Neuronal migration disorder in 205 patients: A decade of a single center experience

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INTRODUCTION

Neuronal migration disorders (NMD) are a spectrum of heterogenous disorders that result from a defect in the critical developmental brain process. The process which is highly genetically regulated, result in mal-positioning and faulty differentiation of cortical grey matter. Table 1 showed NMD classification based on earliest stage of neurodevelopment process with elucidated genetic mutations.

Group1: ABNORMAL CELL PROLIFERATION OR APOPTOSIS	Group2: ABNORMAL CELL MIGRATION	Group3: ABNORMAL POST-MIGRATIONAL DEVELOPMENT
Microcephaly: ***MCPH1***, *CENPJ, CDK5RAP2, WDR62, NDE1,* ***ASPM****, CDK5RAP2, TUBA1A, TUBB2B, TUBB3, TUBG1, LIS1, DCX,* ***CIT****, DYNC1H, KIF5C,* ***CASK, MECP2, CTU2***	**Tubulinopathies**: *TUBA1A,TUBB2B, TUBB3, TUBG1, LIS1, DCX, KIF2A DYNC1H, KIF5C, NDE1,* ***PRUNE1, C12orf57****,* ***KIAA0586, CENPF***	**Polymicrogyria**: *AKT3, CCND2, PIK3R2,* ***OCLN****,* ***ADGRG1****, RTTN, FIG4,* ***CHD7****, SNAP29, EOGT, ARHGAP31, RBPJ, NOTCH1, DLL4, DOCK6,* ***GPSM2****,* ***RNASEH2B****,* ***TUFM, CPT2****.* ***MORC2.*** *1p36.3 DEL, 22q11.2 DEL*
Megalencephaly: *AKT3, EZH2, FGFR3, PIK3CA, PIK3R2*	**Variant lissencephalies:** ***PAFAH1B1****,* ***RAB3GAP1*** *TUBA1A, MACF1, CEP85L, ACTB, ACTG1, RELN, NDE1,* ***LAMB1****, KATNB1, CDK5, TMTC3, CRADD,, PHGDH,* ***ASNS****, DCX,* ***ARX****.*	**Schizencephaly**: *SIX3,* ***SHH****, EMX2, COL4A1,* ***WDR62****, KIF26A, EPG5* ***MT-TH.***
FCD type IIa: ***MTOR****, DEPDC5, PIK3CA,* ***PTEN***	**Gray matter heterotopia**: *ARF1, PVNH3, MAP1B, PVNH5, ERMARD, NEDD4L, ARFGEF2, FLNA, FMR1, LRP2, KIAA1279.* ***Xq28 duplication***	**Holoprosencephaly**: *DEL1q41q42 , SIX3, GLI2, HPE6, PLCH1, SHH, PTCH1, CDON, ZIC2, HPE8, CNOT1, TGIF1, HPE1, STAG2*
FCD type IIb: ***MTOR****, DEPDC5, NPRL3*	**Cobblestone malformations**: ***GPR56****,* ***LAMB1****, LAMB2, LAMC3, SRD5A3,* ***ATP6V0A2, POMT1****, POMT2,* ***POMGNT1****,* ***FKTN****, FKRP, LARGE, CRPPA, POMGNT2, DAG1, RXYLT1, B3GALNT2, POMK, B4GAT1, GMPPB,* ***LAMA2***	**Porencephaly/hydranencephaly** ***FLVCR2***

Table 1: NMD classification adopted from Desikan, R. S.,& Barkovich, A. J. (2016). The genes in bold are the one described in our cohort. Some gene has multiple effect at different pathway.

AIM AND METHOD

This study aims to describe the clinical, radiological, and genetic features of NMD. We conducted a retrospective descriptive analysis of radiologically confirmed neuromigration disorder patients who were diagnosed at Sultan Qaboos University Hospital between year 2012 to 2022.

RESULTS

NMD was confirmed radiologically in 205 patients from 181 families. The male-to-female ratio was 0.95. Seizure was the most common clinical presentation in 50% followed by developmental delay in 20%. 59% of the patients presented before the age of 5 years out of which 35% presented during early infancy. The neurology unit was the first encounter clinic in 56%. Corpus callosum malformation was the most reported radiological features. Figure 1 & 2 show radiological features of *MT-TH* gene and *TUFM* related NMD, respectively. The genetic diagnosis was confirmed in 116 patients. Tuberous sclerosis was the most common diagnosis in 27/116 followed by dystrophoglycanopathy in 26/116. The most common mode of inheritance was autosomal recessive. The consanguinity was reported in 65%. In Table 2, we report 5 newly described clinical features. Table 3, shows 10 previously un-reported genetic variants.

Gene	Clinical features
GPSM2	Bilateral Pelviureteric dilatation
GPR56	Precocious puberty
CTU2	Adrenal insufficiency
LAMA2	Bilateral pigmentary retinopathy and maculopathy with ocular hypertension
C12orf57	Low grade glioma

Table 2: 5 patients with 5 newly reported clinical features.

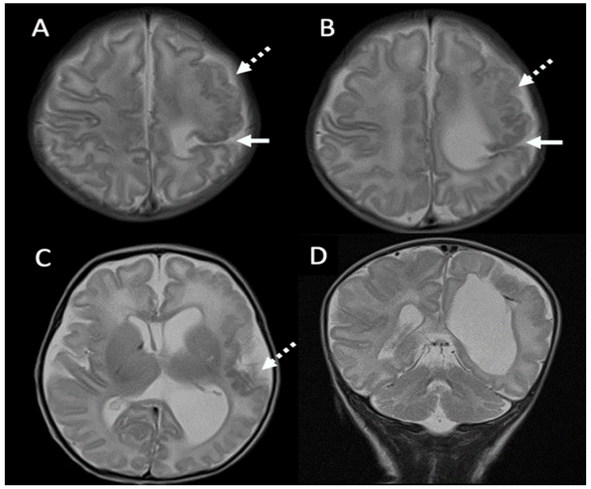

Figure 1. Patient with *MT-TH* gene mutation. MRI was obtained at the age of 11 days. There is open lip schizencephaly (solid arrows) and extensive polymicrogyria (dashed arrows) in the left cerebral hemisphere. Asymmetrical dilatation of the left lateral ventricle and loss of deep white matter in the left cerebral hemisphere.

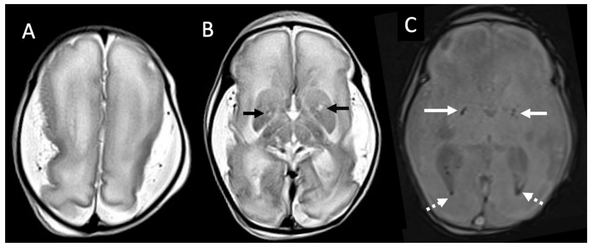

Figure 2. Patient with *TUFM* gene mutation. MRI was obtained at the age of 2 days. (A, B) Axial T2 weighted images show lissencephaly. Bilateral T2 hyperintensities are seen in the basal ganglia (arrows in B). (C) A susceptibility-weighted image shows susceptibility effects in the basal ganglia (solid arrows) and mild intraventricular haemorrhage (dashed arrows).

Gene	Variant
MT-TH	(n.10G>A)
TUFM	c.763C>T?
CTU2	c.1419dup
LAMB1	c.3081G>C
FKTN	c.656T>A
TSC1	c.1509_1510insT c.2121dup
TSC2	EX11_16 DEL
POMT1	c.973T>C
WDR62	c. 2081del

Table 3: 10 variants previously not been reported at HGMD database or Broad ExAC dataset.

Conclusion

NMD are rapidly expanding spectrum with multiple new genes that aid in clinical understanding of these complex conditions. We describe 205 patients from 181 families with radiologically confirmed NMD. Our cohort adds 5 newly reported clinical features and 11 new genetic variants.

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