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Review

Neurodevelopmental Disorders Associated with Biallelic *EIF3F* Variants: A Review

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Abstract

Background: Biallelic *EIF3F* variants cause a rare autosomal recessive neurodevelopmental disorder characterized by developmental delay, intellectual disability, speech impairment, and variable neurological manifestations. This review summarizes the clinical and molecular evidence to clarify genotype-phenotype relationships and identify unresolved disease mechanisms. **Methods**: We conducted a focused narrative review of clinical reports, variant-specific functional studies, and relevant mechanistic literature identified through targeted searches and reference screening. **Results**: Most clinical evidence concerns the recurrent p.(Phe232Val) variant, with only one reported compound-heterozygous individual. Developmental delay, intellectual disability, and speech impairment are prominent clinical features, whereas autism spectrum disorder (ASD), hearing loss, epilepsy, and other manifestations are variably reported. Functional studies in engineered induced pluripotent stem cells demonstrate reduced eIF3f abundance and altered translation, but the consequences for neuronal development remain unclear. Evidence from other experimental systems suggests context-dependent eIF3f functions, although their relevance to the human disorder remains unconfirmed. **Conclusions**: Biallelic *EIF3F* variants are associated with a clinically heterogeneous neurodevelopmental disorder. Integrating the available clinical and molecular evidence highlights important gaps in our understanding of genotype-phenotype relationships and disease mechanisms, underscoring the need for larger, systematically characterized patient cohorts and allele-specific neuronal models to inform future therapeutic research.

Keywords: *EIF3F*; neurodevelopmental disorder; intellectual disability; translation initiation; autism spectrum disorder; recessive inheritance; genotype-phenotype correlation

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1. Introduction

The identification of genes required for protein synthesis has linked disturbed translational regulation to neurodevelopmental disease. *EIF3F*-related neurodevelopmental disorder, also designated intellectual developmental disorder, autosomal recessive 67, was first associated with the homozygous c.694T>G, p.(Phe232Val) variant by Martin et al. [1]. Subsequent clinical studies established a variable phenotype and identified a second allele in one compound-heterozygous individual [2]. Detailed assessment of an additional child further documented the overlap with autism spectrum disorder (ASD) [3].

EIF3F encodes eIF3f, a subunit of mammalian eukaryotic translation initiation factor 3 (eIF3). The complex organizes interactions among the small ribosomal subunit, initiation factors, and messenger RNA. It also regulates selected transcripts, with activation or repression depending on the RNA and experimental context [4]. Consequently, describing the entire eIF3 complex as a general inhibitor of translation obscures its essential role in protein synthesis. Experiments comparing individual subunits likewise show that their effects on complex assembly, translation, and proliferation are not interchangeable [5]. Functional experiments using genome-edited induced pluripotent stem cells carrying the recurrent p.(Phe232Val) variant demonstrated reduced eIF3f protein abundance and altered translation [1]. However, these findings have not established how the variant affects neural development or neuronal function.

An established gene-disease relationship does not by itself resolve the biological chain connecting a variant to impaired brain development. The available clinical evidence is dominated by the recurrent p.(Phe232Val) variant, limiting genotype–phenotype correlations and interpretation of the broader allelic spectrum. Moreover, it remains unclear whether the developmental phenotype results primarily from altered general translation initiation, transcript-selective regulation, eIF3 complex stability, or other context-dependent functions. The relative vulnerability of different neural cell populations and the possible contribution of compensatory mechanisms also remain unresolved. This review addresses that distinction. It integrates clinical observations with variant-specific functional evidence, places broader eIF3f biology in its experimental context, and identifies questions that can be tested in neuronal systems. The focus is the recessive human disorder; findings in other diseases are considered only where they inform plausible mechanisms or experimental design.

2. Scope and Literature Identification

This article is a focused narrative review of *EIF3F*-related neurodevelopmental disorder, integrating clinical, genetic, structural, and mechanistic evidence relevant to the biological functions of eIF3f and its potential contribution to disease pathogenesis. To improve transparency and reproducibility, the literature identification and selection process is summarized in Figure 1.

Targeted literature searches were updated on 22 October 2026 using Europe PMC, including its MEDLINE-indexed records and accessible full-text publications, supplemented by PubMed record verification and searches of publisher websites. The principal search strategy was '(TITLE_ABS:EIF3F OR TITLE_ABS:"eIF3-f" OR TITLE_ABS:EIF3S5) AND FIRST_PDATE:[1900-01-01 TO 2026-10-22]'. A complementary search combined EIF3F with the terms "neurodevelopmental disorder", "intellectual disability", "autism", or "developmental delay". The publication date was restricted to records available up to 22 October 2026. Additional targeted searches were performed using combinations of "EIF3F" or "eIF3-f" with "neuron", "neural", "brain", "compensation", and "organoid". Searches also addressed the role of the eukaryotic translation initiation factor 3 (eIF3) complex in neural differentiation, translational regulation, and mutation-triggered transcriptional adapta-

tion. Exact-title and DOI searches, reference-list screening, and citation tracking were used to identify additional relevant publications. The Human Protein Atlas was consulted to provide contextual information on *EIF3F* expression in adult human brain tissues.

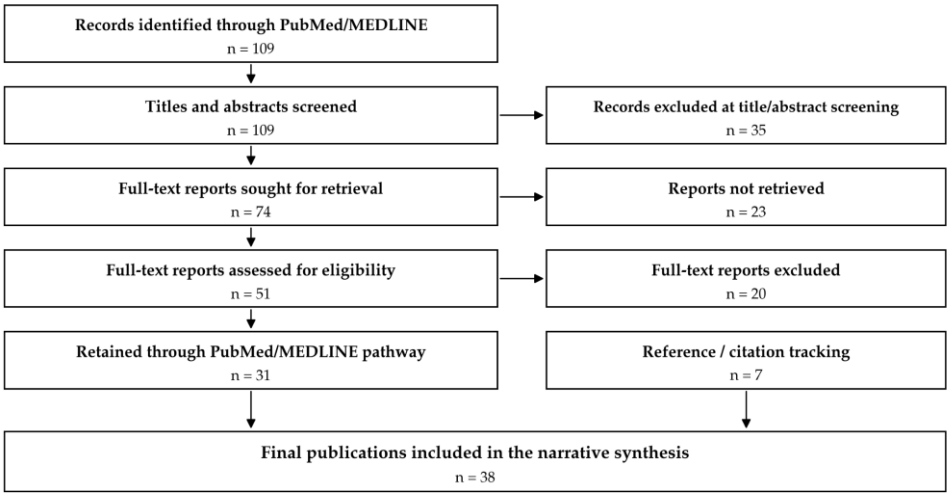


Figure 1. Literature identification and selection process for the narrative review of *EIF3F*-related neurodevelopmental disorder. The flowchart summarizes the identification, screening, retrieval, eligibility assessment, and final selection of publications.

The literature selection process is illustrated in Figure 1. Following identification and consolidation of the relevant PubMed/MEDLINE records, 109 unique records underwent title and abstract screening. Of these, 35 were excluded because they did not meet the thematic scope of the review or lacked sufficient relevance to *EIF3F*-associated neurodevelopmental disorders, eIF3f biology, or the molecular mechanisms under consideration. Full-text retrieval was sought for the remaining 74 reports. Twenty-three reports could not be retrieved, leaving 51 full-text publications for eligibility assessment. Following detailed evaluation, 20 additional reports were excluded because they did not provide sufficiently relevant clinical, genetic, structural, or mechanistic evidence to address the objectives of the review. Consequently, 31 publications were retained through the PubMed/MEDLINE pathway. An additional seven publications were identified through reference-list screening and citation tracking, resulting in a final set of 38 publications included in the narrative synthesis.

Study selection was guided by predefined thematic relevance rather than by formal systematic-review eligibility criteria. Priority was given to peer-reviewed human studies reporting biallelic *EIF3F* variants, detailed clinical phenotypes, genotype–phenotype relationships, and functional investigations of disease-associated alleles. Experimental studies addressing eIF3f function, eIF3 complex assembly, ribosomal interactions, translational regulation, and cellular consequences of altered protein synthesis were also considered. Importantly, mechanistic studies not directly investigating *EIF3F*-associated neurodevelopmental disorder were included only when they provided a biologically relevant framework for interpreting the potential consequences of EIF3F dysfunction. Such studies were selected based on their contribution to understanding eIF3-dependent translation initiation, neural development, cellular homeostasis, or compensatory responses to genetic perturbations. Evidence derived from these broader experimental contexts was distinguished from findings directly demonstrated in patients or disease-specific models, and mechanistic hypotheses were not presented as established disease mechanisms without direct supporting evidence. Where available, accessible full-text articles and clinical supplementary tables were examined to verify reported variants, phenotypic characteristics, and experimental

findings. Quantitative clinical summaries retained the original study-specific denominators to avoid misleading comparisons across heterogeneous cohorts. Publications lacking sufficient individual-level clinical information were not used to calculate pooled phenotypic frequencies or cumulative patient numbers. Conference abstracts, preprints, database submissions, and registry summaries were not considered independent peer-reviewed clinical cohorts. One conference abstract was discussed separately as a preliminary and unconfirmed mechanistic observation and was not incorporated into clinical counts or treated as evidence of an established pathogenic mechanism.

Although the literature identification and selection process was structured and documented, this review was not conducted according to a prospectively registered systematic-review protocol. Duplicate independent screening, formal risk-of-bias assessment, and quantitative meta-analysis were not performed. Accordingly, the final selection of 38 publications represents a focused, thematically guided evidence base for narrative synthesis rather than an exhaustive systematic-review dataset.

3. Clinical and Genetic Evidence

3.1. Foundational Cohorts and Later Reports

Martin et al. [1] identified nine affected individuals from seven families with homozygous p.(Phe232Val). Intellectual disability was present in all nine individuals, with confirmed epilepsy in six of seven individuals with available data, behavioural difficulties in three, and sensorineural hearing loss in three. Hüffmeier et al. [2] subsequently reported 22 affected individuals from 17 families: 21 homozygous for c.694T>G, p.(Phe232Val), and one compound-heterozygous individual carrying c.694T>G, p.(Phe232Val), and c.861dup, p.(Gln288AlafsTer14), in trans. Shared haplotypes in 15 families supported a founder origin.

The later clinical literature extends beyond single-gene case reports. Bar et al. [6] included a homozygous EIF3F finding in participant 33 of an ASD trio-genome reanalysis series. Lob et al. [7] documented an affected homozygote in their clinical supplement. Repiská et al. [8] listed the same recurrent homozygous allele in a Slovak ASD cohort. These reports provide ascertainment in additional clinical settings, but less detailed EIF3F-specific phenotyping than the dedicated cohorts. Patient counts across publications require particular caution. The routine-diagnostics study of Jauss et al. [9] explicitly states that its EIF3F case contributed to a larger study. The Lob supplement cites the 2021 cohort as validation evidence, without establishing whether the individual is independent of it [7]. The Slovak cohort also cites the earlier case report, but the accessible report does not establish participant independence [3,8]. These circumstances preclude simply adding every publication to a single count of unique patients. Reliable natural-history estimates will require consented linkage of de-identified cases across studies and registries. Table 1 distinguishes these sources and their limitations. Age at the last clinical evaluation is included where reported; age-specific information is unavailable for several later ascertainment studies.

Table 1. Clinical and genetic findings reported in individuals with biallelic *EIF3F* variants.

Study	*EIF3F* Finding and Age at Last Evaluation	Contribution	Main Clinical Feature
Martin et al. 2018 [1]	9 individuals, 7 families; homozygous p.(Phe232Val); age: range 4.41–48.93 years	Initial gene association and variant-specific iPSC experiments.	Intellectual disability: 9/9; epilepsy: 6/7 with available data; behavioural difficulties: 3/9; sensorineural hearing loss: 3/9.
Hüffmeier et al. 2021 [2]	22 individuals, 17 families; 21 homozygotes and 1 compound heterozygote p.(Phe232Val)/p.(Gln288AlafsTer14). Mean age at last examination: 12.1 ± 9.6 years.	Expanded phenotype; c.861dup p.(Gln288AlafsTer14) in trans with p.(Phe232Val); founder haplotype.	Among 21 individuals in the main phenotype analysis: global developmental delay 21/21; speech delay 21/21; behavioural problems 12/21; hearing loss 12/21; altered muscle tone 10/21; confirmed epilepsy 3/20.
Bar et al. 2024 [6]	Homozygous EIF3F finding in participant 33 of an ASD trio-genome reanalysis series; patient age not reported in the EIF3F-specific record.	ASD ascertainment using trio-genome reanalysis.	Identified in an ASD ascertainment setting; detailed EIF3F-specific clinical features are limited.
Lob et al. 2025 [7]	Individual ASD414; homozygous c.694T>G; age not reported in the supplementary EIF3F record.	Supplementary clinical record checked; independence from earlier cohorts not established.	Speech delay, bilateral sensorineural hearing loss, sensory processing difficulties.
Lakatosova et al. 2024 [3]	5-year old girl; homozygous c.694T>G; carrier parents	Standardized ASD and developmental assessment; MRI observations.	Single case; imaging findings cannot define a characteristic leukodystrophy.
Repiská et al. 2025 [8]	Homozygous c.694T>G listed in an ASD cohort of 117 children; age of the EIF3F-positive individual not reported.	Individual phenotype and overlap with the earlier Slovak case are insufficiently resolved.	Further ascertainment of the recurrent allele in a behavioural study.
Jauss et al. 2022 [9]	EIF3F finding in a routine-diagnostics cohort; patient-specific age and genotype details are not sufficiently reported for comparison here.	Overlapping publication; should not be counted as an additional independent individual.	No detailed EIF3F-specific clinical phenotype available for comparison in the report considered.

The table lists reports, not a duplicated patient registry. ASD, autism spectrum disorder; iPSC, induced pluripotent stem cell. Clinical counts in the first two rows are reported cohort sizes, not the number with complete data for every feature.

3.2. Core Features and Variable Manifestations

In interpreting the clinical findings, developmental delay, intellectual disability, and autism spectrum disorder are considered distinct clinical concepts, and the terminology used reflects the diagnoses and assessments reported in the original studies. Global developmental delay and speech impairment are among the most consistently reported clinical features, while intellectual disability is a prominent finding in affected individuals. In the 2021 cohort, the main phenotype analysis excluded one individual with a concomitant de novo *MECP2* diagnosis; the remaining denominators differed by feature. Table 2 presents selected observations from that analysis [2]. These proportions describe an ascertained rare-disease cohort and should not be interpreted as population penetrance or individual prognostic estimates.

Table 2. Selected features in the Hüffmeier cohort [2].

Feature	Reported *n/N*	Percentage
Global developmental delay	21/21	100.0%
Speech delay	21/21	100.0%
No speech	5/21	23.8%
Behavioural problems	12/21	57.1%
Hearing loss	12/21	57.1%
Muscular hypotonia or hypertonia	10/21	47.6%
Confirmed epilepsy	3/20	15.0%
Nonspecific brain imaging findings	5/13	38.5%
Microcephaly at later evaluation	6/19	31.6%
Short stature at later evaluation	8/20	40.0%
Gastrointestinal symptoms	5/21	23.8%
Reported developmental regression	3/21	14.3%

n is the number with the feature and *N* is the number with available information. Percentages were calculated from the published *n/N* and rounded to one decimal place. One of the 22 individuals had a concomitant *MECP2* diagnosis and was excluded from these phenotype summaries. No pooling with other cohorts was performed. These are descriptive observations in an ascertained cohort, not estimates of population penetrance. Behavioural problems are not equivalent to a formal ASD diagnosis.

Lakatosova et al. [3] described a child with intellectual disability, marked speech delay, hypotonia, mild bilateral sensorineural hearing loss, and sleep difficulties. Autism spectrum disorder was assessed using standardized diagnostic instruments. MRI showed enlarged perivascular spaces, described as atypical leukoencephalopathy. This observation warrants attention in future imaging studies but does not establish a characteristic leukodystrophy. Likewise, variable dysmorphism and rare structural anomalies are insufficiently specific to support recognition on appearance alone [2,3].

Differences between series may reflect age, referral pathways, symptom definitions, and missing data. Epilepsy represents a clinically relevant but variably reported feature of *EIF3F*-related neurodevelopmental disorder [1,2]. It was reported in 6 of 9 individuals in the initial cohort [1], whereas epilepsy was diagnosed in 3 of 20 individuals in the subsequent cohort [2]. However, the available clinical descriptions do not provide sufficiently consistent information on seizure types, electroencephalographic findings, age at onset, and treatment response to establish a characteristic epilepsy phenotype or define specific epilepsy syndromes associated with biallelic *EIF3F* variants. Further systematic characterization of epilepsy in affected individuals may help refine genotype–phenotype correlations and improve our understanding of the underlying neurobiological mechanisms. Pooling those samples without harmonizing assessment would conceal the discrepancy. Behavioural difficulties should not be considered equivalent to a formal diagnosis of autism spectrum disorder, which requires appropriate clinical assessment using established diagnostic criteria. Longitudinal studies should distinguish delayed acquisition of skills from verified loss of acquired abilities, and record hearing impairment when interpreting language outcomes.

3.3. Variant Spectrum and Interpretation

The recurrent allele dominates the available clinical evidence. The two reported disease-associated variants are the missense variant c.694T>G, p.(Phe232Val), and the frameshift variant c.861dup, p.(Gln288AlafsTer14). Hüffmeier et al. [2] reported one compound-heterozygous individual (P3) who inherited c.694T>G from the mother and c.861dup from the father, confirming that the variants were present in trans. The single compound-heterozygous individual had a severe presentation. However, one individual cannot estab-

lish that the frameshift allele predicts greater severity. Its predicted effect on the transcript or protein was not directly demonstrated in the clinical report [2].

Reduced protein abundance and impaired cellular function support a partial loss-of-function interpretation of p.(Phe232Val), but do not establish the effect of every rare *EIF3F* variant [1]. In particular, the human consequences of two complete null alleles cannot be inferred solely from a viable homozygous missense genotype. Conversely, embryonic lethality after murine gene disruption does not demonstrate that the same outcome occurs in humans [10].

Reports of heterozygous candidate variants require separate interpretation. Huang et al. [11] identified p.(Pro4Ser) among several inherited variants in a brother with intellectual disability, ASD, and psychosis, whereas his sister had a *SHANK3*-containing deletion. The study did not demonstrate a monogenic effect of EIF3F or establish dominant inheritance [11]. Multiple computational predictions do not substitute for segregation, phase, population, and functional evidence. Classification should integrate these data under established variant-interpretation principles, with particular attention to the evidence actually available for a given allele [12].

4. Molecular and Cellular Evidence

4.1. eIF3 Assembly and Selective Translation

Early reconstitution experiments identified a six-subunit combination, including eIF3f, that supported mammalian eIF3 activity in the assay used [13]. This experimental functional core should be distinguished from descriptions of the structural core of the complete complex. Mass-spectrometry mapping resolved an eIF3f–eIF3h–eIF3m module [14]. In murine and cellular experiments, loss of eIF3m destabilized eIF3f and eIF3h and impaired complex integrity [15]. These studies make altered assembly a testable explanation for reduced eIF3f function, but do not show that p.(Phe232Val) disrupts the same interactions.

eIF3-dependent regulation can also be transcript-selective. Lee et al. [4] demonstrated distinct modes of recognition of regulatory RNA elements associated with translational activation or repression. Duan et al. [5] showed that acute depletion of different eIF3 subunits produces different effects on complex organization and translation in cancer cells. Thus, a reduction in bulk protein synthesis does not identify which developmental programs are affected. It also cannot distinguish a primary initiation defect from secondary changes associated with cell state or growth.

Reports linking homozygous *EIF3K* variants and loss-of-function variants in *EIF3A* or *EIF3B* to developmental disorders place *EIF3F* in a wider disease context [16,17]. They support investigation of the eIF3 complex in human development, but do not establish a shared mode of inheritance, downstream mechanism, or treatment response across its subunits.

4.2. Direct Experiments with the Disease Allele

Martin et al. [1] generated CRISPR–Cas9-edited induced pluripotent stem cells carrying heterozygous or homozygous p.(Phe232Val). Homozygous cells had approximately 27% less eIF3f protein than wild-type and heterozygous cells. Translation was reduced in variant-bearing cells; reduced proliferation was observed in homozygotes, while viability was unchanged. These findings provide direct allele-specific evidence in a human cellular background. Figure 2 separates these observations from the clinical association and the unresolved neuronal mechanism.

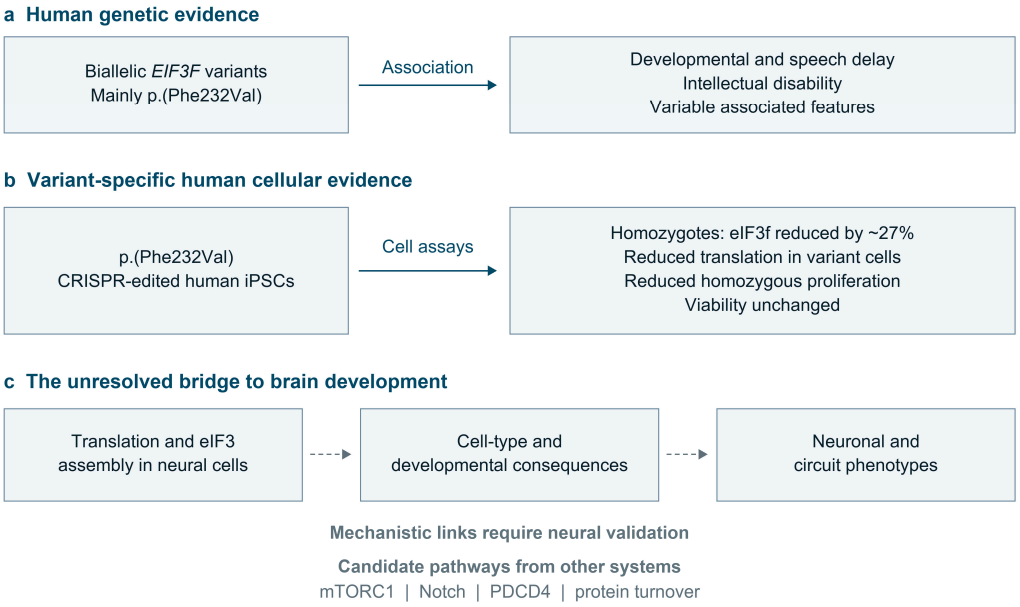


Figure 2. Evidence linking *EIF3F* variants to neurodevelopmental disorder. (**a**) Clinical studies establish the association with biallelic variants [1,2]. (**b**) Engineered iPSC experiments demonstrate allele-associated cellular changes; the approximately 27% reduction refers to eIF3f abundance in homozygotes [1]. (**c**) The downstream neural mechanism remains unresolved. Candidate pathways were identified in other experimental systems and require disease-specific testing. Solid arrows denote evidence in the indicated system; dashed arrows denote proposed links. The panels do not establish a continuous experimentally demonstrated pathway from altered translation to brain dysfunction. Original schematic.

Several limitations should be considered when interpreting these findings. The experiments were conducted in undifferentiated iPSCs rather than neurons or brain organoids. The measured reduction in protein abundance is an assay-specific result, not a biomarker established in patient blood or brain. It is also not equivalent to a 27% reduction in translation or a prediction of clinical severity. A translation effect in heterozygous cells does not establish dominant disease. The experiments also do not establish which molecular alterations contribute to the developmental phenotype, including changes in eIF3 complex stoichiometry, transcript selectivity, or protein turnover. Comparable allele-specific experiments for c.861dup were not identified in the clinical literature reviewed here [1,2].

4.3. Regulation of eIF3f and Evidence from Muscle

Iadevaia et al. [18] showed that EIF3F belongs to a subgroup of translation-factor genes whose transcripts have 5′-terminal oligopyrimidine features and growth-responsive translation. This provides a framework for studying changes in eIF3f abundance, but does not show that the recurrent coding variant alters that regulation.

Muscle experiments provide direct evidence for regulation at the protein level. MAFbx/Atrogin-1 targets C-terminal lysines in eIF3f for polyubiquitination and proteasomal degradation [19]. Further experiments implicated eIF3f as a scaffold connecting mTOR/raptor and S6K1 during muscle differentiation and hypertrophy [20]. In mice, complete gene disruption was associated with early embryonic lethality, whereas partial depletion reduced muscle mass and protein synthesis and increased vulnerability to disuse atrophy [10]. These results support a dosage-sensitive role in muscle homeostasis. They do

not establish that altered muscle tone in affected children results from primary myopathy rather than central or mixed mechanisms.

Endogenous proximity labelling in human muscle cells has more recently identified eIF3-associated, nuclear, and cytoplasmic neighbours of eIF3f [21]. Such approaches could help compare wild-type and variant proteins. Proximity, however, is not equivalent to direct binding, and muscle-specific networks require separate validation in neural cells.

4.4. Phosphorylation and Other Context-Dependent Functions

Apoptosis and mitosis provide distinct examples of eIF3f regulation. Shi et al. [22] identified Thr119 as a CDK11(p46) phosphorylation site and linked phosphorylation to altered association with eIF3 and translational inhibition during apoptosis. An et al. [23] implicated CDK11/p58-dependent phosphorylation at Thr255 and Ser258 in mitotic repression of cap-dependent translation. The kinase isoforms, residues, and cellular states should not be conflated. Neither study tested the recurrent NDD allele in neurons.

Other experiments illustrate the breadth of eIF3f biology. Moretti et al. [24] reported deubiquitinase activity involved in Notch activation. Wen et al. [25] investigated translation inhibition, hnRNP K interaction, and ribosomal RNA degradation in pancreatic epithelial and cancer systems. Ayhan et al. [26] found that eIF3f depletion reduced steady-state accumulation of repeat-associated non-AUG translation products in spinocerebellar ataxia type 8 models. Those findings concern repeat-expansion disease and do not establish RAN translation as a mechanism of *EIF3F*-related NDD.

Hegde et al. [27] demonstrated direct interaction between eIF3f and PDCD4 and increased Bcl-xL IRES-mediated translation after eIF3f depletion in glioblastoma models. The corresponding regulation was not reproduced in the tested non-cancer fibroblasts [27]. This cell-context dependence argues against transferring the result directly to developmental brain disease. Table 3 summarizes representative experimental systems and the questions they leave open.

Table 3. Experimental evidence and the remaining link to neurodevelopmental disease.

System and Intervention	Reported Observation	Implication and Unresolved Question	Source
Human iPSCs edited for p.(Phe232Val)	Lower eIF3f abundance in homozygotes; reduced translation; reduced homozygous proliferation; unchanged viability.	Direct allele-specific evidence. Neural consequences and transcript selectivity remain unresolved.	[1]
Reconstituted and mapped eIF3 complexes; eIF3m-deficient models	eIF3f participates in functional complexes and an f–h–m module; eIF3m stabilizes f and h.	Assembly is a testable mechanism. The disease allele was not tested in these experiments.	[13–15]
Muscle cells and mice; eIF3f degradation or depletion	Regulated ubiquitination, mTOR/S6K signalling, protein synthesis, and muscle mass; null mice fail early in development.	Establishes roles in muscle and development. Does not define a human neuronal phenotype or the fate of human null alleles.	[10,19,20]
Human muscle cells; endogenous BioID tagging	eIF3-associated and additional nuclear and cytoplasmic neighbours identified.	Provides a strategy for variant comparisons. Proximity does not establish direct binding or neural relevance.	[21]

Table 3. *Cont.*

System and Intervention	Reported Observation	Implication and Unresolved Question	Source
Apoptotic and mitotic cell systems; CDK11 isoforms	Phosphorylation associated with translational repression in distinct cellular states.	Supports regulated eIF3f activity. Effects of p.(Phe232Val) on phosphorylation are unknown.	[22,23]
Notch and pancreatic cell systems	Reported Notch deubiquitination and context-dependent translation/rRNA effects.	Generates hypotheses. Neither Notch dysfunction nor rRNA degradation is established in *EIF3F*-related NDD.	[24,25]
SCA8 models; eIF3f knockdown	Reduced steady-state accumulation of polySer and other RAN proteins.	A repeat-expansion context. Protein abundance does not alone resolve effects on synthesis versus turnover in the NDD setting.	[26]
Glioblastoma models; eIF3f depletion and PDCD4 assays	Direct PDCD4 interaction; increased Bcl-xL IRES-mediated translation after depletion.	Context-dependent regulation, absent in the tested non-cancer fibroblasts; not a demonstrated developmental mechanism.	[27]

Only the first row directly tests the recurrent human disease allele. Other rows describe different perturbations and experimental contexts. BioID, proximity-dependent biotin identification; NDD, neurodevelopmental disorder; RAN, repeat-associated non-AUG; SCA8, spinocerebellar ataxia type 8.

4.5. Rationale for Neural Models and Cell Type Vulnerability

The rationale for neural models follows from the developmental phenotype, rather than evidence that EIF3F is neuron-restricted. The Human Protein Atlas classifies its adult brain single-nucleus RNA profile as having low cell-type specificity [28]. This does not mean identical expression or functional dependence across cells. Adult transcript abundance also cannot establish vulnerability during fetal development, local protein abundance, or the consequences of a matched reduction in eIF3f. Together with the muscle and embryonic phenotypes [10], these observations argue for neural prioritization with non-neural comparators, rather than a neuron-exclusive model of disease.

Independent studies provide a biological rationale for examining developmental transitions. In human stem-cell-derived neural progenitors, Mestre-Fos et al. [29] demonstrated eIF3 binding to the 3′-UTR termini of highly translated mRNAs during early differentiation. This interaction correlated with translational activity rather than translational efficiency, but did not establish an EIF3F-specific regulatory mechanism. Lins et al. [30] identified translational regulation of synaptic, metabolic, and cytoskeletal programs as human progenitors differentiated into neurons. In developing mouse cortex, Borisova et al. [31] demonstrated different translation dynamics in early- and later-born lineages and an Ire1α/eIF4A1-dependent contribution to neuronal fate. These studies support testing progenitor-to-neuron transitions and neuronal maturation. They do not identify EIF3F-dependent transcripts or establish a selectively vulnerable cortical subtype.

There is also proof of principle that an eIF3 subunit can influence neuronal activity without a uniform change in general translation: Blazie et al. [32] demonstrated selective regulation by EIF-3.G in nematode cholinergic motor neurons. The subunit and species differ from the human EIF3F disorder. This finding therefore supports measuring transcript-specific and functional neural outcomes, rather than selecting human cholinergic neurons as a presumed primary target. No comparative *EIF3F* allele study retrieved here establishes

that excitatory neurons, inhibitory neurons, or glia have the greatest functional dependence on eIF3f.

4.6. Residual Function and Potential Compensation

Residual function should be distinguished from compensation. Survival of individuals homozygous for p.(Phe232Val), and the partial rather than complete protein reduction in edited iPSCs, are compatible with a hypomorphic allele and an activity threshold [1,2]. They do not demonstrate an induced protective response. Likewise, preserved viability despite altered translation is not evidence that the cellular phenotype has been corrected. The available studies do not establish whether neurons have less functional reserve than other cell types.

Some biochemical redundancy exists within eIF3. Limited-proteolysis and subcomplex experiments identified overlapping contributions to 40S ribosomal binding; Cai et al. [33] proposed that eIF3e, eIF3f, and eIF3h can support binding when intact eIF3g is absent. That observation concerns a particular interaction and direction of substitution. It does not show that another subunit replaces eIF3f, restores all initiation functions, or compensates for p.(Phe232Val) in neurons.

Estrogen receptor alpha (ERα) and estradiol regulate eIF3f abundance through transcriptional repression and mTORC1-dependent translational enhancement [34]. Growth-responsive translation of EIF3F TOP mRNA and stabilization of eIF3f by eIF3m provide potential control points for protein abundance [15,18]. Acute eIF3f depletion in HCT116 cells left residual subcomplexes and co-depleted eIF3k, while impairing proliferation [5]. Persistence or rearrangement of a complex is therefore insufficient to infer rescue. Changes in other subunits may reflect destabilization rather than a successful homeostatic response. These observations justify measuring synthesis, turnover, and complex stoichiometry over time, but do not establish differential compensation in neural and non-neural cells.

Mutation-triggered transcriptional adaptation is a separate mechanism. Studies in other genes have shown that mutant mRNA degradation can induce expression of related genes [35]; more recent experiments identified ILF3 as a link between RNA decay and transcriptional activation in mouse and human cells [36]. Neither study demonstrates this mechanism for EIF3F. It should not be assumed for the recurrent missense allele. For c.861dup, transcript decay must first be demonstrated before testing a decay-dependent adaptive response. Increased expression of a candidate buffering factor would itself require functional validation before being called compensation.

5. Implications for Diagnosis and Clinical Description

The nonspecific phenotype favours broad genomic assessment over recognition from a single clinical sign. This is consistent with general recommendations that exome or genome sequencing be considered early in the evaluation of children with developmental delay or intellectual disability [37]. The EIF3F reports illustrate why negative chromosomal microarray results do not exclude a sequence-level recessive disorder [3]. Homozygous variants should be confirmed and assessed through parental segregation analysis and review of assay coverage. Unexpected inheritance patterns should prompt consideration of alternative explanations. Compound-heterozygous findings require demonstration of phase whenever possible [12].

Clinical reporting should record developmental milestones and adaptive abilities, expressive and receptive language, formal ASD assessment, seizure history, audiology, growth, muscle tone, and relevant imaging. These domains follow the observed phenotype and would improve comparability across studies [2,3]. They do not constitute a validated surveillance schedule. Findings that are atypical or disproportionately severe should prompt

consideration of an additional diagnosis, as illustrated by the individual with a concomitant MECP2 disorder [2].

For families in which both parents carry a pathogenic recessive allele, standard autosomal recessive inheritance implies a one-in-four probability of an affected child in each pregnancy. This genetic expectation must be distinguished from prediction of severity, which remains unreliable. Molecular diagnosis can inform counselling and access to developmental and symptom-directed services, but the studies reviewed here do not establish an EIF3F-specific disease-modifying treatment. Extrapolation from mTOR, Notch, or cancer experiments is insufficient to support pathway-directed treatment in affected children.

6. Priorities for Future Research

6.1. A Deduplicated Natural History Resource

The most immediate clinical need is a longitudinal dataset with a consistent core assessment and a way to identify overlapping publications. It should capture age at evaluation, methods of assessment, negative findings, missing observations, coexisting diagnoses, and variant confirmation. Families with the same recurrent genotype can be informative about variability, but relatedness and shared ancestry need to be considered. Cross-sectional series cannot establish whether an uncommon feature is age-dependent, progressive, incidental, or modified by a second condition.

6.2. Allele-Specific Neural Models and Cell Type Selection

A staged comparison is preferable to choosing a single mature neuron type. Initial experiments should follow patient-derived or genome-edited neural progenitors through cortical glutamatergic neuron differentiation and maturation. Progenitors are relevant because altered lineage allocation or timing could precede synapse formation; cortical projection neurons provide a tractable model of the developmental and cognitive phenotype. Both early- and later-born neuronal states should be sampled because translation requirements differ across cortical lineages [31]. This is a hypothesis-driven starting point, not evidence that cortical excitatory neurons are the uniquely vulnerable population.

GABAergic neurons should be examined in parallel or in mixed excitatory–inhibitory cultures to assess cell-autonomous and network-level effects. Although epilepsy and ASD provide a rationale for this comparison [1–3], they do not establish a primary inhibitory defect. Current evidence does not justify choosing parvalbumin- rather than somatostatin-lineage interneurons as the exclusive target. Astrocyte co-cultures can assess non-cell-autonomous contributions. Oligodendrocyte-lineage studies should be prioritized if white-matter or myelination abnormalities are consistently reported. Currently, a single atypical MRI finding and observations from SCA8 models do not establish a primary myelin-related mechanism [3,26]. Table 4 separates initial models from comparative and exploratory ones.

A preliminary lead extends the question beyond mature neurons. A 2025 conference abstract by Su et al. [38] described brain organoids associated with the recurrent *EIF3F* variant, reporting altered WNT/BMP signalling, premature choroid-plexus and Cajal–Retzius cell emergence, and reduced mature-neuron abundance at later stages. A full peer-reviewed report was not identified in this update. These abstract-level findings support exploratory assessment of early cell-state composition and inclusion of choroid-plexus epithelium, which is not neuronal. They do not establish a specific affected subtype or a validated signalling mechanism; regional identity, developmental timing, and cell proportions require independent control.

Table 4. Proposed cell models for resolving *EIF3F*-related neural vulnerability.

Model and Priority	Rationale	Key Question and Limitation
Neural progenitors and radial-glia-like cells Initial stage	Developmental timing, cell-state transitions, and eIF3-associated translation are relevant to neurogenesis [29,31].	Does the allele alter proliferation, lineage allocation, or timing before neuronal maturation? These are progenitors, not mature neurons.
Cortical glutamatergic projection neurons Initial neuronal model	A tractable model of development and cognition; translation requirements vary across cortical lineages [30,31].	Compare developmental stages, neurites, synaptic proteins, and electrophysiology. No *EIF3F*-specific ranking of cortical subtypes is established.
GABAergic neurons and mixed excitatory–inhibitory cultures Parallel comparison	ASD and epilepsy motivate testing circuit interactions [1–3].	Separate intrinsic defects from network effects. Clinical symptoms alone do not identify a primary inhibitory lesion or select a particular interneuron subtype.
Astrocytes and oligodendrocyte-lineage cells Comparative or conditional	Broad brain expression supports including non-neuronal cells; white-matter findings remain limited [3,28].	Test astrocyte support in co-culture. Prioritize myelination models if replicated findings support them, rather than assuming primary oligodendrocyte disease.
Organoids with early cell-state profiling Exploratory	A conference abstract reports altered choroid-plexus, Cajal–Retzius, and neuronal populations [38].	Control regional identity, maturation, and cell composition. Choroid-plexus epithelium is non-neuronal; this lead awaits full publication and replication.
Matched fibroblasts or myotubes Non-neural comparator	Non-neural eIF3f function and dosage sensitivity are established [10,21].	Compare the same allele and residual protein level across backgrounds. A normal non-neural result would not exclude a neural defect.

These are proposed experimental priorities, not demonstrated rankings of cellular susceptibility. Compare matched allele dosage, protein depletion, differentiation stage, and observation time. Functional compensation requires preservation or restoration of the relevant phenotype, not merely viability or a change in another gene. ASD, autism spectrum disorder.

Comparisons should combine multiple independent clones and genetic backgrounds with introduction or correction of the disease allele. Retaining fibroblasts or myotubes from the same genetic background would help distinguish general eIF3f dependence from neural susceptibility. Protein abundance, residual complex assembly, perturbation duration, and differentiation state should be measured alongside translation and functional outcomes. Preserved neuronal viability alone does not demonstrate functional rescue, particularly when synaptic abnormalities persist. To investigate potential compensatory mechanisms, acute eIF3f depletion should be compared with sustained, allele-specific deficiency. Candidate compensatory pathways should then be experimentally modulated to determine whether they influence neural phenotypes at comparable levels of eIF3f impairment. Replication should treat independent biological preparations as the experimental unit, rather than counting individual cells as independent samples.

6.3. Connecting Translation to Developmental Phenotypes

Paired RNA sequencing and ribosome profiling could distinguish changes in transcript abundance from altered translational efficiency. Proteomics and analysis of eIF3 stoichiometry could then test whether protein output and complex assembly change in

parallel. Measurements of cell-cycle state, differentiation, and cell-type composition are needed because each can alter bulk translation independently of a primary molecular defect. Neuronal maturation, morphology, synaptic development, and electrophysiology would provide downstream readouts. Candidate pathways should be selected from those data rather than assumed from another tissue. In particular, mTORC1, Notch, PDCD4-dependent regulation, and protein turnover remain hypotheses for the NDD setting.

6.4. Establishing a Basis for Therapeutic Studies

Intervention experiments should begin with a reproducible disease-relevant phenotype and a defined rescue criterion. A compound that increases general translation or proliferation may fail to restore neuronal differentiation, and may introduce other effects. Reversal of a molecular readout should therefore be linked to improvement in a neural phenotype, with evaluation of dose, timing, and toxicity. The present evidence supports this experimental agenda; it does not yet identify a validated therapeutic target or predict clinical benefit from restoring eIF3f abundance alone.

7. Conclusions

Biallelic pathogenic *EIF3F* variants are associated with a molecularly defined neurodevelopmental disorder characterized by variable clinical manifestations. Most evidence concerns the recurrent p.(Phe232Val) allele, whereas the broader allelic spectrum and genotype–phenotype relationships remain incompletely defined. Human iPSC experiments connect this allele to reduced protein abundance and altered translation, but the developmental consequences in neural cells remain unresolved. A useful next phase combines deduplicated longitudinal phenotyping with allele-specific neuronal models, genetic rescue, and integrated measurements of translation and neuronal function. Maintaining the distinction between genetic causality, cellular observations, and mechanistic hypotheses is essential for sound variant interpretation and therapeutic research.

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Abbreviations

The following abbreviations are used in this manuscript:

ASD	autism spectrum disorder
CDK11	cyclin-dependent kinase 11
eIF3	eukaryotic translation initiation factor 3
hnRNP K	heterogeneous nuclear ribonucleoprotein K
IRES	internal ribosome entry site
iPSC	induced pluripotent stem cell
MAFbx	muscle atrophy F-box protein
MECP2	methyl-CpG binding protein 2
MRI	magnetic resonance imaging
mTORC1	mechanistic target of rapamycin complex 1
NDD	neurodevelopmental disorder
NPC	neural progenitor cell
PDCD4	programmed cell death 4
RAN	repeat-associated non-AUG
S6K1	ribosomal protein S6 kinase 1

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