Microcephaly: genetics and disease mechanisms

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MaNaMa Neurogenetics, Brussel 7-2-2023

Outline of the talk and points of discussion

1. Definition of Microcephaly (MIC)
2. Elements for diagnostic classification: causes (genetic vs non-genetic), clinical presentation, brain morphology
3. Specific cellular and neurodevelopmental processes involved

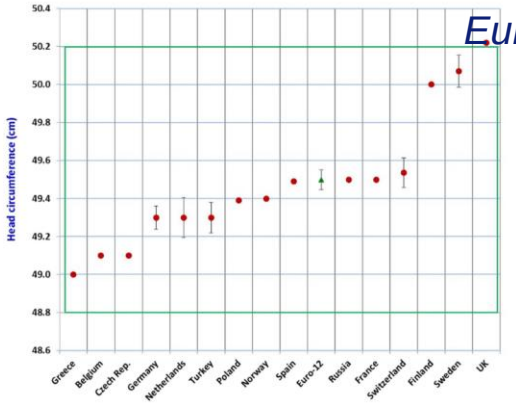
Definition of Microcephaly: OFC below – 2 SD for age and sex

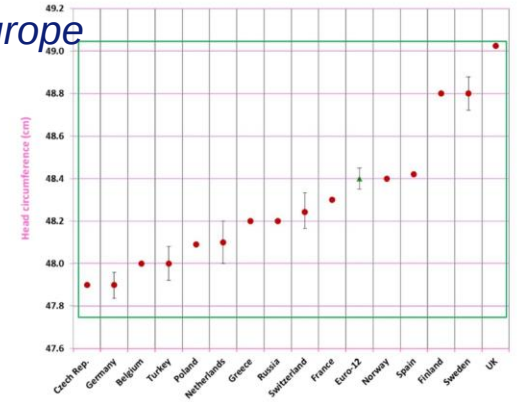
BMJ Open 2014

Worldwide variation in human growth and the World Health Organization growth standards: a systematic review

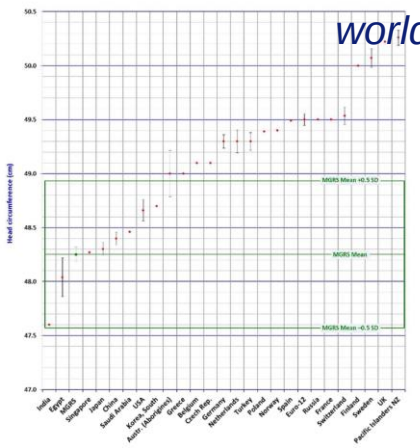
Valerie Natale, Anuradha Rajagopalan

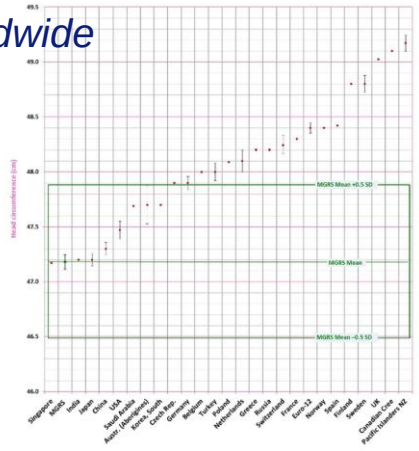
Europe





worldwide





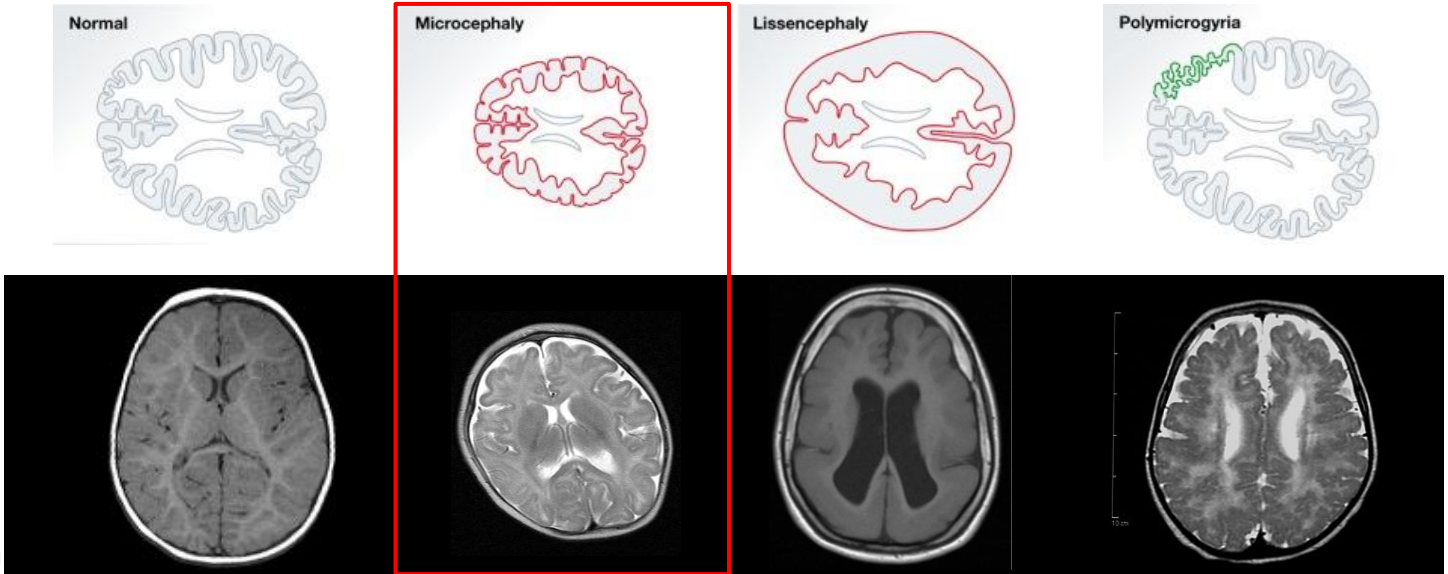
There is variation of normal head size among different ethnic groups, even within "economically advantaged" countries

Using standard growth charts unappropriately can lead to over or underestimation of microcephaly.

Definition: Malformation of Cortical Development (MCD)

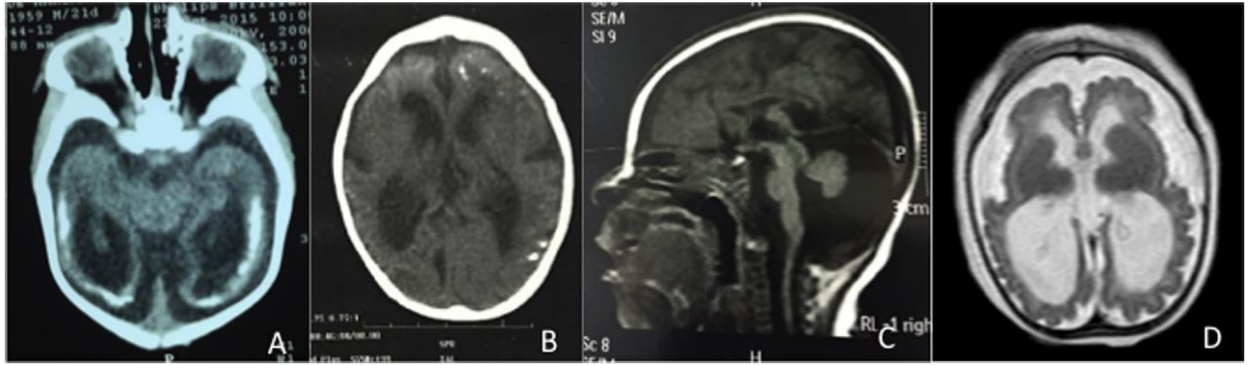
(from J. Aicardi, 1993; AJ Barkovich et al, 2012; Fernandez et al, 2016)

Processes	Abnormalities	Time
1.Neuronal Proliferation/Apoptosis	Micro/Macrocephaly	8-16 w.
2.Migration	Lissencephaly/ Heterotopia	12-20 w.
3.Organization	Polymicrogyria	>24 w.

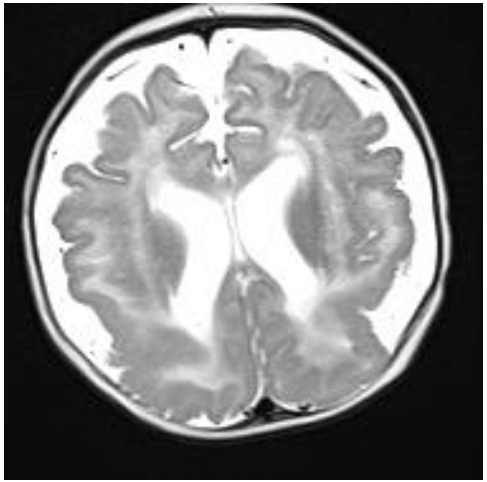


Microcephaly: causes

- Non genetic causes
- Viruses: Zika, CMV, Rubella, HSV, VZV, LCMV



Zika. From: Del Campo, AJMG 2017



CMV

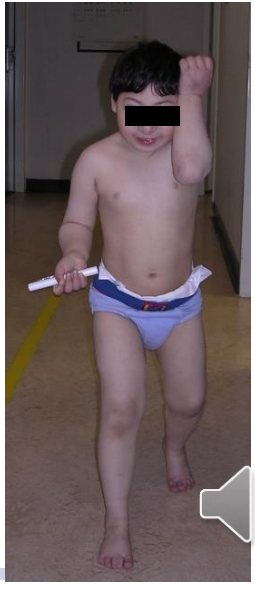
Classification of genetic microcephaly

- Primary microcephaly
  - Isolated (MCPH)
  - Associated with growth retardation (Microcephalic Primordial Dwarfism)
  - Syndromic, associated with MCA
- Secondary (progressive) microcephaly
  - (Mostly) isolated
  - Syndromic, associated with progressive degeneration
- Mutations in about 185 genes are causally related to MIC*
- More than 900 genes related to syndromic MIC

*Oegema R et al. Malformations of cortical development, international consensus recommendations on diagnostic workup. Nat Rev Neurol, 2020

Primary microcephaly- isolated (MCPH)

- OFC at birth below – 2.5 SD for gestational age and sex
- Associated with variable, non progressive ID, motor and speech delay, behavioral issues, epilepsy
- Normal life span
- Monogenetic with mostly autosomal recessive inheritance or CNV
- Developmental disorder of neuro(glial) proliferation or apoptosis regulation, linked to regulation of the cell cycle.



Microcephaly caused by abnormal proliferation: Centrioles, cell cycle and DNA replication checkpoints

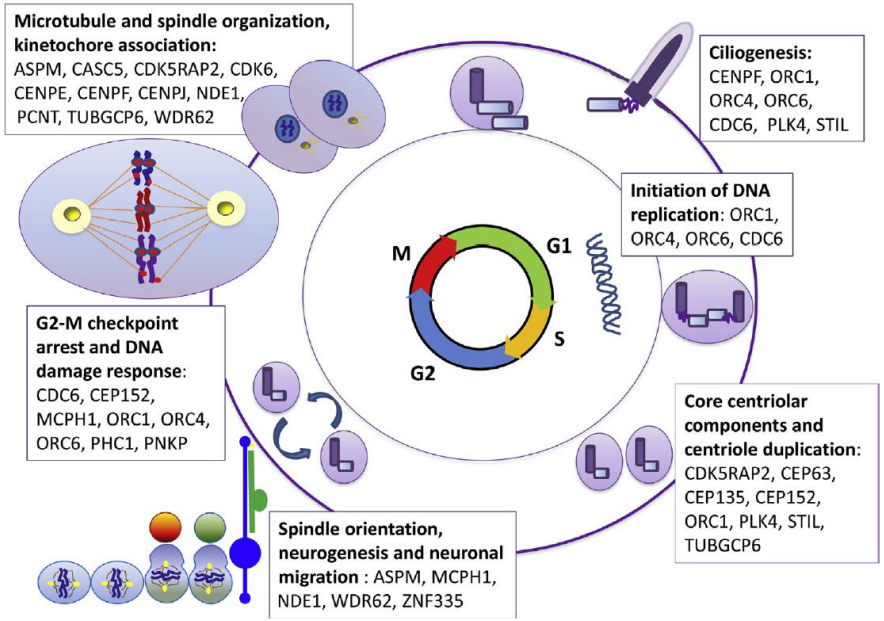
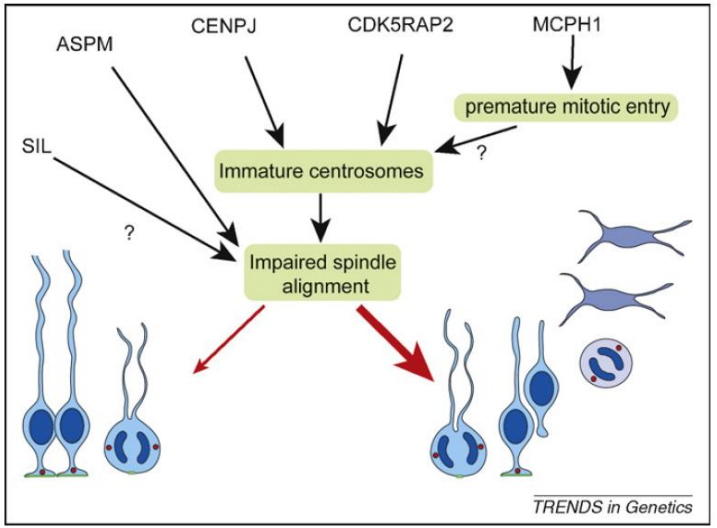


Fig. 1 Illustration of the involvement of MCPH proteins in cell cycle dynamics, the centrosome, ciliogenesis and neuronal migration..

D. Morris-Rosendahl & A. Kaindl, Mol Cell Probes, 2015



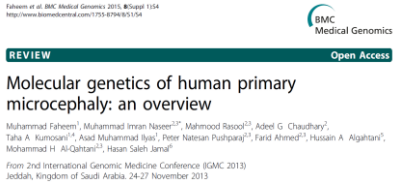
Review

Cell

Primary microcephaly: do all roads lead to Rome?

Gemma K. Thornton and C. Geoffrey Woods

Primary microcephaly, MCPH



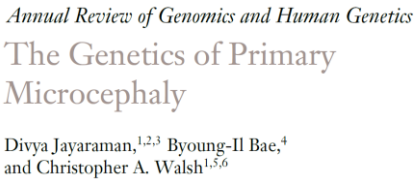
BMC Medical Genomics

REVIEW Open Access

Molecular genetics of human primary microcephaly: an overview

Muhammad Faheem[1], Muhammad Imran Naseer[2,3*], Mahmood Rasool[2,3], Adeel G. Chaudhary[2], Taha A. Kumosani[1,4], Asad Muhammad Ilyas[1], Peter Natesan Pushparaj[2,3], Farid Ahmed[2,3], Hussain A. Algahtani[5], Mohammad H. Al-Qahtani[2,3], Hasan Saleh Jamal[6]

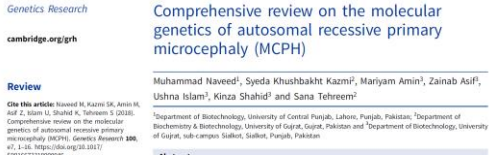
From 2nd International Genomic Medicine Conference (IGMC 2013) Jeddah, Kingdom of Saudi Arabia. 24-27 November 2013



Annual Review of Genomics and Human Genetics

The Genetics of Primary Microcephaly

Divya Jayaraman,[1,2,3] Byoung-Il Bae,[4] and Christopher A. Walsh[1,5,6]



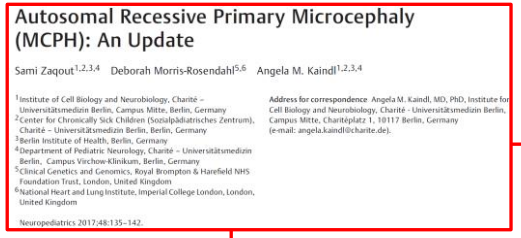
Genetics Research

cambridge.org/grh

Review

Comprehensive review on the molecular genetics of autosomal recessive primary microcephaly (MCPH)

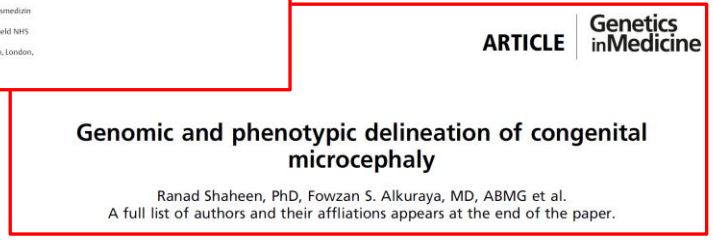
Muhammad Naveed[1], Syeda Khushbakht Kazmi[2], Mariyam Amin[3], Zainab Asif[3], Ushna Islam[3], Kinza Shahid[3] and Sana Tehreem[2]



Autosomal Recessive Primary Microcephaly (MCPH): An Update

Sami Zaqout[1,2,3,4] Deborah Morris-Rosendahl[5,6] Angela M. Kaindl[1,2,3,4]

Neuropediatrics 2017;48:135–142.



ARTICLE Genetics in Medicine

Genomic and phenotypic delineation of congenital microcephaly

Ranad Shaheen, PhD, Fowzan S. Alkuraya, MD, ABMG et al.
A full list of authors and their affliations appears at the end of the paper.

1.Primary MIC can be progressive

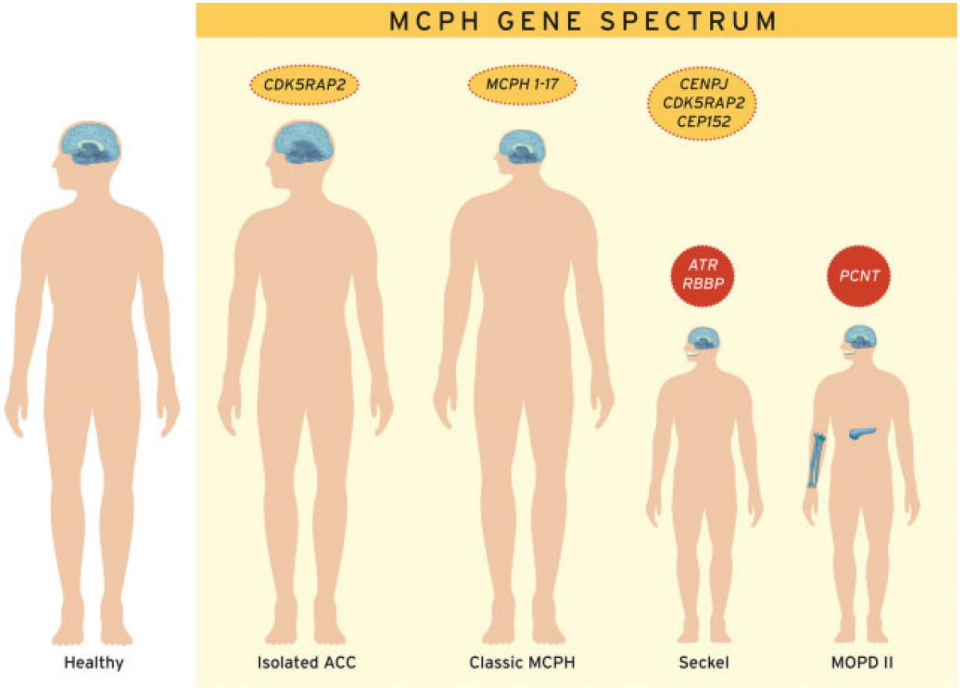
2. Primary MIC can cause growth failure

Table 1 Genes associated with primary microcephaly that encode centrosomal proteins functioning in cent

Locus	Gene	Chromosomal location	Subcellular location	Pathway
MCPH1	*MCPH1*	8p23.1	Nucleus	DNA damage response and regulation of chromosome condensation
MCPH2	*WDR62*	19q13.12	Centrosome (interphase) and spindle poles (mitosis)	Centriole biogenesis
MCPH3	*CDK5RAP2*	9q33.2	Centrosome	Centriole biogenesis
MCPH4	*CASC5*[a]	15q15.1	Kinetochore	Microtubule attachment to centromere and spindle-assembly checkpoint activation in mitosis
MCPH5	*ASPM*	1q31.3	Centrosome (interphase)	Centriole biogenesis
MCPH6	*CENPJ* (also known as *CPAP* or *SAS-4*)	13q12.12–12.13	Centrosome (interphase)	Centriole biogenesis
MCPH7	*STIL*	1p33	Centrosome	Procentriole formation and centriole biogenesis
MCPH8	*CEP135*	4q12	Centrosome	Centriole assembly
MCPH9	*CEP152*	15q21.1	Centrosome	Centriole biogenesis
MCPH10	*ZNF335*	20q13.12	Nucleus	Transcriptional regulation of brain-specific genes controlling cell fate via REST/NRSF
MCPH11	*PHC1*	12p13.31	Nucleus	Negative regulation of GMNN (which itself regulates the cell cycle and inhibits DNA replication)
MCPH12	*CDK6*	7q21.2	Centrosome (mitosis)	Unknown
MCPH13	*CENPE*	4q24	Kinetochore/ centromere	Unknown
MCPH14	*SASS6*	1p21.2	Centrosome	Centriole assembly with CEP135 and CENPJ/CPAP/SAS-4
MCPH15	*MFSD2A*	1p34.2	Plasma membrane	Omega-3 fatty acid transport across blood–brain barrier
MCPH16	*ANKLE2*	12q24.33	Not well characterized	Fly model shows decreased proliferation and increased apoptosis
MCPH17	*CIT*	12q24.23	Midbody	Cytokinesis
MCPH18	*WDFY3* (also known as *ALFY*)	4q21.23	Nucleus and cytoplasm	Autophagy and regulation of Wnt signaling

Autosomal Recessive Primary Microcephaly (MCPH): An Update

Sami Zaqout[1,2,3,4] Deborah Morris-Rosendahl[5,6] Angela M. Kaindl[1,2,3,4]



CURRENT OPINION

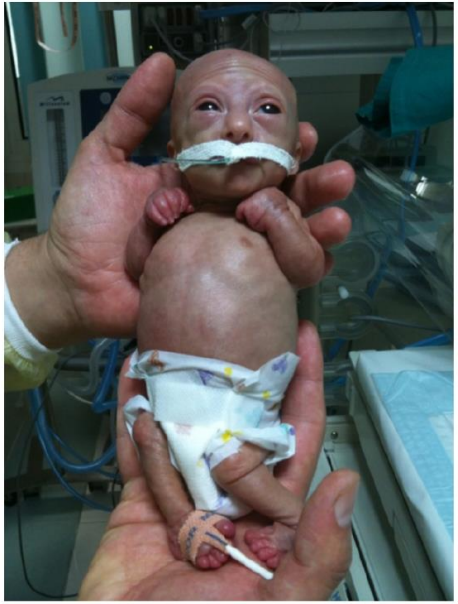
Primordial dwarfism: an update

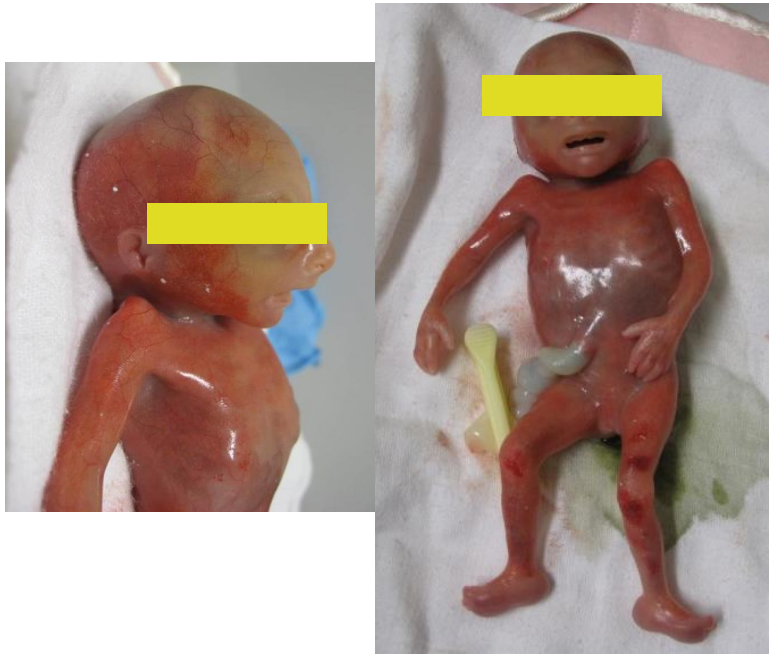
Fowzan S. Alkuraya[a,b]

- Seckel syndrome
  - *ATR, ATRIP, RBBP8, CENPJ, CEP152, DNA2, PLK4, PCNT*
- Primordial dwarfism (NOS)
  - *NIN, POC1A, CRIPT, XRCC4, LARP7*
- Microcephalic Osteodysplatic Primordial Dwarfism type I and type II
  > *PCNT and RNU4ATAC*
- "Other": Meier-Gorlin (*ORC1,-4,-6, CDT1, CDC6*) and 3M syndrome (*CUL7, OBSL1, CCDC8*)

Microcephalic Osteodysplastic Primordial Dwarfism (Majewski type 1)
RNU4ATAC gene

Extreme microcephaly and IUGR





Abolila RA., Egypt J Med Hum Genet, 2012

MOPD- II
PCNT gene

- Primary microcephaly (-4 to -10 SD)
- Facial features reminiscent of “Seckel” syndrome

- IUGR and progressive growth retardation (-4 to -10 SD)

- Skeletal dysplasia:
- Short distal limbs, dysplastic hip, metaphyseal broadening, scoliosis
- Microdontia, abnormal tooth shape
- Skin: acanthosis nigricans and cutis marmorata
- Progressive cerebrovascular disease

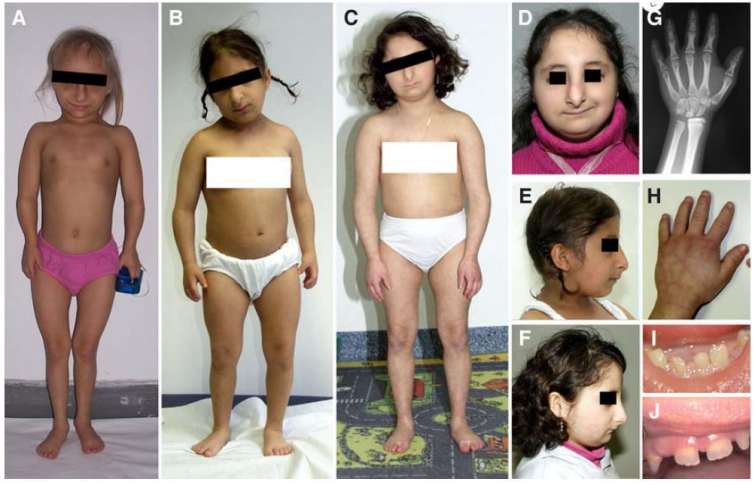
Received: 9 July 2019 | Revised: 20 February 2020 | Accepted: 9 March 2020
DOI: 10.1002/ajmg.a.61585

ORIGINAL ARTICLE

American Journal of medical genetics WILEY

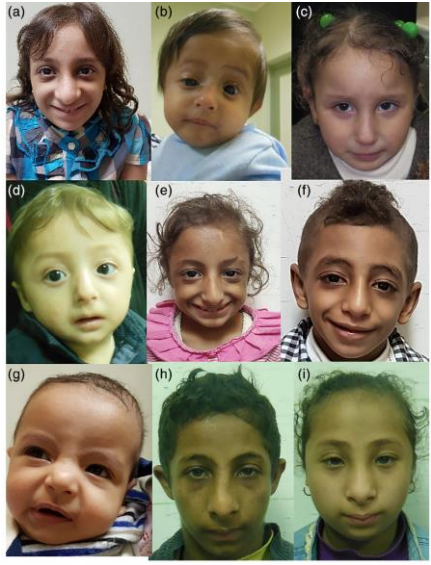
Mutations in the Pericentrin (*PCNT*) Gene Cause Primordial Dwarfism

Anita Rauch,[1*] Christian T. Thiel,[1] Detlev Schindler,[2] Ursula Wick,[1] Yanick J. Crow,[3] Arif B. Ekici,[1] Anthonie J. van Essen,[4] Timm O. Goecke,[5] Lihadh Al-Gazali,[6] Krystyna H. Chrzanowska,[7] Christiane Zweier,[1] Han G. Brunner,[8] Kristin Becker,[9] Cynthia J. Curry,[10] Bruno Dallapiccola,[11] Koenraad Devriendt,[12] Arnd Dörfler,[13] Esther Kinning,[14] André Megarbane,[15] Peter Meinecke,[16] Robert K. Semple,[17] Stephanie Spranger,[18] Annick Toutain,[19] Richard C. Trembath,[20] Egbert Voss,[21] Louise Wilson,[22] Raoul Hennekam,[22,23,24] Francis de Zegher,[25] Helmuth-Günther Dörr,[26] André Reis[1]



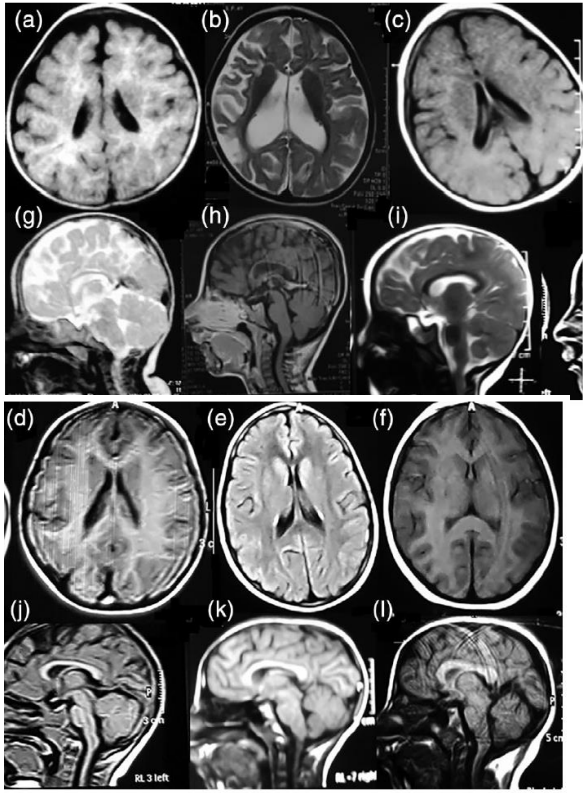
Microcephalic osteodysplastic primordial dwarfism type II: Additional nine patients with implications on phenotype and genotype correlation

Ghada M. H. Abdel-Salam[1,2] | Inas S. M. Sayed[2,3] | Hanan H. Afifi[1,2] | Sherif F. Abdel-Ghafar[2,4] | Maha R. Abouzaid[2,3] | Samira I. Ismail[1,2] | Mona S. Aglan[1,2] | Mahmoud Y. Issa[1,2] | Hala T. EL-Bassyouni[1,2] | Ghada El-Kamah[1,2] | Laila K. Effat[2,4] | Maha Eid[2,5] | Maha S. Zaki[1,2] | Samia A. Temtamy[1,2] | Mohamed S. Abdel-Hamid[2,4]



MOPD- II

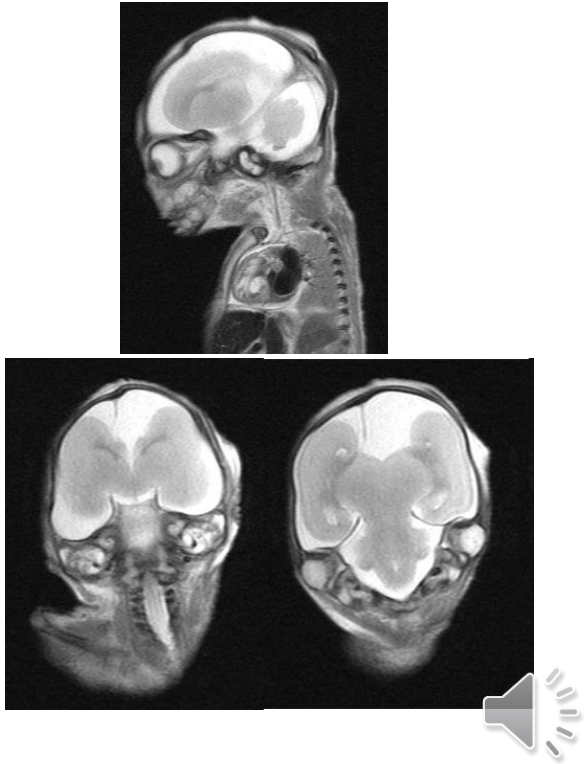
Cortical simplified gyral pattern, moya-moya dis., aneurysms



Abdel-Salam G. AJMG, 2020

MOPD- I

ACC, pachygyria, abn. gyri, interhemispheric cysts

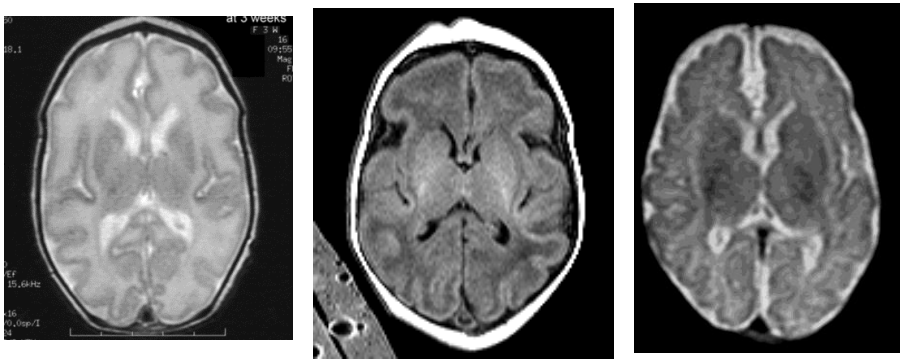


Abdel-Salam G. AJMG, 2013

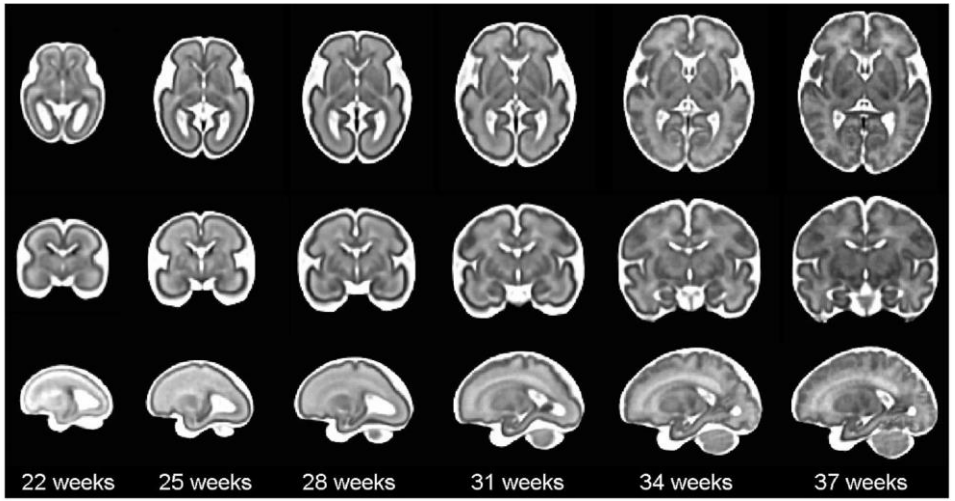
Microcephaly with Simplified Gyral Pattern

Erasmus MC

MCPH



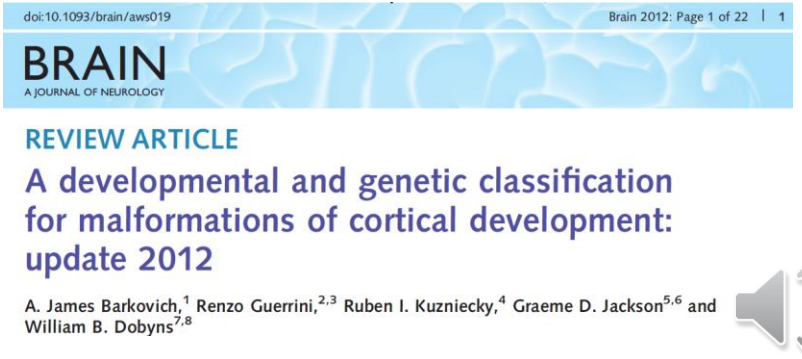
Gestational Week



SCIENTIFIC REPORTS | 7: 476 | DOI:10.1038/s41598-017-00525-w

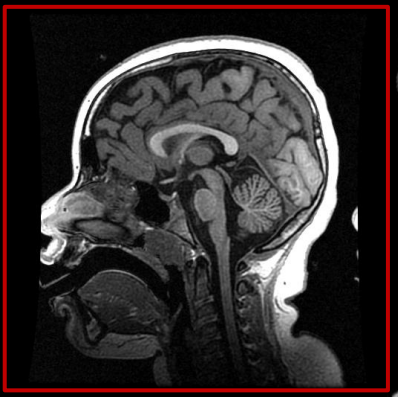
MIC: Morphological classification at brain MRI, utility and limitation

- MIC + Simplified Gyral Pattern (SGP)
- MIC + smooth and thickened cortex (microlissencephaly)
- MIC + SGP + prominent cerebellar and pons dysplasia/hypoplasia
- MIC + hydrocephalus ex-vacuo, hydranencephaly
- MIC + multiple/ different types of cerebral/cerebellar dysgenesis
- MIC + Nodular heterotopia
- MIC + Polymicrogyria appearance
- MIC + Hypomyelination



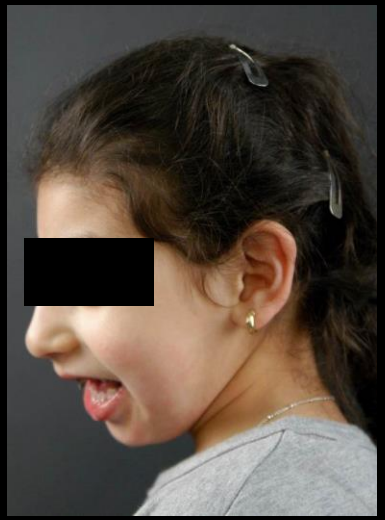
Micro-lissencephaly: small brain with smooth and thick cortex

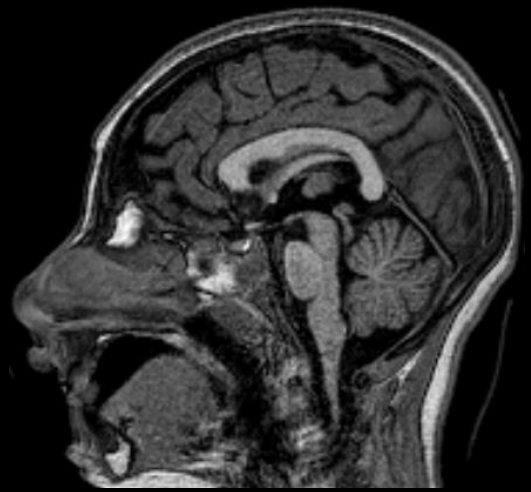
WDR62

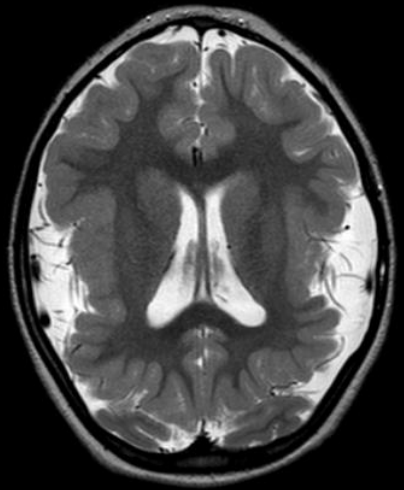


control

Primary Microcephaly with Polymicrogyria (= too many, too small gyri)



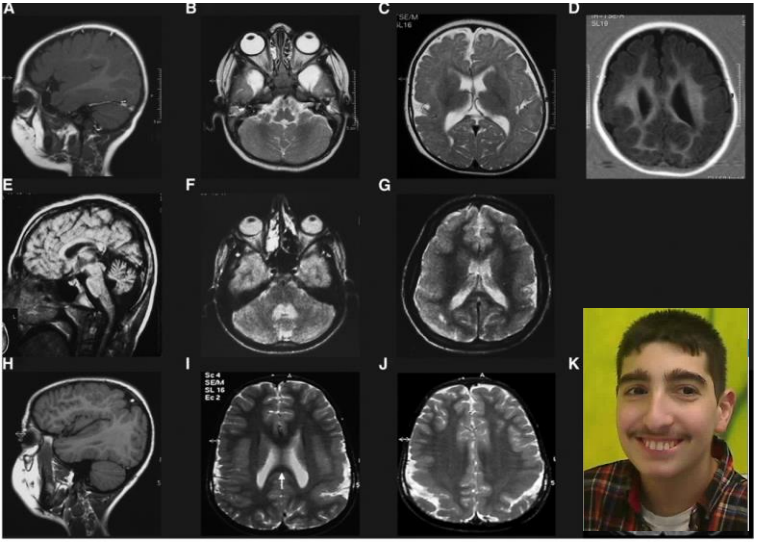




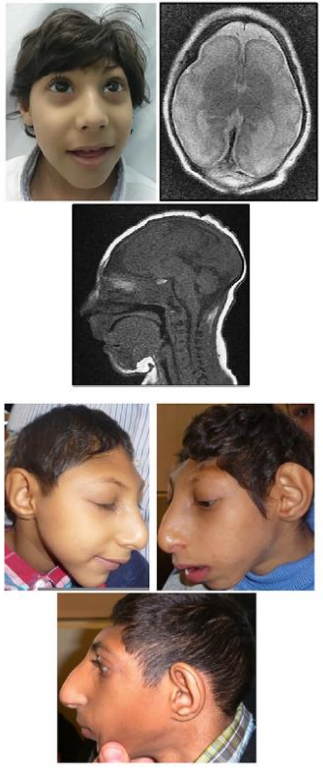
WDR62

Courtesy of Dr A. Accogli, Genova

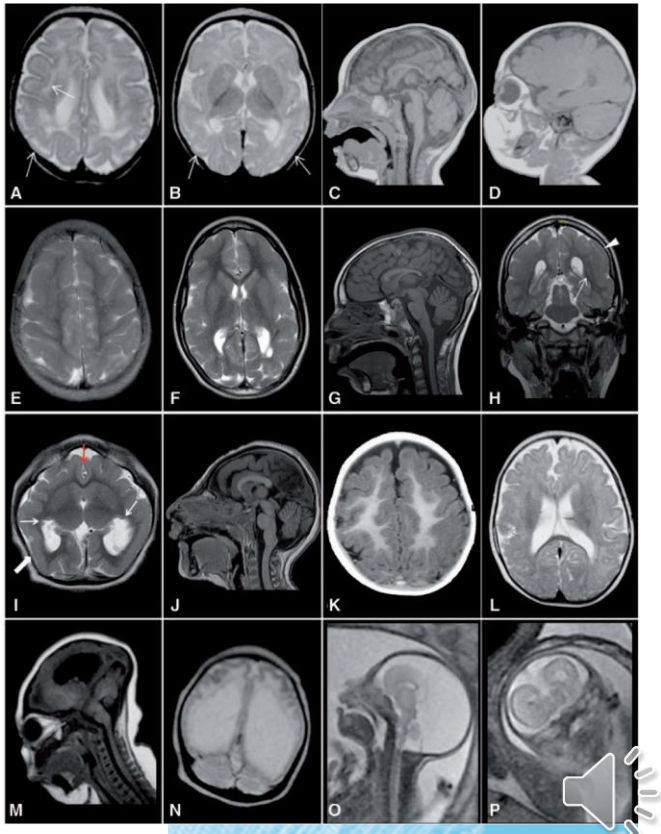
Phenotypic heterogeneity of *RTTN* mutations



The American Journal of Human Genetics *91*, 1–8, September 7, 2012



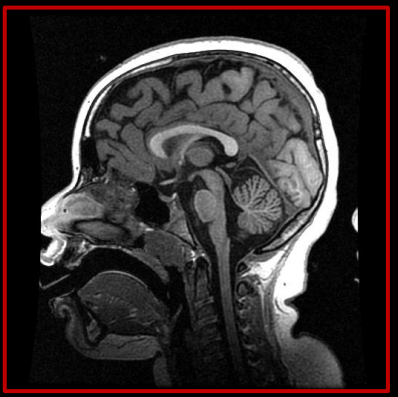
The American Journal of Human Genetics *97*, 1–7, December 3, 2015



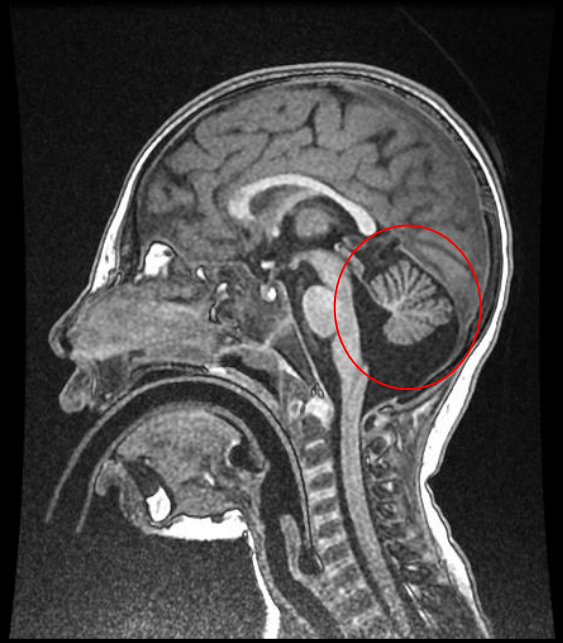
BRAIN 2019: 142; 867–884

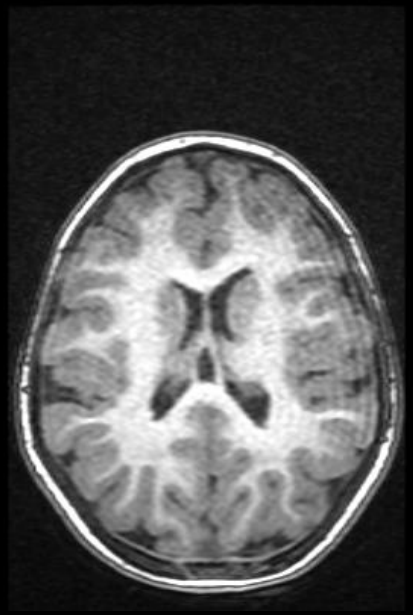
Microcephaly + cerebellar atrophy: PNKP

- MRI age 4 yr; prenatally diagnosed microcephaly, HC at 6 m – 6 SD



control



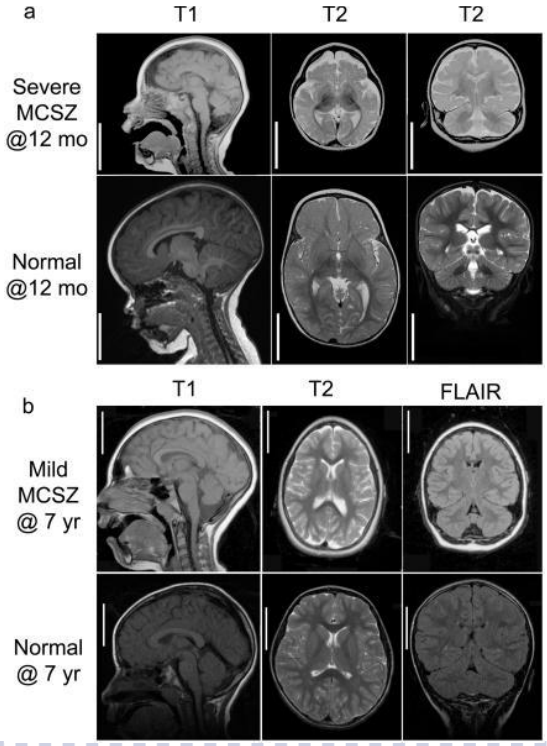


Primary microcephaly with progressive disorder

Erasmus MC

Mutations in *PNKP* cause microcephaly, seizures and defects in DNA repair **2010**

Jun Shen[1,12], Edward C Gilmore[2,3,12], Christine A Marshall[1], Mary Haddadin[4,11], John J Reynolds[5], Wafaa Eyaid[6], Adria Bodell[1], Brenda Barry[1], Danielle Gleason[2], Kathryn Allen[1], Vijay S Ganesh[1], Bernard S Chang[1], Arthur Grix[7], R Sean Hill[2], Meral Topcu[8], Keith W Caldecott[5], A James Barkovich[9] & Christopher A Walsh[1,2,10]



Neurogenetics (2013) 14:43–51
DOI 10.1007/s10048-012-0351-8

ORIGINAL ARTICLE

Progressive cerebellar atrophy and polyneuropathy: expanding the spectrum of *PNKP* mutations

Cathryn Poulton · Renske Oegema · Daphne Heijsman · Jeannette Hoogeboom · Rachel Schot · Hans Stroink · Michèl A. Willemsen · Frans W. Verheijen · Peter van de Spek · Andreas Kremer · Grazia M. S. Mancini

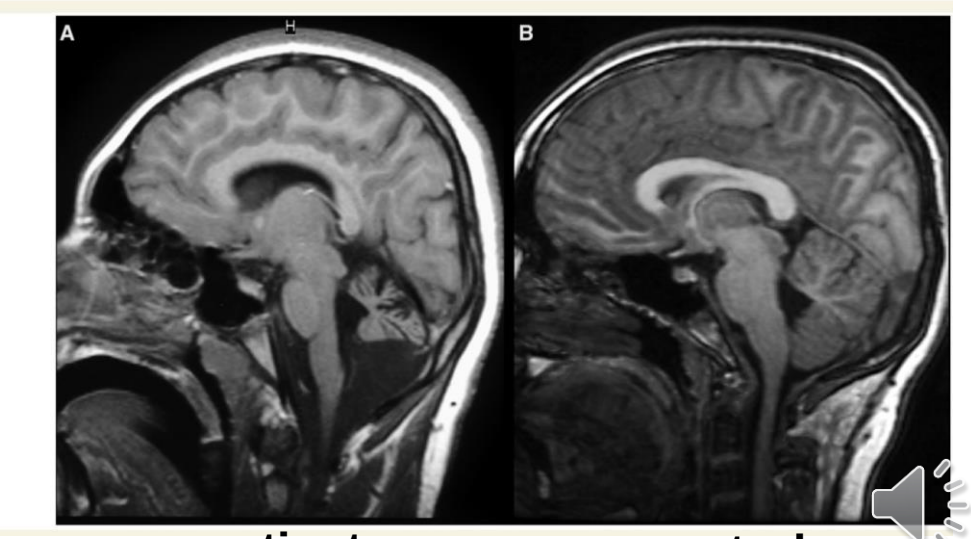
doi:10.1093/brain/awt197 Brain 2013: Page 1 of 2 | e1

BRAIN
A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

A single strand that links multiple neuropathologies in human disease

Renske Oegema,* Cathryn J. Poulton* and Grazia M. S. Mancini



patient control

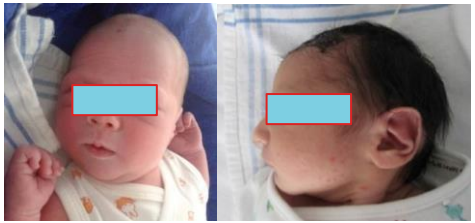
Primary Microcephaly: different outcomes

Annual Review of Genomics and Human Genetics

The Genetics of Primary Microcephaly

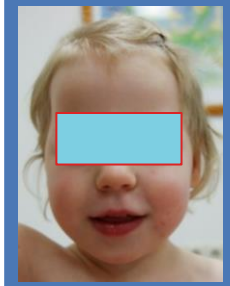
Divya Jayaraman,[1,2,3] Byoung-Il Bae,[4] and Christopher A. Walsh[1,5,6]

HC – 3 SD at birth

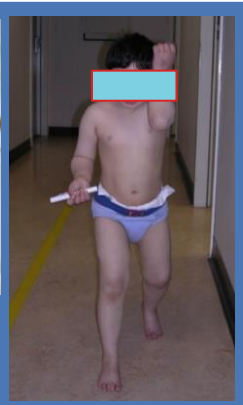


?

HC – 5 SD, non-progressive



Mild speech delay



ID+No speech

SS+ID+No speech

American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 166C:140–155 (2014)

ARTICLE

Genetic Disorders Associated With Postnatal Microcephaly

LAURIE E. SELTZER AND ALEX R. PACIORKOWSKI

HC – 5 SD, progressive

WEST s.

Resp. failure, no epil

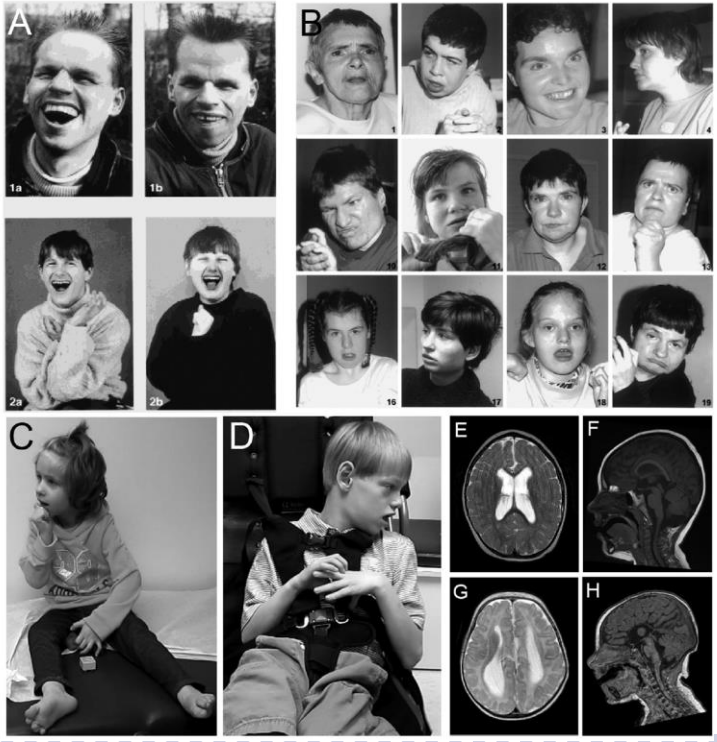
Secondary progressive microcephaly

American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 166C:140–155 (2014)

ARTICLE

Genetic Disorders Associated With Postnatal Microcephaly

LAURIE E. SELTZER AND ALEX R. PACIORKOWSKI

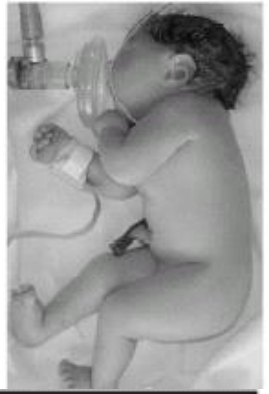


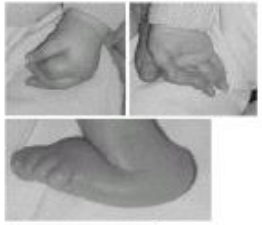
- As part of a recognizable syndrome with MCA:
  - MECP2-related disorder (Rett s.), Rubinstein-Taybi, Mowat-Wilson s., FOXG1-related s., CASK s., Pitt-Hopkins, SLO, Angelman s. etc
- Associated with growth failure, ocular and dysmorphologc features:
  - MICRO-Warbug s., Cockayne s., COFS

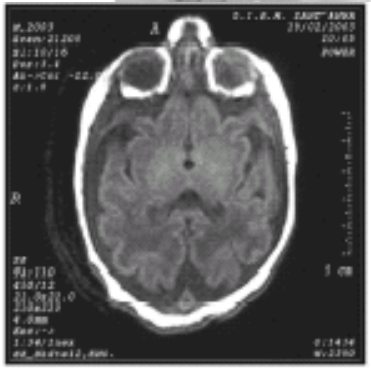
Progressive Microcephaly: Cerebro-Oculo-Facial-Skeletal Syndrome

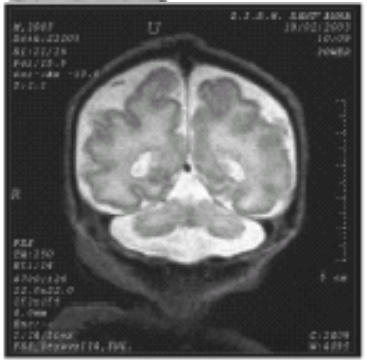
Simplified Gyral Pattern, cerebellar hypoplasia and DNA repair defects

Am. J. Hum. Genet. 69:291–300, 2001

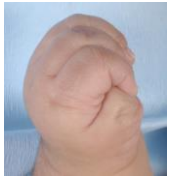




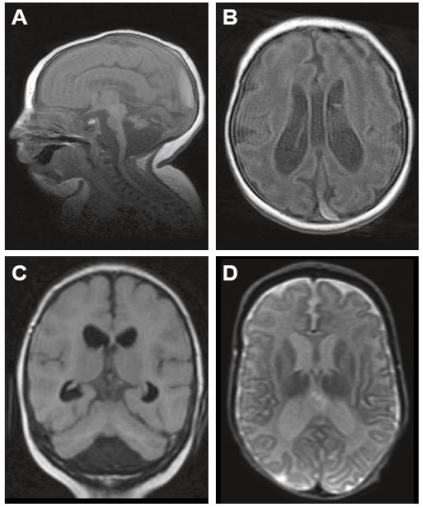




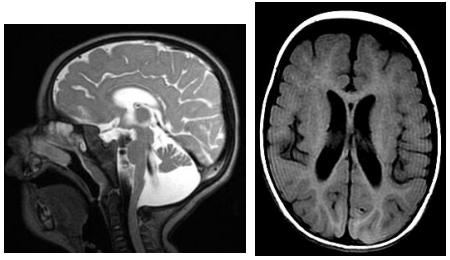
First Reported Patient with Human ERCC1 Deficiency Has Cerebro-Oculo-Facio-Skeletal Syndrome with a Mild Defect in Nucleotide Excision Repair and Severe Developmental Failure



ERCC5



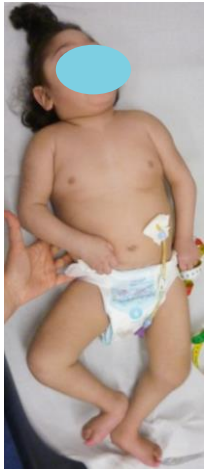
ERCC6



Courtesy Dr A Brooks

SMPD4 mutation mimicks COFS, MEDS and Wolcott-Rallison s.

- Congenital microcephaly with SGP and hypomyelination (71%)
- Progressive microcephaly (90%)
- Congenital distal contractures (85%)
- Death in infancy (33%)
- Respiratory distress/central hypoventilation (85%)
- Epilepsy (68%)
- **Childhood Diabetes M. (27%)***
- Patient fibroblasts show signs of ER stress



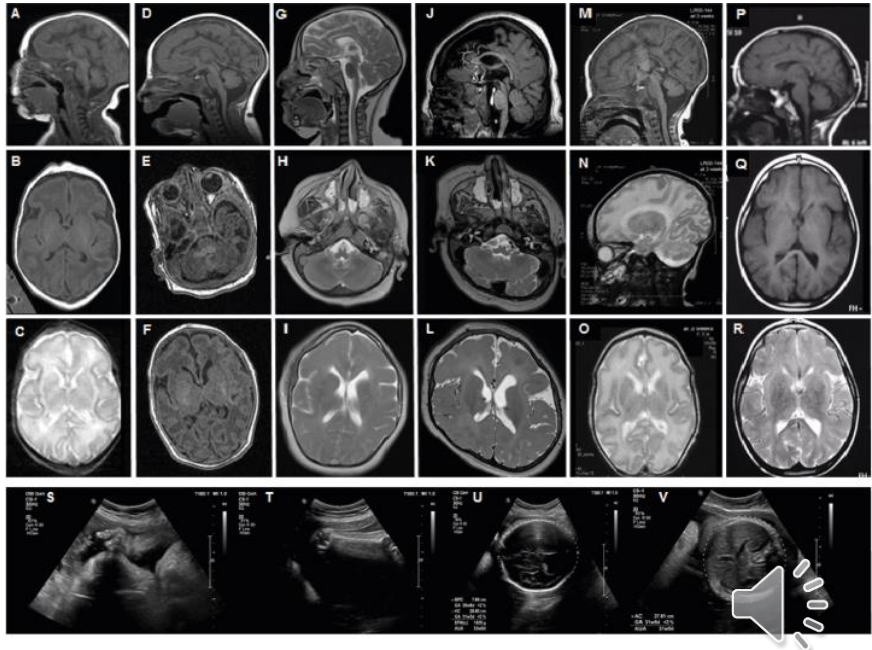
***Smits DJ et al. BRAIN, Feb 2023 in press**

ARTICLE

Loss of SMPD4 Causes a Developmental Disorder Characterized by Microcephaly and Congenital Arthrogryposis

Pamela Magini,[1,40] Daphne J. Smits,[2,40] Laura Vandervore,[2,3] Rachel Schot,[2] Marta Columbaro,[4] Esmee Kasteleijn,[2] Mees van der Ent,[5] Flavia Palombo,[6] Maarten H. Lequin,[7] Marjolein Dremmen,[8] Marie Claire Y. de Wit,[9] Mariasavina Severino,[10] Maria Teresa Divizia,[11] Pasquale Striano,[12,13] Natalia Ordonez-Herrera,[14] Amal Alhashem,[15,16] Ahmed Al Fares,[15,16] Malak Al Ghamdi,[17] Arndt Rolfs,[14] Peter Bauer,[14] Jeroen Demmers,[18] Frans W. Verheijen,[2] Martina Wilke,[2] Marjon van Slegtenhorst,[2] Peter J. van der Spek,[19] Marco Seri,[20] Anna C. Jansen,[3,21] Rolf W. Stottmann,[22] Robert B. Hufnagel,[23] Robert J. Hopkin,[22,24] Deema Aljeaid,[25] Wojciech Wiszniewski,[26,27] Pawel Gawlinski,[27] Milena Laure-Kamionowska,[28] Fowzan S. Alkuraya,[29] Hanah Akleh,[30] Valentina Stanley,[31] Damir Musaev,[31] Joseph G. Gleeson,[31] Maha S. Zaki,[32] Nicola Brunetti-Pierri,[33,34] Gerarda Cappuccio,[33,34] Bella Davidov,[35] Lina Basel-Salmon,[35,36,37] Lily Bazak,[35] Noa Ruhrman Shahar,[35] Aida Bertoli Avella,[12] Ghayda M. Mirzaa,[38,39] William B. Dobyns,[38] Tommaso Pippucci,[1] Maarten Fornerod,[5,41] and Grazia M.S. Mancini[2,41,*]

The American Journal of Human Genetics *105*, 689–705, October 3, 2019



Syndromes with microcephaly, cerebral malformation and hypomyelination

Syndrome Gene (#OMIM)	Protein function	Clinical presentation and brain imaging
EGP5 (# 242840)	key autophagy regulator, implicated in formation of autolysosomes.	AR, Vici syndrome, corpus callosum agenesis, hypopigmentation, cataracts, postnatal microcephaly, failure to thrive, cardiomyopathy, profound developmental delay, immunodeficiency, frontoparietal polymicrogyria, severe hypomyelination.
ERCC6 (# 609413) ERCC8 (# 216400)	DNA double strand bond repair defect	AR, cerebro-oculo-facio skeletal syndrome (COFS/Cockayne syndrome-A and B), congenital microcephaly, low BW, cataract, ID, FTT, deafness, peripheral neuropathy, photosensitivity. MRI: SGP and hypomyelination
PYCR2 (#616420)	Pyrroline-5-carboxylate synthetase, proline biosynthetic enzyme.	AR, Profound psychomotor disability starting at birth. Postnatal progressive microcephaly and hypomyelination (HLD10)
SLC1A4 (# 616657)	ASCT1 transporter for serine, but also alanine and cysteine	AR, Progressive microcephaly, spastic tetraplegia, thin corpus callosum, hypomyelination, cerebral atrophy (SPATCCM).
SMPD4 (# 618622)	Neutral sphingomyelinase-3	AR, congenital arthrogryposis, microcephaly, hypomyelination, progressive NDD
SPTAN1 (# 613477)	spectrin alpha-II gene	AD de novo, variable severe epilepsy, ID (EIEE5). Progressive microcephaly, cerebellar atrophy, brain hypomyelination.
TUBB4A (# 602662)	Tubulin isoform 4A, microtubule sunubit	AD, Onset in infancy with delayed motor development and progressive extrapyramidal movement disorder; variable postanatal microcephaly and hypomyelinating leukoencephalopathy type 6 (HLD6)
TBCD (# 617193)	Chaperone for (dis)assembly of alpha-beta tubulin.	AR, Cerebral atrophy, microcephaly, hypomyelination , severe encephalopathy
VPS11 (# 616683)	vesicular protein sorting associated protein 11, leading to missorting of vesicles in lysosome biogenesis.	AR, Leukoencephalopathy with brain hypomyelination (HLD12), postnatal microcephaly, severe motor impairment, cortical blindness, ID, seizures. Lysosomal storage disorder with sphingolipid abnormalities in urine and signs of storage in skin biopsies.

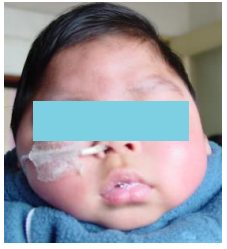
MEDS: Microcephaly, Epilepsy, Diabetes mellitus Syndrome (*IER3IP1*)

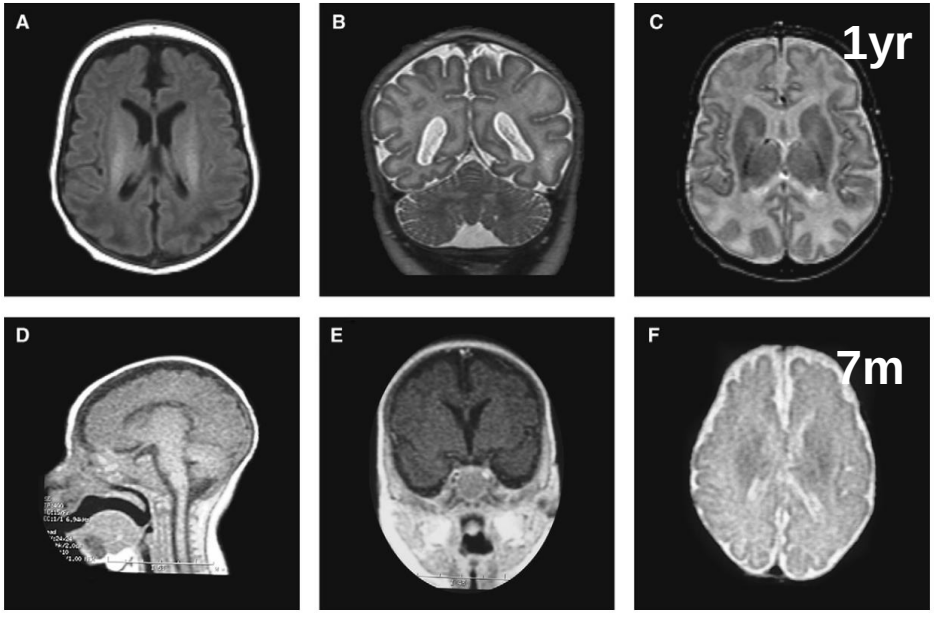
ARTICLE

Microcephaly with Simplified Gyration, Epilepsy, and Infantile Diabetes Linked to Inappropriate Apoptosis of Neural Progenitors

Cathryn J. Poulton,[1] Rachel Schot,[1] Sima Kheradmand Kia,[1] Marta Jones,[3] Frans W. Verheijen,[1] Hanka Venselaar,[4] Marie-Claire Y. de Wit,[2] Esther de Graaff,[5] Aida M. Bertoli-Avella,[1] and Grazia M.S. Mancini[1,*]

The American Journal of Human Genetics *89*, 265–276, August 12, 2011





- ***IER3IP1*** AR mutation
- Congenital microcephaly
- Neonatal persistent IDDM
- Severe therapy-resistant epilepsy
- Death in infancy
- Abnormal apoptosis at brain autopsy

PNAS RESEARCH ARTICLE | MEDICAL SCIENCES

IER3IP1 is critical for maintaining glucose homeostasis through regulating the endoplasmic reticulum function and survival of β cells

Jing Yang[a,1], Jinyang Zhen[a,1], Wenli Feng[a,1], Zhenqian Fan[b], Li Ding[a], Xiaoyun Yang[a], Yumeng Huang[a], Hua Shu[a], Jing Xie[a], Xin Li[a], Jingting Qiao[a], Yuxin Fan[a], Jinhong Sun[a], Na Li[a], Tengli Liu[c,d], Shusen Wang[c,d,e], Xiaona Zhang[a,2], Peter Arvan[f,2], and Ming Liu[a,2]

Edited by Domenico Accili, Columbia University; received March 13, 2022; accepted October 6, 2022 by Editorial Board Member Barbara B. Kahn

PNAS, 2022

IER3IP1 regulates ER secretion and brain size

***IER3IP1* ko induces ER stress, alters oxidative protein folding and cell proliferation**

DEVELOPMENTAL BIOLOGY

A human tissue screen identifies a regulator of ER secretion as a brain-size determinant

Christopher Esk[1]*, Dominik Lindenhofer[1]*, Simon Haendeler[1,2], Roelof A. Wester[1], Florian Pflug[2], Benoit Schroeder[2], Joshua A. Bagley[1], Ulrich Elling[1], Johannes Zuber[3,4], Arndt von Haeseler[2,5], Jürgen A. Knoblich[1,4]†

Loss-of-function (LOF) screens provide a powerful approach to identify regulators in biological processes. Pioneered in laboratory animals, LOF screens of human genes are currently restricted to two-dimensional cell cultures, which hinders the testing of gene functions requiring tissue context. Here, we present CRISPR–lineage tracing at cellular resolution in heterogeneous tissue (CRISPR-LICHT), which enables parallel LOF studies in human cerebral organoid tissue. We used CRISPR-LICHT to test 173 microcephaly candidate genes, revealing 25 to be involved in known and uncharacterized microcephaly-associated pathways. We characterized *IER3IP1*, which regulates the endoplasmic reticulum (ER) function and extracellular matrix protein secretion crucial for tissue integrity, the dysregulation of which results in microcephaly. Our human tissue screening technology identifies microcephaly genes and mechanisms involved in brain-size control.

Science 2020

Microcephaly with Polymicrogyria

ARTICLE

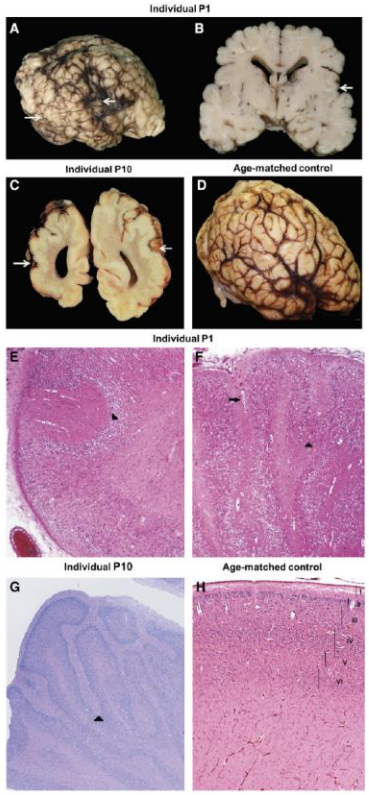
TMX2 Is a Crucial Regulator of Cellular Redox State, and Its Dysfunction Causes Severe Brain Developmental Abnormalities

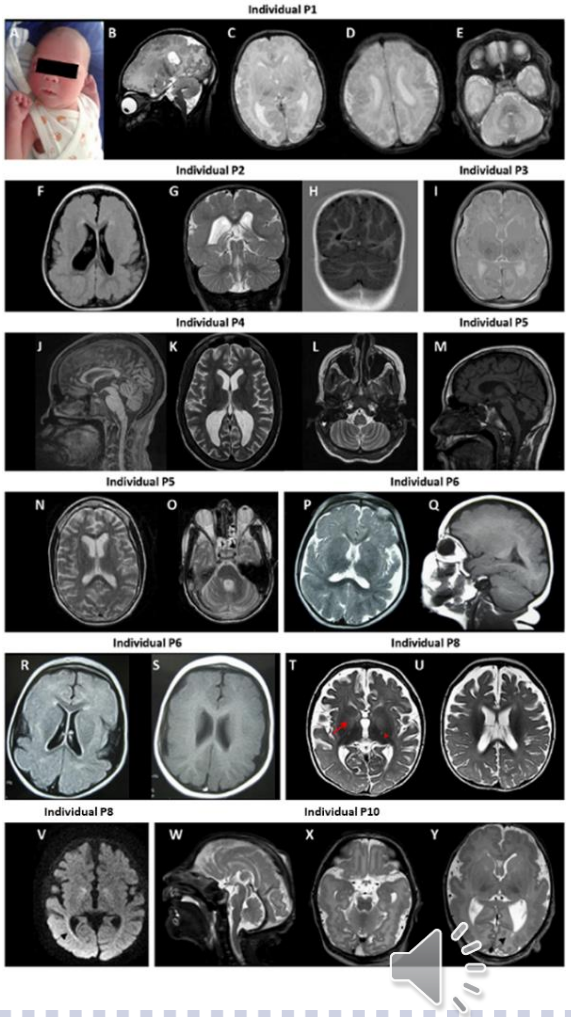
The American Journal of Human Genetics *105*, 1–22, December 5, 2019

Primary microcephaly, Severe NDD, Epilepsy

MRI:
cortical malformation,
diffuse polymicrogyria, pachygyria,
atrophy, similar to CMV infection

Brain pathology:
cortical dislamination and
overmigration of neurons in the pia



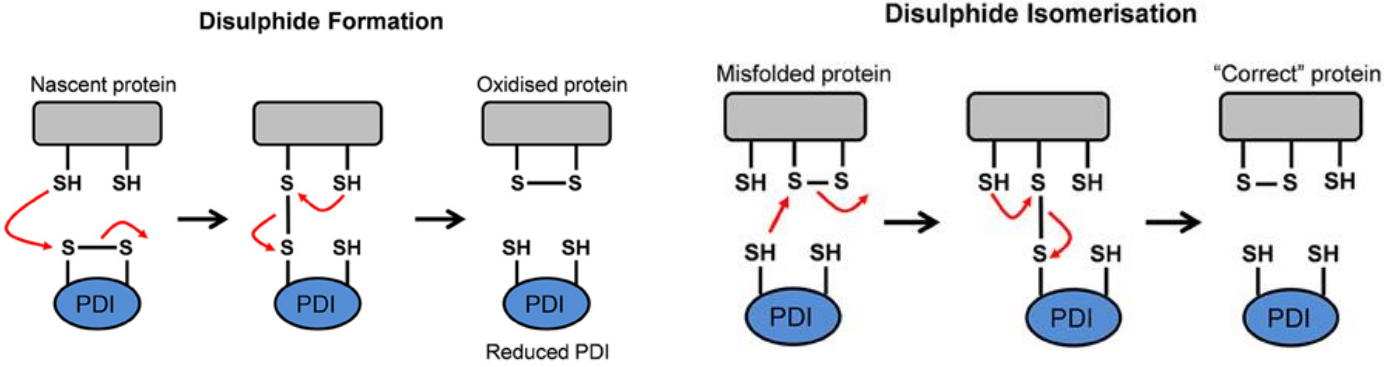


TMX2: Thioredoxin-related Transmembrane Protein 2

Member of the Protein Disulphide Isomerase (PDI) family:

Protein folding, redox regulation and quality control in the ER

- ER localization signal
- Presence ≥ 1Thioredoxin-like domain (CxxC) (TMX2 > atypical SxxC)



Promoting protein folding

Preventing misfolding

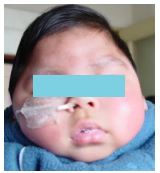
E.R. Perri et al. Frontiers in Cell and Developmental Biology (2016)

Microcephaly related to homeostasis perturbation

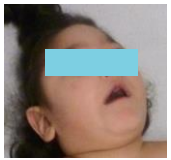
***PYCR2* > MIC + Hypomyelination + FTT**
(Zaki et al Ann Neurol 2016, 80(1):59-70)

***EIF2S3* > MIC + Infantile DM + Hypogonadism (MEHMO syndrome)**
(Skopkova et al Hum Mut 2017, 38:409-425)

***EIF2AK3*/PERK > MIC + Infantile DM + Epiphyseal Dyspl**
Wolcott-Rallison syndrome: MIC is variable!



***IER3IP*1 > MIC + Infantile DM (MEDS syndrome)**
(Poulton C et al Am J Hum Genet 2011, 89(2):265-276)



***SMPD4* > MIC + Hypomyelin+Arthrogryposis + DM**
(Magini et al. Am J Hum Genet, 2019, 105:689-705)

***TMX2* > MIC + Polymicrogyria/COB**
(Vandervore et al Am J Hum Genet Dec. 2019)

cell stress

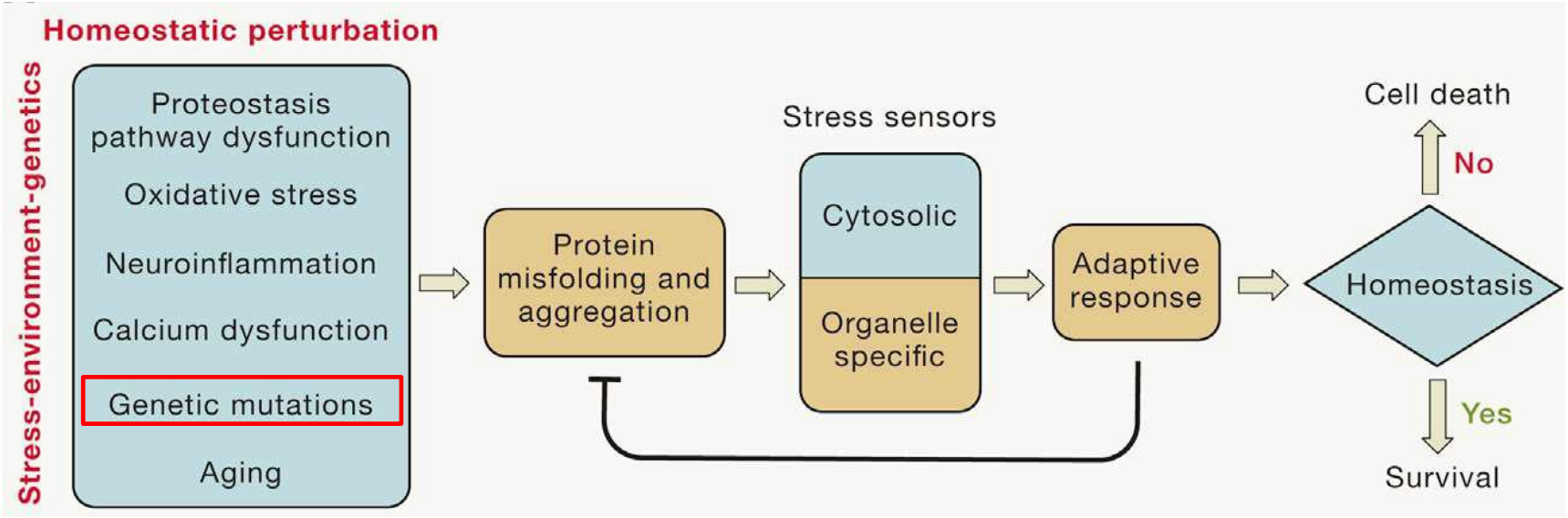
Review

www.cell-stress.com

Endoplasmic reticulum and Golgi stress in microcephaly

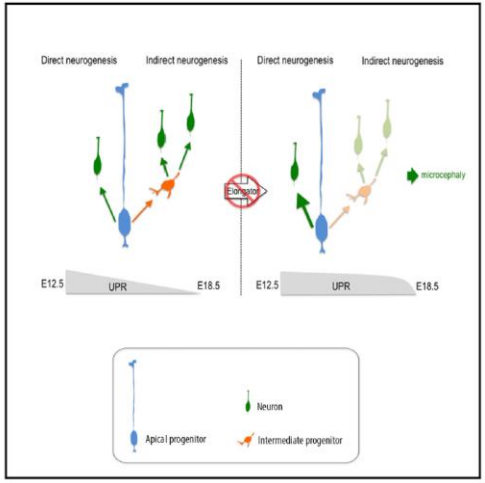
Sandrine Passemard[1,2], Franck Perez[3], Pierre Gressens[1,4,*] and Vincent El Ghouzzi[1,*]

Genetic mutations interfering with brain homeostasis have the same effect of other chronic stress factors

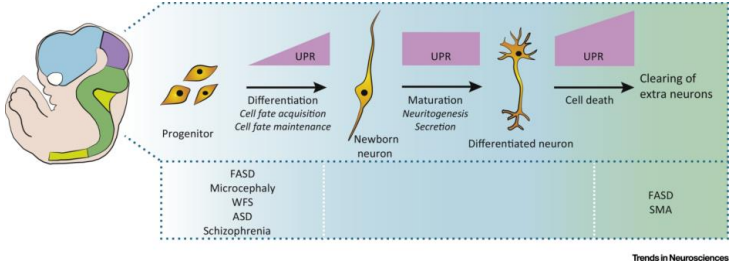


Adapted from: Claudio Hetz, Adapting the proteostasis capacity to sustain brain health-span. Cell 184, March 18, 2021, p.1545-1560

Unfolded Protein Response fine tunes cortical neurogenesis



Laguesse et al. Developmental Cell,35(2015), 553-567.



Godin et al., 2016

- UPR suppression promotes the switch from direct to indirect neurogenesis
- UPR stimulation and ER stress = more direct neurogenesis
- Depletion of intermediate NPC > Microcephaly
- Zika and CMV accelerate neuronal differentiation by dysregulation of autophagy and IER genes > depletion of NPC

nature neuroscience ARTICLES https://doi.org/10.1038/s41593-017-0038-4

Stress-induced unfolded protein response contributes to Zika virus-associated microcephaly

Ivan Gladwyn-Ng[1], Lluís Cordón-Barris[1], Christian Alfano[1], Catherine Creppe[1], Thérèse Couderc[2,3], Giovanni Morelli[1,4], Nicolas Thelen[1], Michelle America[1], Bettina Bessières[5,6], Férechté Encha-Razavi[5], Maryse Bonnière[5], Ikuo K. Suzuki[7], Marie Flamand[8], Pierre Vanderhaeghen[7,9], Marc Thiry[1], Marc Lecuit[2,3,10]* and Laurent Nguyen[1]*

Cells & Development 170 (2022) 203781

Contents lists available at ScienceDirect

Cells & Development

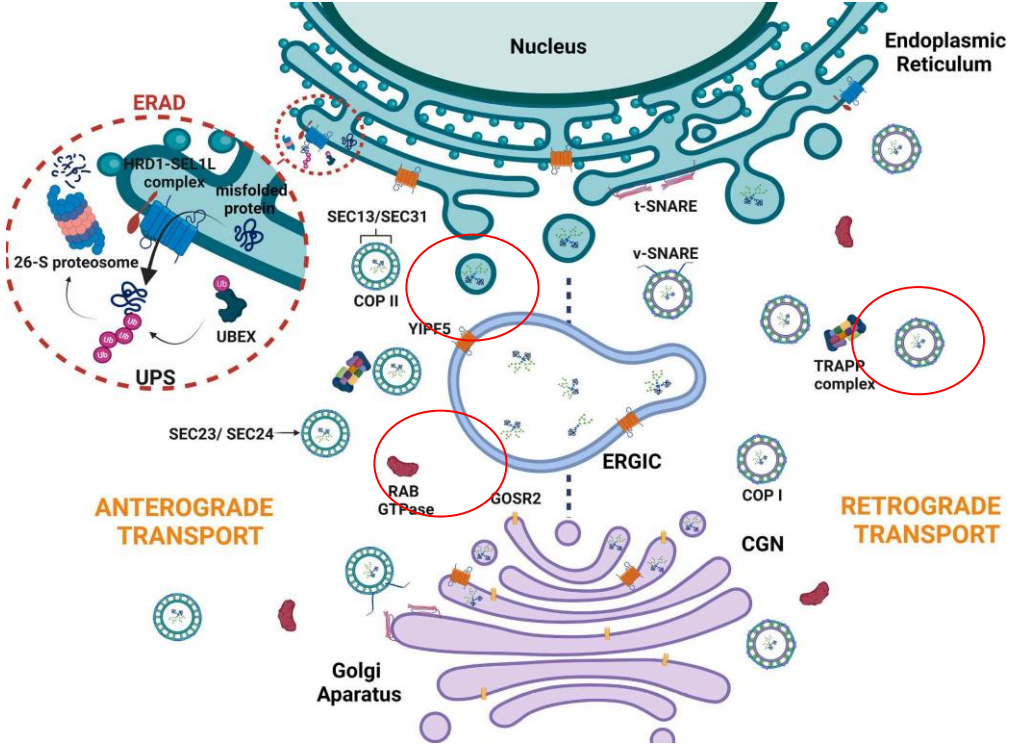
journal homepage: www.journals.elsevier.com/cells-and-development

Review

Emerging roles of endoplasmic reticulum proteostasis in brain development

Giselle Espinosa Vásquez [a,b,c], Danilo B. Medinas [a,b,c,*], Hery Urra [a,b,c,*], Claudio Hetz [a,b,c,d,*]

The early secretory pathway and ER-Associated protein Degradation (ERAD) in neurodevelopmental disorders

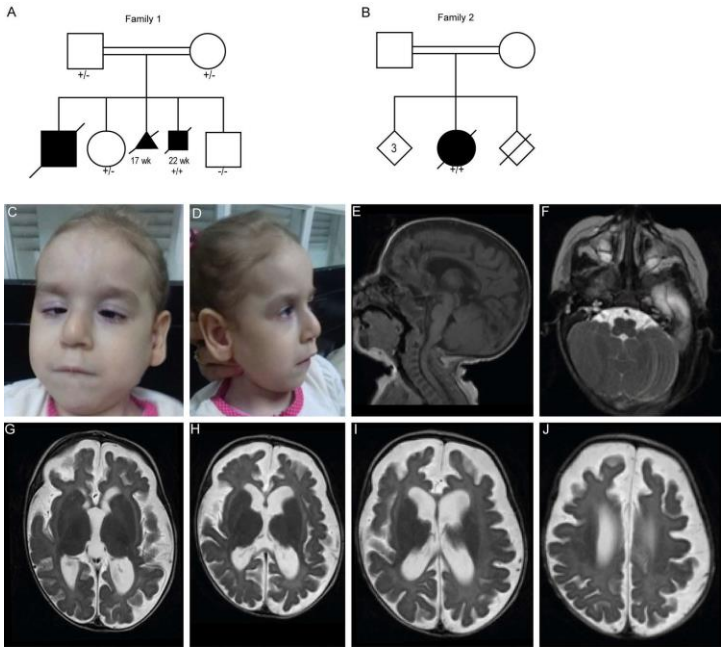


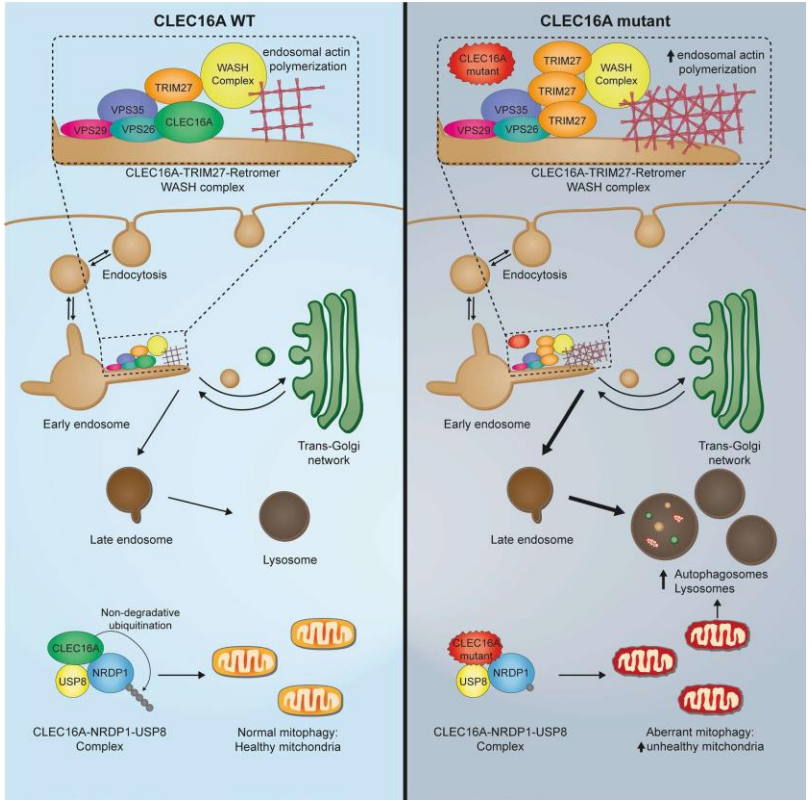
Encircled MIC-related proteins

From: Vasquez et al Cells & Devel 2022, 170:203781 Emerging roles of endoplasmic reticulum proteostasis in brain development.

CLEC16A interacts with retromer and TRIM27, and its loss impairs endosomal trafficking and neurodevelopment.

Smits DJ et al. Human Genetics, online 20 Dec. 2022

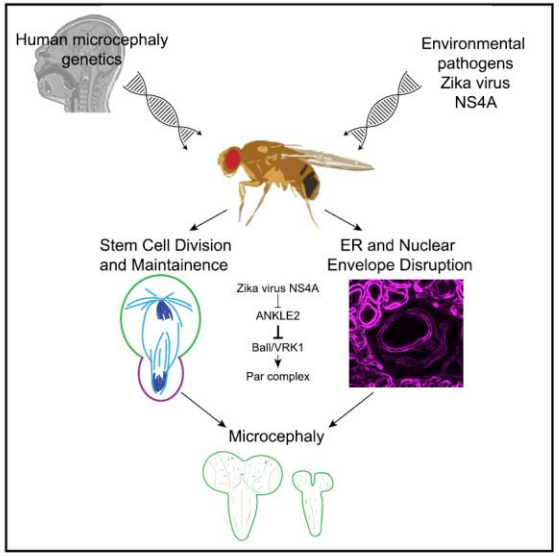




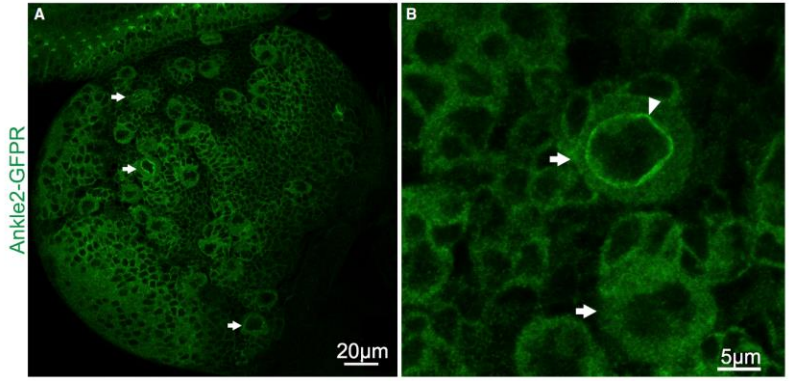
Article

Developmental Cell

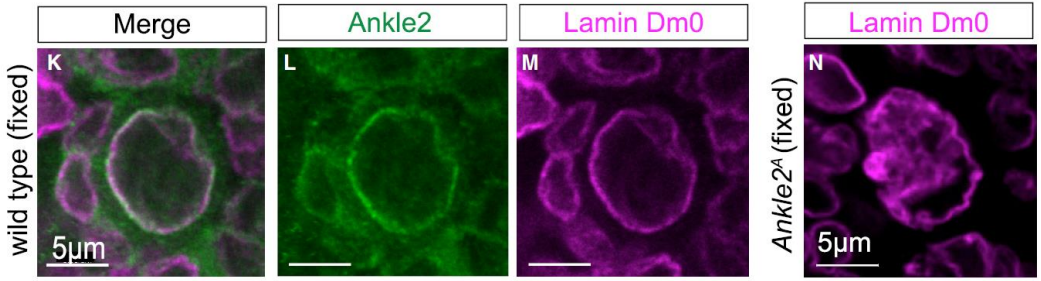
Mutations in *ANKLE2*, a ZIKA Virus Target, Disrupt an Asymmetric Cell Division Pathway in *Drosophila* Neuroblasts to Cause Microcephaly



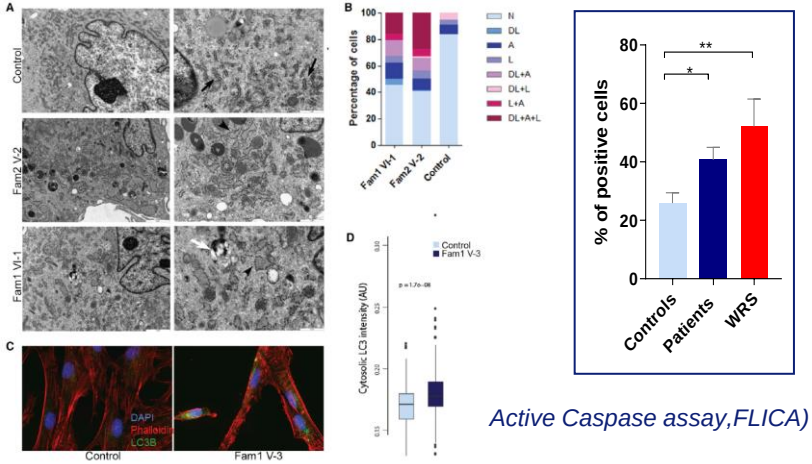
Ankle2 localizes with ER markers and is required for proper ER morphology



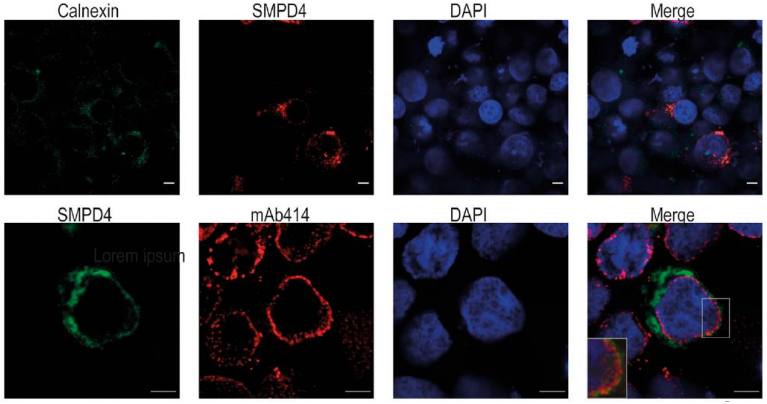
Ankle2 localizes with the nuclear envelope and is required for its morphology



SMPD4 interacts with ER and nuclear envelope proteins



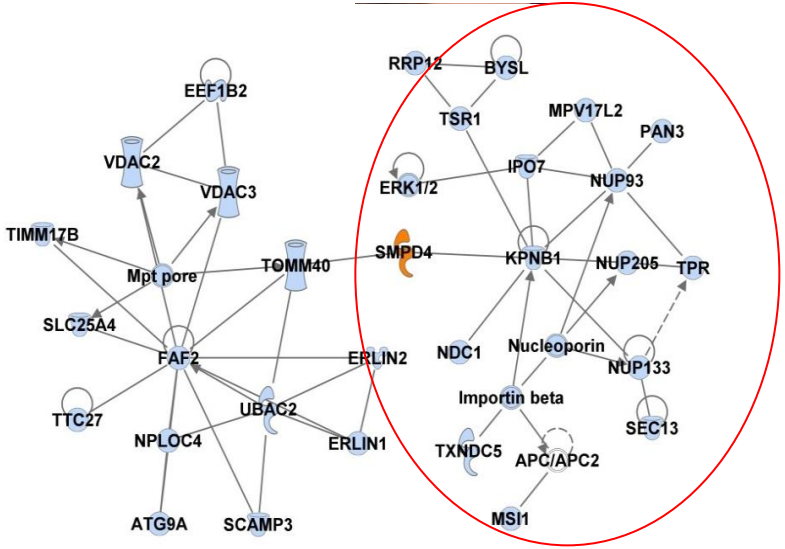
Active Caspase assay,FLICA)



ARTICLE

Loss of SMPD4 Causes a Developmental Disorder Characterized by Microcephaly and Congenital Arthrogryposis

Pamela Magini,[1,40] Daphne J. Smits,[2,40] Laura Vandervore,[2,3] Rachel Schot,[2] Marta Columbaro,[4] Esmee Kasteleijn,[2] Mees van der Ent,[5] Flavia Palombo,[6] Maarten H. Lequin,[7] Marjolein Dremmen,[8] Marie Claire Y. de Wit,[9] Mariasavina Severino,[10] Maria Teresa Divizia,[11] Pasquale Striano,[12,13] Natalia Ordonez-Herrera,[14] Amal Alhashem,[15,16] Ahmed Al Fares,[15,16] Malak Al Ghamdi,[17] Arndt Rolfs,[14] Peter Bauer,[14] Jeroen Demmers,[18] Frans W. Verheijen,[2] Martina Wilke,[2] Marjon van Slegtenhorst,[2] Peter J. van der Spek,[19] Marco Seri,[20] Anna C. Jansen,[3,21] Rolf W. Stottmann,[22] Robert B. Hufnagel,[23] Robert J. Hopkin,[22,24] Deema Aljeaid,[25] Wojciech Wiszniewski,[26,27] Pawel Gawlinski,[27] Milena Laure-Kamionowska,[28] Fowzan S. Alkuraya,[29] Hanah Akleh,[30] Valentina Stanley,[31] Damir Musaev,[31] Joseph G. Gleeson,[31] Maha S. Zaki,[32] Nicola Brunetti-Pierri,[33,34] Gerarda Cappuccio,[33,34] Bella Davidov,[35] Lina Basel-Salmon,[35,36,37] Lily Bazak,[35] Noa Ruhrman Shahar,[35] Aida Bertoli Avella,[12] Ghayda M. Mirzaa,[38,39] William B. Dobyns,[38] Tommaso Pippucci,[1] Maarten Fornerod,[3,41] and Grazia M.S. Mancini[2,41,*]

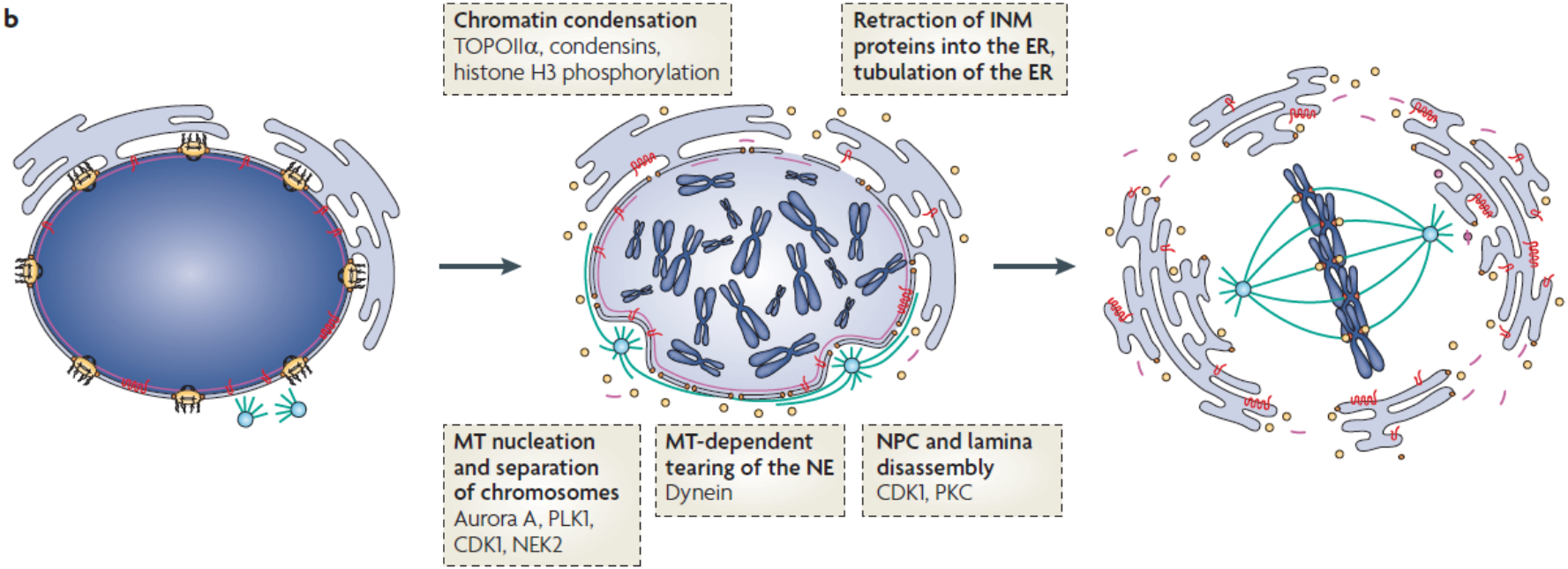


ER protein folding, protein synthesis, protein translocation

ER + Nuclear envelope

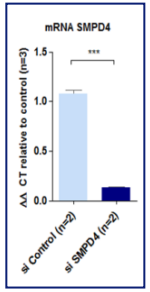
Several components of the nuclear pore complex

Nuclear Pores regulate assembly and disassembly of Nuclear Envelope



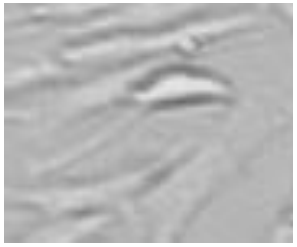
SMPD4 mutation affects cell cycle

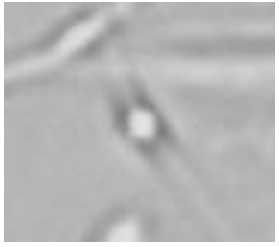
Erasmus MC

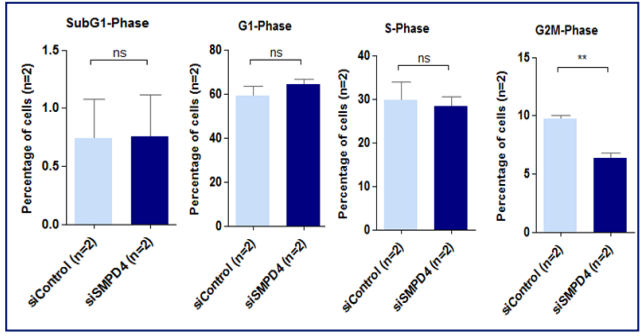


control

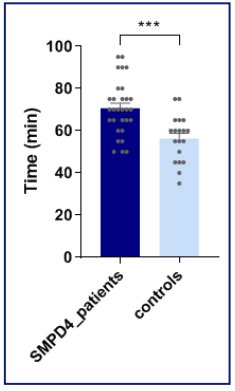
patient







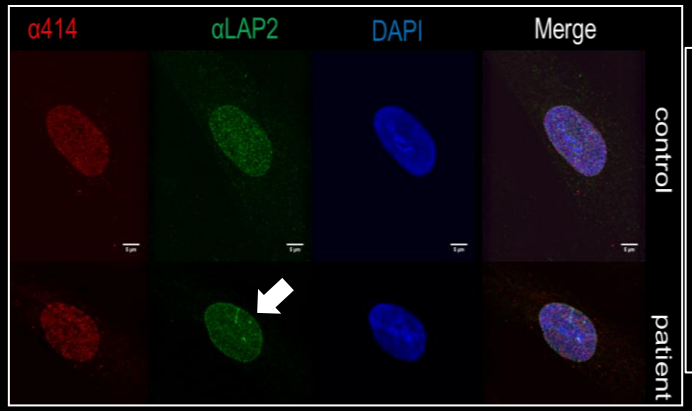
Cell cycle phases (Flow cytometry)

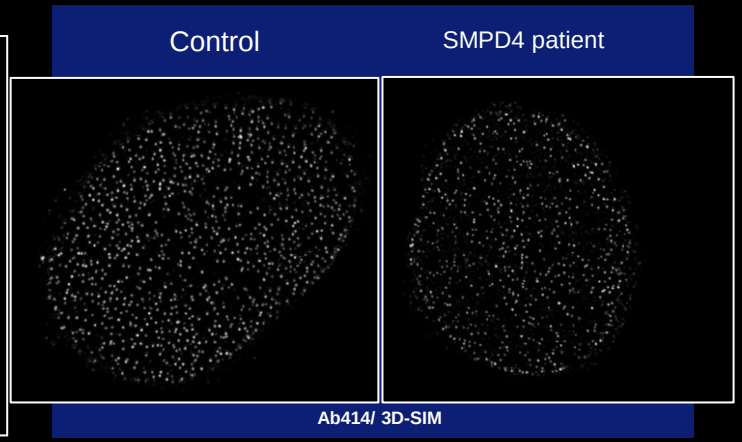


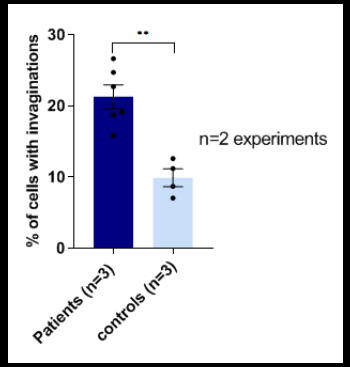
- KD-SMPD4 shows G2/M phase delay
- The duration of mitosis is prolongued in SMPD4 fibroblasts

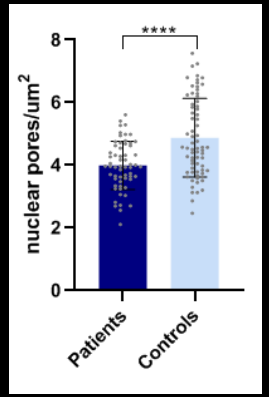
D. Smits et al , BRAIN 2023 in press

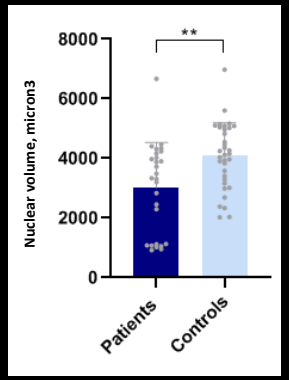
SMPD4 regulates nuclear pore dis/assembly











SMPD4 interphase nuclei show increased membrane invaginations and decreased number of nuclear pores

D. Smits et al, BRAIN 2023, in press

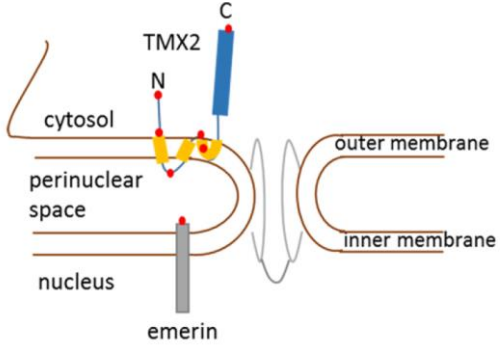
Dual Mechanism in progressive Microcephaly

Erasmus MC

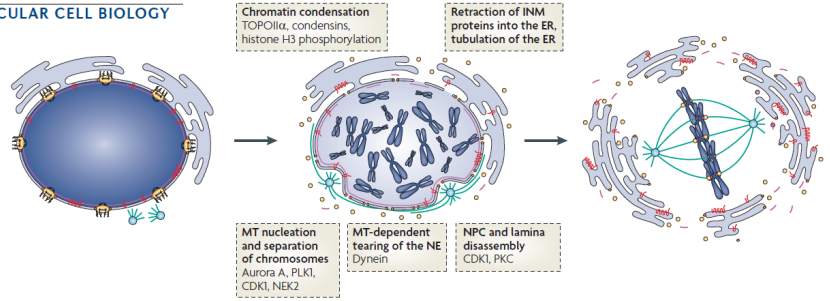
Thioredoxin-related transmembrane protein 2 (TMX2) regulates the Ran protein gradient and importin-β-dependent nuclear cargo transport

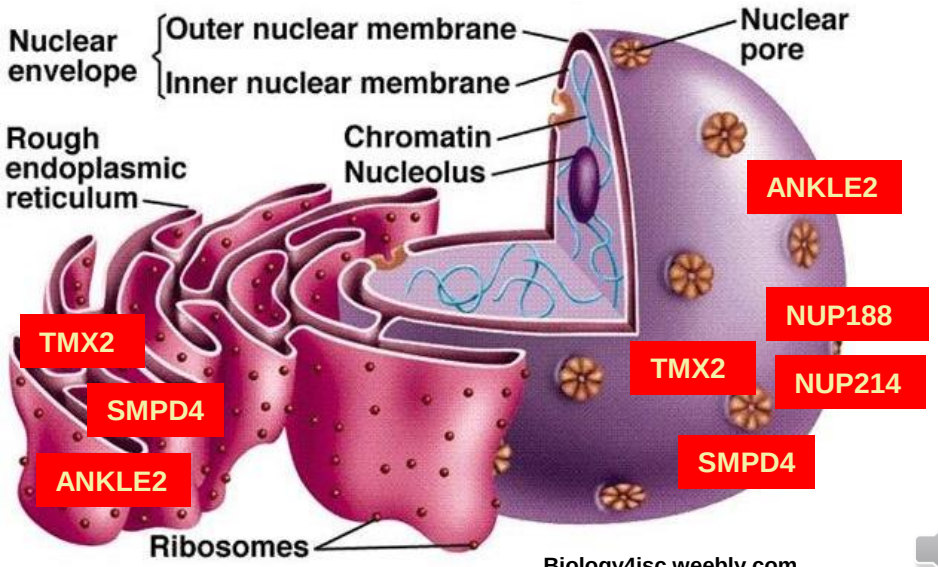
Ami Oguro[1,2] & Susumu Imaoka[1]

SCIENTIFIC REPORTS | (2019) 9:15296 |



NATURE REVIEWS | MOLECULAR CELL BIOLOGY





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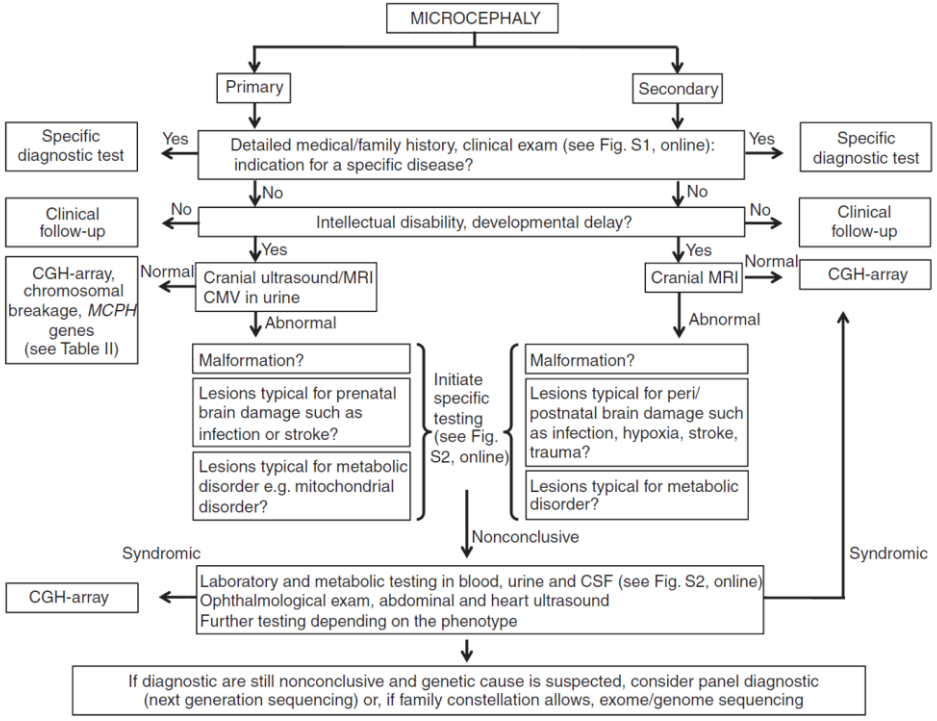
DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Diagnostic approach to microcephaly in childhood: a two-center study and review of the literature

MAJA VON DER HAGEN[1] | MARK PIVARCSI[2,3] | JULIANE LIEBE[1] | HORST VON BERNUTH[4,5] | NATALIYA DIDONATO[6] | JULIA B HENNERMANN[7,8] | CHRISTOPH BÜHRER[9] | DAGMAR WIECZOREK[10] | ANGELA M KAINDL[2,3]



- *Multidisciplinary approach*
- *Stepwise evaluation*
- *Next-gen sequencing*
- *Follow-up*

Erasmus MC:

Clinical Genetics

Daphne Smits, Rachel Schot, Laura Vandervore, Marjon van Slegtenhorst, Martina Wilke, Frans Verheijen, Alice Brooks, Esmee Kasteleijn, Vincenzo Bonifati, Stefan Barakat, Maura van Mook

Cell Biology

Maarten Fornerod, Niels Galjart, Raymond Poot

Pathology

Peter van der Spek, Max Kros, Stefanie Brock

Child Neurology: Marie Claire de Wit

Radiology: Marjolein Dremmen

Proteomics and IOC: Jeroen Demmers, Dick Dekkers, Johan Slotman

ENCORE: exp centr Brain Malformation

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Alexandra Afenjar, Paris
Stephanie Coury, Boston
Boris Keren, Paris
Caroline Nava, Paris
Florence Renaldo, Paris
María José Sanchez, Murcia
Wen-Hann Tan, Boston **and more….**