Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly

Titre	Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly
Type de publication	Article de revue
Auteur	Poirier, K. [1], Lebrun, N. [2], Broix, L. [3], Tian, G. [4], Saillour, Y. [5], Boscheron, C. [6], Parrini, E. [7], Valence, S. [8], Pierre, B. S [9], Oger, M. [10], Lacombe, D. [11], Geneviève, D. [12], Fontana, E. [13], Darra, F. [14], Cances, C. [15], Barth, Magalie [16], Bonneau, Dominique [17], Bernadina, B. D [18], Tich, Sylvie Nguyen The [19], Gitiaux, C. [20], Parent, P. [21], V. Portes, des [22], Pedespan, J. M [23], Legrez, V. [24], Castelnau-Ptakine, L. [25], Nitschke, P. [26], Hieu, T. [27], Masson, C. [28], Zelenika, D. [29], Andrieux, A. [30], Francis, F. [31], Guerrini, R. [32], Cowan, N. J [33], Bahi-Buisson, N. [34], Chelly, J. [35]
Editeur	Nature Publishing Group
Type	Article scientifique dans une revue à comité de lecture
Année	2013
Langue	Anglais
Date	2013
Numéro	6
Pagination	639 - 47
Volume	45
Titre de la revue	Nature genetics
ISSN	1546-1718
Mots-clés	Animals [36], Cell Movement [37], Cercopithecus aethiops [38], COS Cells [39], Cytoplasmic Dyneins/genetics [40], Exome [41], Genetic Association Studies [42], Germ-Line Mutation [43], Humans [44], Kinesin/genetics [45], Lissencephaly/genetics/pathology [46], Magnetic Resonance Imaging [47], Malformations of Cortical Development/genetics/pathology [48], Mice [49], Microcephaly/genetics/pathology [50], Models, Molecular [51], Mutation, Missense [52], Neuroimaging [53], Pedigree [54], Sequence Analysis, DNA [55], Tubulin/genetics [56]

Résumé en anglais	The genetic causes of malformations of cortical development (MCD) remain largely unknown. Here we report the discovery of multiple pathogenic missense mutations in TUBG1, DYNC1H1 and KIF2A, as well as a single germline mosaic mutation in KIF5C, in subjects with MCD. We found a frequent recurrence of mutations in DYNC1H1, implying that this gene is a major locus for unexplained MCD. We further show that the mutations in KIF5C, KIF2A and DYNC1H1 affect ATP hydrolysis, productive protein folding and microtubule binding, respectively. In addition, we show that suppression of mouse Tubg1 expression in vivo interferes with proper neuronal migration, whereas expression of altered gamma-tubulin proteins in Saccharomyces cerevisiae disrupts normal microtubule behavior. Our data reinforce the importance of centrosomal and microtubule-related proteins in cortical development and strongly suggest that microtubule-dependent mitotic and postmitotic processes are major contributors to the pathogenesis of MCD.
URL de la notice	http://okina.univ-angers.fr/publications/ua8340 [57]
DOI	10.1038/ng.2613 [58]
Lien vers le document	http://dx.doi.org/10.1038/ng.2613 [58]
Titre abrégé	Nat Genet

Liens
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[58] http://dx.doi.org/10.1038/ng.2613