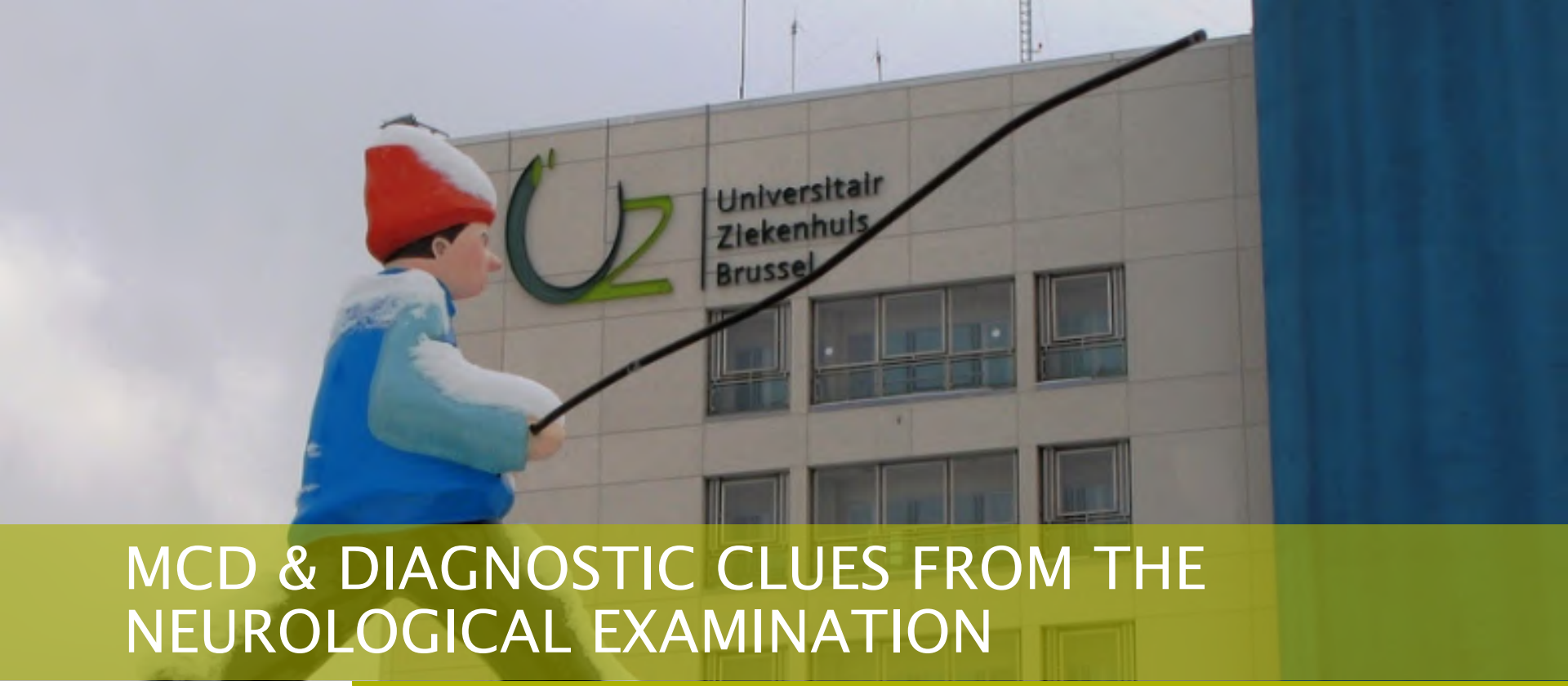


MCD & DIAGNOSTIC CLUES FROM THE NEUROLOGICAL EXAMINATION

Anna Jansen, MD, PhD

Universitair Ziekenhuis Brussel

KidZ Health Castle

VUB

BRAIN MALFORMATIONS

Clues from associated neurological symptoms

1. POLYNEUROPATHY
2. MYOPATHY / MUSCULAR DYSTROPHY
3. SPINAL MUSCULAR ATROPHY
4. SPASTIC PARAPLEGIA
5. MOVEMENT DISORDER

POLYNEUROPATHY

20 year old man

5M
Bifacial weakness, eyelid ptosis

2Y
Developmental language delay

6Y
Mild ID, ASD, ADHD

13Y
Axonal sensorimotor PNP
Carpal tunnel release procedure

15Y
Urinary incontinence
Bilateral pyramidal syndrome

20 YEAR OLD MAN

Diagnostic work-up

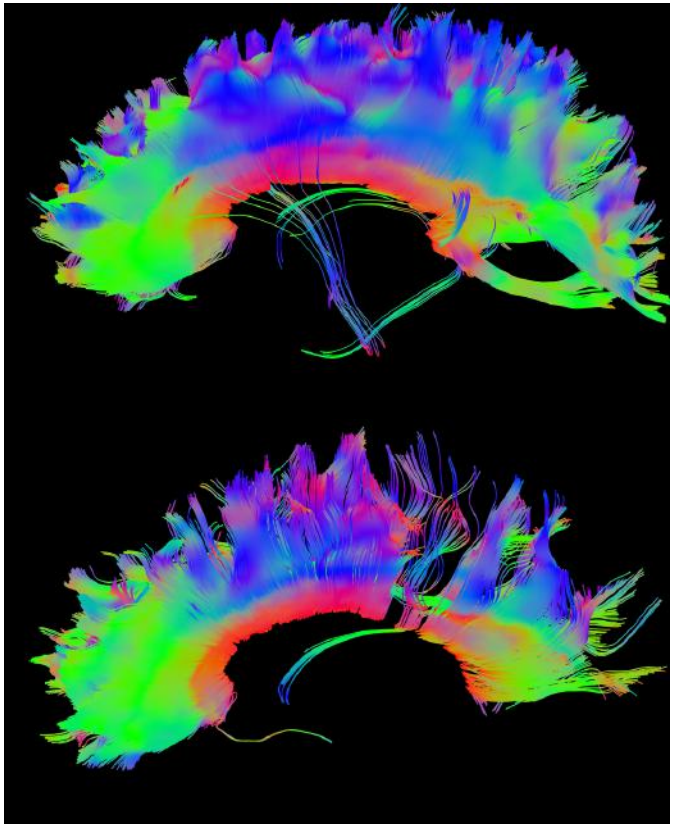
MRI of brain and orbita

- thinning posterior part corpus callosum
- hypotrophic optic nerves
- atrophy extra-ocular muscles

Mitochondrial disorders? Negative

Sequencing analysis of *TUBB3*

- c.1250A>T, p.(Asp417Val)
- *de novo*



Courtesy of Dr Régal

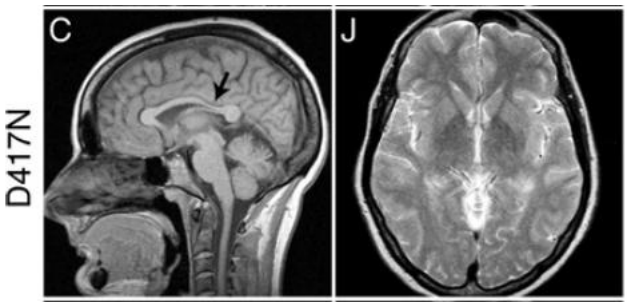
MCD - POLYNEUROPATHY

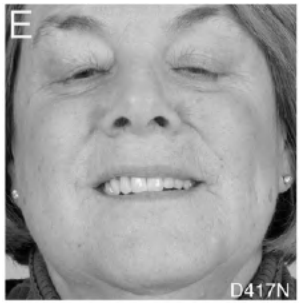
TUBB3

Cell

Human *TUBB3* Mutations Perturb Microtubule Dynamics, Kinesin Interactions, and Axon Guidance

Max A. Tischfield,[1,2,3,4,9] Hagit N. Baris,[3,5,54,55] Chen Wu,[1,2,9,15,54] Guenther Rudolph,[13] Lionel Van Maldergem,[14] Wei He,[1,2,3] Wai-Man Chan,[1,2,3,15] Caroline Andrews,[1,2,3,15] Joseph L. Demer,[16,17,18,19] Richard L. Robertson,[8] David A. Mackey,[20,21] Jonathan B. Ruddle,[20] Thomas D. Bird,[22,23] Irene Gottlob,[24] Christina Pieh,[25] Elias I. Traboulsi,[26] Scott L. Pomeroy,[1,2,9,11] David G. Hunter,[7] Janet S. Soul,[1,11] Anna Newlin,[27] Louise J. Sabol,[28] Edward J. Doherty,[29] Clara E. de Uzcátegui,[30] Nicolas de Uzcátegui,[31] Mary Louise Z. Collins,[32] Emin C. Sener,[33] Bettina Wabbels,[34] Heide Hellebrand,[35] Thomas Meitinger,[36,37] Teresa de Berardinis,[38] Adriano Magli,[38] Costantino Schiavi,[39] Marco Pastore-Trossello,[40] Feray Koc,[41] Agnes M. Wong,[42] Alex V. Levin,[43] Michael T. Geraghty,[44] Maria Descartes,[45] Maree Flaherty,[46] Robyn V. Jamieson,[47,48] H.U. Møller,[49] Ingo Meuthen,[50] David F. Callen,[51] Janet Kerwin,[52] Susan Lindsay,[52,53] Alfons Meindl,[35] Mohan L. Gupta, Jr.,[10,12,56,*] David Pellman,[6,10,12,15] and Elizabeth C. Engle[1,2,3,4,5,7,9,11,15,*]





D417N

CFEOM
CFEOM + polyneuropathy
Isolated CMT2-like disorder

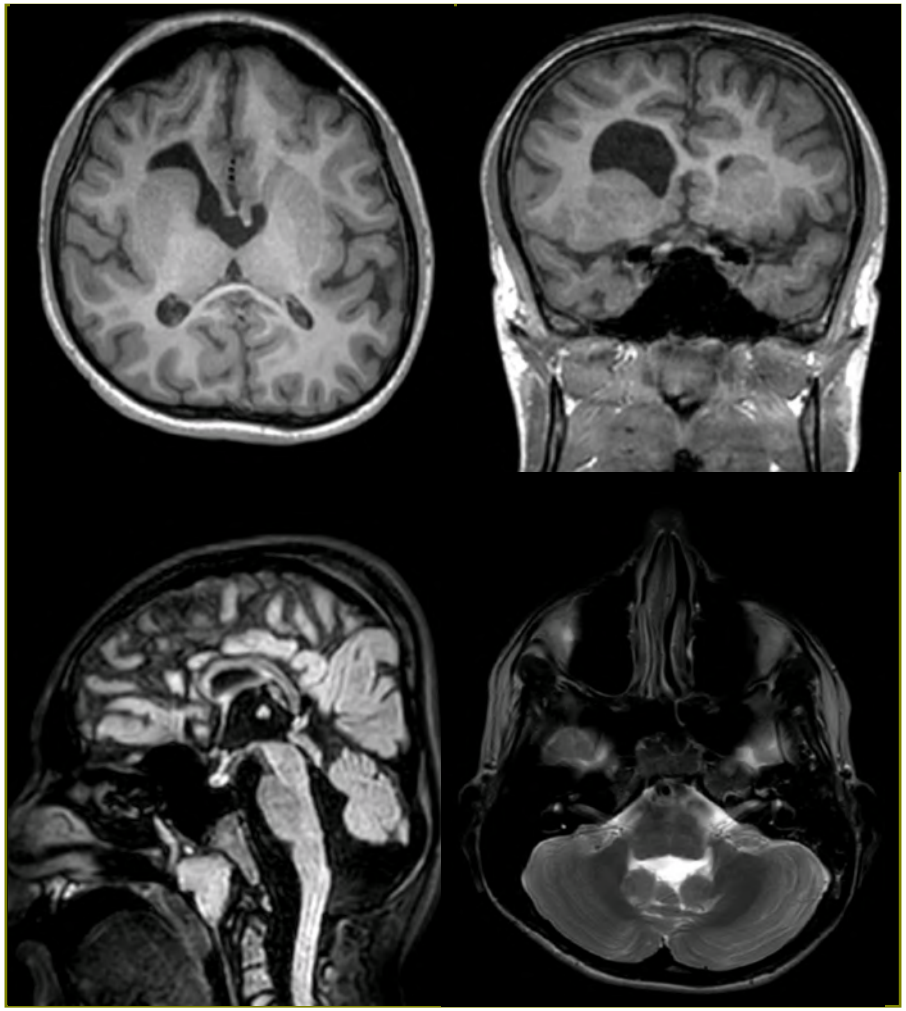
MCD - POLYNEUROPATHY

Tubulinopathy-related dysgyria

11 year old boy

- Normal pregnancy and delivery
- 39 WG with W 3kg, H 49cm, HC 32cm (-1.9SD)
- Age 4 months: poor visual pursuit
- Age 5 months: focal seizures, HC 38.5cm (-3.2SD)
- Age 11 years:
  - HC 45cm (-6SD)
  - Refractory focal seizures
  - Severe ID, communication limited to sounds
  - Dyskinetic cerebral palsy GMFCS IV, MACS IV
  - Central visual impairment, **no CFEOM**
  - **EMG and NCV normal**

De novo c.1172G>T, p.(Arg391Leu)

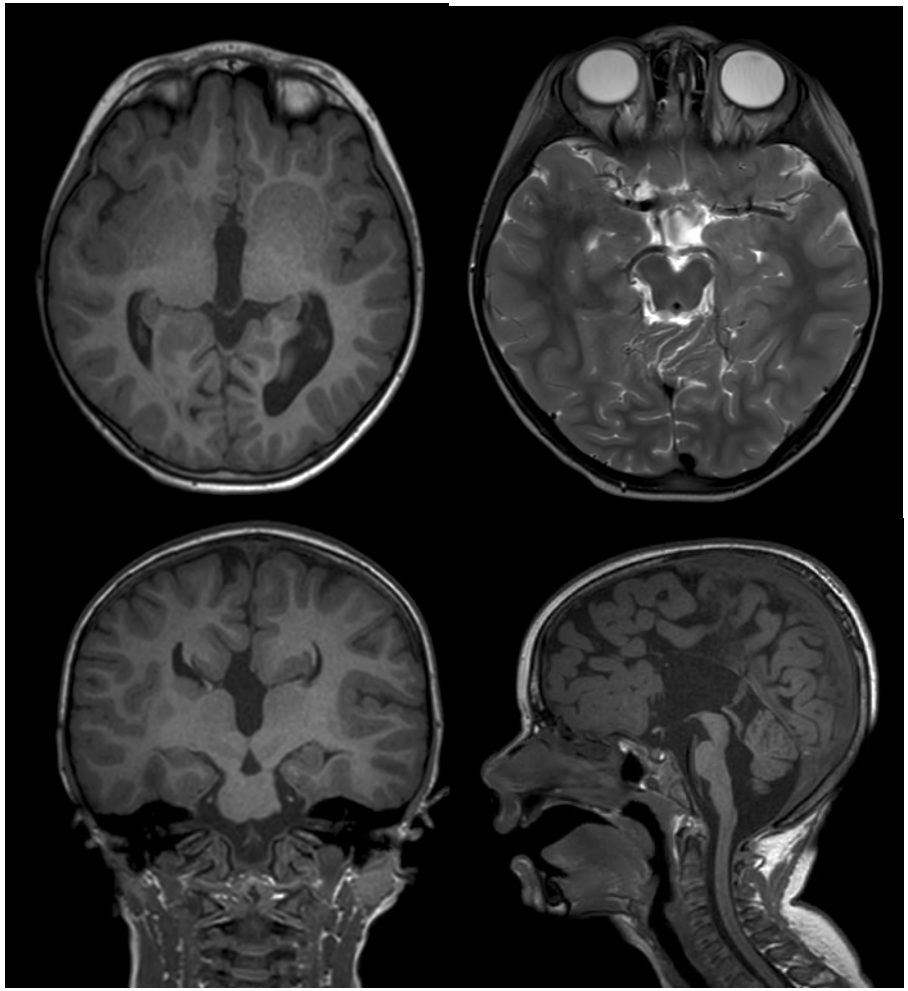


MCD - POLYNEUROPATHY

Tubulinopathy-related dysgyria

4-year old girl

- Normal pregnancy and delivery
- Axial hypotonia, strabismus, unilateral ptosis
- Age 2: BSID-II DQ<55, language delay
- Age 4:
  - SON-IQ 53 (non-verbal IQ test)
  - Motor DQ 55 with spastic diplegia
  - Expressive and receptive language both poor, dysarthric speech, drooling
  - **EMG and NCV normal**
  - Asymmetric ptosis, **no typical CFEOM**



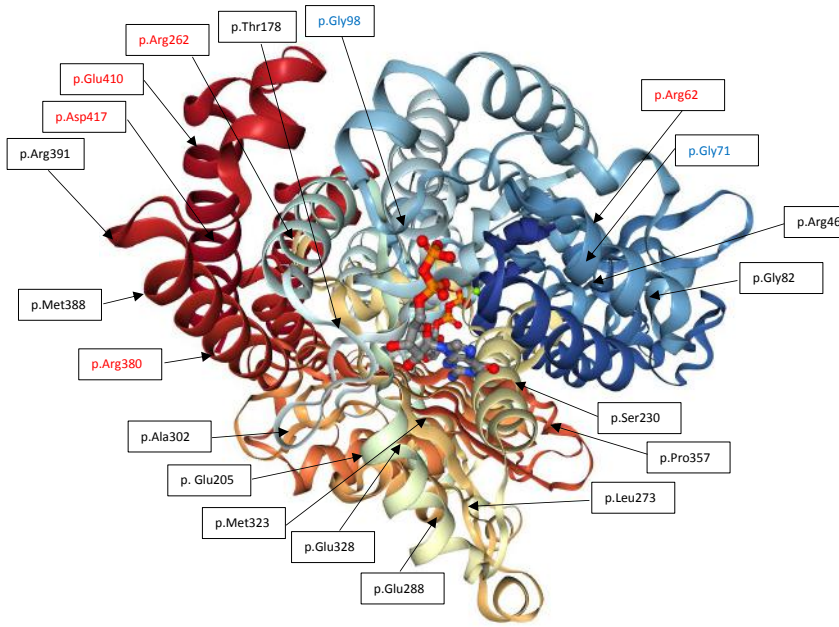
De novo c.292G>A, p.(Gly98Ser)

MCD - POLYNEUROPATHY

Am J Med Genet A. 2016 February ; 170(2): 297–305. doi:10.1002/ajmg.a.37362.

Two Unique *TUBB3* Mutations Cause Both CFEOM3 and Malformations of Cortical Development

Mary C. Whitman[1,2,3], **Caroline Andrews**[3,4,5,6], **Wai-Man Chan**[3,4,5,6,7], **Max A. Tischfield**[3,4,5], **Steven F. Stasheff**[8], **Francesco Brancati**[9], **Xilma Ortiz-Gonzalez**[10], **Sara Nuovo**[11], **Francesco Garaci**[12], **Sarah E. MacKinnon**[1], **David G. Hunter**[1,2], **P. Ellen Grant**[13], and **Elizabeth C. Engle**[1,2,3,4,5,6,7,14,15,16,*]



MCD - POLYNEUROPATHY

Polymicrogyria

Homozygous Nonsense Mutations in *KIAA1279* Are Associated with Malformations of the Central and Enteric Nervous Systems

Alice S. Brooks,[1] Aida M. Bertoli-Avella,[1] Grzegorz M. Burzynski,[6] Guido J. Breedveld,[1] Jan Osinga,[6] Ludolf G. Boven,[6] Jane A. Hurst,[7] Grazia M. S. Mancini,[1] Maarten H. Lequin,[2] Rene F. de Coo,[4] Ivana Matera,[6,8] Esther de Graaff,[1] Carel Meijers,[3] Patrick J. Willems,[9] Dick Tibboel,[5] Ben A. Oostra,[1] and Robert M. W. Hofstra[6]

Am. J. Hum. Genet. 77:120–126, 2005

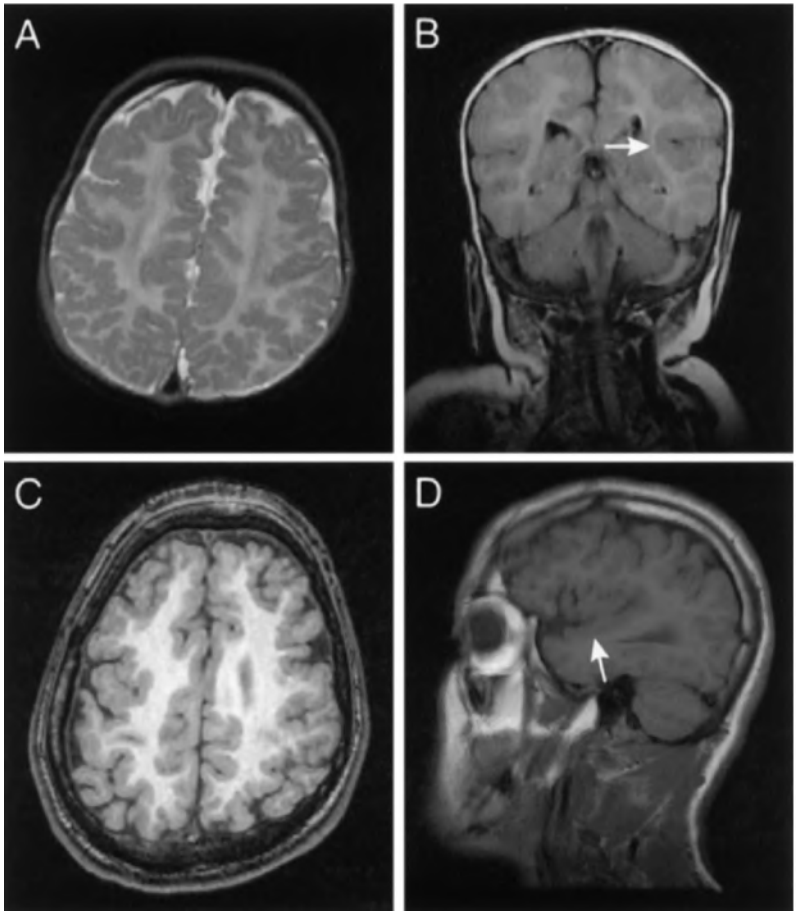
Goldberg-Shprintzen Megacolon syndrome

Microcephaly

Intellectual disability

Hirschsprung's disease

Polymicrogyria



MCD - POLYNEUROPATHY

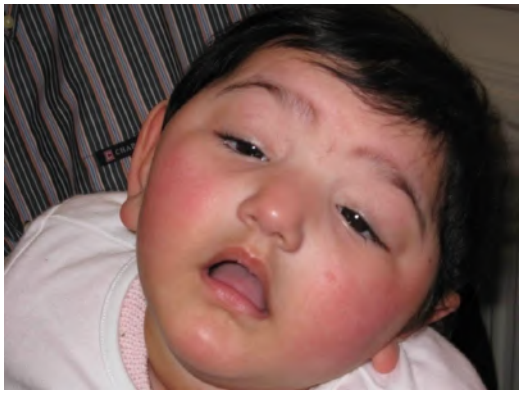
Polymicrogyria

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics

Goldberg–Shprintzen Megacolon Syndrome with Associated Sensory Motor Axonal Neuropathy

Hormos Salimi Dafsari,[1] Susan Byrne,[1] Jean-Pierre Lin,[1] Matthew Pitt,[2] Jan D. H. Jongbloed,[3] Frances Flinter,[4] and Heinz Jungbluth[1,5,6]*



- Microcephaly
- Blepharophimosis, blepharospasm
- Short stature
- **Primary axonal neuropathy with secondary degradation over time**
- Brain MRI not performed/not reported
- Recessive mutation in *KIAA1279*

MCD- POLYNEUROPATHY

Polymicrogyria

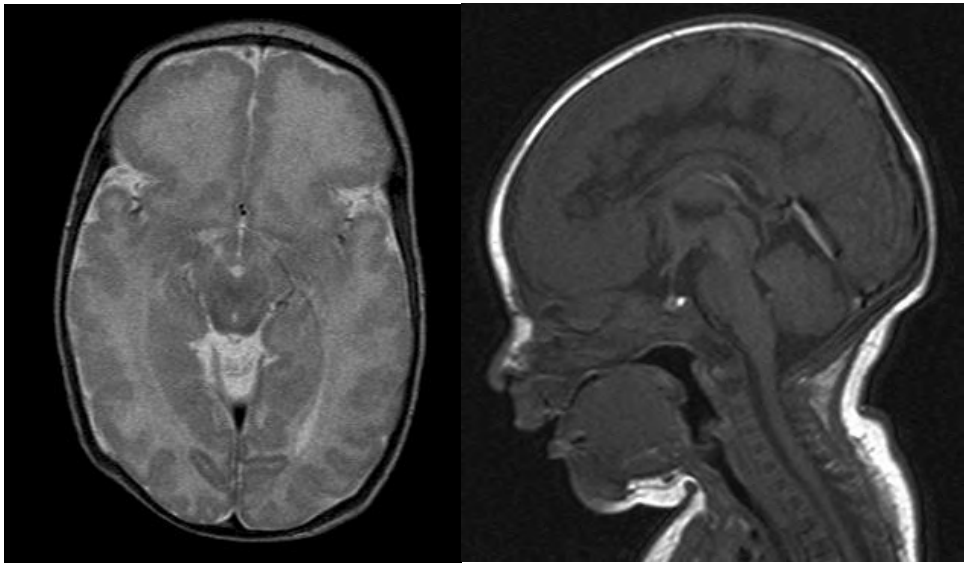
MUTATION UPDATE

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

Mutation Spectrum in *RAB3GAP1*, *RAB3GAP2*, and *RAB18* and Genotype–Phenotype Correlations in Warburg Micro Syndrome and Martsolf Syndrome

Mark T. Handley,[1‡] Deborah J. Morris-Rosendahl,[2,29‡†] Stephen Brown,[1] Fiona Macdonald,[3] Carol Hardy,[3] Danai Bem,[4] Sarah M. Carpanini,[1] Guntram Borck,[5] Loreto Martorell,[6] Claudia Izzi,[7] Francesca Faravelli,[8] Patrizia Accorsi,[9] Lorenzo Pinelli,[10] Lina Basel-Vanagaite,[11,12] Gabriela Peretz,[11] Ghada M.H. Abdel-Salam,[13] Maha S. Zaki,[13] Anna Jansen,[14] David Mowat,[15] Ian Glass,[16] Helen Stewart,[17] Grazia Mancini,[18] Damien Lederer,[19] Tony Roscioli,[20,21] Fabienne Giuliano,[22] Astrid S. Plomp,[23] Arndt Rolfs,[24,25] John M. Graham,[26] Eva Seemanova,[27] Pilar Poo,[28] Àngels García-Cazorla,[28] Patrick Edery,[29] Ian J. Jackson,[1] Eamonn R. Maher,[4,30] and Irene A. Aligianis[1]*



- Postnatal microcephaly (-4 à -6SD)
- Eye abnormalities (congenital cataract, microcornea, microphthalmia)
- Microgenitalia
- **Progressive axonal peripheral neuropathy**

- Frontoparietal PMG, thin CC

homozygous p.Thr18Pro mutation in *RAB3GAP1*

MCD – POLYNEUROPATHY

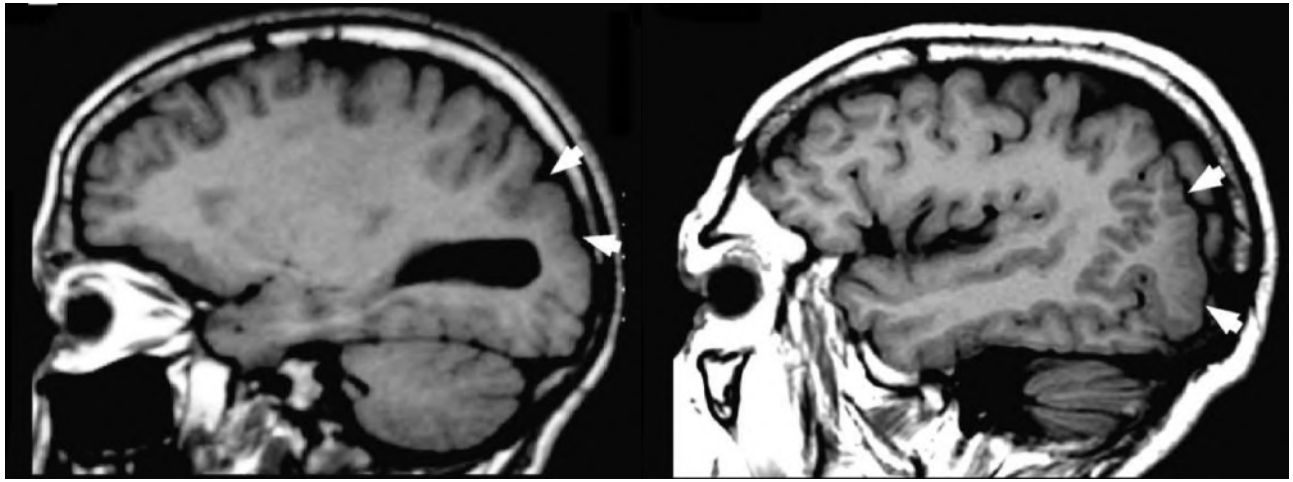
Polymicrogyria

Role of the phosphoinositide phosphatase *FIG4* gene in familial epilepsy with polymicrogyria

Baulac et al Neurology® 2014;82:1068–1075

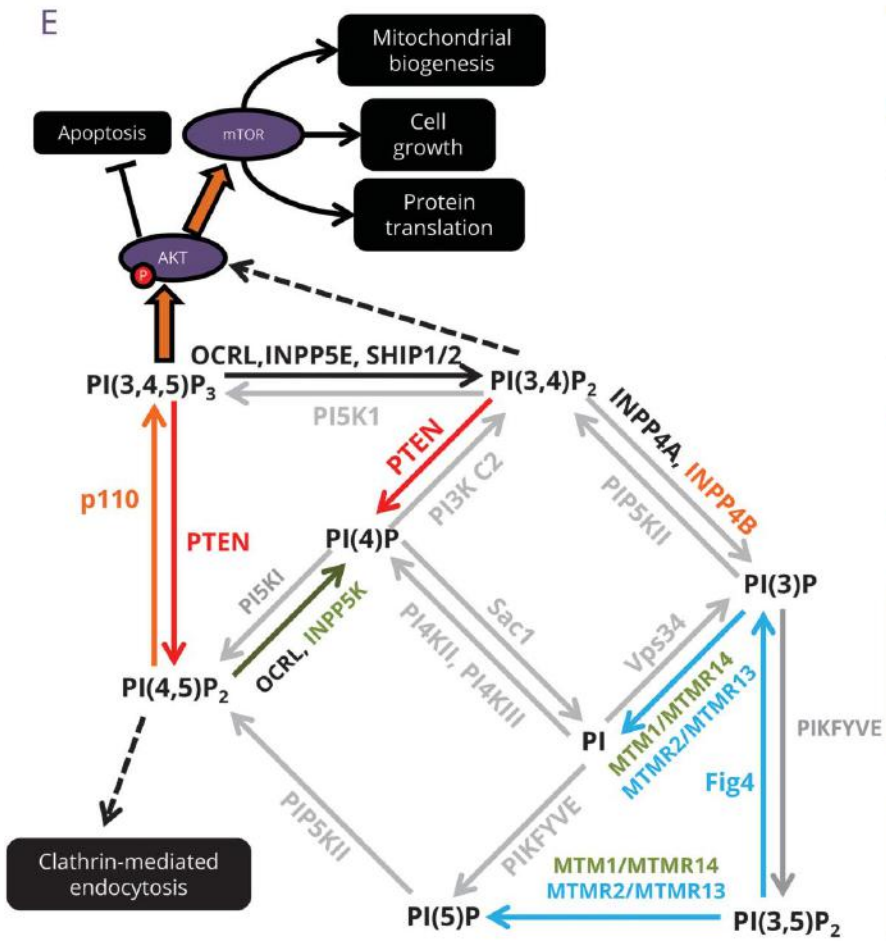
Recessive mutations in *FIG4*

- Yunis-Varón syndrome (MCA)
  - cleidocranial dysplasia
  - digital anomalies
  - brain malformations
  - early death
- Temporo-occipital PMG
- **Charcot-Marie-Tooth type 4J**
  - demyelinating polyneuropathy
  - severe axonal loss



MCD – POLYNEUROPATHY

Macrocephaly



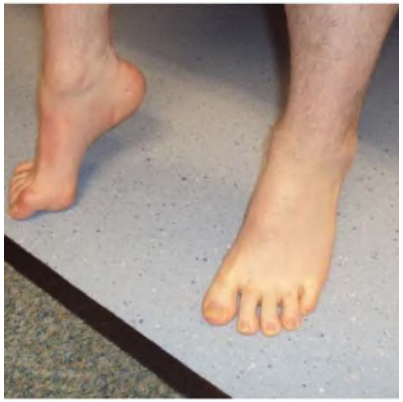
Cancer
P110
INPP4B

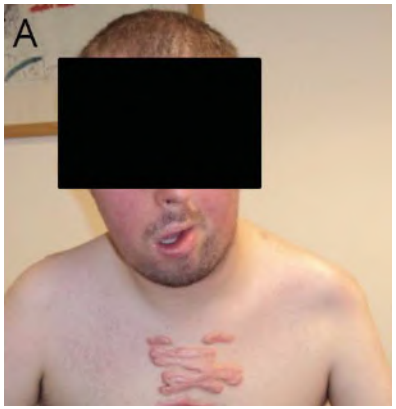
Syndromal
OCRL
INPP4A
INPP5E
SHIP1/2

Cancer + Neuropathy
PTEN

Neuropathy
CMT4B1/MTMR2
CMT4B2/MTMR13
CMT4J/FIG4

Myopathy
MTM1
MTMR14
INPP5K





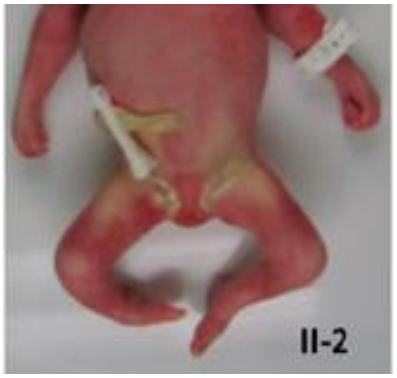
MCD – POLYNEUROPATHY

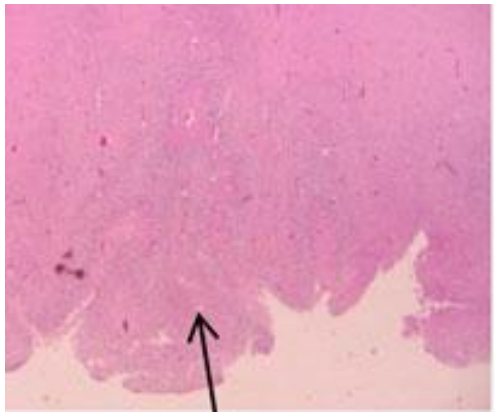
Polymicrogyria

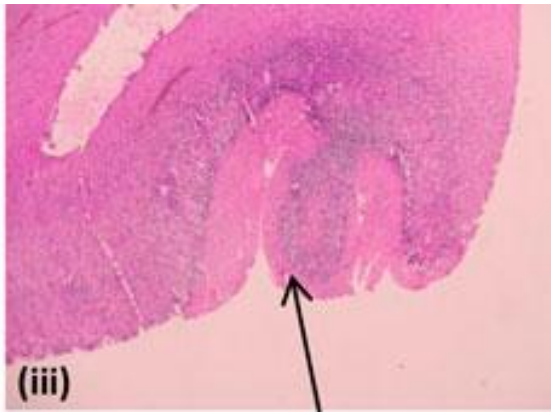
Germline recessive mutations in *PI4KA* are associated with perisylvian polymicrogyria, cerebellar hypoplasia and arthrogryposis

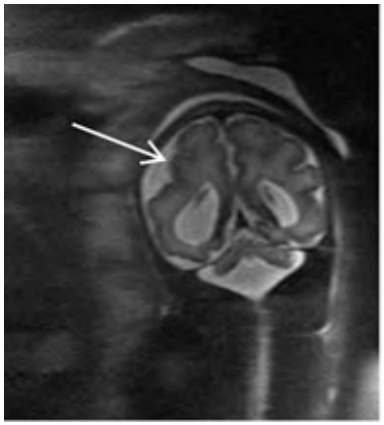
Alistair T. Pagnamenta[1], Malcolm F. Howard[1], Eva Wisniewski[2], Niko Popitsch[1], Samantha J.L. Knight[1], David A. Keays[3], Gerardine Quaghebeur[4], Helen Cox[6], Phillip Cox[7], Tamas Balla[2], Jenny C. Taylor[1] and Usha Kini[5,*]

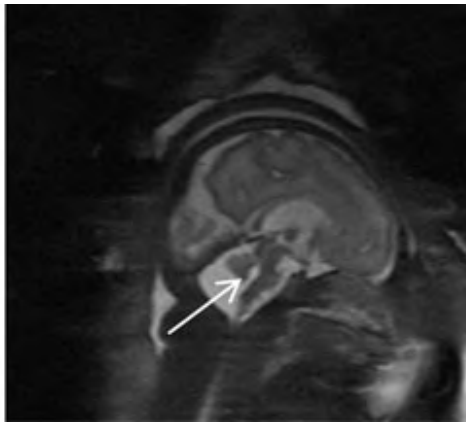
Human Molecular Genetics, 2015, Vol. 24, No. 13 3732–3741









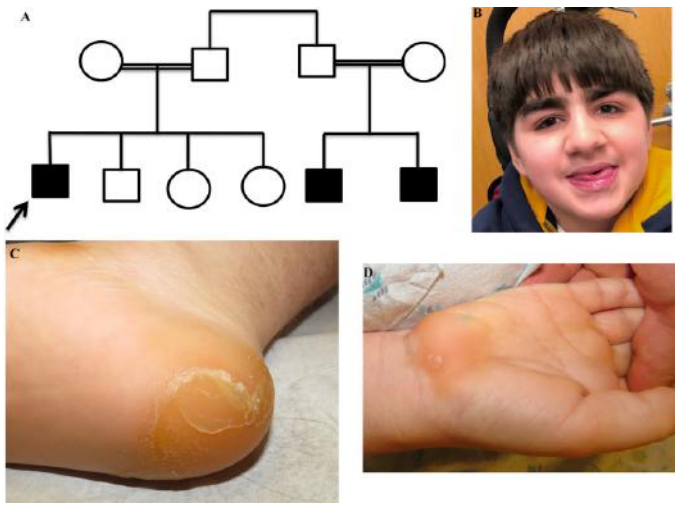


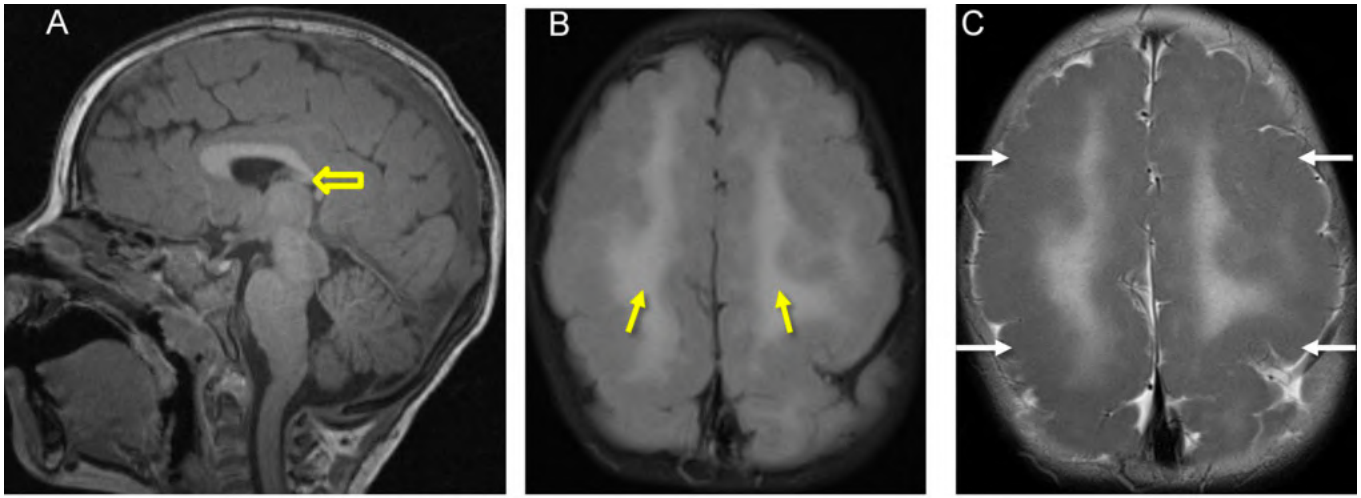
MCD - POLYNEUROPATHY

PMG/cobblestone malformation

CEDNIK: Phenotypic and Molecular Characterization of an Additional Patient and Review of the Literature

Tina Hsu, BA[1], Carrie C. Coughlin, MD[2,3], Kristin G. Monaghan, PhD, FACMG[4], Elise Fiala, MS[5], Robert C. McKinstry, MD, PhD[3,6], Alex R. Paciorkowski, MD[7], and Marwan Shinawi, MD, FACMG[5]





Recessive mutations in *SNAP29*

MCD – CONGENITAL MUSCULAR DYSTROPHY

PMG/Cobblestone malformation

Global developmental delay

Myopia +++

Increased creatine kinase levels

POMGnT1

c.511C>T (p.Arg171*); c.1342G>C (p.Gly448Arg)

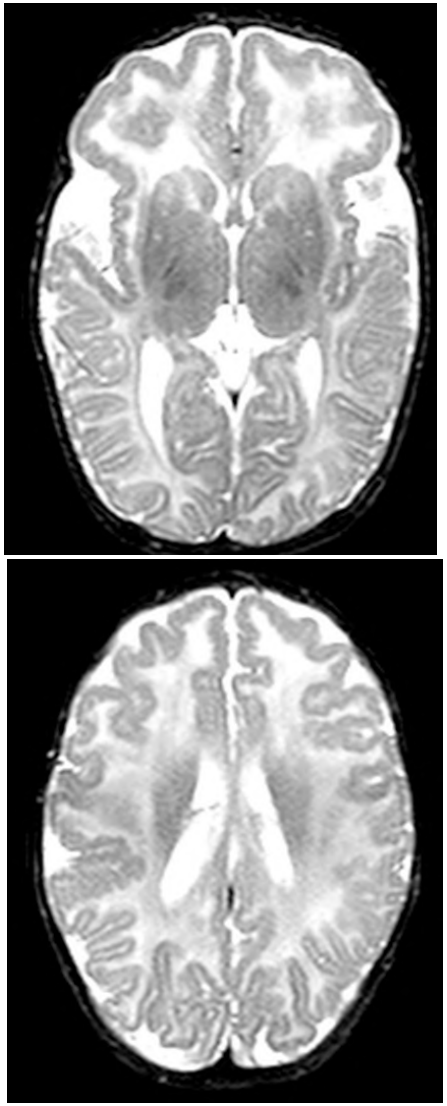
Cobblestone malformation

Dystroglycanopathy genes

B3GALNT2, B4GAT1, DAG1, FKRP, FKTN, LARGE1, GALNT2, GTDC2, ISPD, POMT1, POMT2, POMGNT1, POMGNT2, POMK, SLC35A1, TMEM5

Lamininopathy, CDG and other COB dysplasia genes

ATP6V0A2, COL3A1, GPR56/ADGRG1, LAMA2, LAMB1, LAMC3, SNAP29, SRD5A3



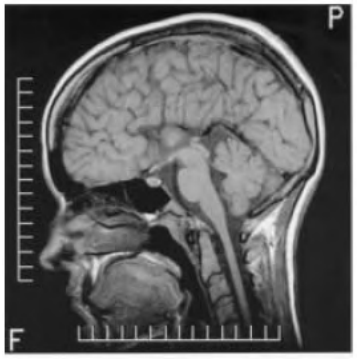
MCD – POLYNEUROPATHY

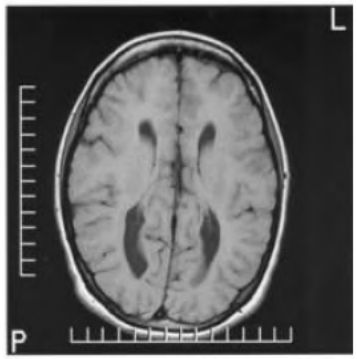
Agenesis corpus callosum

NEUROLOGICAL PROGRESS

Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum

Nicolas Dupré, MD, MSc,[1] Heidi C. Howard, PhD,[1] Jean Mathieu, MD, MSc,[2] George Karpati, MD,[3] Michel Vanasse, MD,[4] Jean-Pierre Bouchard, MD,[5] Stirling Carpenter, MD,[6] and Guy A. Rouleau, MD, PhD[1]





Pathogenic variants in *KCC3 (SLC12A6)*

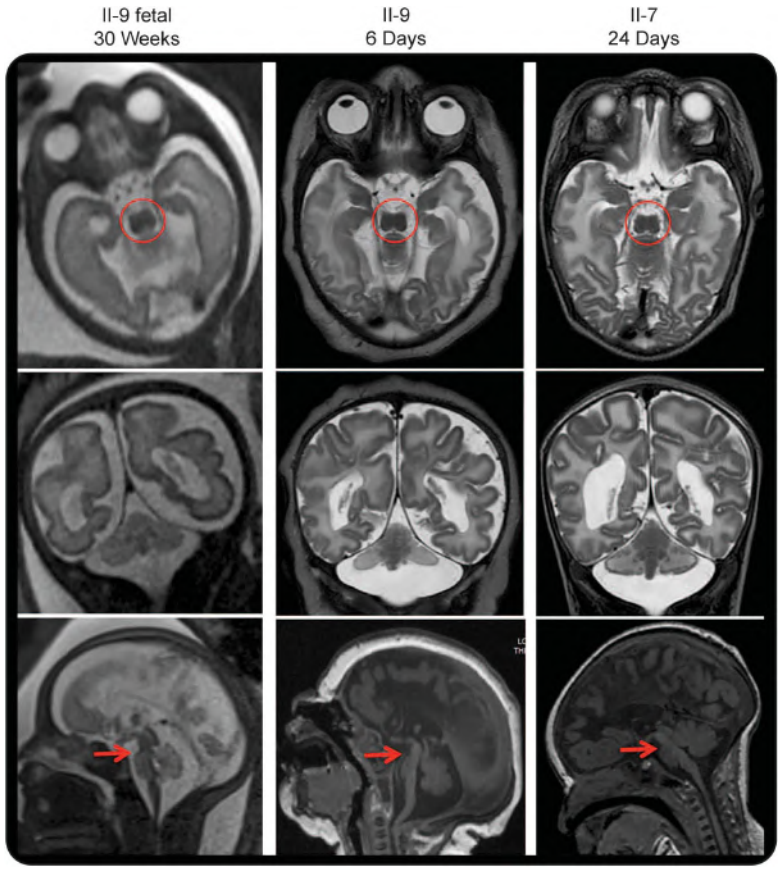
- Onset first year of life
- Neonatal hypotonia
- Progressive distal and proximal symmetric limb weakness
- Amyotrophy
- **Severe sensorymotor neuropathy**
- Psychosis
- Shortened lifespan

MCD – POLYNEUROPATHY

Agenesis corpus callosum and pontocerebellar hypoplasia type 9

Complete callosal agenesis, pontocerebellar hypoplasia, and axonal neuropathy due to AMPD2 loss

Marsh et al Neurol Genet 2015;1:e16



Pathogenic variants in *AMPD2*

- Postnatal microcephaly
- Profound ID
- Epilepsy
- Brain MRI: ACC and PCH
- **Axonal neuropathy**
- Shortened lifespan

MCD - MYOPATHY

ACC – PMG and BSH

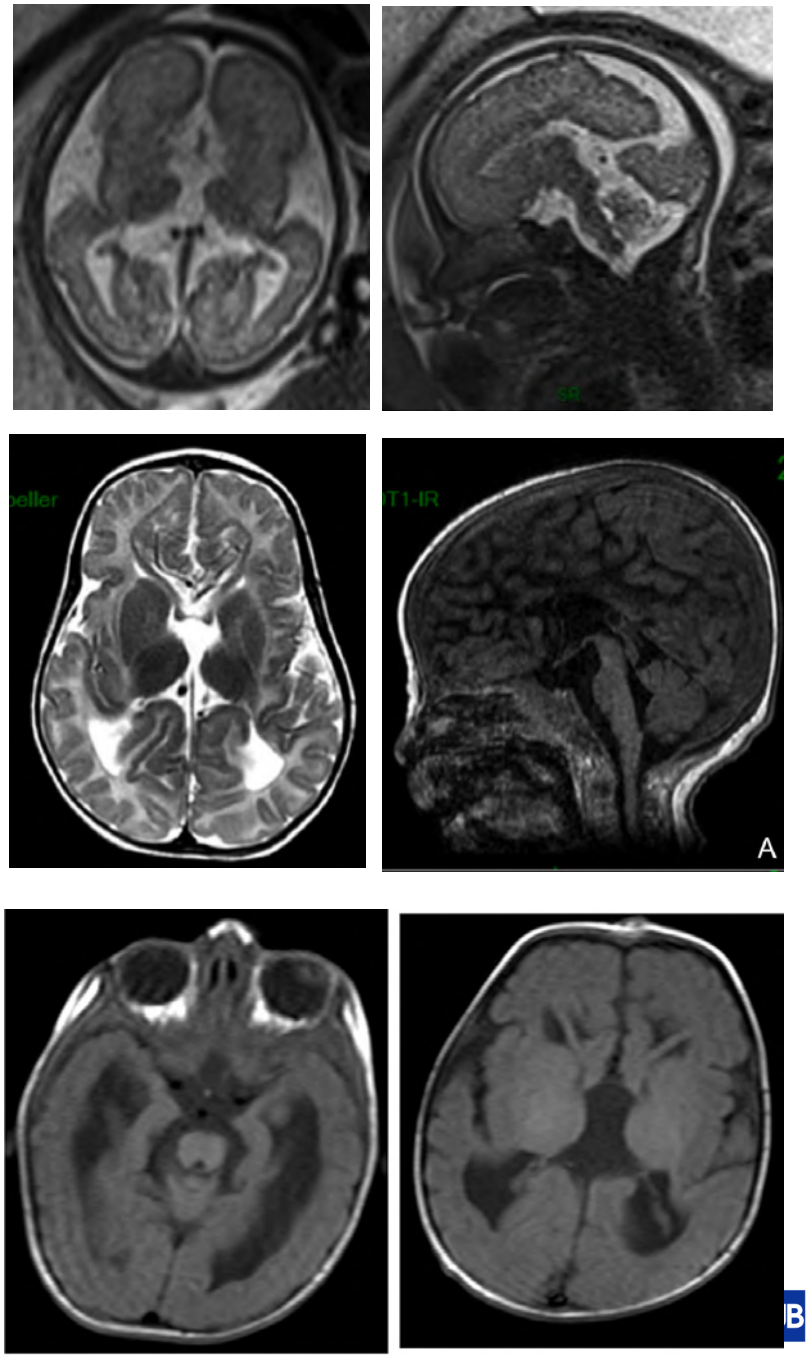
Prenatal and Postnatal Presentations of Corpus Callosum Agenesis with Polymicrogyria Caused By *EGP5* Mutation

Camille Maillard,[1,2] Mara Cavallin,[1,2] Kevin Piquand,[1,2] Marion Philbert,[1,2] Jean Philippe Bault,[3,4] Anne Elodie Millischer,[5] Despina Moshous,[1,6,7] Marlène Rio,[8] Cyril Gitiaux,[9] Nathalie Boddaert,[5,10] Cecile Masson,[11] Sophie Thomas,[1,2] and Nadia Bahi-Buisson[1,2,9]*

Am J Med Genet Part A 173A:706–711.

Pathogenic variants in *EPG5*

- Microcephaly
- MCA (cataracts, cleft, hypospadias)
- Dilated cardiomyopathy
- Cutaneous albinism
- Defective humeral response with recurrent infections
- Brain MRI: ACC, CBLBH, cortical malformation



Am J Med Genet. 2018;**176A**:499–501.

MCD – HMSN / SMALED / MYOPATHY / HSP

Pachygyria / polymicrogyria

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

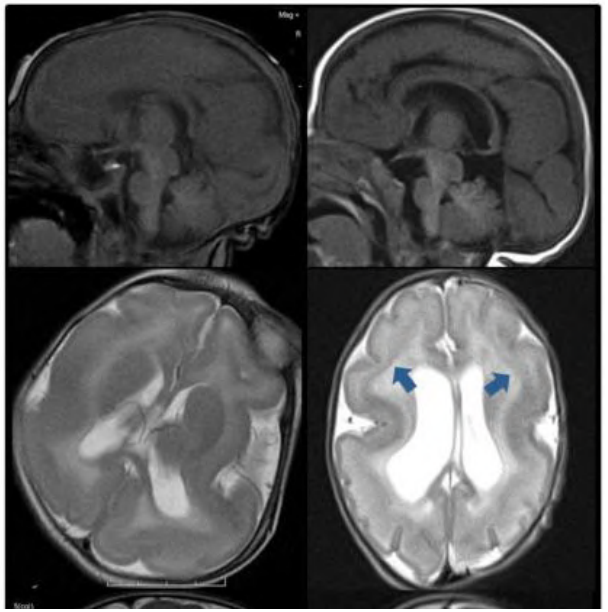
Karine Poirier[1,2], Nicolas Lebrun[1,2], Loic Broix[1,2,*], Guoling Tian[3,*], Yoann Saillour[1,2], Cécile Boscheron[4], Elena Parrini[5,6], Stephanie Valence[1,2], Benjamin SaintPierre[1,2], Madison Oger[1,2], Didier Lacombe[7], David Geneviève[8], Elena Fontana[9], Franscesca Darra[9], Claude Cances[10], Magalie Barth[11,12], Dominique Bonneau[11,12], Bernardo Dalla Bernadina[9], Sylvie N'Guyen[13], Cyril Gitiaux[1,2,14], Philippe Parent[15], Vincent des Portes[16], Jean Michel Pedespan[17], Victoire Legrez[18], Laetitia Castelnau-Ptakine[1,2], Patrick Nitschke[19], Thierry Hieu[19], Cecile Masson[19], Diana Zelenika[20], Annie Andrieux[4], Fiona Francis[21,22], Renzo Guerrini[5,6], Nicholas J. Cowan[3], Nadia Bahi-Buisson[1,2,14,**], and Jamel Chelly[1,2,**]

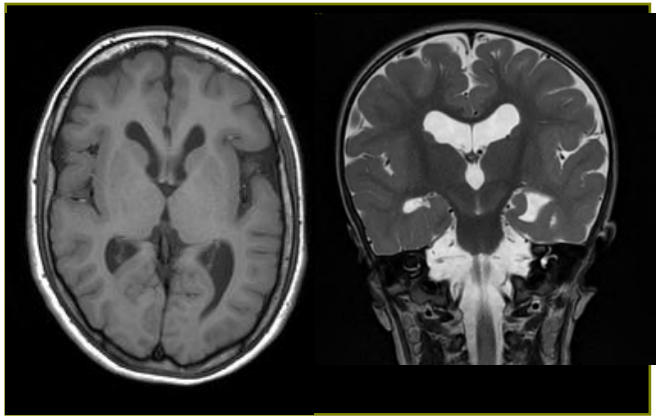
Expanding the phenotypic spectrum associated with mutations of *DYNC1H1*

Sarah J. Beecroft [a,b], Catriona A. McLean [c], Martin B. Delatycki [d,e], Kurian Koshy [f], Eppie Yiu [d,g], Goknur Haliloglu [h], Diclehan Orhan [i], Phillipa J. Lamont [j], Mark R. Davis [k], Nigel G. Laing [a,b,k], Gianina Ravenscroft [a,b,*]

Novel dynein *DYNC1H1* neck and motor domain mutations link distal SMA and abnormal cortical development

Chiara Fiorillo, MD, PhD[1], Francesca Moro, PhD[1], Julie Yi[2], Sarah Weil, PhD[2], Giacomo Brisca, MD[3], Guja Astrea, PhD, MD[1], Mariasavina Severino, MD[4], Alessandro Romano, PhD[5], Roberta Battini, MD[1], Andrea Rossi, MD[4], Carlo Minetti, MD[3], Claudio Bruno, MD[3], Filippo M. Santorelli, MD[1], and Richard Vallee, PhD[2]





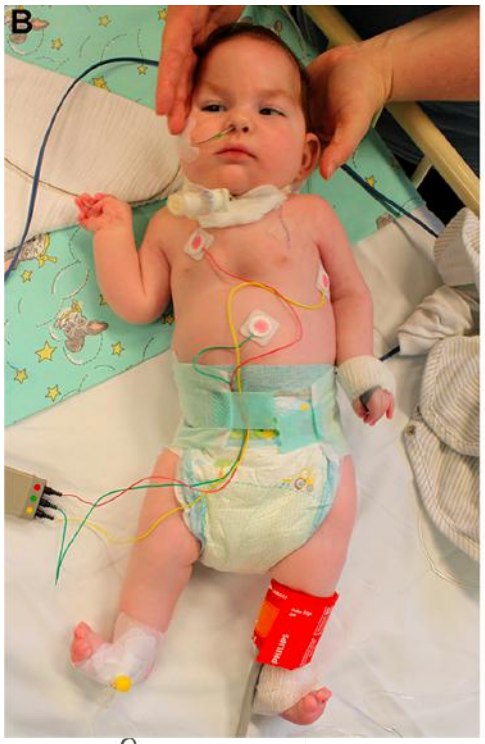
Courtesy Dr Destrée

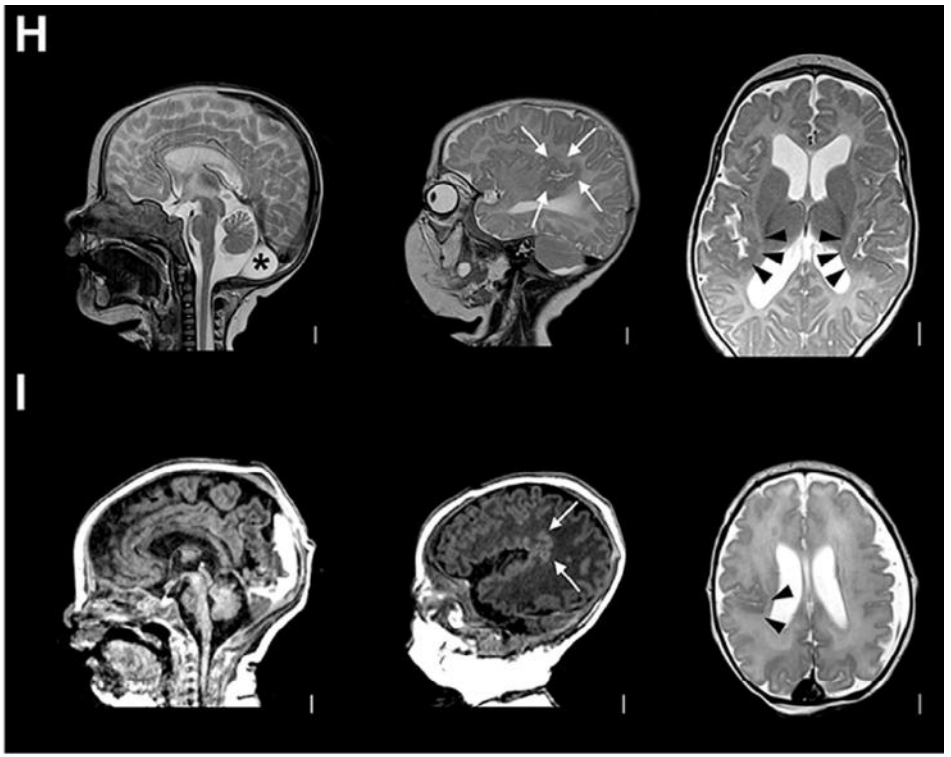
MCD - SMALED

Polymicrogyria

Recurrent *de novo BICD2* mutation associated with arthrogryposis multiplex congenita and bilateral perisylvian polymicrogyria

Gianina Ravenscroft [a,*], Nataliya Di Donato [b], Gabriele Hahn [c], Mark R. Davis [d], Paul D. Craven [e], Gemma Poke [f], Katherine R. Neas [f], Teresa M. Neuhann [g], William B. Dobyns [h], Nigel G. Laing [a,d]





MCD – SPASTIC PARAPLEGIA

'Polymicrogyria'

CLINICAL/SCIENTIFIC NOTES | OPEN ACCESS

***AP4S1* splice-site mutation in a case of spastic paraplegia type 52 with polymicrogyria**

Susana Carmona, PhD, Clara Marecos, MD, Marta Amorim, MD, Ana C. Ferreira, MD, Carla Conceição, MD, José Brás, PhD, Sofia T. Duarte, MD, PhD,* and Rita Guerreiro, PhD*

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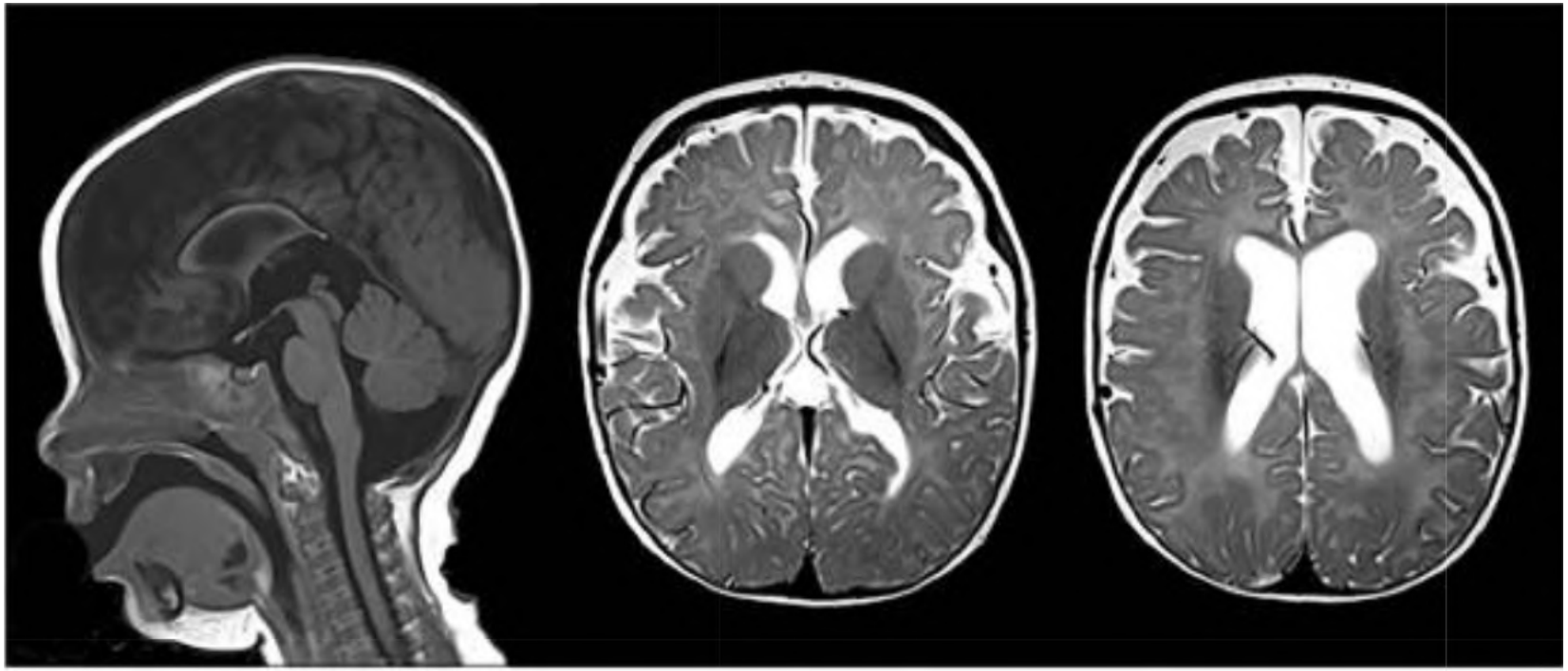
Neurol Genet 2018;4:e273. doi:10.1212/NXG.0000000000000273

Bi-allelic variants in adaptor protein complex 4 (AP-4) SPG47 (AP4B1), SPG50 (AP4M1), SPG51 (AP4E1) and SPG52 (AP4S1)

Retrograde dysfunction of the long descending fibers of the corticospinal tract

- Hypotonia – diplegia – tetraplegia
- Intellectual disability
- Poor/absent speech
- Febrile seizures/epilepsy



MCD – SPASTIC PARAPLEGIA

Microcephaly – thin CC - CBH

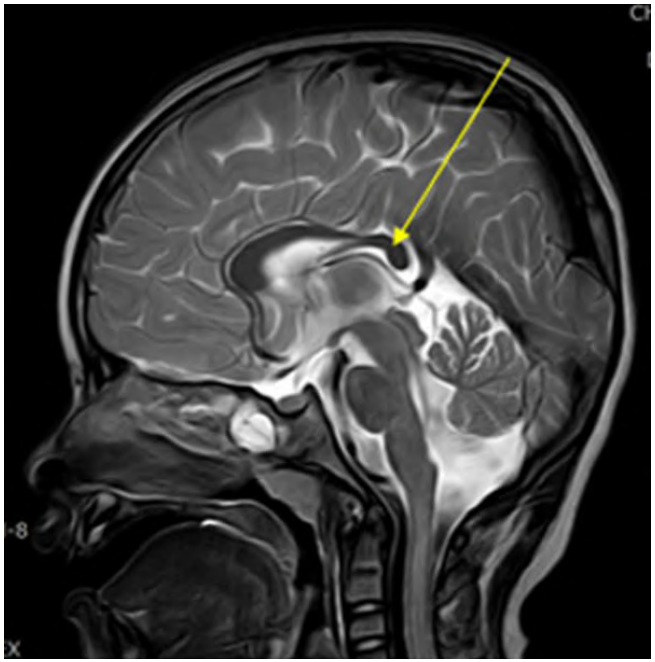
SCIENTIFIC REPORTS

OPEN

Received: 15 May 2017
Accepted: 13 September 2017
Published online: 02 October 2017

Autosomal dominant transmission of complicated hereditary spastic paraplegia due to a dominant negative mutation of *KIF1A*, SPG30 gene

Chong Kun Cheon[1,2], So-Hee Lim[3], Yoo-Mi Kim[1], Doyoun Kim[4], Na-Yoon Lee[3], Tae-Sung Yoon[3], Nam-Soon Kim[3], Eunjoon Kim[4,5] & Jae-Ran Lee[3]



Spastic paraplegia with

- mild intellectual disability with language delay
- epilepsy
- optic nerve atrophy
- microcephaly

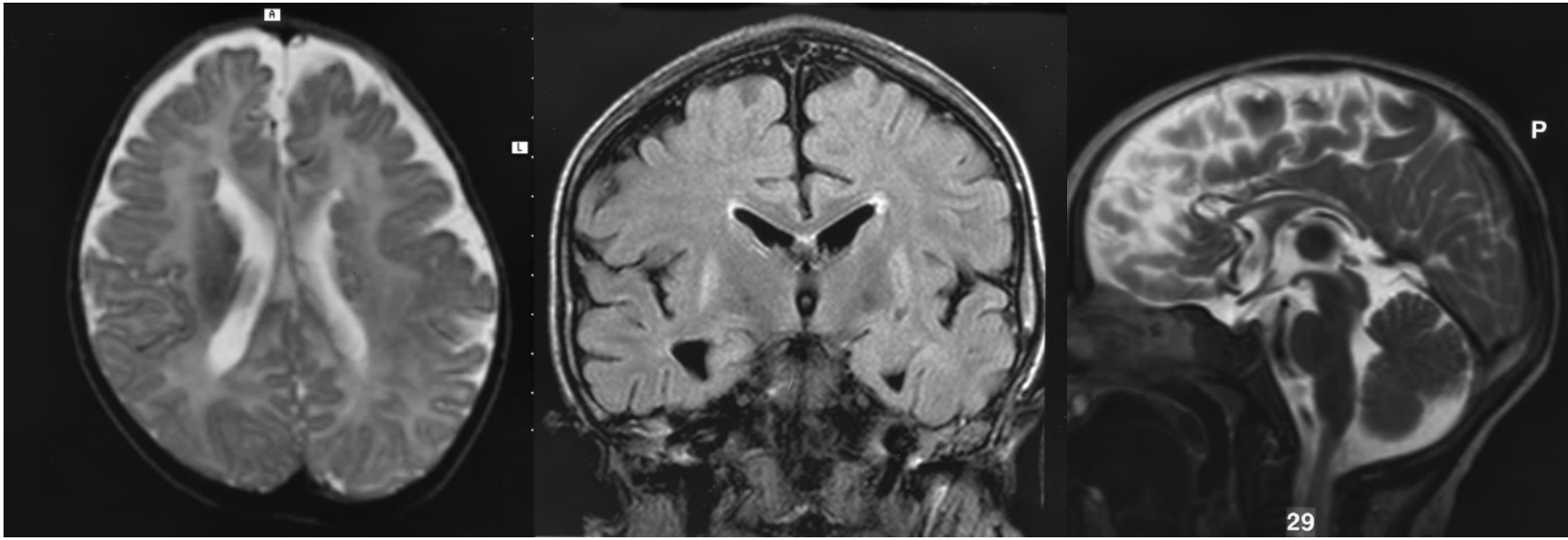
- thinning of corpus callosum
- periventricular white matter lesion

MCD – MOVEMENT DISORDER

Heterotopia

Elaborating the phenotypic spectrum associated with mutations in *ARFGEF2*: Case study and literature review

Ibrahim Tanyalçin [a], *Helene Verhelst* [b], *Dicky J.J. Halley* [c], *Tim Vanderhasselt* [d], *Laurent Villard* [e,f], *Cyril Goizet* [g,h], *Willy Lissens* [a], *Grazia M. Mancini* [c], *Anna C. Jansen* [i,j,*]



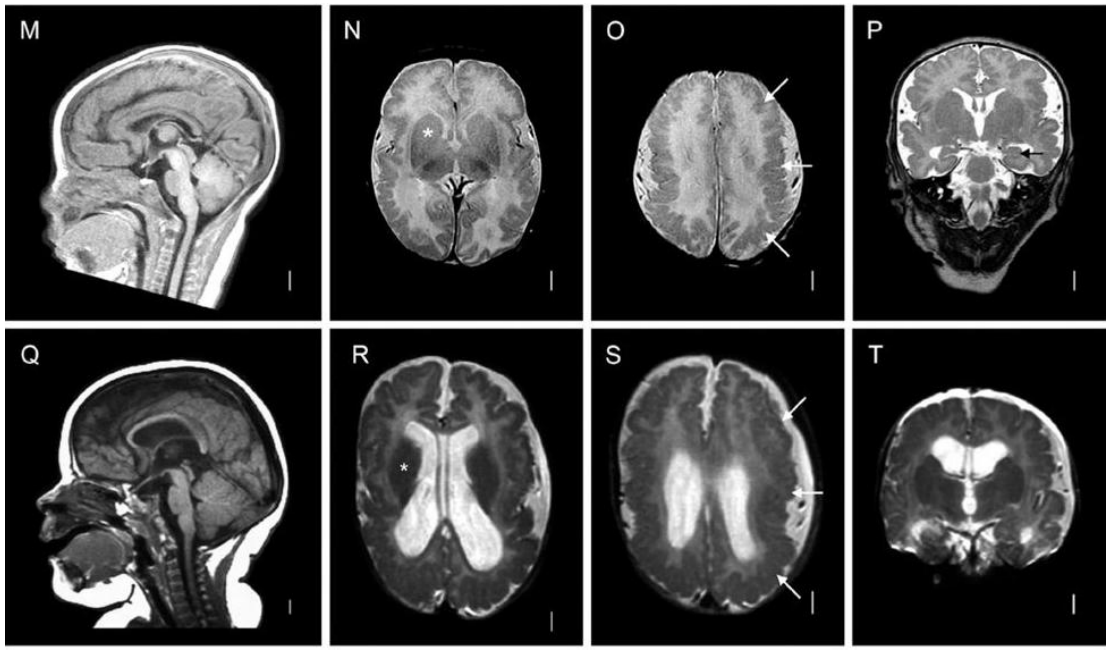
homozygous c.242_249delins7 (p.Pro81fs) mutation in *ARFGEF2*

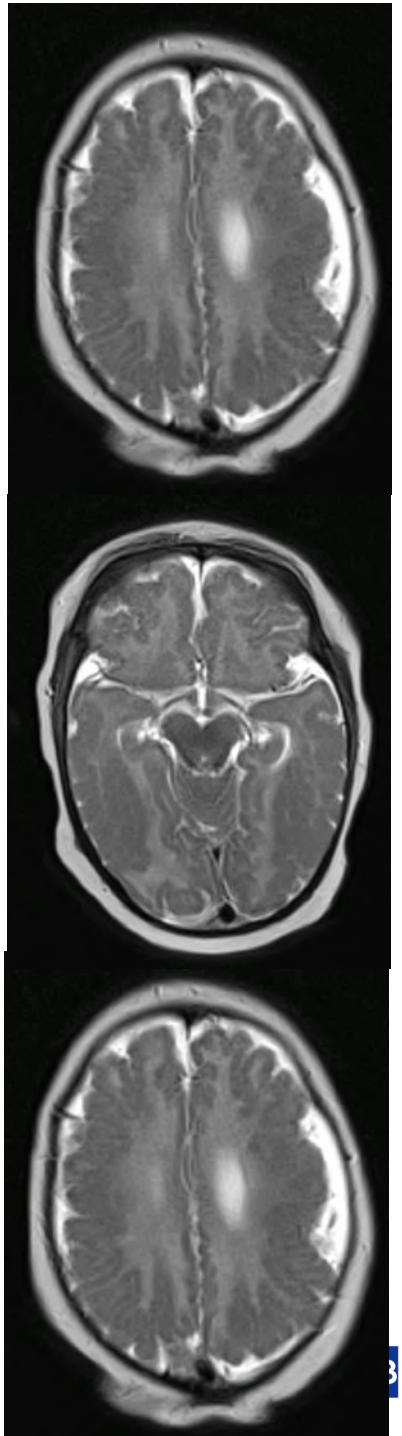
MCD – MOVEMENT DISORDER

Polymicrogyria

GRIN2B encephalopathy: novel findings on phenotype, variant clustering, functional consequences and treatment aspects

Platzer et al. J Med Genet. 2017 July ; 54(7): 460–470





De novo c.2437C>G, p.(Leu813Val) in *GRIN2B*

SUMMARY

MCD & neurological syndromes

Polyneuropathy

- PMG: TUBB3, SNAP29, KIAA1279, RABopathies, FIG4, BICD2
- PMG/LIS: DYNC1H1
- ACC: AMPD2, SLC12A6

Myopathy with ACC, CBLH: EPG5

Hereditary spastic paraplegia

- PMG: AP4S1
- Micro: KIF1A

Muscular dystrophies

- cobblestone malformation: dystroglycanopathy, laminopathy, CDG, other

Movement disorders

- Heterotopia: ARFGEF2
- Polymicrogyria: GRIN2B

THANK YOU

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