, which is homologous to the SUI1 domain of DENR [27]. The PUA domain acts as the RNA-binding domain and has been found in various protein families [28, 29]. It is frequently located after the DUF1947 domain (as in MCTS1 and eIF2D). According to the studies of the eIF2D and MCTS1–DENR complexes with the 40S ribosomal subunit, these domains are responsible for the protein association with the ribosome and participate in stabilization of the tRNA acceptor stem [25, 30]. The SUI1 domain has been identified only in three families of eukaryotic proteins: eIF2D, DENR, and translation initiation factor eIF1. The SUI1 domains of all three factors occupy the same site on the ribosome [26, 30, 31], but the proteins are otherwise structurally different. In eIF2D, the SUI1 domain is preceded by the SWIB/MDM2 domain connected to it through a linker [26, 32],

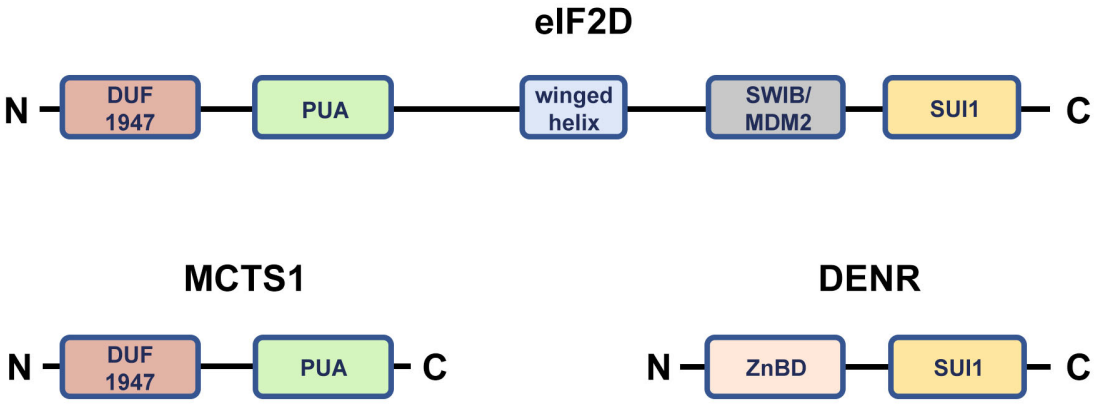


**Fig. 1.** Domain organization of eIF2D, MCTS1, and DENR [25, 26]. Structural domains are shown as rectangles. Homologous domains are indicated with the same colors.

**Table 1.** Involvement of DENR and eIF2D in the nervous system functioning and associated disorders

| TRANSLATION FACTOR | PSYCHONEUROLOGICAL DISEASES | | |
|---|---|---|---|
| DENR | **Disease/Dysfunction** | **Mechanism** | **References** |
| | schizophrenia | mutation | [12] |
| | autism spectrum disorder (ASD) | mutation | [13, 14] |
| | clinical depression | dysregulation of gene expression | [15] |
| | **NEURODEGENERATIVE DISEASES** | | |
| | **Disease/Dysfunction** | **Mechanism** | **References** |
| | Parkinson's disease | dysregulation of gene expression | [16] |
| | **OTHER CHANGES INDIRECTLY AFFECTING NERVOUS SYSTEM FUNCTIONING** | | |
| | **Disease/Dysfunction** | **Mechanism** | **References** |
| | regulation of circadian rhythms | 1. dysregulation of gene expression<br>2. regulation of *CLOCK* gene expression | [17-19] |
| | impairment of terminal arborization of cortical neurons | mutation | [20] |
| | impaired migration of cortical neurons | mutation | [20] |
| | regulation of RAN translation | dysregulation of gene expression* | [21, 22] |
| eIF2D | **PSYCHONEUROLOGICAL DISEASES** | | |
| | **Disease/Dysfunction** | **Mechanism** | **References** |
| | schizophrenia | dysregulation of gene expression | [23] |
| | **OTHER CHANGES INDIRECTLY AFFECTING NERVOUS SYSTEM FUNCTIONING** | | |
| | **Disease/Dysfunction** | **Mechanism** | **References** |
| | regulation of RAN translation | dysregulation of gene expression* | [22, 24] |

Note. * Caused by gene knockdown.

the two domains and the linker forming a single, rigid structure. In the analogous position, DENR contains the zinc-binding domain that mediates its interaction with MCTS1 [25, 33].

The functions of eIF2D and DENR remain obscure. Based on the accumulated body of evidence, these proteins are involved in the non-canonical translation initiation, with the functional activity of DENR being different from that of eIF2D. DENR in the content of the dimer is capable of initiating translation of open reading frames (ORFs) preceded by short upstream ORFs (uORFs) located in the 5′-untranslated regions (5′-UTRs) [10, 11]. Yeast orthologs of eIF2D and DENR are involved in the ribosome recycling and mediate dissociation of the complex formed by the 40S ribosomal subunit, deacylated tRNA, and mRNA [34, 35]. Hence, it is possible that eIF2D and DENR participate in the ribosome recycling in humans as well.

Although the functions of eIF2D and DENR-MCTS1 dimer are poorly understood, the early studies of these factors have unequivocally demonstrated their involvement in the tRNA positioning in the ribosomal P-site [27, 36]. The precise role of these proteins remains ambiguous: it is unclear whether they stabilize tRNA in the P-site to promote translation initiation or trigger tRNA dissociation to enable ribosome recycling. Furthermore, the question of how these functions are divided between eIF2D and MCTS1–DENR heterodimer remains unresolved, given their similar domain architecture.

The dysregulation of the eIF2D and DENR expression is frequently associated with pathologies. Thus, DENR expression is increased in various types of cancer [37]. Upregulated DENR expression is associated with late-stage malignancies, including lung, breast, renal, and colorectal carcinomas. It was reported that elevated DENR expression may be a risk factor in the glioma development in dogs [38]. In contrast, eIF2D expression is downregulated in certain cancer types [39]. Furthermore, according to the obtained data, DENR might be involved in the regulation of cell cycle, as well as in DNA repair and splicing [38]. Mutations in the *DENR* and *eIF2D* genes and their altered expression are associated with neurological diseases, including, for example, schizophrenia and autism spectrum disorders (ASDs) [12, 13, 23].

## EIF2D AND DENR AS POTENTIAL BIOMARKERS OF PSYCHONEUROLOGICAL DISORDERS

Translational control in neurons is essential for cognitive brain functions. The critical importance of protein synthesis regulation for normal brain functioning is indicated by the existence of a broad spectrum of disorders linked to altered translation rates, such as autism and neurodegenerative diseases. It is currently believed that the translation initiation factor eIF2α, mTORC1 complex, and translation elongation factor eEF2 are the principal regulators of neuronal translation [40]. The fundamental significance of translational control in neurons strongly suggests that the inventory of regulatory factors essential for normal neuronal function is destined to grow.

The *eIF2D* and *DENR* genes have been identified as biomarkers for diagnosing psychoneurological disorders. It was demonstrated that the *eIF2D* expression is typically elevated in patients suffering from schizophrenia for more than ten years. The expression of *eIF2D* can be assessed in blood samples, which eliminates the need for brain biopsy, a procedure generally unacceptable in clinical practice [23]. However, it is important to mention that during the early stages of schizophrenia, the *eIF2D* expression is typically downregulated [23].

Recently, it was found that *DENR* is a risk gene in schizophrenia, and that the C37Y missense mutation in its Zn-binding domain is associated with ASD [12, 13]. According to the study by a research group from Finland [14], this mutation was associated with ASD in two out of three patients with NFID (Northern Finland intellectual disability). Therefore, available data indicate a link between *DENR* and both schizophrenia and ASD.

The association of DENR with schizophrenia and autism suggests that this protein may play a role in the pathogenesis of these disorders. Molecular genetics studies have identified a substantial genetic overlap between schizophrenia and ASD. For example, it was shown that individuals with deletions or duplications in the *22q11.2* locus have a significantly increased risk of developing both these disorders, while disruptions in the locus containing the *C4* (complement component 4) gene were found in patients with schizophrenia, as well as in those with ASD [41]. Further studies in this direction will confirm whether DENR represents another example of genetic overlap between schizophrenia and autism and can serve as a composite biomarker for the diagnostics and risk prediction for both disorders.

The functional impairments of DENR have a noticeable impact on the nervous system activity. Beside the known ASD-linked C37Y mutation in the zinc-binding domain, it was demonstrated that the *de novo* missense mutations C37Y and P121L disrupt the terminal arborization of cortical neurons [20]. DENR was found to affect migration of cortical neurons in mice *in vivo* [20]. Furthermore, *DENR* expression was found to be upregulated in depression, resulting in a higher DENR concentration in blood samples [15].

Therefore, the functional significance of DENR in neuronal processes points out two promising research directions: investigation of links between mutations in the *DENR* gene, alterations in its expression, and psychoneurological disorders and, if these links are confirmed, assessment of the diagnostic potential of DENR as a composite biomarker for these disorders. Currently, the lack of experimental data on eIF2D prevents it from being considered as a reliable biomarker of psychoneurological diseases.

## DENR, SLEEP DISORDERS, AND PATHOGENESIS OF NEURODEGENERATIVE DISEASES

Sleep dysfunction negatively affects brain and behavioral functions. In particular, it disrupts circadian rhythms, which impairs the clearance of misfolded neurotoxic proteins involved in the development of neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases [42]. As shown in young mice, the levels of DENR in the cortical neurons increase during sleep [17]. Sleep disruption downregulates expression of translation-related genes, including *DENR* [18]. DENR participates in the regulation of circadian rhythms through the control of CLOCK biosynthesis, although the exact mechanism remains unclear [19]. The dysfunction of CLOCK is associated with common psychoneurological disorders, such as schizophrenia,

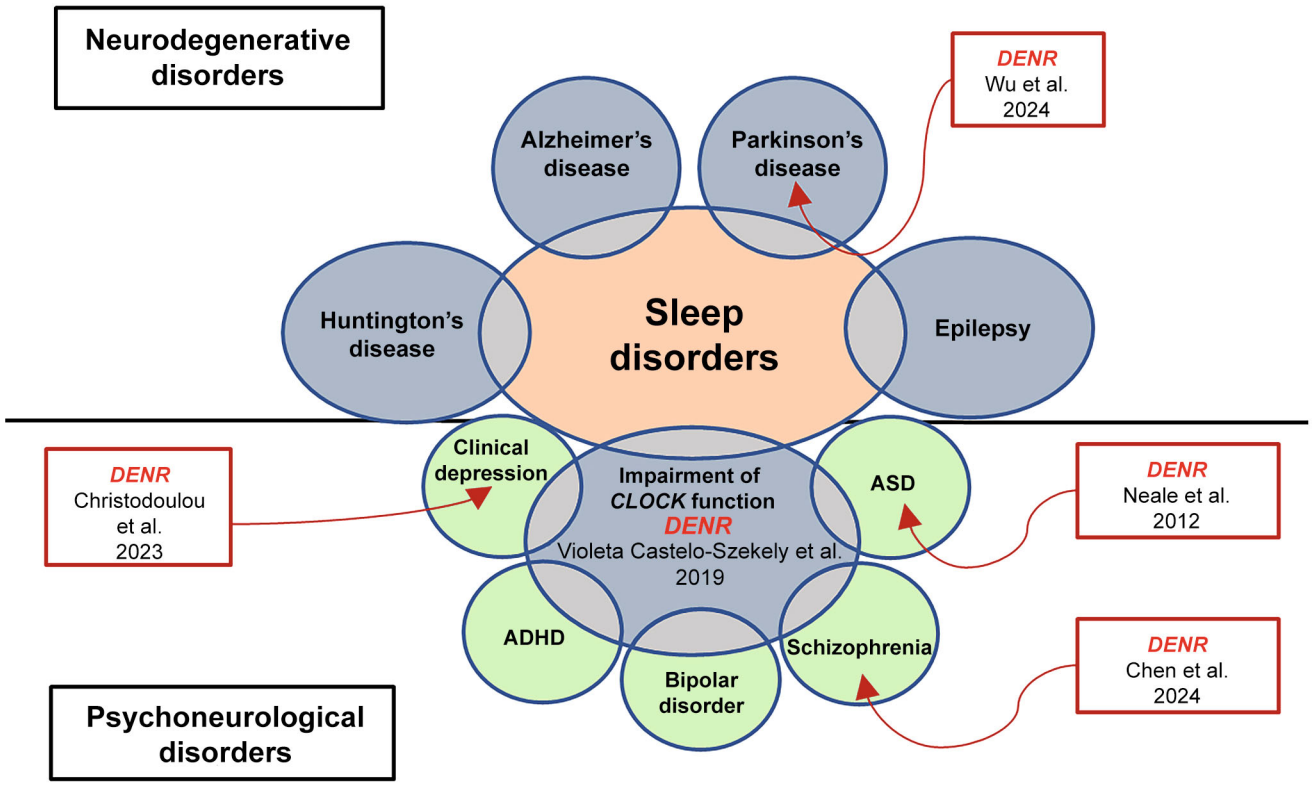


**Fig. 2.** The role of DENR in neurodegenerative (upper panel) and psychoneurological (bottom panel) pathologies associated with sleep disorders: gray and green, diseases presumably linked, directly or indirectly, respectively, with sleep disorders; red, disorders with reported changes in the *DENR* expression or mutations in *DENR* (references provided).

ASD, attention deficit hyperactivity disorder (ADHD), major depressive disorder, bipolar disorder, etc. [43]. As a member of circadian clock gene family expressed in the hypothalamic suprachiasmatic nucleus, the *CLOCK* gene, along with other genes, plays a pivotal role in the transcription–translation feedback loop. These genes are necessary for sustaining the sleep-wake cycle [44]. The knockdown of *DENR* reduces translation of the *CLOCK* mRNA, which might lead to the circadian clock dysfunction [19].

In addition to impairments in the *CLOCK* gene function, alterations in the *DENR* expression and mutations in this gene have been found in a number of psychoneurological and neurodegenerative disorders. Thus, it was shown that the *DENR* expression is suppressed in patients with the Parkinson's disease. Based on the experimental data and results of bioinformatic analysis, *DENR* was proposed as a potential biomarker for the Parkinson's disease [16]. In contrast, *DENR* expression in patients with depression is upregulated [15]. DENR has also been considered in the context of pathogenesis of psychoneurological diseases. For example, *DENR* has recently been identified as a risk gene in schizophrenia, and a missense mutation in its zinc-binding domain is associated with ASD [12, 13].

Taken together, these data suggest that DENR could be an important contributor to the molecular mechanisms underlying various psychoneurological and neurodegenerative disorders. As illustrated in Fig. 2, numerous pathologies associated with sleep disorders are characterized by mutations in the *DENR* gene or changes in its expression. Current evidence suggests that DENR can serve as a multifunctional biomarker for assessing the risk of a broad range of psychoneurological and neurodegenerative disorders.

## EIF2D, DENR, AND DYSREGULATION OF NON-CANONICAL TRANSLATION INITIATION IN PATHOGENESIS OF NEURODEGENERATIVE DISORDERS

It has been suggested that abnormal expansion of specific nucleotide repeats in a genome might be the underlying cause of neurodegenerative disorders, including ALS and spinocerebellar ataxia [45, 46]. Nucleotide repeat expansion results in the translation of repetitive RNA sequences, thus generating peptides with repeated amino acid motifs. These aberrant translation products exhibit a propensity for aggregation and neurotoxicity. The translation initiation for such repeats occurs via a mechanism independent of the canonical AUG start codon and is known as the repeat-associated non-AUG (RAN) translation.

Dysregulation of the RAN translational machinery has been detected in the myotonic dystrophy type 2 and Huntington's disease [47-50]. It has been shown that in Huntington's disease, RAN translation takes place in the protein-coding genomic regions [51]. The studies of familial ALS have revealed mutations in the non-protein-coding *C9orf72* locus, which also undergoes RAN translation [52, 53].

Multiple studies have identified non-canonical translation initiation factors as participants in the RAN translation. Specifically, the knockdown of *eIF2D* in *Caenorhabditis elegans* enhanced RAN translation of the *C9orf72* locus by more than 50% [21], whereas the knockdown of *DENR* in HEK293 cells reduced it by 50% [22]. The same effect was observed for the knockdown of the *MCTS1* gene encoding the heterodimerization partner of DENR, but not for the *eIF2D* knockdown [22].

In Drosophila, the knockdown of *DENR* suppressed translation of expanded repeats in the *C9orf72* locus, while decreased *DENR* expression promoted the viability of flies expressing these repeats [22]. DENR may represent a promising therapeutic target in the treatment of diseases driven by the expansion of *C9orf72* repeats, such as ALS and spinocerebellar ataxia. Future research may include investigating the role of DENR as a regulatory factor of RAN translation in other disorders associated with repeat expansion in various genomic regions.

The participation of eIF2D in the RAN translation in the *C9orf72* locus has been questioned [24]; therefore, the role of this protein in the RAN translation requires further investigation.

Collectively, the data obtained indicate that DENR could be a potential biomarker for diagnosing RAN translation-associated disorders, such as the Huntington's disease and myotonic dystrophy type 2. However, its validation will require additional studies of the RAN translation mechanisms to elucidate the regulatory function of DENR and to define its role in the pathogenesis of neurodegenerative disorders linked to the RAN translation. The evidence on the eIF2D involvement in the RAN translation remains conflicting, which emphasizes the need for additional studies in order to define its exact function in this process and related neurodegenerative pathogenesis. New experimental evidence could help evaluate the prospects of using eIF2D as a potential biomarker for neurodegenerative disorders.

## CONCLUSION

A growing prevalence of psychoneurological and neurodegenerative disorders necessitates timely therapeutic interventions, which in turn requires the availability of effective early diagnostic systems. Current evidence indicates that the efficacy of conventional diagnostic approaches based on psychological testing and physical examinations is inadequate, while available biochemical and molecular genetic diagnostic systems have yet to achieve a satisfactory performance. In this regard, the development of new diagnostic approaches should continue, including of those aimed at the biomarker identification.

Understanding molecular mechanisms of diseases facilitates identification of candidates for biological markers. Here, we analyzed the role of translation factors DENR and eIF2D in the development and pathogenesis of psychoneurological and neurodegenerative diseases. Both DENR and eIF2D genes have been identified as promising biomarkers for the Parkinson's disease and schizophrenia [34, 21]. Given potential action mechanisms analyzed in this work, DENR could soon be considered a biomarker for a broad range of psychoneurological and neurodegenerative diseases to improve the accuracy of diagnostics and enable earlier therapeutic interventions. While eIF2D has been identified as a biomarker for schizophrenia, its utility for diagnosing other diseases remains uncertain. Therefore, further investigation into the role of eIF2D in the pathogenesis of psychoneurological and neurodegenerative disorders is required. It is important to emphasize that DENR has already been suggested as a biomarker for a broad spectrum of disorders, whereas eIF2D represents a more specific yet promising candidate biomarker.

**Abbreviations**

| | |
|---|---|
| ALS | amyotrophic lateral sclerosis |
| ASD | autism spectrum disorder |
| RAN | translation repeat-associated non-AUG translation |

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**Ethics approval and consent to participate**

This work does not contain any studies involving human subjects or animals.

**Conflict of interest**

The author of this work declares that she has no conflicts of interest.

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