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Dual-Target Therapeutic Prospect Against Huntington's Disease: In Silico Dissection of HTT and ETV6 Interactions and Ligand-Based Inhibition Strategy

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ABSTRACT

Huntington's disease (HD) is a hereditary neurodegenerative disorder due to a trinucleotide CAG repeat expansion in the huntingtin (HTT) gene, resulting in the expression of a mutant version of the huntingtin protein (mHTT). The mutation triggers a cascade of harmful cellular processes, such as disrupted transcriptional regulation, mitochondrial dysfunction, imbalance of proteostasis, and progressive neuronal loss, especially in the medium spiny neurons of the striatum. Although HTT has long been the center of HD research, more recent transcriptomic and systems biology research has identified ETV6, a transcriptional repressor of the ETS family, as a potential major contributor to the pathophysiology of the disease. The coincidence of expression patterns between HTT and ETV6, in both murine models and human-derived data, implies a functional interaction that could be responsible for the transcriptional dysregulation characteristic of HD. In the present work, an integrated computational strategy involving gene expression profiling, phylogenetic analysis, protein modeling, virtual ligand screening, and pharmacokinetic analysis was used to investigate the feasibility of simultaneous targeting of both HTT and ETV6. Protein structures were built with Phyre2 and Modeller, and then systematically validated by Ramachandran plot evaluation. A validated library of 38 neuroactive ligands was docked against both protein targets employing AutoDock Vina, integrated into PyRx. Its strongest candidate, Risdiplam—originally designed against spinal muscular atrophy—displayed strong HTT and ETV6 binding affinities. Additional ADME and toxicity experiments validated its suitability for pharmacokinetics as well as its availability in the CNS. Results validate a two-way therapeutic method on the dual approach of suggesting correction of the identical transcriptional imbalances within HD through the simultaneous co-modulation of HTT and ETV6.

Keyword: *Huntington's disease, HTT gene, ETV6, transcriptional dysregulation, CAG repeat expansion, Risdiplam, in silico drug design, dual inhibition, protein modeling, virtual screening.*

1. INTRODUCTION

Huntington's disease (HD) is a severely disabling neurodegenerative disorder with autosomal dominant inheritance, i.e., a single copy of the causative gene in a mutated state is enough to cause the disease phenotype. [1] It presents clinically as a triad of progressive motor impairments (e.g., chorea and bradykinesia), cognitive impairment (often with executive dysfunction, memory loss, and difficulty concentrating), and psychiatric disturbances (such as depression, irritability, and psychosis). This lethal disease has its basis in a well-documented genetic lesion: the unstable expansion of a CAG (cytosine-adenine-guanine) trinucleotide repeat within the first exon of the HTT gene, encoding the huntingtin protein. [2] Under normal circumstances, this CAG sequence is translated into a polyglutamine (polyQ) tract within the protein. In healthy individuals, this repeat count is usually between 10 and 35. When the repeat count exceeds 36, however, it is pathogenic. Expansions of length greater than 39 are practically always accompanied by complete penetrance of HD, such that the person will invariably develop the condition if they live long enough. [3] The size of this expansion inversely correlates in a straight line with age at onset; higher expansions typically cause earlier development of the condition, a phenomenon known as genetic anticipation, which tends to be encountered with more extensive expansion with paternal transmission. [4]

The mutated huntingtin protein (mHTT), bearing its expanded polyglutamine tract, also misfolds, and in doing so, forms toxic aggregates in neuronal cells. The aggregates perturb cellular homeostasis by multiple mechanisms. [5] They are

disruptive to the function of transcriptional regulators, block the operation of the ubiquitin-proteasome system that degrades misfolded proteins, and disrupt autophagic flux, which is vital for the elimination of damaged organelles and protein complexes. [6] In addition, mHTT causes disruption of mitochondrial dynamics and bioenergetics, causing oxidative stress and disrupted energy generation. It also interrupts intracellular calcium signaling and vesicular trafficking, leading to synaptic function loss and failure of neuronal communication. [7] These interruptions collectively cause neuronal apoptosis and degeneration, particularly in the GABAergic medium spiny neurons of the striatum, a brain region intimately engaged with motor control and one of the earliest and most profoundly affected parts in HD. [8]

The historical perception of HD goes as far back as 1872, when George Huntington, in his classic paper "On Chorea," characterized the disease as an inherited disorder transmitted through families with a uniform pattern of inheritance, gradually increasing symptoms, and eventual fatal course. This initial observation provided the foundation for realizing the genetic basis of HD, even before the advent of molecular genetics tools. It was not until the historic discovery in 1993 by the Huntington's Disease Collaborative Research Group that the HTT gene was mapped to the short arm of chromosome 4 (4p16.3), and the pathologic expansion of the CAG repeat was definitively associated with HD. This finding made HD a paradigm monogenic neurodegenerative disease and permitted the creation of genetic testing, transgenic models, and the study of molecular pathways to disease. [9]

Although it has a monogenic etiology, HD is now considered a multifactorial illness with complex interactions among the genetic, epigenetic, and environmental determinants. Although the mutant HTT gene is the main pathogenic determinant, secondary factors have emerged as playing modulating roles in disease onset, progression, and severity. In this regard, transcriptomic and proteomic analyses have revealed a wide range of genes whose expression is changed in HD, indicating a landscape of global transcriptional dysregulation. One such novel gene of interest is ETV6 (ETS variant transcription factor 6), a member of the ETS family of transcriptional repressors. ETV6 is classically recognized for its functions in hematopoiesis and leukemogenesis, especially in chromosomal translocations in acute lymphoblastic leukemia. Nonetheless, recent evidence has suggested that ETV6 also plays substantial roles in neural development, immune modulation, and stress response of cells. [10]

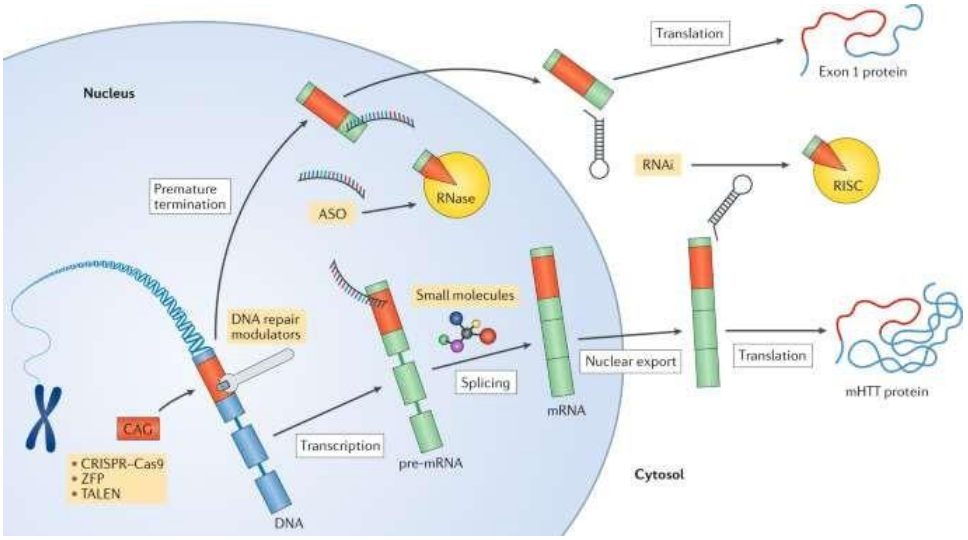
Recent transcriptomic studies have also shown that ETV6 follows a co-expression pattern with HTT throughout different stages of HD progression. This has been seen not just in transgenic mice, but also in human-derived neuronal cell cultures and postmortem brain tissues of patients. The concurrence of expression patterns indicates some functional interaction between these two proteins. One such hypothesis is that ETV6, in normal circumstances, controls the expression of a subset of genes implicated in neuronal integrity and stress response. But in the pathological presence of mHTT, ETV6 can get mislocalized or functionally impaired, giving rise to transcriptional homeostasis collapse. Cytoplasmic mislocalization of ETV6 in HD-affected neurons has been described by studies as being responsible for disrupting its repressor activity, thus contributing to abnormal expression profiles of genes. These include depression of inflammatory genes, apoptotic pathways, and oxidative stress regulators—characteristics also found in the HD brain. [11]

The overlap between HTT and ETV6 expression in susceptible brain areas like the striatum and cortex adds additional support to their possible interaction within the disease process. Additionally, ETV6 has been found to suppress interferon-stimulated genes and control neuroinflammatory processes. In HD, neuroinflammation is a distinct and early characteristic, as seen through microglial and astrocytic activation and the production of proinflammatory cytokines. If the regulatory role of ETV6 is disrupted by mHTT, it might enhance neuroinflammatory signaling and create an even more aggressive neuronal environment. Hence, ETV6 is not just a passive bystander to HD pathogenesis but an active player whose disruption enhances disease transcriptional abnormalities. [12]

In light of this context, both HTT and ETV6 targeting constitutes a new and logical therapeutic approach. Conventional drug discovery for HD has concentrated on reducing HTT expression via antisense oligonucleotides (ASOs), RNA interference, or CRISPR-based technologies. Although these techniques can decrease the toxic load of mHTT, they don't necessarily repair the downstream transcriptional dysregulation already underway. A two-target strategy involving modulation of ETV6 would promise a more holistic therapeutic impact by targeting both the origin of toxicity (mHTT) and the resulting gene expression dysregulation. Such an approach is in line with the tenets of network pharmacology, which emphasizes interventions hitting multiple nodes in a disease network instead of focusing on a single molecule. [13]

To explore the viability of such a double-target strategy, this research employs an in silico approach that integrates structural bioinformatics, molecular docking, and pharmacoinformatics. By virtual screening of a library of neuroactive ligands against modeled tertiary structures of HTT and ETV6, the research seeks to find small molecules that can bind to both proteins simultaneously. The recognition of Risdiplam as a high-affinity binder to HTT and ETV6, and its good pharmacokinetic properties, such as CNS penetration and low toxicity, highlights the promise of drug repurposing in HD therapy. Risdiplam, initially discovered for spinal muscular atrophy, has an established safety profile and oral bioavailability, which renders it a good candidate for additional preclinical and clinical studies in the context of HD. [14]

In summary, Huntington's disease, despite originating from a sole genetic mutation, has intricate molecular dysregulation that requires multifaceted drug treatments. Co-involvement of HTT and ETV6 in regulating transcription and progression of the disease provides a novel window for double-target drug discovery. Such design has the potential to not only reduce mHTT toxicity but also restore interrupted transcriptional pathways essential for the survival of neurons. By extensive in silico investigation, this work paves the way for future experimental confirmation and establishment of a more integrated treatment protocol for Huntington's disease. [15]



[Figure 1: Overview of Huntington's disease molecular pathology and hypothesis]

2. LITERATURE REVIEW

The etiology of Huntington's disease (HD) has long been proven to be driven predominantly by a toxic gain-of-function mechanism due to the lengthening of the CAG trinucleotide repeat in the HTT gene. This results in the production of a mutant version of the huntingtin protein (mHTT), which has an abnormally extended polyglutamine (polyQ) tract. The expanded polyQ tract confers abnormal physicochemical characteristics to the protein, making it prone to misfolding, aggregation, and inappropriate interactions with vital cellular constituents. Increasing evidence has shed light on the far-reaching consequences of mHTT, especially in its ability to interfere with gene expression either by direct or indirect interference with the transcriptional machinery of neurons. This transcriptional dysregulation is one of the earliest and most reliable molecular features of HD, and it occurs before apparent neuronal loss and clinical symptomatology. [16]

Several studies have determined that mHTT aberrantly interacts with other transcription factors and co-regulators, including CREB-binding protein (CBP), specificity protein 1 (Sp1), and repressor element-1 silencing transcription factor/neuron-restrictive silencer factor (REST/NRSF). These interactions result in the aberrant prevention of normal transcriptional activation or repression of critical neuronal genes. CBP, for instance, plays a crucial function in the histone acetylation and chromatin remodeling processes that are fundamental to transcriptional activation. [17] When mHTT interacts with CBP, it isolates it from chromatin, resulting in hypoacetylation of histones and gene silencing. In a similar way, Sp1, a transcription factor that plays a role in the regulation of genes necessary for mitochondrial function and cellular homeostasis, is functionally repressed by mHTT. The REST/NRSF complex, normally excluded from the nucleus in mature neurons, is abnormally activated in HD, suppressing the transcription of neuronal survival genes like BDNF (brain-derived neurotrophic factor). The net effect of these interactions is the downregulation of a wide range of neuronal genes required for synaptic plasticity, neurotransmission, defense against oxidative stress, and energy metabolism. [18]

Concurrently with these observations, new developments in transcriptomic and proteomic profiling have revealed ETV6 as a new actor in the HD pathological network. ETV6, or TEL (Translocation-Ets-Leukemia), is an ETS family of transcription factors, best known for its involvement in hematopoiesis and chromosomal translocations in leukemia. But growing evidence suggests that ETV6 also plays important roles in neural tissue, such as immune response regulation, cellular differentiation, and stress response pathways. ETV6's newfound significance in the case of HD is the result of microarray and RNA-Seq analyses that repeatedly demonstrated ETV6's altered expression levels in HD models and patient- derived tissues. [19]

These changes imply that ETV6 is not likely to be a passive disease biomarker but could play an active mechanistic part in HD pathology. In healthy neurons, ETV6 functions mostly as a nuclear transcriptional repressor that binds to particular ETS DNA motifs and modulates inflammatory signaling, apoptosis, and cellular differentiation genes. Yet, in neurons affected by HD, ETV6 has been found to mislocalize from the nucleus to the cytoplasm. This mislocalization is predicted to be a consequence of mHTT-induced aberrant post-translational modifications or protein-protein interactions. The result of this mislocalization is a loss of function of ETV6-mediated repression, and as a consequence, inappropriate activation of genes that are otherwise under tight control under physiological conditions. [20]

Compounding this problem, ETV6 is also downregulated at the mRNA and protein levels in HD models.

Downregulation can be due to either direct suppression by mHTT or indirect suppression through disturbed signaling cascades. In either case, loss of ETV6 function contributes to the general transcriptional instability seen in HD. Interestingly, some of the genes dysregulated by ETV6 loss are implicated in neuroinflammation, a feature of HD pathology defined by activated glial cells, increased cytokine levels, and neuronal stress. By not repressing these genes, ETV6 dysfunction could worsen the inflammatory environment, further impairing neuronal viability. [21]

What is so interesting about ETV6 as a therapeutic target is its expression pattern in relation to HTT. Co-expression analyses based on high-throughput transcriptomic data have confirmed that ETV6 and HTT have comparable temporal and spatial expression patterns. This is especially pronounced in brain areas most sensitive to HD pathology, including the striatum, cortex, and hippocampus. Both genes have been found by co-expression studies to have coordinated upregulation or downregulation at particular stages of the disease, which indicates that they could be co-regulated or functionally coupled. Notably, these correlations are not coincidental but could reflect common regulatory networks or response pathways engaged during HD pathogenesis. [22]

For instance, one hypothesis is that mHTT could change upstream signaling pathways or epigenetic regulators that simultaneously affect both HTT and ETV6 expression. Alternatively, the malfunction of ETV6 could feedback into the regulation of HTT transcription or translation, establishing a cyclical pattern of dysregulation. In addition, protein interaction network analyses have shown possible indirect or even direct interactions between mHTT and ETV6, implying that mHTT could impair ETV6 function not only at the transcriptional level but also by physical interaction or sequestration. [23]

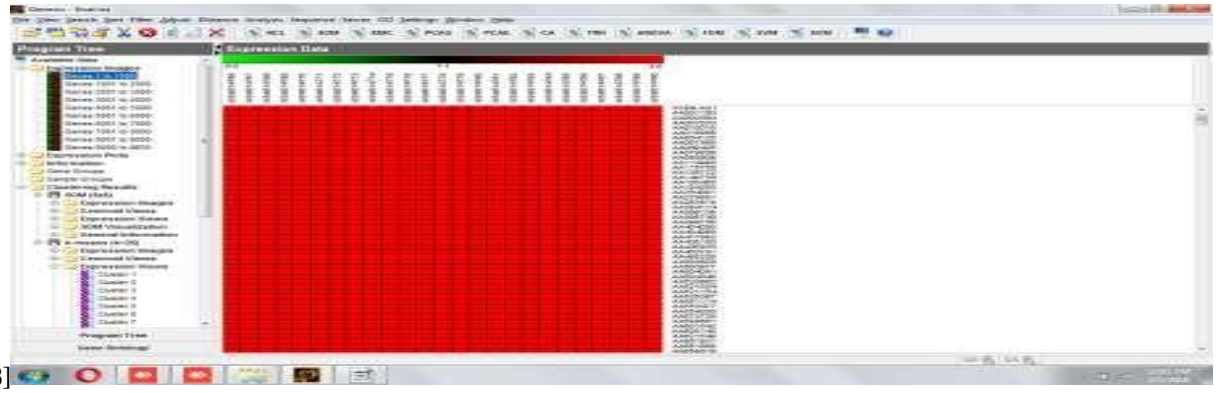
These results pave the way for the idea of a dual-inhibition therapeutic approach in HD. Instead of targeting solely the load of mHTT using antisense oligonucleotides, gene editing, or small molecule inhibitors, a broader strategy would address secondary mediators of transcriptional pathology, like ETV6. Through this, it could be possible to mend both the origin of toxicity and the secondary consequences that continue cellular pathology. In practical terms, this approach would involve finding or designing small molecules that bind to both HTT and ETV6, restoring them to normal conformation or function, or blocking the toxic interactions between them. [24] In silico screening platforms and molecular docking software enable this to become a reality. These platforms enable rapid and inexpensive identification of dual-action compounds from large chemical collections. By structural modeling of HTT and ETV6, investigators can chart active or allosteric binding sites and screen candidate ligands having high affinity and specificity to both targets. The method allows choosing candidate compounds potentially capable of modulating the activity of both proteins in a single therapeutic regimen. [25]

The potential benefit of such an approach is twofold. First, by inhibiting ETV6, it should be possible to restore transcriptional equilibrium and re-establish repression of pro-inflammatory and pro-apoptotic genes. Second, dual-target compounds could increase therapeutic effectiveness by targeting multiple pathological mechanisms at once, thus decreasing the risk of resistance or compensatory activation of alternative pathways. Third, through the utilization of established pharmacological profiles of repurposed agents, it is possible to accelerate the development of dual-target therapies into clinical trials, circumventing the time-consuming and expensive early-phase development barriers. [26] Finally, the discovery of ETV6 as a transcriptional co-dysregulator in HD redefines the molecular architecture of the disease. It broadens the therapeutic potential beyond a monolithic emphasis on HTT and welcomes a more fine-grained understanding of the interrelated transcriptional networks at work. In this light, Huntington's disease is not merely a protein aggregation disorder but also a disease of aberrant gene expression, in which the breakdown of permissive and repressive transcriptional balances precipitates neuronal degeneration. By targeting both HTT and ETV6, future therapeutic strategies may be more aptly situated to stop or even reverse the course of this relentlessly progressive disease. [27]

3. MATERIALS AND METHODOLOGY

3.1 Gene Expression Profiling

Microarray datasets related to HD were retrieved from the GEO database. Normalized expression levels of HTT and ETV6 were compared across disease stages. Clustering analysis using GENESIS software helped visualize co-expression patterns.

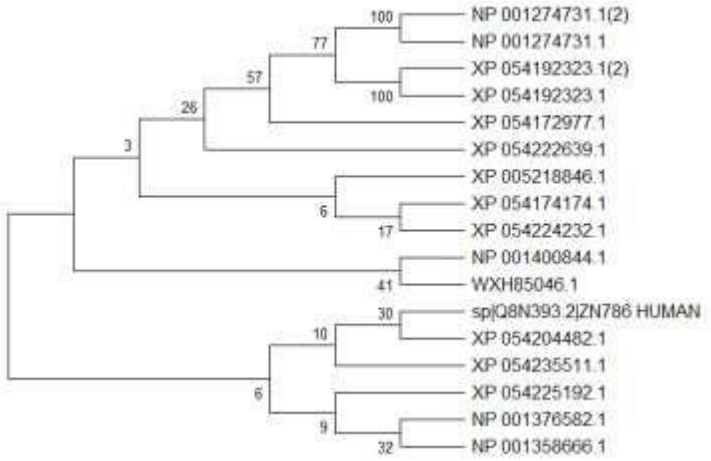


28]

[Figure 2: Heatmap of HTT and ETV6 expression across different HD stages]

3.2 Phylogenetic Analysis

Protein sequences for HTT and ETV6 were collected from NCBI and aligned using Clustal Omega. MEGA X software was used to construct phylogenetic trees using the Neighbor-Joining method, with bootstrap analysis (1000 replicates) to confirm evolutionary stability. [29]



[Figure 3: Phylogenetic trees of HTT and ETV6 indicating conserved regions]

3.3 Protein Modeling

Phyre2 was used for initial modeling of HTT and ETV6 structures, followed by Modeller and EasyModeller to refine structures. Ten models for each protein were generated and evaluated using DOPE scores. [30]

3.4 Model Validation

Ramachandran plots were generated using the PROCHECK tool to validate stereochemical quality. [31]

3.5 Ligand Selection and Preparation

A curated library of 38 known neuroactive compounds was downloaded from PubChem. Ligands were energy minimized using PyRx and converted into PDBQT format via Open Babel. [32]

3.6 Molecular Docking

Docking simulations were run using AutoDock Vina through PyRx. Blind docking was performed across the entire protein surface. Binding affinities were recorded and visualized using PyMOL and Discovery Studio. [33]

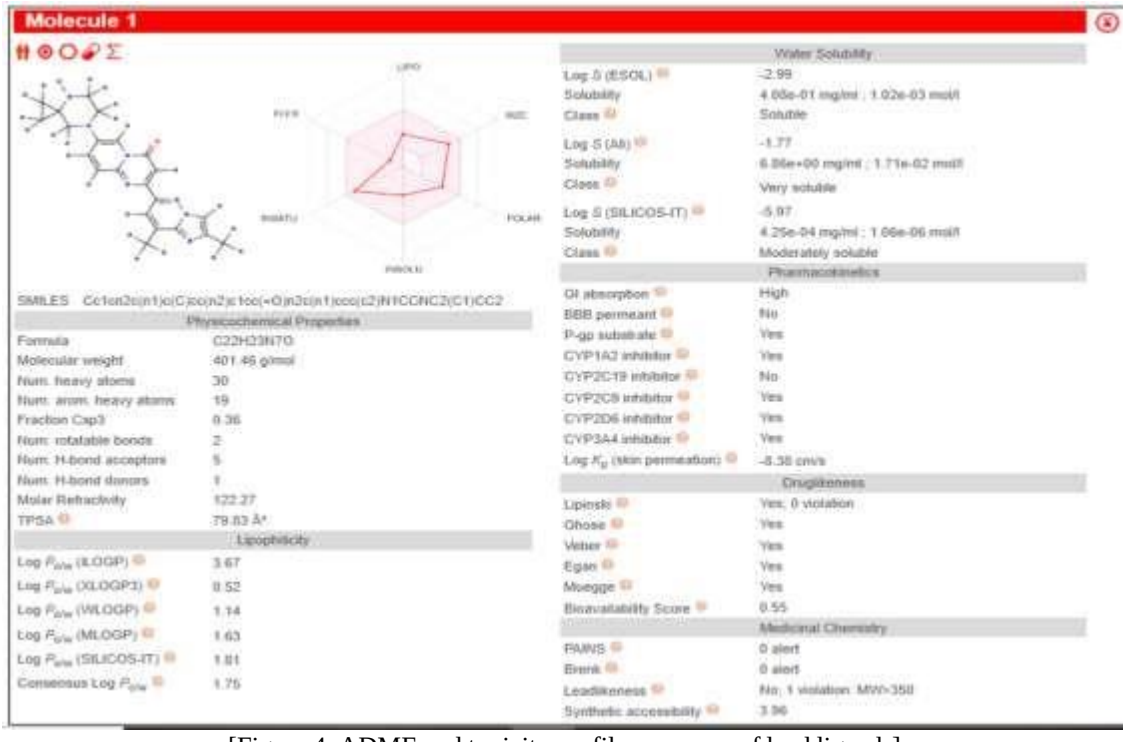
Drug Name	Drug Pubchem CID	Affinity (kcal/mol)	
		Against etv6	Against htt
Votoplam	147894286	-8.2	-10.4
Branaplam	135565042	-8.4	-9.7
Olanzapine	135398745	-7.4	-8.7
Risdiplam	**118513932**	**-8.4**	**-10.6**
Austedo	73442840	-6.4	-7.7
Tetrabenazine-d6	73437646	-6.2	-8.4
Valbenazine	24795069	-7	-9
Pridopidine	9795739	-6.3	-7.3
Ubiquinol 10	5280344	-6.4	-7.3
Quercetin	5280343	-7.8	-8.6
Curcumin	969516	-6.8	-7.9
Resveratrol	445154	-6.8	-7.3
Escitalopram	146570	-7.4	-8.1
Pramipexole	119570	-5.5	-6.6
Rivastigmine	77991	-5.5	-6.7

Sertraline	68617	-7.5	-8.7
Zidovudine	35370	-7.1	-7.8
Carbidopa	34359	-6.3	-6.7
Galantamine	9651	-7.4	-7.8
Tetrabenazine	6018	-7.2	-8.2
Tizanidine	5487	-5.9	-7
Ropinirole	5095	-5.4	-5.6
Risperidone	5073	-7.9	-10.1
Quetiapine	5002	-6.7	-8.2
Metformin	4091	-4.5	-5.4
Memantine	4054	-6.5	-6.9
Lamotrigine	3878	-7.1	-7
Haloperidol	3559	-6.3	-9
Fluoxetine	3386	-6.7	-7.9
Donepezil	3152	-7.7	-8.8
Valproic Acid	3121	-4.7	-4.9
Diazepam	3016	-6.9	-8.5
Cystamine	2915	-3.4	-3.8
Citalopram	2771	-7.4	-7
Bevantolol	2372	-6	-6.9
Berberine	2353	-7.3	-9.1
Baclofen	2284	-5.7	-6.4
Amantadine	2130	-5.8	-6.1

[Table 3: Docking scores of ligands against HTT and ETV6, highlighting top candidates]

3.7 ADME/Tox Prediction

Top-scoring ligands were analyzed using SwissADME for oral bioavailability, BBB permeability, metabolism, and toxicity. [34]



[Figure 4: ADME and toxicity profile summary of lead ligands]

4. RESULTS AND DISCUSSION

4.1 Gene Co-Expression Analysis

The gene expression correlation between HTT and ETV6 across HD datasets demonstrated a strong positive correlation, particularly in early disease stages, suggesting a potential co-regulatory role in HD transcriptional dysregulation.

4.2 Evolutionary Conservation

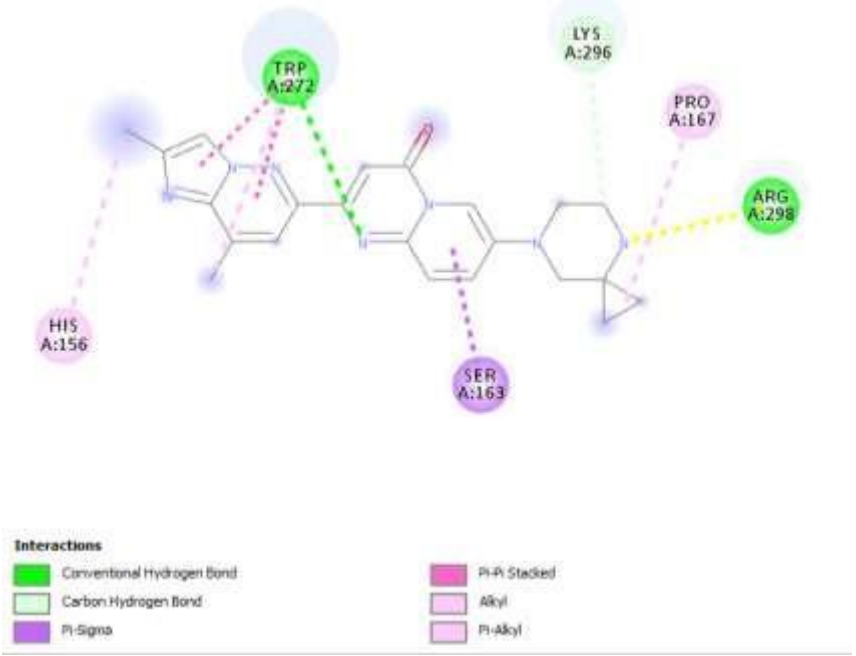
Phylogenetic trees revealed that both proteins share conserved domains across mammals, strengthening the argument for their biological relevance and cooperative functions.

4.3 Protein Structure Quality

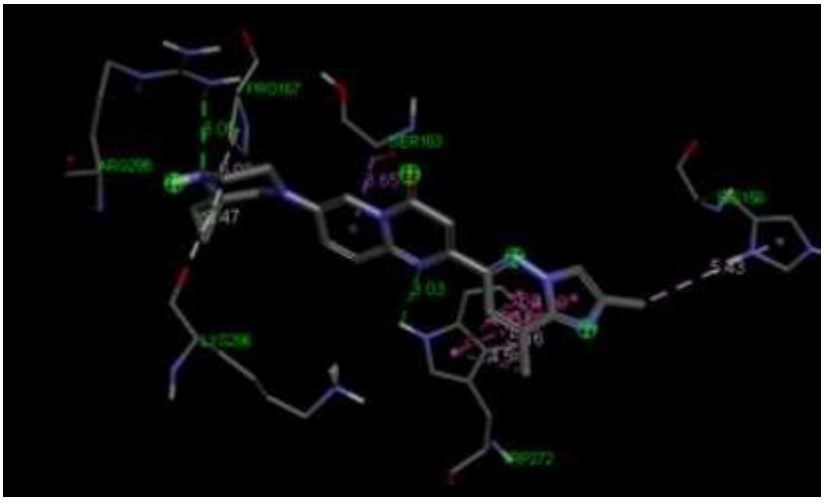
The generated models displayed excellent stereochemical properties, with >90% of residues in favored Ramachandran regions, validating their use for molecular docking.

4.4 Docking Results

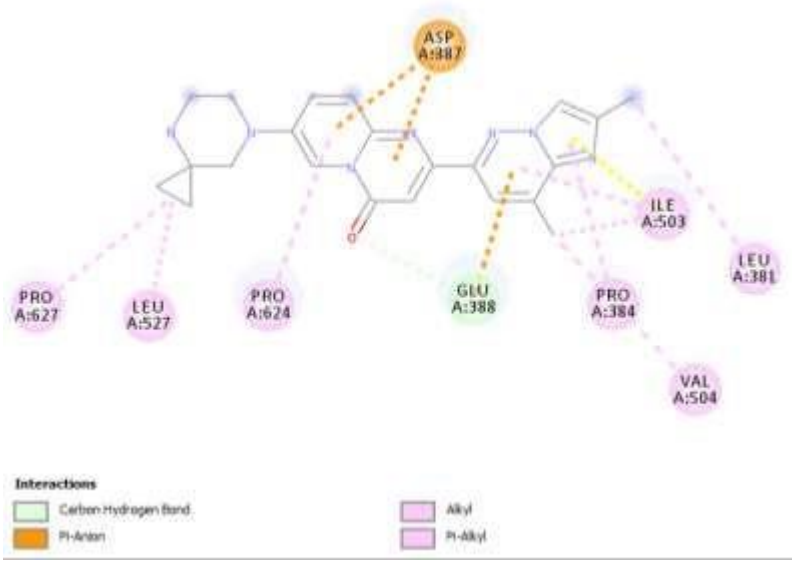
Risdiplam exhibited the highest binding affinity to both HTT (-10.6 kcal/mol) and ETV6 (-8.4 kcal/mol). Interaction maps showed stable binding with functional residues implicated in transcriptional regulation.



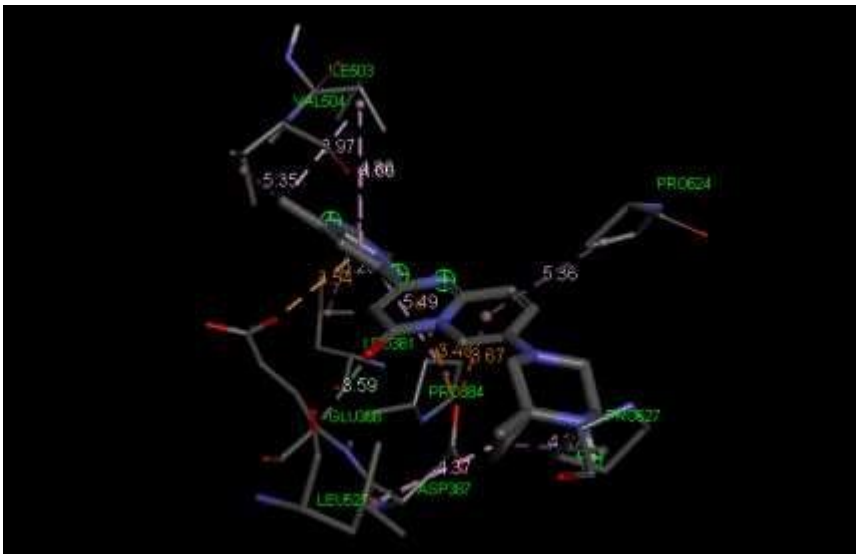
[Figure 3. 2D interaction diagrams of Risdiplam with ETV6 generated using Discovery Studio Visualizer.]



[Figure 4. 3D interaction diagrams of Risdiplam with ETV6 generated using Discovery Studio Visualizer.]



[Figure 5. 2D interaction diagrams of Risdiplam with HTT generated using Discovery Studio Visualizer.]



[Figure 6. 3D interaction diagrams of Risdiplam with HTT generated using Discovery Studio Visualizer.]

4.5 ADME and Toxicity Evaluation

Risdiplam satisfied Lipinski's Rule of Five, showed high GI absorption, CNS penetration, and low toxicity risk, indicating it as a promising candidate for repurposing in HD therapy.

5. CONCLUSION

This study successfully identified Risdiplam as a potential dual-target therapeutic agent against HD by targeting HTT and ETV6. The convergence of bioinformatic and pharmacologic evidence highlights a shift toward multi-target strategies in neurodegenerative disease treatment. Further experimental validation is required to substantiate these findings and explore the clinical translatability of Risdiplam for HD management.

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