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Supplementary webappendix

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Supplementary Legend for Figure 1. Axial T2-weighted images at the level of the mid-lateral ventricles showing different malformations of cortical development (MCD). Long arrows show representative areas of cortical malformation (A-D, F, I-O), subcortical band heterotopia (H) or periventricular nodular heterotopia. The short black arrow shows a small periventricular nodular heterotopia (O). Asterisks denote abnormal white matter (B), focal transmantle dysplasia (D), wide inter hemispheric space due to absent corpus callosum (E), a shunt (I), and an open-lip cleft (M). The disorders of brain growth shown include severe congenital microcephaly with a polymicrogyria-like cortical malformation associated with homozygous *WDR62* mutations (A), dysplastic megalencephaly (here hemimegalencephaly) on the right with heterozygous *PTEN* p.Tyr68His mutation (B), megalencephaly and frontal-perisylvian polymicrogyria in an infant with heterozygous *PIK3R2* p.Gly373Arg mutation (C), and focal cortical dysplasia most consistent with type 2b (focal transmantle dysplasia imaged at 7T) (D). Diffuse disorders of neuronal migration include severe lissencephaly with cerebellar hypoplasia and absent corpus callosum with heterozygous *TUBA1A* p.Thr51Ile mutation (E), polymicrogyria-like cortical malformation due to heterozygous *TUBB2B* p.Gly98Arg mutation (F), severe grade 3 classic lissencephaly with heterozygous LIS1 p.Ile216Lys mutation (G), and diffuse subcortical band heterotopia in a female with heterozygous *DCX* p.Ala204Asp mutation (H). Cobblestone cortical malformations shown include frontal predominant cobblestone malformation in a child with muscle-eye-brain disease and compound heterozygous *POMGnT1* mutations (I), frontal predominant cobblestone malformation in a child with autosomal recessive cutis lax and homozygous *ATP6V0A2* p.T280fsX285 mutation (J), and posterior predominant cobblestone mutation in a child with congenital muscular dystrophy and homozygous *LAMA2* mutation (K). The next image shows a peroxisomal cortical malformation from a child with Zellweger syndrome (L). Postmigrational MCD shown include classic schizencephaly with an open-lip cleft in the left frontal region (M), and perisylvian polymicrogyria in a child with the common 3 Mb deletion 22q11.2 (N). The last two images show a child with posterior periventricular nodular heterotopia with overlying polymicrogyria (O), and bilateral diffuse periventricular nodular heterotopia in a female with a heterozygous *FLNA* p.Q1346fsX1349 mutation (P). These images come from subjects LR12-220 (A), LR12-123 (B), LR12-303 (C), LR13-rg1 (D), LR09-393 (E), LR02-406 (F), LR10-132 (G), LR12-295 (H), LR12-478 (I), LR07-081 (J), LR09-117a1 (K), LP98-074 (L), LR11-246 (M), LR07-120 (N), LR11-208 (O), and LP99-157a2 (P).

Supplementary Table 1. Phenotype spectrum observed with 8 tubulinopathy genes

	LCH severe	LCH moderate	LIS p>a	PMG-like, CBLH	CBLH
TUBA1A	+	+	+	+	+
TUBA8	–	–	–	variant	–
TUBB5	–	–	–	+	+
TUBB2B	+	+	–	+	–
TUBB3	–	–	–	+	–
TUBG1	–	–	+	–	–
DYNC1H1	–	+	+	–	–
KIF2A	–	–	+	–	–

Abbreviations: a, anterior; CBLH, cerebellar hypoplasia; ILS, isolated lissencephaly sequence; LCH, lissencephaly with cerebellar hypoplasia; PMG, polymicrogyria; p, posterior.

Supplementary Table 2. Comparative imaging features of MCD

	Brain symmetry (R-L)		Cortical thickness		Cortical surface texture		Other features			
	Symmetric	Asymmetric	>1 cm	<1 cm	Smooth	Pebbled	ACC	CBLH	PNH	WM
MEG-DMEG-FCD II	+	+	+	+	–	+	–	–	R	+
LIS-SBH	+	R*	+	–	+	–	±	±	–	–
PMG-like (tubulin)	+	+	–	+	–	+	+	+	R	–
PMG typical	+	+	–	+	–	+	–	R	±	–
COB	+	–	+	+	+	+	–	+	–	+
FCD I	–	+	–	+	–	–	–	–	–	–
PNH	+	+	na	na	na	na	±	+	na	–

Abbreviations: ACC, agenesis of the corpus callosum; CBLH, diffuse cerebellar hypoplasia; COB, cobblestone malformation; DMEG, dysplastic megalencephaly; FCD I, focal cortical dysplasia type 1; FCD II, focal cortical dysplasia type 2; L, left; LIS, lissencephaly; MEG, megalencephaly; MCD, malformations of cortical development; PMG, polymicrogyria; PNH, periventricular nodular heterotopia; SBH, subcortical band heterotopia; R, right; R*, rare feature; WM, abnormal white matter signal (excludes prominent perivascular spaces as these are common to most MCD)

Supplementary Table 3: Causative genes and phenotype spectrum in cobblestone-type cortical malformations

Gene*	Cyto	Phenotypes	References
Dystroglycanopathies: COB with CMD (anterior predominant, a>p)			
B3GALNT2	1q42.3	WWS MEB	1
B3GNT1	11q13.2	MEB	2
FKRP	19q13.32	WWS MEB CBL-CMD	3–5
FKTN	9q31.2	WWS FCMD	6, 7
GTDC2	3p22.1		8
ISPD	7p21.2	WWS	9–12
LARGE	22q12.3	WWS MEB	13
POMGnT1	1p34.1	MEB	14, 15
POMT1	9q34.13	WWS	16, 17
POMT2	14q24.3	WWS MEB MIC-CMD	18, 19
TMEM5	12q14.2		11
N- and O-linked glycanopathies: COB with CDG (anterior predominant, a>p)			
ATP6V0A2	12q24.31	Debre cutis laxa	20, 21
B4GALT1	9p13	DWM with CDG	22, 23
SNAP29	22q11.2	CEDNIK	24, 25
SRD5A3	4q12	CHIME-like	26
Lamininopoathies: COB only or COB with CMD (posterior predominant, p>a)			
LAMA2	6q22.33	COB p>a, CMD	27, 28
LAMB1	7q31.1	COB p>a	29
LAMC3	9q34.13	COB p>a	30
Collagenopathy: COB only (very preliminary group)			
GPR56	16q13	COB a>p	31–33
COL18A1	21q22.3	Knobloch	34

Key: COB, cobblestone malformation; CBL-CMD, mental retardation, cerebellar cysts and CMD; CEDNIK, CEDNIK syndrome; Cyto; cytogenetic location; Debre cutis laxa, DWM-CDG, Dandy-Walker malformation with CDG; Debré-type autosomal recessive cutis laxa; FCMD, Fukuyama congenital muscular dystrophy; Knobloch, Knobloch syndrome; MEB, Muscle-eye-brain disease; WWS, Walker-Warburg syndrome. a>p, anterior more severe than posterior; p>a, posterior more severe than anterior.
* Protein names are listed in Supplementary Table 4

Supplementary Table 4: Full names for all genes and proteins quoted in this article (abbreviations are listed in alphabetical order)

a1b3 integrin - α1 integrin/β3 integrin complex
ACTB - actin, beta
ACTG1 - actin, gamma 1
AKT - protein kinase B
AKT3 - v-akt murine thymoma viral oncogene homolog 3
AMPK - AMP-activated protein kinase
ARFGEF2 - ADP-ribosylation factor guanine nucleotide-exchange factor 2
ARX - aristaless related homeobox
ATP6V0A2 - ATPase, H+ transporting, lysosomal V0 subunit a2
B3GALNT2 - beta-1,3-N-acetylgalactosaminyltransferase 2
B3GNT1 - UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 1
B4GALT1 - UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 1
CHD7 - chromodomain helicase DNA binding protein 7
COL18A1 - collagen, type XVIII, alpha 1
CNR - cederin-related neuronal receptor
DCX – doublecortin
DYNC1H1 - dynein cytoplasmic 1, heavy chain 1
EOMES (or PAX6 or TBR-2) - eomesodermin
EZH2 – lysine N-methyltransferase 6
FH - fumarate hydratase
FKRP - fukutin related protein
FKTN - fukutin
FLNA - filamin A
FOXO - forkhead box O
GSK3 - glycogen synthase kinase 3
GTDC2 - glycosyltransferase-like domain containing protein 2
GPR56 - G protein-coupled receptor 56
GPSM2 - G-protein signaling modulator 2
HIFα - hypoxia inducible factor 1, α subunit
IKK - IKKα, IKKβ, and NEMO/IKKγ compex
ISPD - isoprenoid synthase domain containing
IκB - nuclear factor of κ light polypeptide gene enhancer in B-cells inhibitor
KIAA1279 – kinesin binding protein KIAA1279
KIF2A - kinesin heavy chain member 2°
KIF5C - kinesin family member 5C
LAMA2 - laminin, alpha 2
LAMC3 - laminin, gamma 3

LAMB1 - laminin, beta 1
LARGE - like-glycosyltransferase
LIS1 - platelet-activating factor acetylhydrolase 1b, regulatory subunit 1
mDAB1 - dab, reelin signal transducer, homolog 1 (Drosophila)
MTOR - mammalian target of rapamycin
MTORC1 - MTOR complex 1
MTORC2 - MTOR complex 2
NF1 - neurofibromin 1
NDE1 - nudE neurodevelopment protein 1
NFκB - nuclear factor κ-light-chain-enhancer of activated B cells
NKCC1 - Na-K-2Cl- cotransporter
NSD1 – nuclear receptor binding SET domain protein 1
NSDHL - NAD(P) dependent steroid dehydrogenase-like
OCLN - occludin
P - inorganic phosphate
P60S6K - 60 kDa ribosomal protein S6 kinase
PAFAH1B1 (or LIS1) – platelet-activating factor acethylhydrolase 1b, regulatory subunit 1
POMGnT1 - protein O-linked mannose N-acetylglucosaminyltransferase 1 (beta 1,2-)
PHLPP - PH-domain leucine-rich-repeat protein phosphatase
PIP2 - phosphatidylinositol 4,5-bisphosphate
PIP3 - phosphatidylinositol 3,4,5-trisphosphate
POMT1 - protein-O-mannosyltransferase 1
POMT2 - protein-O-mannosyltransferase 2
RNF135 - ring finger protein 135
PAX6 - paired box 6
PI3K - phosphatidylinositol 3-kinase
PIK3R2 - phosphoinositide-3-kinase, regulatory subunit 2
PIK3CA phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PTEN - phosphatase and tensin homolog
RAB3GAP1 - RAB3 GTPase activating protein subunit 1
RAB3GAP2 - RAB3 GTPase activating protein subunit 2
RAB18 - RAB18, member RAS oncogene family
RELN – reelin
SNAP29 - synaptosomal-associated protein, 29kDa
SRD5A3 - steroid 5 alpha-reductase 3
SRPX2 - sushi-repeat containing protein, X-linked 2
TMEM5 - transmembrane protein 5
TSC1 - tuberous sclerosis 1
TSC2 - tuberous sclerosis 2
TUBA1A - tubulin, alpha 1

TUBA8 - tubulin, alpha 8
TUBB/TUBB5 - tubulin, beta class I/
TUBB2B - tubulin, beta 2B class IIb
TUBB3 - tubulin, beta 3 class III
TUBG1 - tubulin, gamma 1
VEGF - vascular endothelial growth factor.
VLDLR - very low density lipoprotein receptor
WDR62 - WD repeat-containing protein 62
YWHAE - tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon

REFERENCES for supplementary Table 2

1. Stevens E, Carss KJ, Cirak S, et al. Mutations in B3GALNT2 Cause Congenital Muscular Dystrophy and Hypoglycosylation of alpha-Dystroglycan. Am J Hum Genet 2013; 92: 354–65.

2. Buysse K, Riemersma M, Powell G, et al. Missense mutations in beta-1,3-N-acetylglucosaminyltransferase 1 (B3GNT1) cause Walker-Warburg syndrome. Hum Mol Genet 2013; 22: 1746–54.

3. Beltran-Valero de Bernabe D, Voit T, Longman C,et al. Mutations in the FKRP gene can cause muscle-eye-brain disease and Walker-Warburg syndrome. J Med Genet 2004; 41: e61.

4. Brockington M, Yuva Y, Prandini P, et al. Mutations in the fukutin-related protein gene (FKRP) identify limb girdle muscular dystrophy 2I as a milder allelic variant of congenital muscular dystrophy MDC1C. Hum Mol Genet 2001; 10: 2851–9.

5. Mercuri E, Topaloglu H, Brockington M, et al. Spectrum of brain changes in patients with congenital muscular dystrophy and FKRP gene mutations. Arch Neurol 2006b; 63: 251-7.

6. Kobayashi K, Nakahori Y, Mizuno K, et al. Founder-haplotype analysis in Fukuyama-type congenital muscular dystrophy (FCMD). Hum Genet 1998; 103: 323–7.

7. Manzini MC, Gleason D, Chang BS, et al. Ethnically diverse causes of Walker-Warburg syndrom (WWS):FCMD mutations are a more common cause of WWS outside of the Middle East. Hum Mutat 2008; 29: E231–41.

8. Manzini MC, Tambunan DE, Hill RS, et al. Exome sequencing and functional validation in zebrafish identify GTDC2 mutations as a cause of Walker-Warburg syndrome. Am J Hum Genet 2012; 91: 541–7.

9. Cirak S, Foley AR, Herrmann R, et al. ISPD gene mutations are a common cause of congenital and limb-girdle muscular dystrophies. Brain 2013; 136: 269–81.

10. Roscioli T, Kamsteeg EJ, Buysse K, et al. Mutations in ISPD cause Walker-Warburg syndrome and defective glycosylation of alpha-dystroglycan. Nat Genet 2012; 44: 581–5.

11. Vuillaumier-Barrot S, Bouchet-Seraphin C, Chelbi M, et al. Identification of Mutations in TMEM5 and ISPD as a Cause of Severe Cobblestone Lissencephaly. Am J Hum Genet 2012; 91: 1135-43.

12. Willer T, Lee H, Lommel M, Yoshida-Moriguchi T, et al. ISPD loss-of-function mutations disrupt dystroglycan O-mannosylation and cause Walker-Warburg syndrome. Nat Genet 2012; 44: 575-80.

13. Longman C, Brockington M, Torelli S, et al. Mutations in the human LARGE gene cause MDC1D, a novel form of congenital muscular dystrophy with severe mental retardation and abnormal glycosylation of alpha-dystroglycan. Hum Mol Genet 2003; 12: 2853–61.

14. Diesen C, Saarinen A, Pihko H, et al. *POMGnT1* mutation and phenotype spectrum in muscle-eye-brain disease. J Med Genet 2004; 41: e115.

15. Yoshida A, Kobayashi K, Manya H, et al. Muscular Dystrophy and Neuronal Migration Disorder Caused by Mutations in a Glycosyltransferase, POMGnT1. Dev Cell 2001; 1: 717-24.

16. Beltran-Valero de Bernabe D, Currier S, Steinbrecher A, et al. Mutations in the O-Mannosyltransferase Gene POMT1 Give Rise to the Severe Neuronal Migration Disorder Walker-Warburg Syndrome. Am J Hum Genet 2002; 71: 1033–43.

17. Currier SC, Lee CK, Chang BS, et al. Mutations in POMT1 are found in a minority of patients with Walker-Warburg syndrome. Am J Med Genet A 2005; 133: 53–7.

18. Mercuri E, D'Amico A, Tessa A, et al. POMT2 mutation in a patient with 'MEB-like' phenotype. Neuromuscul Disord 2006a; 16: 446–8.

19. van Reeuwijk J, Janssen M, van den Elzen C, et al. POMT2 mutations cause alpha-dystroglycan hypoglycosylation and Walker-Warburg syndrome. J Med Genet 2005; 42: 907-12.

20. Kornak U, Reynders E, Dimopoulou A, et al. Impaired glycosylation and cutis laxa caused by mutations in the vesicular H+-ATPase subunit ATP6V0A2. Nat Genet 2008; 40: 32-4.

21. Van Maldergem L, Yuksel-Apak M, Kayserili H, et al. Cobblestone-like brain dysgenesis and altered glycosylation in congenital cutis laxa, Debre type. Neurology 2008; 71: 1602–8.

22. Hansske B, Thiel C, Lubke T, et al. Deficiency of UDP-galactose:N-acetylglucosamine beta-1,4-galactosyltransferase I causes the congenital disorder of glycosylation type IId. J Clin Invest 2002; 109: 725–33.

23. Peters V, Penzien JM, Reiter G, et al. Congenital disorder of glycosylation IId (CDG-IId) -- a new entity: clinical presentation with Dandy-Walker malformation and myopathy. Neuropediatrics 2002; 33: 27–32.

24. Fuchs-Telem D, Stewart H, Rapaport D, et al. CEDNIK syndrome results from loss-of-function mutations in SNAP29. Br J Dermatol 2011; 164: 610–6.

25. Kudlyk T, Willett R, Pokrovskaya ID, Lupashin V. COG6 interacts with a subset of the Golgi SNAREs and is important for the Golgi complex integrity. Traffic 2013; 14: 194-204.

26. Cantagrel V, Lefeber DJ, Ng BG, et al. SRD5A3 is required for converting polyprenol to dolichol and is mutated in a congenital glycosylation disorder. Cell 2010; 142: 203-17.

27. Jones KJ, Morgan G, Johnston H, et al. The expanding phenotype of laminin alpha2 chain (merosin) abnormalities: case series and review. J Med Genet 2001; 38: 649-57.

28. Philpot J, Cowan F, Pennock J, et al. Merosin-deficient congenital muscular dystrophy: the spectrum of brain involvement on magnetic resonance imaging. Neuromuscul Disord 1999; 9: 81–5.

29. Radmanesh F, Caglayan AO, Silhavy JL, et al. Mutations in LAMB1 Cause Cobblestone Brain Malformation without Muscular or Ocular Abnormalities. Am J Hum Genet 2013; 92: 468-74.

30. Barak T, Kwan KY, Louvi A, et al. Recessive LAMC3 mutations cause malformations of occipital cortical development. Nat Genet 2011; 43: 590–4.

31. Luo R, Jin Z, Deng Y, Strokes N, Piao X. Disease-associated mutations prevent GPR56-collagen III interaction. PLoS One 2012; 7: e29818.

32. Piao X, Chang BS, Bodell A, et al. Genotype-phenotype analysis of human frontoparietal polymicrogyria syndromes. Ann Neurol 2005; 58: 680–7.

33. Piao X, Hill RS, Bodell A, et al. G protein-coupled receptor-dependent development of human frontal cortex. Science 2004; 303: 2033–6.

34. Keren B, Suzuki OT, Gerard-Blanluet M, et al. CNS malformations in Knobloch syndrome with splice mutation in COL18A1 gene. Am J Med Genet A 2007; 143: 1514–8.