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# Tau tubulin kinase 2 is required to initiate mammalian ciliogenesis

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Despite the critical importance of cilia in development and disease, the biochemical pathways that initiate ciliogenesis at the mother centriole are not well understood. Here we describe the identification of a serine-threonine protein kinase, *Ttk2*, as an essential component of the ciliary initiation pathway. The mouse mutant *bartleby* (*bby*) was isolated in a genetic screen in our lab based on phenotypes consistent with a severe disruption in Hh signaling, and immunostaining and scanning electron microscopy revealed that *bby* mutants lack cilia. The *bby* phenotype is caused by a nonsense mutation in the gene encoding Tau Tubulin Kinase 2 (*Ttk2*), truncating the protein within the kinase domain. Independent studies have shown that human mutations in *Ttk2* are associated with the human neurodegenerative disorder spinocerebellar ataxia type 11. We show that *Ttk2::GFP* localizes to the distal mother centriole in cells prior to ciliary axoneme extension, and to the transition zone between the basal body and axoneme in ciliated cells. In *Ttk2bby* mutant cells, components of the IFT complexes, such as IFT88 and IFT140, are not recruited to the transition zone. Thus *Ttk2* acts at a step upstream to IFT in the process of cilia formation and is a critical component of a pathway regulating the initiation of ciliogenesis. Although several kinases have roles in ciliogenesis, *Ttk2* is thus far the only kinase found to have an essential role in cilia formation. Moreover, identification of *Ttk2* substrates and upstream regulators has the potential to reveal other regulators of this important step in ciliogenesis.

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