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## Bi-allelic mutations in *TRAPPC2L* result in a neurodevelopmental disorder and have an impact on RAB11 in fibroblasts

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### Abstract

**Background** The combination of febrile illness-induced encephalopathy and rhabdomyolysis has thus far only been described in disorders that affect cellular energy status. In the absence of specific metabolic abnormalities, diagnosis can be challenging.

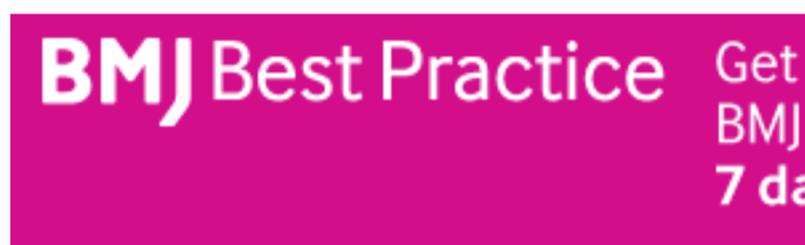
**Objective** The objective of this study was to identify and characterise pathogenic variants in two individuals from unrelated families, both of whom presented clinically with a similar phenotype that included neurodevelopmental delay, febrile illness-induced encephalopathy and episodes of rhabdomyolysis, followed by developmental arrest, epilepsy and tetraplegia.

**Methods** Whole exome sequencing was used to identify pathogenic variants in the two individuals. Biochemical and cell biological analyses were performed on fibroblasts from these individuals and a yeast two-hybrid analysis was used to assess protein-protein interactions.

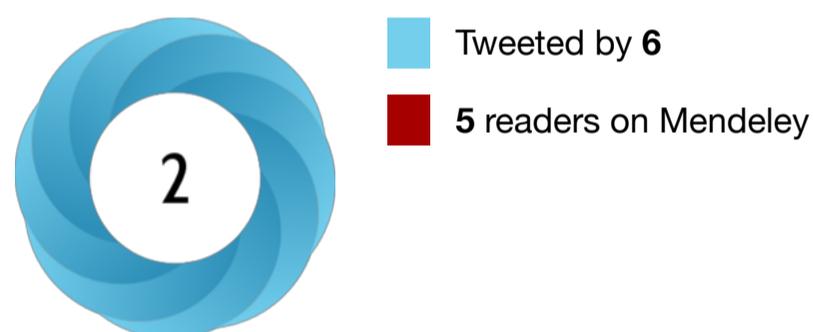
**Results** Probands shared a homozygous *TRAPPC2L* variant (c.109G>T) resulting in a p.Asp37Tyr missense variant. TRAPPC2L is a component of transport protein particle (TRAPP), a group of multisubunit complexes that function in membrane traffic and autophagy. Studies in patient fibroblasts as well as in a yeast system showed that the p.Asp37Tyr protein was present but not functional and resulted in specific membrane trafficking delays. The human missense mutation and the analogous mutation in the yeast homologue Tca17 ablated the interaction between TRAPPC2L and TRAPPC10/Trs130, a component of the TRAPP II complex. Since TRAPP II activates the GTPase RAB11, we examined the activation state of this protein and found increased levels of the active RAB, correlating with changes in its cellular morphology.

**Conclusions** Our study implicates a RAB11 pathway in the aetiology of the TRAPPC2L disorder and has implications for other TRAPP-related disorders with similar phenotypes.

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Footnotes

MPM, CG, DK and WFEK contributed equally.

**Contributors:** MPM performed the membrane trafficking assays, all microscopy and edited the manuscript. CG phenotyped the patients and wrote the manuscript. DK has cared for subject S2 since the age of 10 months, coordinated all investigations, collected samples, gathered data, participated in writing the case report and edited the manuscript. WFEK analysed the clinical data, drafted the tables and clinical figures and edited the manuscript. NA performed the yeast two-hybrid analyses and edited the manuscript. DMC and MSe analysed the clinical data and edited the manuscript. TBH, KD, AI and HP performed and interpreted exome analysis. TP and FP processed, analysed and validated the whole

exome sequencing data. DSD performed the biochemical analyses and edited the manuscript. DS performed the autophagy experiments. GC performed and analysed the muscle biopsy. KLLvG critically reviewed the manuscript. JZ was involved in clinical and genetic discussions, confirmed segregation of TRAPPC2L in the family of subject S2 and edited the manuscript. CF performed the clinical genetic characterisation of subject S2, performed genetic counselling and edited the case report and the manuscript. She also did the Sanger sequencing of the candidate genes and confirmed segregation of TRAPPC2L in the family. JAM analysed the muscle biopsy for mitochondrial function, assisted with the interpretation of enzymatic and genetic results and interpreted the exome data. MSa designed the study, interpreted the data and wrote the manuscript. PMvH conceptualised the study, analysed and interpreted the clinical data and wrote the manuscript.

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