CellPress

Review

# Human TBK1: A Gatekeeper of Neuroinflammation

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**The importance of TANK binding kinase-1 (TBK1), a multimeric kinase that modulates inflammation and autophagy, in human health has been highlighted for the first time by the recent discoveries of mutations in *TBK1* that underlie amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), normal tension glaucoma (NTG) or childhood herpes simplex encephalitis (HSE). Gain-of-function of *TBK1* are associated with NTG, whereas loss-of-function mutations result in ALS/FTD or in HSE. In light of these new findings, we review the role of *TBK1* in these seemingly unrelated, yet allelic diseases, and discuss the role of TBK1 in neuroinflammatory diseases. This discovery has the potential to significantly increase our understanding of the molecular basis of these poorly understood diseases.**

## TBK1 at Multiple Crossroads

**Tumor necrosis factor (TNF) receptor-associated factor NF-κB activator (TANK)-binding kinase 1 (TBK1)** (see Glossary), also known as NF-κB-activating kinase (NAK) or T2K, has recently attracted the attention of human geneticists, immunologists, and neurologists alike for its critical role in central nervous system (CNS) pathology. It is a ubiquitously expressed serine–threonine kinase belonging to the 'noncanonical IκB kinases' (IKKs) recognized for its critical role in regulating type I interferon (IFN) production [1]. TBK1 is involved in the activation of various cellular pathways leading to IFN and proinflammatory cytokine production following infection [1], autophagic degradation of protein aggregates [27] or pathogens [2–4], and homeostatic cellular functions such as cell growth and proliferation [5]. Research in genetics has experienced an increased pace of discovery owing to advances in sequencing technologies that have begun to reveal numerous new genetic etiologies underlying various diseases [115]. The recent discoveries of TBK1 heterozygous mutations in four human diseases have demonstrated the nonredundant role of this multifaceted protein in the CNS in particular [6–11] (Figure 1). Here we review the pleiotropic role of TBK1 in light of new discoveries of human germline *TBK1* mutations underlying neuroinflammatory diseases including HSE, ALS, **FTD**, and NTG. These novel findings have emerged following the first identification of a series of genetic etiologies defining disease (HSE) or after a period of stagnant gene discovery (ALS, FTD, NTG). The data implicate new molecular pathways in disease pathogenesis. Consequently, discerning these pathways may lead to a better understanding of the causal mechanisms underlying such neurological disorders. Moreover, knowledge gained from further molecular investigation could be used to develop new and perhaps more effective therapies for these neurological diseases, which currently have limited treatment options.

## TBK1 in Inflammatory Pathways

TBK1 was first identified as a TANK-interacting protein in mice [12], with a role in controlling NF-κB-mediated responses as demonstrated in luciferase reporter assays of HEK293T cells

### Trends

HSE, in a subset of children, is caused by impaired antiviral interferon (IFN) production due to monogenic mutations in the toll-like receptor 3 (TLR3)–IFN signaling pathway, including mutations in *TBK1*.

Due to advances in sequencing technologies, several new amyotrophic lateral sclerosis (ALS) or ALS–frontotemporal dementia (ALS-FTD) genes have been identified, five of which are known to be involved in autophagy (*SQSTM1*, *VCP*, *OPTN*, *UBQLN2*, and *TBK1*). These mutations are thought to contribute to disease pathogenesis, possibly due to impaired autophagy.

The genetic etiology of normal tension glaucoma (NTG) has recently been attributed to copy number variants (CNVs) found in chromosome region 12q14, specifically leading to duplications of the *TBK1* gene. This duplication has been found to increase *TBK1* transcript levels, suggesting a gain-of-function role for *TBK1* in NTG.

Recent developments in the field of selective autophagy have implicated this evolutionarily conserved process in innate immunity and pathogen clearance, including in neuronal cells.

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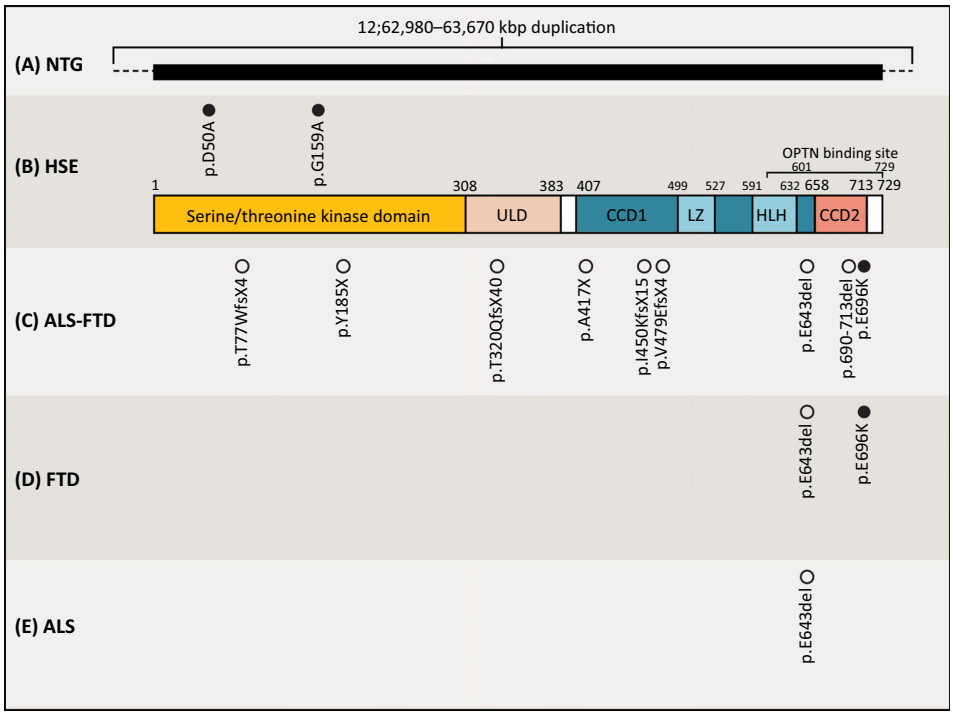


Trends in Molecular Medicine

Figure 1. Disease-Causing Mutations in Human *TBK1*. TBK1 is an 84-kDa, 729-amino-acid protein comprising a kinase domain, a ubiquitin-like domain (ULD), and coiled-coiled domains 1 and 2 (CCD1, CCD2). The kinase domain is critical for the phosphorylation of various substrates such as interferon- regulatory factor 3 (IRF3) [15] whereas the ULD domain regulates kinase activation and interactions with other proteins in the TBK1 pathway [97]. The CCD1 domain harbors leucine zipper (LZ) and helix–loop–helix (HLH) domains, which specifically control dimerization. The C-terminal CCD2 harbors an adaptor-binding motif facilitating the interaction of TBK1 with its adaptors TANK, NF-κB-activating kinase (NAK)-associated protein 1 (NAP1), similar to NAP1 TBK1 adaptor (SINTBAD) and OPTN [33,89]. Germline human *TBK1* mutations have been reported to be disease causing in (**A**) normal tension glaucoma (NTG), (**B**) herpes simplex encephalitis (HSE), (**C**) amyotrophic lateral sclerosis–frontotemporal dementia (ALS-FTD), (**D**) FTD, and (**E**) ALS; these mutations are shown with respect to their amino acid positions within the TBK1 protein. The black horizontal box in (A) indicates duplications in kilobases reported to include *TBK1*. Open circles represent loss-of-function (LoF) variants; filled circles represent missense variants (Table 1). Abbreviation: TBK1, tumor necrosis factor receptor-associated factor NF-κB activator (TANK)-binding kinase 1.

cotransfected with TBK1 and the NF-κB promoter [13]. However, in contrast to canonical IKKs (IKKα and IKKβ) that control NF-κB activation, the noncanonical IKKs (TBK1 and IKKε) have since been found to play a more important role in the activation of transcription factors of the IFN-inducing IFN-regulatory factor (IRF) family [14]. TBK1 has been shown to play a key role in multiple cellular pathways, particularly inflammation and autophagy. TBK1 sits at the crossroads of multiple pathways, including NF-κB and IRF3, and controls multiple target genes, including type I and type III IFNs.

**Pattern recognition receptors (PRRs)** such as toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and cytosolic DNA receptors all play important roles in the recognition of invading pathogens leading to IFN production (Figure 2, Key Figure). The engagement of such innate immune sensors by their cognate ligands, such as lipopolysaccharide (LPS), double-stranded RNA (dsRNA), or DNA, results in the production of cytokines that alert neighboring cells (including immune cells) of danger and foreign invasion, subsequently promoting the early events of defense against infection. Engagement of TLR3 by dsRNA recruits its adaptor TIR domain-containing adaptor-inducing IFN-β (TRIF), eventually activating TBK1,

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