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Advancements in the Study of Clinical Features and Molecular Functions in Heterogeneous TAF1-associated Clinical Phenotypes

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Abstract: *Purpose of review*: TATA-binding protein (TBP)-associated factor 1 (TAF1) encodes the largest component of the transcription factor IID (TFIID) complex, which binds to core promoters and serves as a scaffold for assembly of the RNA polymerase II transcription complex. Variants in TAF1 are associated with X-linked dystonia-parkinsonism (XDP) and X-linked syndromic mental retardation-33 (MRXS33). This review provides a concise summary of the genetic and clinicopathological features of TAF1 variants related to phenotype. *Recent findings*: XDP is an adult-onset X-linked progressive neurodegenerative disorder presenting dystonia and parkinsonism and caused by a SINE-VNTR-*Alu* (SVA)-type retrotransposon within *TAF1.* TAF1/MRXS33 intellectual disability syndrome is characterized by global developmental delay, intellectual disability, facial dysmorphia, generalized hypotonia, and neurological abnormalities due to the missense variants in TAF1. Various symptoms of TAF1 missense mutations may be related to mutations in different functional regions of the protein. The clinical manifestations of XDP and MRXS33, both caused by variants of TAF1, present prominent heterogeneity, which could be influenced by whether the TAF1 mutation is located in the coding region, the time when TAF1 expression decreases, and the effect on downstream gene expression. *Summary*: TAF1 is linked to many different phenotypes because of its variable regulation of coding and noncoding elements, which makes its mechanistic roles in disease challenging to interpret. However, it is important to note that strategies to correct TAF1 splicing could provide therapeutic benefits in different diseases.

Keywords: XDP; MRXS33; SVA; TAF1; Phenotypes

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1. Introduction

The transcription factor IID (TFIID) complex consists of TATA-binding protein (TBP) which includes 13 TBP-associated factors (TAFs). This complex promotes transcriptional initiation by recognizing promoter DNA and combining it with additional universal transcription factors for assembly into functional pre-initiation complexes [1]. *TAF1,* encoding the largest component of TFIID (1893 amino acids), includes various complex functional domains that interact with other proteins or with DNA. Thus, it is reasonable that variants in *TAF1* could cause

diverse phenotypes. Indeed, variants in *TAF1* are associated with X-linked dystonia-parkinsonism (XDP) and X-linked syndromic intellectual developmental disorder-33 (MRXS33). XDP is an adult-onset X-linked progressive neurodegenerative disorder presenting dystonia and parkinsonism and caused by a SINE-VNTR-Alu (SVA)-type retrotransposon in intron 32 of *TAF1* [2]. It is suggested that the retrotransposon disrupts the splicing of *TAF1* mRNA and decreases the expression of *TAF1*. TAF1/MRXS33 intellectual disability syndrome is characterized by general developmental delay (GDD), intellectual disability (ID), facial deformities, generalized hypotonia, and variable neurological abnormalities due to missense variants in *TAF1*. Compared with the XDP, the publications linked to MRXS33 were limited and indicated considerable pleiotropy and clinical variability. The age of onset and clinical manifestations of XDP and MRXS33 are different, and the clinical symptoms are diverse. This paper aims to provide a brief explanation by summarizing the clinical symptoms of these two diseases; how the symptoms relate to different *TAF1* gene mutation patterns and the functions of different domains of the TAF1 protein; and recent advancements in research, both in vitro and in vivo, to understand these diseases.

2. Clinical characteristics of XDP and MRXS33 with TAF1 variants

XDP is an X-linked recessive disorder endemic to Panay Island in the Philippines, affecting 1 in 4000 males on the island [3]. One of the unique clinical features of XDP is the initial presentation of focal dystonia, which generalizes to multiple body regions over time. The dystonic phase of XDP predominates for the first 10–15 years after the patient develops symptoms before the Parkinsonian's symptoms become more predominant. Although the majority of individuals affected by XDP are male, XDP symptoms may also occur in female patients, producing focal, non-progressive dystonia; a staggering gait; and tremors [4]. Previous data indicated that the mean age of onset in men was 39 years, with a range of 12 to 64 years [5]. However, the mean age of onset in women was 52 years, with a range of 26 to 75 years [4]. Parkinsonian features tend to develop as the disease progresses, which may replace or accompany dystonic symptoms [3,5–6]. The non-motor features of XDP, as described in recently published studies, consist of cognitive impairment, alterations of mood (anxiety and depression), executive dysfunction, and impairments in abstract thinking and motor programming [7–9]. To date, over 500 males and 14 females have been identified as having XDP. The basal ganglia, from both clinical studies of patients and pathological studies of post-mortem tissue, have been an important study part of XDP research [5,10–12]. A review of magnetic resonance imaging (MRI) studies in patients with XDP showed that all cases with novel findings had hyperintense putamina rims, and 72% showed caudate head atrophy; however, putamina was detected in only 30% of the images, mostly during the later stage of parkinsonism [11]. Published studies of XDP genetics have confirmed one 2627 bp SVA retrotransposon insertion in intron 32 of *TAF1*, which exhibited a result on the splicing and expression of the TAF1 gene. In 2017, Bragg et al. found a full sequence of an XDP-specific SVA and identified one domain: the hexameric sequence, (CCCTCT)n with a variable number of repeats [13]. In a large sample of probands, the number of repeats of the hexamer ranged from 35 to 52 repeats and demonstrated a perfectly significant negative relationship with the onset age of disease in patients. This foundation was the first evidence confirming a direct correlation between sequence repeats in XDP patients and disease manifestation, thus indicating that the SVA played a significant role in disease pathogenesis. Westenberger et al. supported this notion and further suggested that the number of repeats of the hexamer had significant negative correlations with the onset age of XDP and with *TAF1* expression, and also positive correlations with the severity of disease and deficits of cognitive [14]. In 2021, a further study found that the number of repeats of the hexamer and the degree of repeat instability were higher in the basal ganglia and

cerebellum than in the blood [15].

Other than the special TAF1 variants associated with XDP, missense variants in *TAF1* have been shown to result in TAF1/MRXS33 intellectual disability syndrome (MIM# 300966). Indeed, variants of subunits of TFIID, such as *TBP, TAF2, TAF6,* and *TAF13*, have implied a possible correlation with neurodegenerative diseases and developmental delay. MRXS33 syndrome was initially reported by O'Rawe et al. in eleven independent families with nine distinct single nucleotide variants and two duplications including *TAF1* [16]. Patients displayed GDD, ID, characteristic facial deformities, generalized hypotonia, and variable neurologic abnormalities. It is worth noting that skewed X chromosome inactivation (XCI) was found in all affected and carrier females who tested, comprising asymptomatic heterozygous females in six independent families and one female proband [1]. Thus, it would be reasonable to propose that the XCI skewing test be performed to verify the pathogenic missense variants in *TAF1*. To date, sixty-one ID patients with missense variants in *TAF1* have been reported from forty-eight unrelated families (**Table 1**) [1,16–24]. Of these patients, 57 were male, and 4 were female (3 with de novo mutations, 1 unknown, and 2 with skewed XCI). TAF1 amino acid mutation sites were marked on the TAF1 protein (**Figure 1**), and most mutations were found in triple barrel-winged helix (WH)-α-helical (DUF3591) domain, which interacted with TAF7 and affected gene expression profiles during human development, and tandem bromodomains (BrDs), which are readers of acetyl-lysine residues at the center of histone acetylation signaling network [25–26]. The patients' clinical information is summarized in **Table 1**, and this study classified the clinical manifestations into abnormal birth history; developmental delay; postnatal growth delay (including microcephaly); craniofacial malformation; cardiac malformation; musculoskeletal malformation (including abnormal sacral segmentation); ear, nose, mouth, eye, and throat problems; autism spectrum disorder (ASD); and epilepsy (**Table 1**). The paper also summarizes the clinical features of different *TAF1* missense variants located in different domains (**Table 1**). In addition to developmental delay, craniofacial malformation (41/61, 67.2%), musculoskeletal malformation (37/61, 60.7%), and postnatal growth delay (28/61, 45.9%) were the most common clinical manifestations of *TAF1* missense variants. Meanwhile, patients with amino acid mutation sites located in DUF3591, BrDs, and the non-functional region between the zinc knuckle motif and BrDs are more prone to clinical manifestations of ASD and epilepsy. However, further clinical information is needed to ascertain whether the developmental delay is more severe when the mutations are located in these parts, whether there are more specific clinical features, and why. A summary of brain MRI profiles demonstrates that hypoplasia of the corpus callosum is the most common neuroimaging feature in patients, followed by cerebellar atrophy and ventriculomegaly (**Table 1**).

Table 1. Summary of clinical Features of different TAF1 Missense variants located in different domains

Patient number	Male number	De Novo number	The domain of protein	Abnormal Birth History	Development Retardation	Postnatal Growth Retardation	Craniofacial Malformation	Cardiac Anomalies	Musculoskeletal Deformity	Ear, Nose, Mouth, Eyes, and Throat problem	ASD	Seizure
3	3	1	TAND	0	3	1	1	1	1	1	0	1
9	9	5		1	9	4	4	1	4	4	1	0
15	11	7	DUF3591	3	15	10	12	8	10	10	7	6
11	11	4		1	11	4	10	1	8	4	1	0
1	1	1	Zinc knukle	0	1	0	0	1	0	0	0	0
5	5	1		1	5	3	4	3	5	5	4	1
17	17	5	BrDs	2	17	6	10	6	9	3	7	6

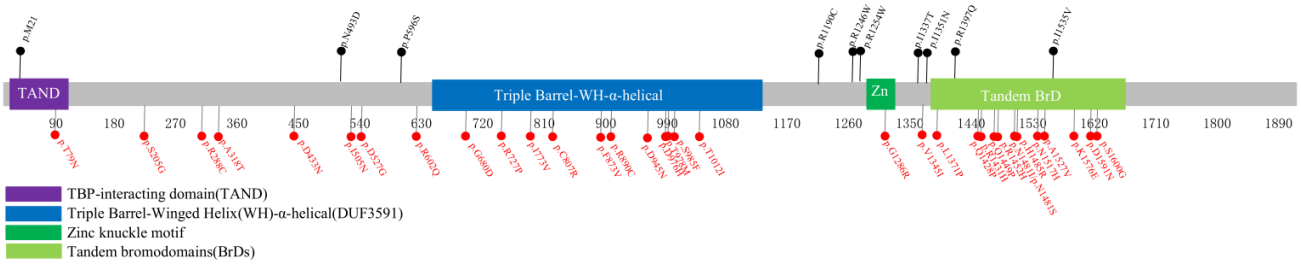

Figure 1. TAF1 functional motifs and the variants identified in the study cohort. Solid black circles at the top indicate reported variants that represent two or more patients, and the solid red circles listed below indicate reported variants that represent one patient. Boxed parts indicate structural TAF1 domains of known functions (RefSeq: NM_004606.4). TAF1, TATA-box binding protein associated factor 1

Table 2 summarizes the different clinical features of XDP and MRXS33. *TAF1* is a large gene, with at least 38 essential exons and several alternative exons, and past research has mapped its many splice variants in various cell types [27]. The published *TAF1* missense mutations associated with developmental delay are all located before exon 32; gnomAD and previous articles have reported that mutations located after exon 32 have no clinical manifestations, while the inheritance pattern of XDP shows that insertion of the SVA in intron 32 causes an adult onset and has no effect on intelligence. Whether the difference in clinical manifestations between the two is related to the form as well as the site of the mutation is an unresolved question that merits further investigation. More and larger cohorts are needed to investigate the relationship between domain function and the clinical phenotypes or pathogenicity of *TAF1* variants.

Table 2. Clinical features of XDP and MRXS33

	TAF1 variants	Age of onset	Clinical characteristics	Neuroimaging
XDP	SVA in intron 32	Late 30s to early 40s	Dystonia; parkinsonism; cognitive impairment	striatal atrophy
MRXS 33	Missense variants; splice variants; duplication	Infancy	Intellectual disability; delayed speech and language development; delayed gross motor development; craniofacial; microcephaly; generalized hypotonia	Hypoplasia of the corpus callosum; cerebellar hypoplasia; central nervous system hypomyelination; ventriculomegaly

3. In vitro and molecular pathology studies of TAF1

The specific *TAF1* transcripts have a reduced expression, which has been identified in blood, post-mortem brain, and fibroblast samples obtained from XDP patients [28]. The initial study by Makino et al. observed a reduced expression of a neuron-specific splice variant of *TAF1* in the human post-mortem XDP caudate nucleus [29]. This isoform designated n*TAF1*, is distinguished by the addition of six nucleotides compared with the canonical transcript (cTAF1). Recently, more studies have focused on induced pluripotent stem cells (iPSCs) and neural cells differentiated from iPSCs obtained from XDP individuals, suggesting that *TAF1* is reduced in patient-derived iPSCs and spiny projection neurons induced from iPSCs [2,13]. However, a study examining the alternative

splicing pattern of *TAF1* mRNA in XDP and control iPSCs identified that similar levels of *TAF1* mRNA containing the microexon 34' are detected between XDP and control, as well as *TAF1* transcription is similar between XDP and control brains [30]. Excision of SVA by genome editing of the XDP iPSC using CRISPR/Cas9-mediated gene editing rescued these defects, restored correct splicing, and normalized TAF1 transcript levels. Likewise, multiple studies have shown that the main genetic cause of XDP is decreased *TAF1* gene expression, whereas excision of SVA by gene editing increases *TAF1* expression [31]. At present, there are three pathological mechanisms that may be involved in XDP: First, the XDP-specific nucleotide change (DSC3) is located in the exon after intron 32 of *TAF1*, which can affect a large number of expression of genes related to vesicular transport and dopamine function. In XDP patients, dopamine transporter imaging by single-photon emission computed tomography (SPECT) demonstrated decreased dopamine reuptake in presynaptic terminals in the bilateral putamen, and ultrasound changes in the substantia nigra were observed [32–34]. Therefore, DSC3-mediated dopamine-centric gene dysfunction may be the molecular pathological mechanism of Parkinson-like symptoms in XDP patients. Second, changes in oxidative stress induced by *TAF1* may be involved in the occurrence of XDP. As early as 2016 and 2017, scholars have studied differential gene expression in fibroblasts from patients with XDP and fibroblasts from normal controls, showing the enrichment of genes related to the ability of cells to handle oxidative stress and the transduction of NF-κB signaling pathway-related inflammatory mediators are involved in the pathogenesis of XDP [28, 35]. Third, increased glutamate receptor expression in XDP neurons results in neuronal excitotoxicity [36]. In conclusion, there is abundant evidence from in vitro studies that the SVA insertion into intron 32 of *TAF1* is associated with the occurrence of XDP, but the specific mechanism remains to be further explored.

There are limited studies on the relationship between MRXS33 and *TAF1* missense mutation and the molecular pathological mechanism. O'Rawe et al. collected blood for RNA-seq studies in a family with two probands (p.Ile1337Thr) [16]. That study found 213 genes to be differentially expressed between the affected male probands and their unaffected families. Transcription factor target enrichment analysis revealed a significant enrichment of genes regulated by E-box proteins (CANNTG promoter motifs), and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis revealed an enrichment of genes involved in Parkinson's disease, Alzheimer's disease, Huntington's disease, and cardiac-muscle contraction. In a subsequent study, a novel variant in TAF1 (p.Ser1600Gly) resulting in MRXS33 showed that there was a different expression of neuronal ion channel genes between *TAF1*-deleted and control SH-SY5Y cells using a special PCR array covering 86 channel genes [24]. Eight genes were confirmed, including *ASIC2, ASIC3, KCNJ14, CACNG4, KCNAB3, CACNA1G, HCN2*, and *KCNH2*, among which the latter three genes were downregulated, and *CACNA1G* was further evaluated, revealing that overexpression in TAF1 variant p.Ser1600Gly, remarkably down expression in *CACNA1G* and the protein level of CACNA1G (CaV3.1). The calcium imaging results were in line with the reduction in CaV3.1 protein. Both TAF1 depletion and the TAF1 variant p.Ser1600Gly could lead to defects in the length of dendrites and the number of interactions in neurons differentiated from SH-SY5Y cells, as well as cell proliferation by downregulation of *CCND1* in SH-SY5Y cells. This finding indicates that the TAF1 variant p.Ser1600Gly may cause clinical manifestations such as ID through loss of function.

In conclusion, *TAF1* mutations may cause loss of function in vitro studies, whether it is a *TAF1* missense variant in MRXS33 or an SVA insertion in intron 32 in XDP. According to RNA-seq and ChIP-seq, the difference in symptoms between the two may be related to neuronal development and ion channels, with the latter mutation being related to oxidative stress and glutamate receptor activation. However, it should be highlighted that the RNA-seq results are preliminary, and more experiments should be performed to confirm the expression of the key genes and molecular pathways.

4. Studies on in vivo levels of TAF1

To date, XDP studies on in vivo levels of *TAF1* have mainly focused on the brain tissue of patients; there are few XDP-related animal models. Autopsy studies of patients with XDP have shown that the loss of medium spiny neurons (MSNs) and astrocytes in the dorsal striatum correlates with the clinical presentation of XDP patients [10, 37]. In XDP tissue, a marked loss of neuropeptide Y (NPY) interneuron staining was observed in the caudate nucleus and putamen, primarily exerting a slow modulation of its postsynaptic targets (MSNs) [37]. Altered MSN modulation triggers hyperexcitability of cortical inputs, leading to neurotoxicity. Makino et al. used quantitative RT-PCR to find that the n*TAF1* isoform was significantly reduced in the XDP caudate nucleus as well as in the cortex and nucleus acumens [29]. These findings suggest that reduction of n*TAF1* may lead to neuronal loss in XDP brains. Similarly, Cirnaru et al. also found in animal experiments that targeted reduction of *ctaf1* and/or *ntaf1* in neonatal mice and rats resulted in a dyskinesia phenotype and a reduction in striatal cholinergic interneurons [38]. Although the mouse and rat animal models established by Cirnaru et al. cannot represent the genetic animal models of XDP, they are the first animal models to show the specific roles of n*TAF1* and c*TAF1* in the nervous system.

Previous studies have shown that *TAF1* expression is necessary for early embryonic development in mice and *C. elegans*, so changes in *TAF1* expression may produce severe consequences [39–41]. Therefore, few animal models have been established to investigate dysfunctional *TAF1* missense mutations associated with MRXS33. First, to explore the pathogenic mechanism involved in MRXS33 caused by a mutation in the *TAF1* gene, O'Rawe et al. designed a splice-blocking morpholino (MO) and CRISPR/Cas9 targeting to knockdown or disrupt *taf1* [16]. The area of the optic tectum, occupying the majority of the space within the midbrain, was smaller in embryos injected with the *taf1* MO than in control embryos. This observation provided evidence for a functional link between a neuronal phenotype and *TAF1* mutations. In agreement with this observation, a recent study created the first complete knockout model of the *TAF1* orthologue in zebrafish by using CRISPR/Cas9 to investigate *taf1*'s role during embryogenesis, revealing that *taf1* knockout zebrafish embryos display lethal malformations implying embryonic lethality [1]. In conclusion, it can be inferred from the study that *TAF1* played an essential role in embryonic development and specifically in neurodevelopmental processes. Moreover, transcriptome analysis and Protein Analysis Through Evolutionary Relationships (PANTHER) of *taf1* zebrafish knockout suggest that *taf1* regulates genes that are important for neurodevelopmental processes [1]. Because of the embryonically of *TAF1* deletion, the animal model of MRXS33 which understands how mutations in *TAF1* contribute to neurological deficits failed. Thus, aside from the previous zebrafish model, a novel animal model in which the *TAF1* gene is deleted in rat pups was achieved by using CRISPR/Cas9 technology and somatic brain transgenesis mediated by lentiviral transduction [42]. Either guide RNA (gRNA)-control or gRNA-*TAF1* lentiviral vectors were administered to rat pups by intracerebroventricular (ICV) injection on postnatal day 3, followed by a battery of behavioral tests on postnatal days 14 and 35 [42]. As predicted, the rat model replicated the clinical features of *TAF1* ID syndrome, with young rats showing motor deficits similar to those of juvenile humans. Histopathological analysis showed that *TAF1* deletion led to cerebellar and cortex abnormalities, where Purkinje cells were observed to be decreased in number as determined by Calbindin staining. The results suggested a possible cellular basis for the motor defects and morphological changes in the cerebellum and cerebral cortex, especially the loss of Purkinje cells. Further electrophysiological examination performed on Purkinje cells showed that the frequency of spontaneous excitatory postsynaptic currents (sEPSCs) was significantly decreased below the control level with *TAF1* editing, and this change was associated with reduced CaV3.1 protein expression in the *TAF1*-edited animals [43–44]. Then, it was found that treatment of SAK3, a T-type calcium channel enhancer, protected Purkinje and granule cells from apoptosis, restored sEPSCs in *TAF1*-edited Purkinje cells, and prevented the loss of cortical neurons and

GFAP-positive astrocytes by *TAF1* gene editing [45–46]. Overall, a *TAF1*-edited rat animal model suggests that *TAF1*-related dyskinesia may be associated with cerebellar Purkinje cell changes induced by presynaptic CaV3.1 deletion, but this animal model does not replicate all clinical manifestations of MRXS33, and new animal model and treatment strategies need to be developed.

In the currently developed animal model, knockdown of *Taf1* expression by gene editing causes a dyskinesia phenotype in postnatal rats and mice. However, posttranscriptional reduction of c/n*Taf1* expression does not cause cerebral or cerebellum morphological alterations, and knockdown of *Taf1* expression by CRISPR-targeted exon 1 contrasted with Purkinje cell loss and cortical abnormalities. Although the clinical symptoms presented in these two animal models do not fully represent XDP or MRXS33 but may serve as a hint: *TAF1* noncoding mutations cause XDP due to post-transcriptional modification, whereas *TAF1* missense mutations in *TAF1* cause MRXS33 due to loss of function.

5. Summary

Based on current knowledge, TAF1 is an important component of TFIID, regulating the expression of other genes that could account for the diseases associated with variants in *TAF1*. However, which downstream gene changes are caused by *TAF1* mutations and how the mutations relate to XDP and MRXS33 neuropathology are questions that remain to be fully investigated. In addition, the *TAF1* missense mutations found to be associated with MRXS33 were all located before exon 32, while the SVA insertion was in intron 32, and the decreased expression of *TAF1* in XDP may be related to post-transcriptional modification. The clinical manifestations related to *TAF1* mutation are related to the mutation located in the translated or untranslated region, but whether it is related to the location in different functional regions or before or after exon 32 needs further study. The downstream gene changes caused by different mutations and the molecular pathology of XDP or MRXS33 need to be fully studied. Only with this knowledge can treatments for *TAF1* mutation-related diseases be developed; importantly, it is expected that strategies to correct *TAF1* splicing could provide therapeutic benefits in a variety of diseases.

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