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ORIGINAL ARTICLE

Neuropathology of genetically defined malformations of cortical development—A systematic literature review

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Abstract

Aims: Malformations of cortical development (MCD) include a heterogeneous spectrum of clinical, imaging, molecular and histopathological entities. While the understanding of genetic causes of MCD has improved with the availability of next-generation sequencing modalities, genotype-histopathological correlations remain limited. This is the first systematic review of molecular and neuropathological findings in patients with MCD to provide a comprehensive overview of the literature.

Methods: A systematic review was performed between November 2019 and February 2020. A MEDLINE search was conducted for 132 genes previously linked to MCD in order to identify studies reporting macroscopic and/or microscopic findings in patients with a confirmed genetic cause.

Results: Eighty-one studies were included in this review reporting neuropathological features associated with pathogenic variants in 46 genes (46/132 genes, 34.8%). Four groups emerged, consisting of (1) 13 genes with well-defined histological-genotype correlations, (2) 27 genes for which neuropathological reports were limited, (3) 5 genes with conflicting neuropathological features, and (4) 87 genes for which no histological data were available. Lissencephaly and polymicrogyria were reported most frequently. Associated brain malformations were variably present, with abnormalities of the corpus callosum as most common associated feature.

Conclusions: Neuropathological data in patients with MCD with a defined genetic cause are available only for a small number of genes. As each genetic cause might lead to unique histopathological features of MCD, standardised thorough neuropathological assessment and reporting should be encouraged. Histological features can help improve the understanding of the pathogenesis of MCD and generate hypotheses with impact on further research directions.

KEYWORDS
cobblestone malformation, genotype-phenotype correlation, lissencephaly, malformation of cortical development, migration disorder, polymicrogyria

INTRODUCTION

Malformations of cortical development (MCD) are a group of rare and heterogeneous disorders caused by altered neuronal proliferation or apoptosis, migration and post-migrational differentiation.

MCD is currently classified based upon the earliest step of cortical development that is disturbed, the suspected pathogenic mechanism and brain imaging findings [1]. MCD can be caused by congenital infections (e.g. cytomegalovirus infection), vascular insults, chromosomal aberrations and single gene mutations. To date, about 200 genes have been linked to the development of MCD [2]. Despite the advances in genetics due to the recent introduction of next-generation sequencing, diagnosis remains challenging because of genetic and clinical heterogeneity and up to 60% of patients remain without a causal diagnosis [3]. While there has been a rapid improvement of our understanding of the underlying molecular mechanisms and causes of MCD, histopathological studies of migration disorders have been reported mainly prior to the introduction of next-generation sequencing. Nevertheless, the histological analysis of brain tissue has proven to be a valuable tool in our understanding of normal brain development, as has been shown for the mechanisms underlying neuronal migration [4]. Furthermore, examples of existing genotype-neuropathological correlations have provided unique insight in the mechanisms of disturbed neuronal migration and organisation in humans, as seen in cobblestone malformation linked to pathogenic variants in *GPR56* [5].

Histological spectrum of MCD

Many pathologists are not familiar with the clinical, imaging, molecular and microscopic features of these rare disorders and few histological classifications of MCD are available in the literature.

Microcephaly and megalencephalies are caused by disorders in neuronal proliferation or apoptosis resulting in heterogeneous histological features. These include mild to severe cortical dysplasia, polymicrogyria and heterotopias. Other features such as gliosis, hypertrophy and atypia, are variably present [6]. Abnormal migration can result in (1) lissencephaly, including agyria and pachygyria, (2) heterotopia or (3) cobblestone malformations. Histologically, classic lissencephaly is characterised by a smooth brain surface with a thick cortex consisting of a reduced number of disorganised cortical neuronal layers. Variations of the microscopic presentation have been described depending on the underlying genetic aetiology [7, 8]. While pathogenic variants in *PAFAH1B1* (formerly called *LIS1*) result in a four-layered cortex with severely reduced white matter, pathogenic variants in *DCX* cause lissencephaly in males with prominent heterotopias in the white matter and pathogenic variants in *ARX* causing complete loss of protein function lead to a three-layered cortex. Heterotopia, including periventricular nodular heterotopia (PNH) and subcortical band heterotopia (SBH), histologically present as localised bands or nodules of neurons that fail to migrate and remain deep in the hemisphere [9]. PNH, most commonly caused by variants in *FLNA*, and SBH, caused mainly by variants in *DCX*, occur most frequently in females as part of X-linked disorders with more severe phenotypes in males [9, 10]. In cobblestone malformations the cortex is severely disorganised with complete loss of normal lamination. This is caused by over-migration of neurons across the pial basement membrane into the subarachnoid space. The leptomeninges often appear fused with underlying entrapped blood vessels deep in the cortex [5, 11]. Genotypic differences in the histological appearance of cobblestone malformation have led to the subclassification of cobblestone type A (linked to variants in *POMT1*, *POMT2*, *FKRP*), type B (described for variants in *LARGE*) or type C (linked to variants in *POMGNT1*) [12]. Polymicrogyria is the result of abnormal post-migrational maturation of the cortex causing undulating bands of neurons frequently associated with fusion of the molecular layer and entrapment of pial vessels [13, 14]. Based on the number of cortical layers, polymicrogyria was initially differentiated into unlayered, four-layered or six-layered polymicrogyria but variation of the number of cortical layers in the same patient have been observed [14]. Schizencephalic clefts are usually lined by polymicrogyric cortex. Focal cortical dysplasia (FCD) is currently classified as disorder developing secondarily to disrupted post-migrational development but the underlying pathophysiological mechanisms remain to be elucidated [1]. It has further been subclassified histologically as described by Blümcke et al., [15] a review of which is beyond the scope of this paper. Recently, the need for an update of this classification has been stressed, which would take into account the latest insights into pathology and pathophysiology [16].

This article reviews the neuropathological data on malformations of cortical development with a defined molecular diagnosis with a focus on lissencephaly, cobblestone malformation and polymicrogyria. The aim of this review was to provide an overview of the state-of-the-art literature for pathologists, to gain more insight in the histological spectrum of these malformations and the neuropathology-genotype correlations, and to encourage future research on the correlation of neuropathology, imaging features and genetics of MCD.

METHODS

This systematic review follows the publishing guidelines as described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), when applicable to the objectives of this review [17]. It has not been registered with PROSPERO.

Inclusion criteria

Eligibility criteria were determined a priori and required that studies performed macroscopic and/or microscopic analysis of brain tissue of foetal, paediatric or adult cases with MCD and a confirmed genetic cause. Genetic causes included pathogenic variants in one of the genes listed in Table S1 associated with either

lissencephaly, agyria, pachygyria, simplified gyral pattern, subcortical band heterotopia, periventricular nodular heterotopia, polymicrogyria, cobblestone malformation, dysgyria, abnormal cortical lamination, microcephaly with a simplified gyral pattern, porencephaly or schizencephaly, or unspecified migration disorders. In order to be as comprehensive as possible, the list of genes associated with MCD has been created based on the curated gene list from the Neuro-MIG consortium, the NGS MCD panel gene list (www.brightcore.beversion 5) from the local genetics centre, and the personal literature records of one reviewer (SB) (Table S2). After initial consideration of 269 genes that are currently linked to MCDs and congenital brain malformations (Table S2), genes linked to other cortical malformations such as FCD and megalencephaly, genes that have been described to give brain malformations that do not affect the cortex (e.g. genes causing brainstem/cerebellar malformations but without cortical malformations, e.g. Joubert syndrome) and genes that have not been reported in human patients, were excluded.

Only studies published in English were included. Studies included in this review are either case reports, case series, cohort studies or narrative reviews that also presented new additional patients.

Exclusion criteria

Studies providing neuropathological data, but no molecular diagnosis were excluded. Studies reporting neuropathological findings in mice or other animal MCD models were also excluded. MCD caused by other aetiologies (e.g. infectious causes, chromosomal aberrations (except for deletions including *PAFAH1B1* causing Miller–Dieker syndrome) were excluded. Meeting abstracts and editorials were excluded.

Genes reported to cause FCD but no other migration disorder were also excluded from this review (e.g. *TSC1*, *TSC2*, *RHEB*, *DEPDC5*).

Search strategy

A search on PubMed and OMIM was performed by one reviewer (SB) between 11/2019 and 02/2020 with subsequent search for randomly selected genes by a second reviewer (AJ) as internal control.

Figure 1 represents the search strategy used for one selected gene (Figure 1). A combination of search terms was used and combined with each gene abbreviation and MESH term. Screening of title, subsequent screening of selected full text articles and manual search of keywords in the text ("autopsy", "patholo*", "histolog*", "post-mortem") was used to detect eligible studies.

Gene abbreviations were also entered into OMIM in order to retrieve additional studies. Reference lists from included studies were also screened in order to identify additional studies.

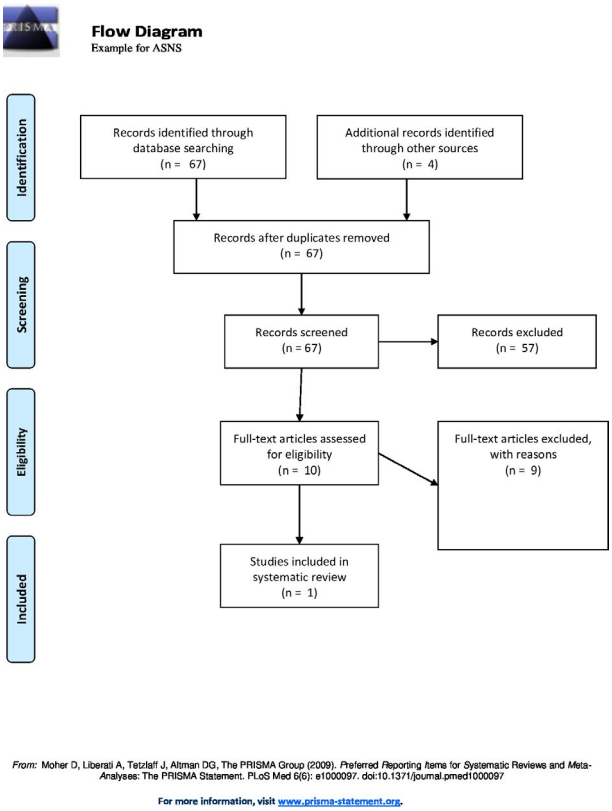

FIGURE 1 Example of results of literature search for ASNS

Study selection

The titles of each retrieved study were screened to determine whether the study fulfilled the inclusion or exclusion criteria. Full texts of possibly eligible studies were reviewed and assessed for eligibility as described in the search strategy.

Data abstraction

Full-text articles of included studies were reviewed by SB for data extraction using an Excel sheet template designed for this review. Random data audit of selected included studies was carried out by AJ.

For each eligible study, the following data were extracted and recorded: author(s), year of publication, patient age, name of affected gene, mode of inheritance, imaging phenotype, information on macroscopic features, histological features of the cortex, basal ganglia, hippocampus, corpus callosum, brainstem, cerebellum, white matter, presence of heterotopia and other features; and information on immunohistochemistry.

The quality of the neuropathological exam was assessed for each study including the extent of the description of histological features and whether microscopic images were available for verification of the described malformations. Score 1 was assigned to articles with extensive reports of the neuropathological features and histological

TABLE 1 Results of the literature review with included studies and histological features per affected gene

Gene	MoI	Imaging features (MRI)	References	Age	Images	Macroscopy	Cortex
ACTB	AD	LIS, SBH, ACC	[28]	Twins died in early 20s	No	Yes	Normal
ACTG1	AD	LIS, microLIS, heterotopias, ACC	[41]	29GW + 26GW	No	Yes	MicroLIS
ACTG1	AD	LIS, microLIS, heterotopias, ACC	[42]	35GW	Yes	No	LIS
AKT3	AD	MEG-PMG-polydactyly-hydrocephalus syndrome (MPPH)	[22]	3 paediatric cases	Yes	No	FCD2a/HME
AKT3	AD	MEG-PMG-polydactyly-hydrocephalus syndrome (MPPH)	[43]	6Y	Yes	Yes	FCD, PMG
AKT3	AD	MEG-PMG-polydactyly-hydrocephalus syndrome (MPPH)	[23]	1Y	No	Yes	FCDIIa, PMG
ARX	XL	LIS	[44]	38GW + 40GW + 35GW	Yes	Yes	LIS
ARX	XL	LIS	[7]	1M + 18M	Yes	No	LIS
ARX	XL	LIS	[24]	35GW	Yes	Yes	LIS
ARX	XL	LIS	[45]	11M	Yes	Yes	LIS
ARX	XL	LIS	[46]	3M	No	Yes	LIS
ARX	XL	LIS	[47]	26D	No	Yes	n/a
ASNS	AR	SGP	[48]	8M	Yes	Yes	Atrophy
B3GNT1/B4GAT1	AR	COB	[49]	2GW + 24GW + 21GW	No	No	COB
C2CD3	AR	PMG, SGP	[32]	15GW	No	No	PMG
C2CD3	AR	PMG, SGP	[33]	13GW + 14GW	No	No	n/a
CEP55	AR	SGP, hydranencephaly	[50]	30GW + 32GW + 35GW	Yes	Yes	Atrophy, disorganisation
CIT	AR	SGP, microLIS	[51]	39GW	Yes	Yes	MicroLIS
COL3A1	AR	PMG, COB	[52]	15Y	No	Yes	n/a
COL4A1	AD	Schizencephaly, porencephaly, FCD	[53]	n/a	Yes	No	n/a
COL4A1	AD	Schizencephaly, porencephaly, FCD	[54]	34GW (2 cases)	No	No	n/a
COL4A1	AD	Schizencephaly, porencephaly, FCD	[55]	6Y	No	No	FCD1a, porencephaly
CRADD	AR	LIS	[30]	31GW	No	No	SGP
DCX	XL	LIS, SBH	[24]	35GW	Yes	Yes	LIS
DCX	XL	LIS, SBH	[56]	n/a (male)	Yes	No	LIS
DCX	XL	LIS, SBH	[57]	n/a (female)	Yes	No	SBH
DCX	XL	LIS, SBH	[58]	n/a (male)	No	No	SBH
DCX	XL	LIS, SBH	[59]	35GW–36GW (3 male fetuses)	Yes	No	LIS
DCX	XL	LIS, SBH	[21]	36GW + 37 GW	Yes	Yes	LIS

Heterotopias	Basal ganglia	Hippocampus	CC	Brainstem	Cerebellum	White matter
n/a	n/a	n/a	n/a	n/a	n/a	n/a
No	Immature, fragmented	n/a	ACC, dysmorphic	Hypoplasia	Hypoplasia	n/a
Yes	n/a	n/a	ACC	n/a	n/a	Astrogliosis, fragmented astroglial processes, reduced number of microglia and oligodendrocytes
n/a	n/a	n/a	n/a	n/a	n/a	n/a
Yes	n/a	Hypoplasia, gliosis	n/a	n/a	n/a	Disorganised
Yes	n/a	n/a	n/a	n/a	n/a	n/a
Yes	Hypoplasia, atrophic thalami	Abnormal	ACC	Hypoplasia	Dysmorphic	Reduced
Yes	n/a	n/a	n/a	Hypoplasia	Normal	Reduced
Yes	Hypoplasia	Hypoplasia	ACC	Normal	Hypoplasia	Reduced
Yes	n/a	n/a	ACC	Hypoplasia	Hypoplasia	Reduced
Yes	Hypoplasia	n/a	ACC	Heterotopic neurons	Normal	Gliosis
n/a	n/a	n/a	n/a	n/a	n/a	n/a
No	Atrophy	Atrophy	Hypoplasia	Hypoplasia	Hypoplasia	Reduced
No	n/a	n/a	ACC	Hypoplasia	Hypoplasia	n/a
No	n/a	n/a	n/a	n/a	Vermis agenesis, cortex hypoplasia	n/a
n/a	n/a	n/a	n/a	n/a	n/a	n/a
No	Normal	n/a	n/a	No basis pontis	Hypoplasia	n/a
No	Hypoplasia	Hypoplasia	ACC	Hypoplasia	Hypoplasia	n/a
n/a	n/a	n/a	n/a	n/a	n/a	n/a
n/a	n/a	n/a	n/a	n/a	n/a	n/a
Yes	n/a	n/a	n/a	n/a	Hypoplasia, Purkinje cell heterotopia	n/a
n/a	n/a	n/a	n/a	n/a	n/a	n/a
n/a	n/a	n/a	n/a	n/a	n/a	n/a
Yes	Hypoplasia	Hypoplasia	Thick	Dysplastic nuclei	Hypoplasia	Reduced
SBH	n/a	n/a	n/a	n/a	n/a	Reduced
SBH	n/a	n/a	n/a	n/a	n/a	n/a
SBH	n/a	n/a	n/a	n/a	n/a	n/a
SBH	n/a	Hypoplasia	ACC/Dysplasia	n/a	n/a	n/a
SBH	Normal	n/a	Hypoplasia	Normal	Normal	Reduced

(Continues)

TABLE 1 (Continued)

Gene	MoI	Imaging features (MRI)	References	Age	Images	Macroscopy	Cortex
DCX	XL	LIS, SBH	[7]	2Y + 7D	Yes	Yes	LIS
DYNC1H1	AD	PMG, LIS	[60]	3 foetal cases	Yes	No	PMG
DYNC1H1	AD	PMG, LIS	[61]	36GW + 22GW	Yes	Yes	PMG
EPG5	AR	SGP, PMG, schizencephaly	[62]	n/a	Yes	Yes	Coarse
EPG5	AR	SGP, PMG, schizencephaly	[63]	13M	Yes	Yes	Normal
EPG5	AR	SGP, PMG, schizencephaly	[26]	30GW	Yes	Yes	Normal
EPG5	AR	SGP, PMG, schizencephaly	[27]	21GW	Yes	Yes	Focal cortical microdysgenesis
FIG4	AR	PMG	[64]	4M + 4M + foetal case	No	No	Neuronal loss and vacuolation in layers 3 and 5
FKRP	AR	COB, LIS	[12]	24GW	No	No	COB
FKTN	AR	PMG, COB, LIS	[65]	10D	No	No	PMG
FKTN	AR	PMG, COB, LIS	[66]	5D	No	Yes	n/a
FKTN	AR	PMG, COB, LIS	[67]	26GW	Yes	Yes	n/a
GPR56	AR	PMG	[5]	35GW (+2 siblings)	Yes	Yes	PMG/COB
GPR56	AR	PMG	[13]	n/a	No	No	PMG/COB
IER3IP1	AR	SGP	[68]	26M	Yes	Yes	SGP
ISPD	AR	COB, LIS, PMG, SBH	[19]	n/a	No	No	COB
ISPD	AR	COB, LIS, PMG, SBH	[69]	21GW	No	Yes	Absent gyration
ISPD	AR	COB, LIS, PMG, SBH	[70]	n/a	No	No	COB
KBP	AR	PMG, MIC	[71]	36GW	Yes	Yes	PMG
LARGE	AR	COB, PMG	[12]	22GW + 23GW + 27GW	No	Yes	COB
LARGE	AR	COB, PMG	[37]	9M	Yes	Yes	PMG
NDE1	AR	LIS, SGP, MIC	[72]	10M	No	Yes	MicroLIS
NHEJ1	n/a	PMG, heterotopia	[73]	33GW	Yes	Yes	PMG
NSDHL	XL	PMG/LIS/COB	[74]	29GW	Yes	Yes	PMG
OCLN	AR	PMG, LIS	[35]	n/a	No	No	PMG
OCLN	AR	PMG, LIS, pseudo-TORCH	[25]	n/a	Yes	No	PMG
OCLN	AR	PMG, LIS, pseudo-TORCH	[36]	6Y	No	Yes	n/a
PAFAH1B1	AD	LIS	[75]	1Y	No	No	LIS
PAFAH1B1	AD	LIS	[7]	19 W–19Y (6 patients)	Yes	No	LIS
PAFAH1B1	AD	LIS	[21]	36GW	Yes	Yes	LIS
PAFAH1B1	AD	LIS	[24]	35GW	Yes	Yes	LIS
PAFAH1B1	AD	LIS	[76]	38GW	No	Yes	LIS
PHGDH	AR	LIS	[29]	11GW + 20GW + 20GW	Yes	Yes	Normal
PIK3CA	AR	MEG-Capillary malformation-PMG syndrome	[23]	3Y	Yes	No	FCD2a, PMG

Heterotopias	Basal ganglia	Hippocampus	CC	Brainstem	Cerebellum	White matter
Yes	n/a	n/a	n/a	Hypoplasia	Heterotopias	Hypomyelination
Yes	n/a	n/a	ACC	n/a	Hypoplasia, heterotopias	n/a
Yes	Dysmorphic	Hypoplasia	ACC	Hypo/Dysplasia	Hypo/Dysplasia	Hypoplasia
No	n/a	Hypoplasia	ACC	Hypoplasia	n/a	n/a
No	n/a	n/a	ACC	Hypoplasia	Hypoplasia	n/a
No	Normal	Normal	ACC	Hypoplasia	Normal	Delayed myelination
Yes	n/a	n/a	ACC	n/a	n/a	n/a
n/a	Vacuolation of BG and thalamus	n/a	ACC	Vacuolation of olivary bodies	Vacuolation of dentate nucleus	n/a
n/a	n/a	n/a	Hypoplasia, Dysmorphic	Hypoplasia	Hypo/Dysplasia	n/a
n/a	n/a	n/a	n/a	n/a	n/a	n/a
n/a	n/a	n/a	n/a	n/a	n/a	n/a
n/a	n/a	n/a	n/a	n/a	n/a	n/a
Yes	n/a	Normal	Normal	Over-migration of neurons into leptomeningeal space	Vermis agenesis, cortex hypoplasia, focal over-migration of neurons	n/a
No	Normal	Normal	n/a	Normal	Dysplastic	Normal
n/a	n/a	n/a	n/a	n/a	Hypoplasia	Reduced
No	n/a	n/a	n/a	Hypo/Dysplasia	Hypo/Dysplasia	n/a
No	n/a	n/a	ACC	n/a	n/a	n/a
Yes	n/a	n/a	Hypoplasia	Hypoplasia	Hypoplasia	n/a
n/a	Normal	n/a	Hypoplasia	Hypoplasia	Normal	n/a
n/a	n/a	n/a	Hypoplasia, Dysmorphic	Hypoplasia	Hypo/Dysplasia	n/a
No	Dysplasia	Hypoplasia	Hypoplasia	Hypoplasia	Dysplastic	Abnormal
No	n/a	n/a	n/a	n/a	Hypoplasia	n/a
Yes	n/a	n/a	n/a	n/a	n/a	Periventricular astrocytic gliosis
Yes	Absent/Dysplasia?	n/a	ACC	Left hypoplasia	Hypo/Dysplasia, heterotopias	Abnormal
No	Hypoplasia	Normal	Hypoplasia	Hypoplastic pyramidal tracts	Normal, gliosis	n/a
No	n/a	n/a	n/a	n/a	Calcifications	n/a
n/a	n/a	n/a	n/a	Calcifications	Calcifications	Reduced, calcifications
Yes	n/a	n/a	n/a	n/a	n/a	n/a
Yes	n/a	Normal	n/a	Hypoplasia	Heterotopias	Reduced
Yes	Normal	n/a	Dysplasia	Hypoplasia	Normal	Reduced
Yes	Hypoplasia	Dysmorphic	ACC	Hypoplasia	Heterotopias	Reduced
Yes	n/a	n/a	n/a	n/a	n/a	n/a
No	Hypoplasia	Hypoplasia	n/a	Hypoplasia	Hypoplasia	Microcalcifications
No	n/a	n/a	n/a	n/a	n/a	n/a

(Continues)

TABLE 1 (Continued)

Gene	MoI	Imaging features (MRI)	References	Age	Images	Macroscopy	Cortex
PIK3CA	AR	MEG-Capillary malformation-PMG syndrome	[77]	62D	Yes	No	Neuronal depletion, dysplastic neurons focally (FCD?)
PIK3CA	AR	MEG-Capillary malformation-PMG syndrome	[22]	2M–1Y (4 cases)	Yes	No	FCDIIa
PI4KA	AR	PMG	[78]	16GW–32GW (3 cases)	Yes	Yes	PMG
PIGA	XLR	SGP	[79]	10 W	No	Yes	Abnormal lamination
POMGNT1	AR	COB	[20]	7 foetal cases	No	No	COB
POMGNT1	AR	COB	[12]	12 foetal cases	Yes	Yes	COB
POMGNT1	AR	COB	[80]	22GW	No	Yes	LIS
POMK	AR	COB	[81]	14GW–16GW (4 cases)	No	Yes	n/a
POMT1	AR	COB	[12]	22 foetal cases	Yes	Yes	COB
POMT1	AR	COB	[20]	13 foetal cases	No	No	COB
POMT1	AR	COB	[82]	19GW	Yes	Yes	COB
POMT2	AR	COB	[20]	3 foetal cases	No	No	COB
POMT2	AR	COB	[12]	5 foetal cases	Yes	Yes	COB
RTTN	AR	PMG	[83]	28GW	Yes	Yes	SGP
TMEM5	AR	COB	[19]	n/a	No	No	COB
TMX2	AR	PMG	[84]	14D + 2D	Yes	Yes	PMG
TUBA1A	AD	Dysgyria	[18, 85, 86]	10 cases, 23–36GW	Yes	Yes	MicroLIS
				25GW–35GW (6 cases)	No	No	LIS
				23GW–37GW (3 cases)	Yes	Yes	PMG
TUBA1A	AD	Dysgyria	[40]	23GW–35GW (3 cases)	Yes	Yes	LIS
TUBA1A	AD	Dysgyria	[87]	36GW	Yes	Yes	PMG
TUBA1A	AD	Dysgyria	[88]	23M	Yes	Yes	LIS
TUBB2A	AD	Dysgyria	[89]	2Y	No	No	n/a
TUBB2B	AD	Dysgyria	[18]	16GW + 27 GW	Yes	Yes	MicroLIS
				35GW	No	No	LIS
				25GW–28 GW (3 cases)	No	No	PMG
TUBB2B	AD	Dysgyria	[18, 90]	27GW	Yes	Yes	PMG
TUBB2B	AD	Dysgyria	[91]	15GW	Yes	Yes	MicroLIS
TUBB3	AD	Dysgyria	[18, 92]	27GW	Yes	Yes	MicroLIS
USP18	AR	PMG	[34]	22GW	Yes	Yes	PMG
WDR62	AR	PMG, LIS, SGP, schizencephaly, MIC,	[93]	27GW	Yes	Yes	SGP
ZEB2	AD	SGP	[94]	17GW	No	Yes	n/a
ZEB2	AD	SGP	[95]	35GW	No	Yes	n/a

Heterotopias	Basal ganglia	Hippocampus	CC	Brainstem	Cerebellum	White matter
No	n/a	Dysplastic	n/a	n/a	n/a	Bilateral periventricular leukomalacia
n/a	n/a	n/a	n/a	n/a	n/a	n/a
n/a	n/a	n/a	Normal	Hypoplasia, dysplastic olivary nuclei	Hypo/Dysplasia	n/a
No	n/a	n/a	Hypoplasia	Dysplasia	Hypoplasia	Reduced
n/a	n/a	n/a	n/a	n/a	Dysplasia	n/a
n/a	n/a	n/a	Hypoplasia, ACC	Hypoplasia	Dysplasia	n/a
n/a	n/a	n/a	ACC	n/a	n/a	n/a
n/a	n/a	n/a	n/a	n/a	Vermis agenesis	n/a
n/a	Normal	n/a	Hypo/Dysplasia	Hypo/Dysplasia	Hypo/Dysplasia	n/a
n/a	n/a	n/a	n/a	n/a	Dysplasia	n/a
n/a	n/a	n/a	ACC	Hypoplasia	Hypoplasia	n/a
n/a	n/a	n/a	n/a	n/a	Dysplasia	n/a
n/a	Normal	n/a	Hypo/Dysplasia	Hypo/Dysplasia	Hypo/Dysplasia	n/a
Yes	Poorly striated	Hypoplasia	Hypoplasia	Normal	Normal	Heterotopias
n/a	n/a	n/a	n/a	Hypo/Dysplasia	Hypo/Dysplasia	n/a
Yes	Normal	Normal	Hypoplasia	Normal	Normal	WM junction blurred, calcifications
Yes	Hypoplasia	n/a or not individualized	ACC	Hypoplasia	Hypoplasia	n/a
Yes	Dysmorphic	Normal or n/a	ACC	Hypoplasia	Hypoplasia	n/a
Yes	Dysmorphic	Dysmorphic	ACC, hypoplasia	Hypoplasia	Hypoplasia	n/a
Yes	Dysmorphic	Hypo/dysplasia	ACC or dysmorphic	Hypoplasia	Hypoplasia, vermis agenesis	Reduced
No	n/a	n/a	Hypoplasia	Hypoplasia	Hypoplasia, dysplasia	n/a
No	Dysmorphic	Hypo/dysplasia	ACC	Hypoplasia	Dysplasia	n/a
No	n/a	n/a	Hypoplasia	Hypoplasia	Hypoplasia	n/a
No	Normal	Absent	ACC	Hypoplasia	Hypoplasia	n/a
Yes	Absent	Normal	ACC	Hypoplasia	Hypoplasia	n/a
Yes	Hypoplasia	Normal	ACC	Normal	Hypoplasia, dysplasia	Disorganised CST
Yes	Dysmorphic	n/a	ACC	n/a	Heterotopias	Heterotopias
No	n/a	n/a	n/a	Hypoplasia	Hypoplasia	Reduced
Yes	Hypoplasia	Normal	ACC	Hypoplasia	Hypoplasia	n/a
Yes	n/a	n/a	n/a	n/a	n/a	Calcifications, haemorrhage
Yes	n/a	n/a	n/a	n/a	n/a	n/a
n/a	n/a	n/a	ACC	n/a	n/a	n/a
n/a	n/a	n/a	Hypoplasia	n/a	n/a	n/a

(Continues)

TABLE 1 (Continued)

Gene	MoI	Imaging features (MRI)	References	Age	Images	Macroscopy	Cortex
ZEB2	AD	SGP	[96]	21GW	No	Yes	n/a
ZEB2	AD	SGP	[97]	21GW	No	Yes	n/a

Note: Studies have been aggregated in one row when the patient included in Table 1 has been reported several times in different studies.

Abbreviations: ACC, agenesis of corpus callosum; AD, autosomal dominant; AR, autosomal recessive; COB, cobblestone malformation; D, days; GW, gestational week; HMEG, hemimegalencephaly; LIS, lissencephaly; M, months; MIC, microcephaly; MOI, mode of inheritance; n/a, not available; PMG, polymicrogyria; PNH, periventricular nodular heterotopia; SBH, subcortical band heterotopia; SGP, simplified gyral pattern; XL, X-linked; Y, years.

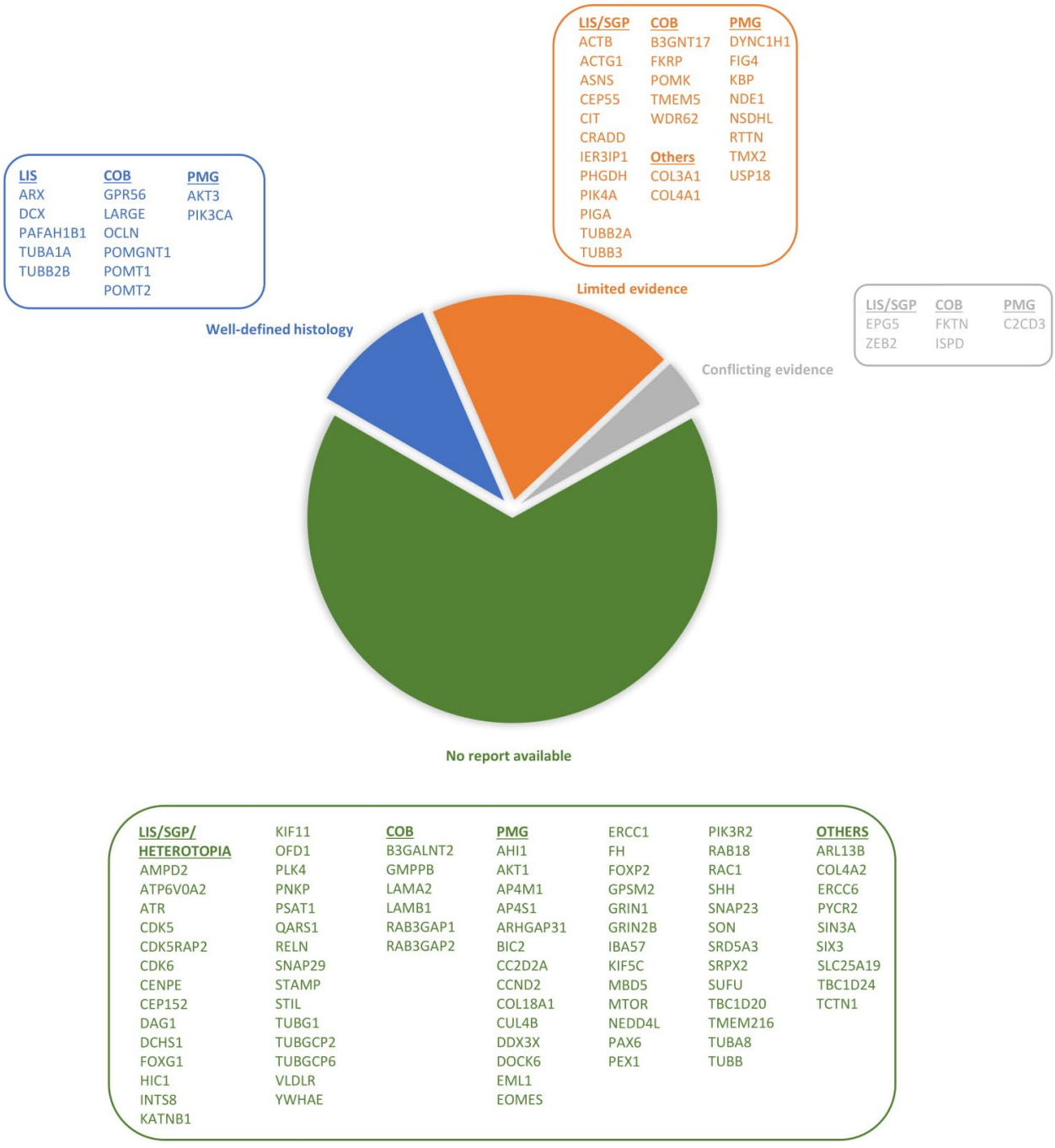

FIGURE 2 Subclassification of MCD genes included in the literature search per availability of neuropathological data. Abbreviations: COB, cobblestone malformation; LIS, lissencephaly; PMG, polymicrogyria; SGP, simplified gyral cortex

Heterotopias	Basal ganglia	Hippocampus	CC	Brainstem	Cerebellum	White matter
n/a	n/a	n/a	ACC	n/a	n/a	n/a
n/a	n/a	n/a	ACC	n/a	n/a	n/a

images. Score 2 was assigned to articles featuring extensive reports without images or brief reports but with images for verification; and score 3 was designated to articles with short reports of the neuropathological features without images.

Data synthesis

Due to the high level of heterogeneity of the genetic variants included in the neuropathological studies, we did not conduct a meta-analysis or other quantitative analysis.

A qualitative systematic review approach was applied to investigate the relationship between genetic variants and neuropathological features.

RESULTS

A list of the 132 genes for which a literature search for neuropathological features has been conducted can be found in the online resources (Table S1).

Inclusion criteria were met for 81 studies which reported neuropathological data for 46 of 132 genes (34.8%) (Table 1). Nine of these studies included heterogeneous patient cohorts with variants in different genes [7, 12, 18–24]. Macroscopic findings were described in 51 studies (but not always for all genes), whereas 30 studies did not provide information of macroscopic features.

Macroscopic or microscopic images were available in 43 studies (although images were not always available for all genes described in studies describing several genes, e.g. *LARGE* [12]). Images were not available in 38 studies.

A total of 215 brains were examined, including 160 foetal brains (74.4%), 41 paediatric cases (19.1%) and three adult brains (1.4%). For 11 cases, the age of the patients was not specified (5.1%).

In the different studies, 103 different malformations were described. Lissencephaly or a description compatible with lissencephaly was available for 29.1% of patients. Polymicrogyria or a description fitting the definition of PMG was reported in 21.4% of cases, cobblestone malformation in 14.6%, simplified gyral pattern (SGP) in 3.9%, atrophy in 1.9%, and FCD in combination with other cortical malformations in 5.8% respectively. Four studies reported MCD on imaging, but the cortex was reported to be normal on histology (3.9%). In 14 studies (13.6%), histological features of the cortex were not reported.

Emerging evidence from retrieved literature

For 21 of the 46 genes two or more studies have been published reporting neuropathological features. These studies highlight the emergence of *four* subgroups in which genes and the available literature can further be classified (Figure 2).

Genes with well-characterised histopathological features

For *AKT3*, *ARX*, *DCX*, *GPR56*, *LARGE*, *OCLN*, *PAFAH1B1*, *PIK3CA*, *POMGNT1*, *POMT1*, *POMT2*, *TUBA1A* and *TUBB2B*, two to seven studies describe recurring neuropathological features. There is also important overlap with the associated imaging features. *PAFAH1B1*, *DCX and ARX* cause lissencephaly with well-defined features of cortical dyslamination. Genotype–phenotype correlations with respect to the cortical organisation in abnormal layers has been reviewed elsewhere [7, 8]. *POMGNT1*, *POMT1* and *POMT2* cause similar neuropathological features in line with cobblestone malformation and within the same group when further subclassified as described by Devisme et al. [12]. Although a clear genotype-neuropathological correlation for each individual gene is apparently lacking, it is nevertheless possible to narrow down the diagnosis to a small group of genes. Pathogenic variants affecting *LARGE* have also been reported to cause cobblestone malformations. This is the only gene that causes variations in severity of cobblestone malformation within the same patient, resulting histologically in a variable ratio of extracortical layer/cortical plate, a finding that might offer a diagnostic clue for pathologists [12]. For *GPR56* and *OCLN*, the histopathological features are relatively unique and allow the pathologist to pinpoint the diagnosis to the respective gene [5, 25] (see later). Tubulinopathy-associated malformations (*TUBA1A*, *TUBB2B*) have heterogeneous imaging and neuropathological presentations, but the combination of frequently present features results in a pattern allowing the recognition of these genotypes in most patients [18]. *AKT3* and *PIK3CA* cause megalencephaly with focal cortical dysplasia type IIa and polymicrogyria. Brain tissue in these patients is often obtained during epilepsy surgery, thus forming an exception to the aforementioned genes which are usually available for histological examination only through autopsy.

Genes with only one or two neuropathological reports (limited evidence)

For genes included in this group, there are currently only a limited number of reports of the neuropathological findings available in the literature (Figure 2). Additional neuropathological studies are necessary to confirm or expand the histological spectrum associated with variants in these respective genes.

Two reports for *ACTG1* and for *DYNC1H1* report overlapping histological features in line with imaging features, including (micro-) lissencephaly and polymicrogyria respectively. Nevertheless, the number of reported patients remains limited and differences in terminology complicate comparison.

Genes for which variable neuropathological data are available

Genes for which variable macroscopic and histological features have been reported are listed in Figure 2. For *C2CD3*, *ISPD*, *FKTN* and *ZEB2*, cortical features are not comparable due to either the absence of histological images or because only macroscopic examination has been reported. Comparison is further complicated because the reports are heterogeneous regarding the assessment of the different structural regions of the central nervous system, such as basal ganglia, brainstem and cerebellum.

Four studies reported neuropathological features of cases associated with pathogenic variants in *EPG5*. Three of these reports show overlapping brain malformations including microcephaly, pontocerebellar malformations, hypoplasia of the corticospinal tracts and agenesis of the corpus callosum, whereas cortical malformations suggestive of an underlying migration disorder were not reported. This contrasts with imaging findings (absent gyrification) in Touraine et al. [26]. A fourth study by Aggarwal et al. [27] reported abnormal cortical lamination on histological sections, whereas the cortex was reported to be normal on foetal MRI.

Genes without available neuropathological data

For 87 genes (65.9%) neuropathological data were not available (Figure 2).

Correlation with neuroimaging features

Lissencephaly

For pathogenic variants in *ACTB*, *ACTG1*, *ARX*, *CRADD*, *DCX*, *PAFAH1B1* and *PHGDH*, the main imaging feature is lissencephaly. Histologically, this could be confirmed for *ACTG1*, *ARX*, *DCX* and *PAFAH1B1*. On histological preparations, the cortex was described as having a simplified gyral pattern for *CRADD*, and as normal for *ACTB* and *PHGDH* (Table 1). However, the three publications describing these genes did not provide images of the cortical features for correlation [28–30]. Nevertheless, an *ACTB* variant has been described in a patient with neurodegeneration, iron accumulation in pallidal and nigral neurons as well as rod-like eosinophilic structures in the neocortex, which are distinctive and findings and could possibly form a diagnostic clue [28].

Dysgyria

Cortical malformations associated with pathogenic variants in either of the tubulin genes are referred to as dysgyria on imaging studies. Histology has proven to be a useful tool to further narrow down the phenotype to lissencephaly, microlissencephaly or polymicrogyria for *TUBA1A* and *TUBB2B*. However, the heterogeneity of imaging and neuropathological features within patients carrying a variant in either *TUBA1A* or *TUBB2B* suggests residue specific effects on protein function causing variable phenotypes [31]. Currently, neuropathology has only been reported in one patient with a variant in *TUBB2A* without a detailed description of the cortical lamination, and in *TUBB3* resembling microlissencephaly.

Polymicrogyria

AKT3, *C2CD3*, *COL3A1*, *DYNC1H1*, *FKTN*, *FIG4*, *KBP*, *NDE1*, *NHEJ1*, *NSDHL*, *OCLN*, *PI4KA*, *PIK3CA*, *RTTN*, *USP18*, *TMX2* and *WDR62* are primarily linked to cortical features that resemble polymicrogyria on MRI.

Polymicrogyria was confirmed histologically in patients carrying variants in *DYNC1H1*, *FKTN*, *KBP*, *NHEJ1*, *NSDHL*, *OCLN*, *PI4KA*, *USP18* and *TMX2*, with variation between reports concerning the numbers of cortical layers, undulating bands of neurons, festooning and breaches in the pial membrane. Polymicrogyria was also described in a patient with a pathogenic variant in *C2CD3* [32], but no information on the histological features of the cortex was available in an additional patient with a pathogenic variant in *C2CD3* [33].

In contrast to imaging features, histological appearances consistent with microlissencephaly were reported in a patient with a variant in *NDE1*. A simplified gyral pattern was reported for *RTTN* and *WDR62*. For a patient with a variant in *COL3A1*, only a macroscopic description was available.

Variants in *USP18* and *OCLN* are associated with brain malformations resembling congenital infections, including haemorrhages and calcification, as well as cortical malformations histologically compatible with polymicrogyria [25, 34–36]. Calcification and polymicrogyria were also reported in *NSDHL*.

Polymicrogyria-like cortical malformations have been reported for *GPR56* and *LARGE* [5, 35, 37]. Both genes are primarily linked to cobblestone malformation but it has been suggested that breaches in the pial membrane and over-migration of neurons into the leptomeninges is a continuum with polymicrogyria and cobblestone malformation at the less and more severe end, respectively.

Variants in *FIG4* have been reported in patients with polymicrogyria, amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease and Yunis–Varon syndrome. Histology reports of patients with CMT disease are available in the literature whereas only one study could be retrieved describing cases of *FIG4*-associated polymicrogyria and Yunis–Varon syndrome. Although phenotypes differ, histological similarities exist between patients with CMT disease and PMG/Yunis–Varon syndrome. For both patient groups, neuronal loss with vacuolation of the cytoplasm has been reported. This is in line with the likely pathogenic mechanism of a disruption of intracellular degradation of vesicles [38].

AKT3 and *PIK3CA* variants have been detected in resection specimen in patients with megalencephaly, focal cortical dysplasia type IIa and focal polymicrogyria. Megalencephalies are described in detail elsewhere [39].

Cobblestone malformations

Imaging features and histology overlap for all genes that have been described in patients with cobblestone malformation (*B3GNT1*, *FKRP*, *ISPD*, *LARGE*, *POMGNT1*, *POMK*, *POMT1*, *POMT2*, *TMEM5*.

GPR56 has been reported to give a continuum of PMG and cobblestone malformations, as mentioned earlier.

Associated brain malformations

The most frequently reported associated brain malformation was hypoplasia or agenesis of the corpus callosum (54.1%, Figure S1). Abnormalities of the cerebellum, most frequently hypoplasia, vermis agenesis or dysplasia, were reported in 52 studies (53.1%, Figure S1). The brainstem was reported to be abnormal in 45 studies (45.9%). The brainstem nuclei exhibited decreased neuronal density, ectopic neurons or were completely displaced in some patients. Surrounding leptomeninges and the aqueduct of Sylvius were also reported to be abnormal. These findings were especially common in individuals with cobblestone malformations [12]. Malformations of the hippocampus are only occasionally reported on MRI but were reported in 18.4% of the included studies. Most commonly, the hippocampus was abnormally rotated and hypoplastic. Other abnormalities included dysplasia with disorganisation of pyramidal neurons and poorly formed dentate gyri in a patient with a variant in *TUBA1A* [40]. The basal ganglia were hypoplastic, evident by decreased neuronal density, or dysplastic, for example because of fusion of the putamen and the caudate nucleus, in 24.5%.

Neuronal heterotopias were reported in 40 studies, absent in patients in 25 studies and no information on the presence or absence of heterotopias was available in 34 studies (Table 1).

Other features that were reported in several studies include, for example gliosis, absent olfactory bulbs, encephalopathy, hydrocephalus/ventriculomegaly, calcification and thickened leptomeninges.

Immunohistochemistry

Immunohistochemistry was used in 28 studies to support the diagnosis. In most studies, layer markers such as NeuN and MAP2 were used to characterise the wrongly migrated neurons, stains such as vimentin to highlight the radial glial network necessary for correct migration, and stains such as GFAP to subtype the different cells. Fifty-three studies did not report the use of additional immunohistochemical stains.

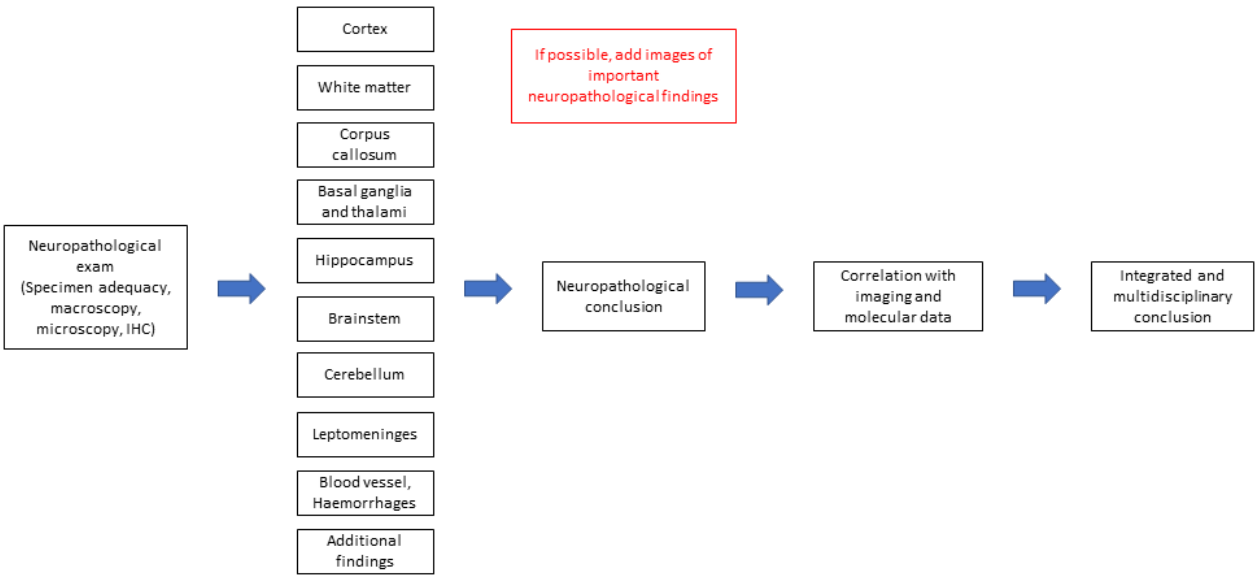

FIGURE 3 Suggested reporting workflow for neuropathological assessment of MCD cases

Quality of reports

For each publication, we assigned a score from 1 to 3 for the availability of histological images and extent of detailed information that was available from the publication (Table S3). Forty-three articles provided both images and a detailed report of neuropathological features (score 1). Twenty-two articles provided either a detailed description of neuropathological features without images or histological images with limited amount of information in the main text (score 2). Sixteen articles mentioned a neuropathological exam briefly but provided neither detailed information nor images (score 3).

DISCUSSION

Malformations of cortical development are heterogeneous and rare disorders but recent advances in genetics have helped to improve our understanding of the underlying pathophysiological mechanisms.

Molecular-histological correlations are often lacking, an exception being the histological spectrum for genes commonly linked to lissencephaly, cobblestone malformations and for a number of tubulin genes [8, 12, 18].

Neuropathological data are available for several genes, but histology remains difficult to assess for surgical pathologists for several reasons.

First, pathologists are often only vaguely familiar with the histological features of these disorders, their differential diagnoses and genetic causes. This also renders the use of terminology difficult and causes important interobserver variability. Few histological classifications are available and those are mostly based on the most common phenotypes, thus being difficult to apply to cases carrying a novel variant.

Second, most examined brain tissue is available after termination of pregnancy. Both improved quality and increased availability of (foetal) MRI offer an opportunity for detection of subtle brain malformations as well as early detection of MCD during pregnancy. These findings can help facilitate neuropathological examination during autopsy and target sampling. However, not only are foetal brains more fragile and prone to manipulation than adult brains, termination of pregnancy and prolonged time to expulsion and fixation carry the risk that autolysis interferes with both macroscopic and microscopic investigations. The foetal brain might also exhibit immature features of the "developing" migration disorder, differing from what is described in mature brains in the general literature. This is particularly true for very early terminations of pregnancy around 20 weeks' gestation. When comparing histological images of foetal cases with adult or paediatric cases, age differences might cause an important pitfall of interpatient heterogeneity rendering comparison difficult.

Third, although there are several reviews available with suggested classification schemes, such as for lissencephaly, cobblestone malformations and FCD, there is significant phenotypic heterogeneity between patients carrying variants in different genes, even when MRI imaging features suggest similar cortical malformations. Furthermore, variation in cortical malformations on the histological level between patients carrying a variant in the same gene, as well as variation in cortical features in different cortical regions in the same patients render the task of the pathologist even more difficult. (1) Overlap between the different clinical and imaging features, (2) phenotypic heterogeneity in patients with variants in the same genes and (3) resemblance of phenotypes within patients with pathogenic variants in different genes, makes it difficult to purely rely on a classification but requires a more individual approach of all clinical features in every single patient [98]. This holds also true for the neuropathological features in individual patients. While overlapping phenotypes exist, for many genotypes the histological spectrum appears broad and larger cohorts are needed to define these spectra. Further research is needed to show whether variants in every MCD gene cause a distinctive histological phenotype due to its unique impact on cortical development.

Therefore, this review highlights the importance of standardised assessment and reporting as diverging neuropathological features in a limited number of patients complicates interpretation. To facilitate comparison of individual studies and patients, it is important for pathologists to provide a detailed description of the macroscopic and histological features and, if possible, images of these findings. Data on the histology of other brain structures are often not available, leaving the question whether these structures were normal or not assessed macroscopically and sampled for microscopic evaluation. We suggest following a structured approach of reporting including the main structural domains of the brain and any additional findings as suggested in Figure 3 [99]. Even if it is not possible to classify the malformation as, for example lissencephaly or polymicrogyria, detailed description of pathological features helps comparing histology and this can be summarised in a concluding sentence (e.g. 'migration disorder with 4-layered cortex suggestive of lissencephaly'). Detailed description of microscopic appearance also helps interpreting the impact of altered protein function on the underlying pathophysiological mechanisms of MCD. This can help create new hypotheses and indicate directions for further study, both in vitro and in vivo, for example in organoids and in animal models of MCD respectively. We also encourage the reporting of neuropathological features of MCD patients when available in order to be able to draw neuropathology-phenotype correlations in the future.

This is the first extensive review of neuropathological data associated with MCD. We focused this review on the literature of 132 genes associated with either lissencephaly, simplified gyral pattern, dysgyria, polymicrogyria or cobblestone malformations. These genes were selected out of more than 250 genes that are currently linked to MCDs and congenital brain malformations (Table S2). This selection offers an extensive amount of data on the current neuropathological information available for MCDs. Excluding MCDs such as the megalencephaly-FCD spectrum is a limitation of this study but allows a more homogenous study population with cortical malformations. The disorders included here are caused by abnormal neuronal proliferation, migration or post-migrational maturation and

brain tissue is mostly obtained during autopsy due to a severe clinical and imaging phenotype. FCD and megalencephaly are also linked to abnormal neuronal migration, but they are also caused by neuronal overgrowth, mostly due to mutations in the PI3K-AKT-MTOR pathway, thus offering an additional pathogenic mechanism. In addition, samples are often obtained during epilepsy surgery, which is not usually performed in patients with the MCDs included in this review. Nevertheless, some cases of FCD and megalencephaly were included in the review when concomitant polymicrogyria was present, highlighting the overlapping importance of correct cortical migration in both disorders.

Improved understanding and definition of phenotypic features together with correlation of imaging data and histology, ultimately provides a possibility to improve the diagnostic process and counselling of the affected families. The data collected in this review offer a comprehensive overview of the imaging and neuropathological features of 132 genes associated with common subtypes of MCD and can be useful to clinicians in the diagnostic process of a MCD patient. While this review concentrates on neuropathological features, it is important to consider that MCD might be part of a congenital malformation syndrome. Therefore, careful examination of all organ systems in search for extra-CNS malformations is indispensable for all MCD patients. MCDs are sometimes associated with specific syndromes, and combinations of malformations can give hint towards a certain diagnosis (Table S1). As such, the combination of muscular dystrophy, retinal dysplasia and cobblestone malformation is caused by mutations in, for example *B3GNT1*, *FKTN*, *FKRP*, *LARGE*, *POMGNT1*, *POMT1*, *POMT2*. Cobblestone-like cortical malformations and retinal dysplasia without muscular dystrophy but with gonadal dysplasia have been reported in individuals with mutations in *TMEM5*, whereas gonadal dysplasia is common only in association with variants in *POMT2* [18]. Facial dysmorphisms are a common finding in many MCD patients and often non-specific. Distinctive facial features have been reported in patients with mutations in *ACTG1* with Bartaiser–Winter syndrome. Affected individuals present with trigonocephaly, hypertelorism, ptosis and microlissencephaly or anterior-predominant pachygyria [19, 41].

A limitation of this study is that the literature search was based on the screening of article titles instead of abstracts. This was done as the large number of genes included resulted in numerous articles to consider for inclusion. Although screening article titles carries a risk to miss papers that report neuropathology, our threshold to screen full-text articles was very low whenever the title was suggestive of a detailed clinical description of one or several patients or when the title was inconclusive.

CONCLUSION

Neuropathology for each genetic cause might be unique. Overlapping histological features can help make rough classifications. Standardised and throughout assessment of different brain structures both macroscopically and microscopically is therefore indispensable. Correlation of imaging data and suspected pathogenic mechanisms provides a better understanding of the phenotypic spectrum.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

Conceptualisation: [Stefanie Brock]; Methodology: [Stefanie Brock], [Filip Cools]; Literature search and data analysis: [Stefanie Brock], [Anna Jansen]; Drafting of the manuscript: [Stefanie Brock]; Revising the manuscript: [Stefanie Brock], [Filip Cools], [Anna Jansen].

ETHICAL APPROVAL

This work did not require additional ethics approval and patient consent.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/nan.12696.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Supplementary Material

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