



Truncating mutations in *YIF1B* cause a progressive encephalopathy with various degrees of mixed movement disorder, microcephaly, and epilepsy

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Several intracellular proteins are involved in mediating vesicular transport of protein and lipid cargo from the endoplasmic reticulum (ER) to the Golgi apparatus (GA) in eukaryotic cells. Errors in membrane trafficking between ER and GA have been implicated in brain disorders [1, 7], showing that these processes are critical for neuronal biogenesis. An important protein in these processes is YIF1B, an intracellular 314-residue transmembrane protein. Hippocampal neurons from Yif1B knockout (KO) mice showed that Yif1B is implicated in anterograde trafficking and Golgi architecture [1], where depletion of Yif1b caused disorganization, fragmentation, and volume reduction of the GA in pyramidal neurons.

Mohammed AlMuhaizea, and Rawan AlMass have equal contribution.

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Here we describe six patients from five unrelated families presenting with profound developmental and motor delay with dystonia, dysphagia, hypotonia, epilepsy and microcephaly, and homozygous truncating variants in *YIF1B* encountered by whole exome sequencing (WES), identifying *YIF1B* as a novel disease gene in humans (Fig. 1, Supplementary Fig. 1, Supplementary Table 1, online resource for detailed clinical information).

Clinical examinations revealed that all patients had an unremarkable pregnancy and birth, and no major dysmorphic features. Hypotonia and global developmental delay were noticed in infancy with smiling and partial babbling as their best achieved social and language skills. Motor development remained profoundly affected without head control, rolling or sitting. By age 2–3 years distal, limb choreiform movements started in four individuals which evolved into axial and limb dystonia with dyskinesia by the age of 4–8 years. Dystonia was unresponsive to levodopa or carbidopa but partially improved

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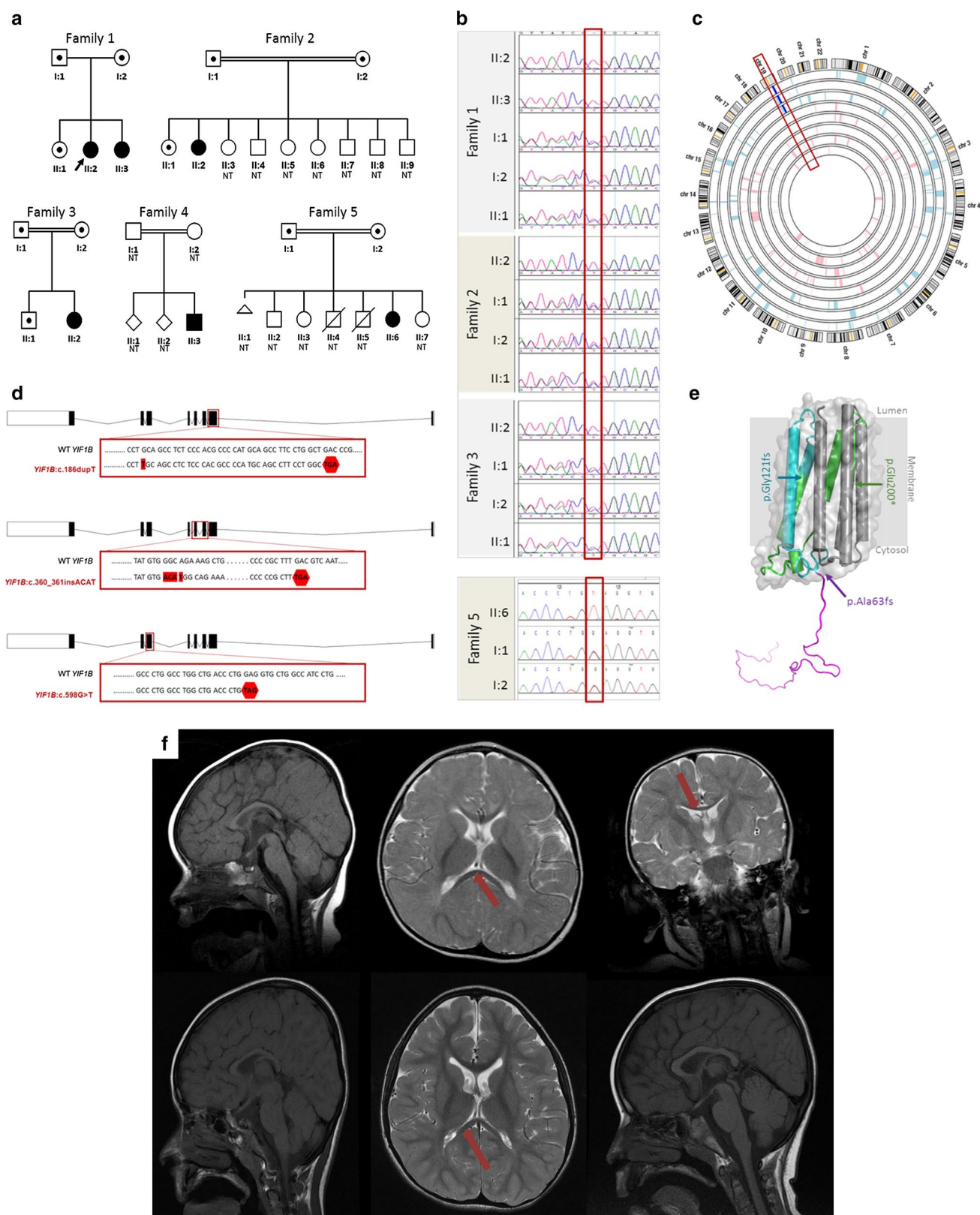
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on trihexyphenidyl. Two individuals developed epileptic seizures at 6- to 8-months. EEG showed multiple bilateral epileptiform discharges and abnormal background

indicating diffuse dysfunction. Microcephaly was found in all but one individual. There were no exaggerated startle, organomegaly or neurocutaneous stigmata. Hearing

Fig. 1 **a** Pedigrees of six affected individuals from five families. **b** Sanger sequencing reveals segregation of the variants in the tested families. **c** An ROH was detected on chromosome 19 including *YIF1B*. **d** Scheme of *YIF1B* transcripts, affected exons, and resulting truncations. **e** 3D structural model for YIF1B. Helices are shown as cylinders, and the predicted molecular surface of the structured transmembrane portion of YIF1B is indicated. The flexible cytosolic region is shown in an arbitrary conformation. Protein regions retained in the variants are shown in magenta (p.Ala63fs) and magenta/cyan (p.Gly121fs) and magenta/cyan/green (p.Glu200*). The residues resulting from the frame shifts were not included (see Supplementary Figs. 2 and 3). **f** Brain MRI. Mild thinning of the corpus callosum was noted in all patients with the founder mutation

was normal. One case presented with cortical blindness. Repeated MRI brain imaging showed mild thinning of the corpus callosum in the majority of cases without other structural abnormalities, with brain atrophy in one case (Fig. 1f). Other standard metabolic investigations in serum and liquor were unremarkable. Hence, all individuals with truncating *YIF1B* variants shared a similar phenotypical spectrum. All affected residues encountered were highly conserved and identified variants (c.186dupT:p.Ala64fs; c.360_361insACAT:p.Gly121fs; c.598G > T:p.Glu200*) were absent from gnomAD and other databases of healthy individuals with no other homozygous loss-of-function variants found (Supplementary Fig. 1b online resource).

YIF1B is widely expressed at mRNA and protein levels in all tissues including neuronal cells, in particular raphe neurons (Supplementary Figs. 2–4, online resource). Functional and network analyses identified 171 genes that are co-regulated with *YIF1B* in over 46,000 human RNAseq samples ($r \geq 0.9$), that were enriched in genes involved in neurological and development disorders, and nervous system development and function (p value < 0.01) (Supplementary Fig. 5a, b and Supplementary Tables 2, 3, online resource).

In rat, the YIF1B ortholog interacts with serotonin receptor 1 (5-HT1AR) which is a Gi/Go protein-coupled receptor in dendrites of serotonin neurons of the raphe nuclei. Co-localization of Yif1B and 5-HT1AR was observed in intermediate compartment small vesicles, showing Yif1B involvement in transient intracellular trafficking and modulation of 5-HT1AR transport to dendrites [2, 3]. Hence, defects on Yif1B may lead to the impairment of the physiological functioning of 5-HT1AR [4]. YIF1B also interacts with the lysosomal protein TAPL in humans [5]. In HeLa cells, overexpressing truncated YIF1B reduced TAPL's lysosomal localization and co-localization with truncated YIF1B in the *cis*-Golgi [6]. In addition, Yif1B interacts with Rab6, a recycle trafficking protein. Therefore, alterations of this interaction may lead to aggregates' accumulation in neurons, which has been reported to cause neurodegenerative diseases [1]. These findings show that to fulfill its biological function, YIF1B interacts with different proteins and controls

their trafficking. Consequently, mutations affecting protein binding sites or subcellular localization of YIF1B are expected to cause trafficking deficiencies of its interaction partners.

Computational protein modelling of YIF1B predicted that the first ~ 68 residues form a cytosolic disordered region and indicated the presence of transmembrane helices in the remaining ~ 250 residues (Fig. 1e, Supplementary Fig. 6a, b, online resource). The p.Gly121fs variant leads to the insertion of 31 non-related residues which are predicted to be unstructured (Supplementary Fig. 6a–c online resource). Although we cannot rule out that this variant might retain some capacity to insert into membrane, its biological function is most likely lost. The p.Ala63fs variant leads to the introduction of 12 unrelated residues following Pro62 before the stop codon, resulting in truncation before the first helix, indicating a complete loss of function. The variant p.Glu200* has 3.5 transmembrane helices missing, which is, therefore, predicted to be non-functional.

Hence, the reported disease phenotypes are corresponding to the effects of a complete loss-of-function of YIF1B. Collectively, our data provide a demonstration of the importance of *YIF1B* in humans and argue that this gene is involved in a novel neurogenetic disorder. Further functional studies are required to unravel the precise pathogenetic mechanisms of this novel disease entity.

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Author contributions NK conceived and designed the experiments. RAM, AAH, JH, JAS, LAQ and AB performed experiments. DC, MS, PB, ABA, AB analyzed data. DC performed bioinformatics, pathway and network analyses. SA performed protein modeling. MAM, LAQ collected specimen. MAM handled biopsies, undertook patient care and management, collected clinical data, and delineated the patients' phenotype (F1, F2, and F3). AC helped MAM to recruit one patient. TB, MSC, PB, AB-A, JI, PK collected clinical data (F4, F5). NK, TSB, EMS, MAM, DC, JH, IHK wrote the paper.

Compliance with ethical standards

Conflict of interest MSC, PB and ABA are employees of CEN-TOGENE AG. AB is an employee of GeneDx. The other authors declare no conflict of interest.

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