The American Journal of Human Genetics, Volume *92*

Supplemental Data

Mutations in *BICD2* Cause Dominant Congenital Spinal Muscular Atrophy and Hereditary Spastic Paraplegia

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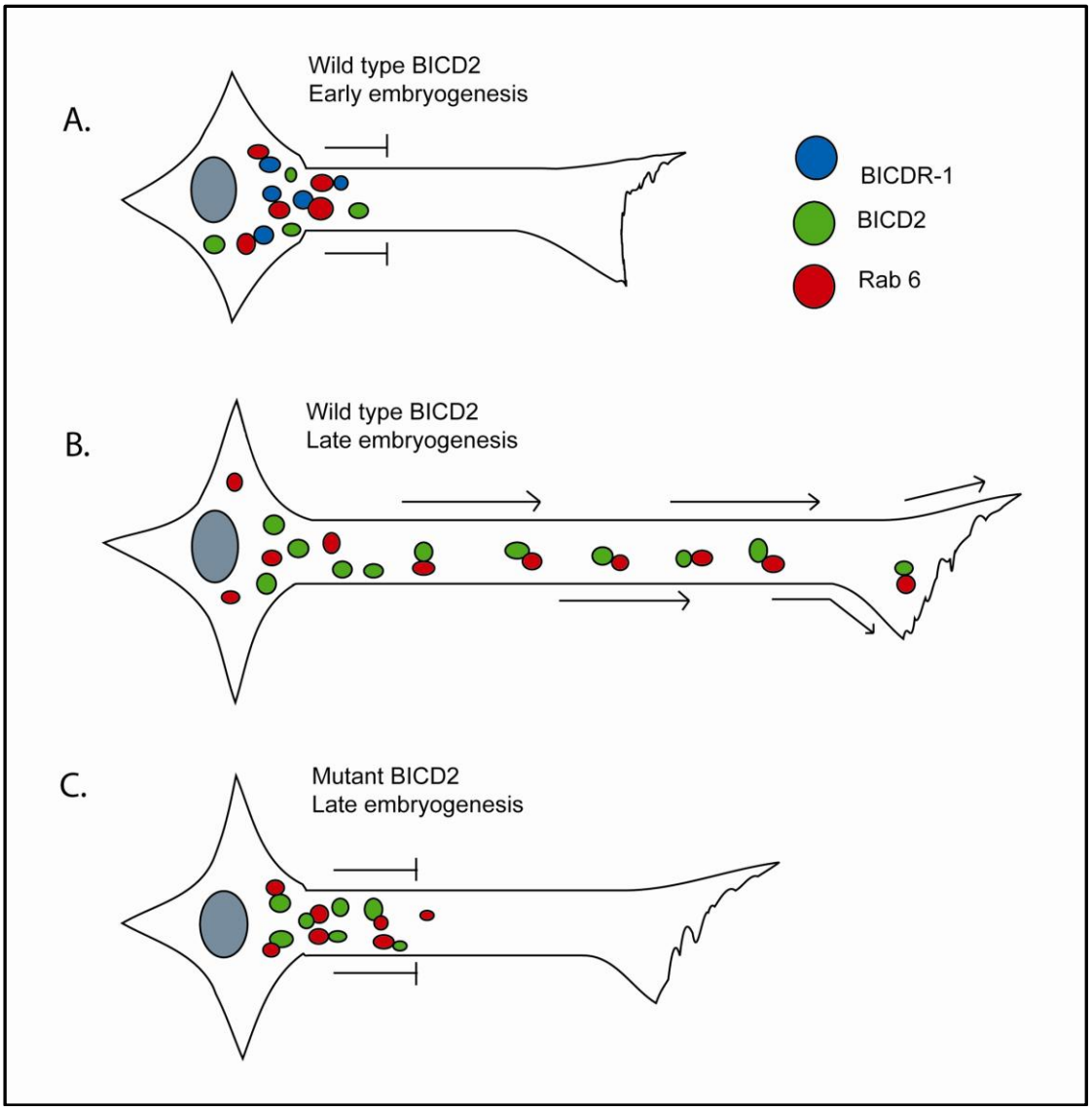

Figure S1. A Proposed Disease Mechanism for DCSMA Caused by Mutations in *BICD2*

(A) The proposed pathomechanism of DCSMA due to mutations in *BICD2*. In early embryogenesis, Bicaudal related protein-1 (BICDR-1) sequesters Rab6 positive vesicles to the pericentrosome preventing their anterograde transport to growth cones.

(B) In late embryogenesis (Post day 10 in mice), BICDR-1 is down regulated, allowing anterograde transport of Rab6 positive vesicles part mediated by BICD2 from the Golgi to the growth cone required for neurite extension (Silencing of Rab6 and overexpression of BICDR-1 in late embryogenesis impairs neurite outgrowth). (C) In the case of mutant BICD2, the increased binding affinity to the dynein/ dynactin complex shifts the balance in favour of retrograde transport and impairs transport of Rab6 positive vesicles to peripheral growth cones - impairing neurite outgrowth.

Supplemental Acknowledgments

AMR is funded by the National Institutes of Neurological Diseases and Stroke and office of Rare Diseases (U54NS065712), and an IPSEN clinical research fellowship. ECO is funded by a National Health and Medical Research (NHMRC) postgraduate scholarship. RS is supported by a University of Tübingen IZKF grant 1970-0-0. MAG is supported by an FWF (P23223-B19) grant. MPM is supported by a Thyne Reid Foundation grant. DNH and JES (USA1) are supported by the Inherited Neuropathies Consortium RDCRN, NINDS- 1U54NS0657. MMR is funded by a Medical Research Council (MRC), MRC Centre grant (G0601943), and by the National Institutes of Neurological Diseases and Stroke and office of Rare Diseases (U54NS065712). Work undertaken at University College London Hospitals/University College London was partly funded by the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. NFC and KNN are funded by NHMRC Centre for Research Excellence grant #1031983 and NHMRC Project Grant #1022707.