

Comprehensive genotype-phenotype correlation in lissencephaly

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Abstract: Malformations of cortical development (MCD) are a heterogeneous group of disorders with diverse genotypic and phenotypic variations. Lissencephaly is a subtype of MCD caused by defect in neuronal migration, which occurs between 12 and 24 weeks of gestation. The continuous advancement in the field of molecular genetics in the last decade has led to identification of at least 19 lissencephaly-related genes, most of which are related to microtubule structural proteins (tubulin) or microtubule-associated proteins (MAPs). The aim of this review article is to bring together current knowledge of gene mutations associated with lissencephaly and to provide a comprehensive genotype-phenotype correlation. Illustrative cases will be presented to facilitate the understanding of the described genotype-phenotype correlation.

Keywords: Lissencephaly (LIS); LIS1; doublecortin (DCX); tubulinopathy

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Introduction

The rapidly evolving genetic landscape has revealed more than 100 genes associated with malformations of cortical development (MCD), a heterogeneous group of disorders with diverse genotypic and phenotypic variations. Substantial insights into the mechanisms underlying lissencephaly (LIS) led most to believe that these processes map onto molecular processes/pathways and are interdependent on one another, explaining the wide array of clinical and imaging phenotypes. The cerebral cortex comprises of two groups of neurons with differing migration modes: (I) radial migration from the ventricular zone and (II) tangential migration from ganglionic eminence. Neurons that undergo radial migration are primarily excitatory projection neurons while neurons that migrate in a tangential manner are mainly inhibitory interneurons.

LIS1 and *DCX* are the commonest LIS-related gene mutations, first discovered in 1993 and 1998 respectively (1-3). The continuous advancement in the field of molecular genetics in the last decade has led to identification of 19 LIS-associated genes thus far, many of which are related to

microtubule structural proteins (tubulin) or microtubule-associated proteins (MAPs) (4). These LIS-related genes include *LIS1*, *DCX*, *ACTB*, *ACTG1*, *ARX*, *CDK5*, *CRADD*, *DYNC1H1*, *KIF2A*, *KIF5C*, *NDE1/NDEL1*, *TUBA1A*, *TUBA8*, *TUBB*, *TUBB2B*, *TUBB3*, *TUBG1*, *RELN* and *VLDLR* (2,5-15) (Figure 1). In view of the rapidly expanding LIS-related genetic mutations and heterogeneous phenotypes, a more comprehensive classification system is crucial. Just recently, a new imaging-based classification system for LIS was proposed by Di Donato *et al.* (4).

A comprehensive analysis of clinical features, familial distribution (if present) and neuroimaging findings is crucial to facilitate a more targeted genetic testing in patients with LIS. For instance, an X-linked pattern of inheritance would suggest the involvement of *DCX* or *ARX* genes while an autosomal recessive pattern of inheritance would suggest involvement of reelin-pathway-related genes or the *CDK5* gene. LIS and facial dysmorphism are characteristics of Miller-Dieker syndrome (MDS), Baraitser-Winter syndrome (BWS) and Norman Roberts syndrome (NRS). On the other hand, the presence of genital abnormality such as cryptorchidism, micropenis and

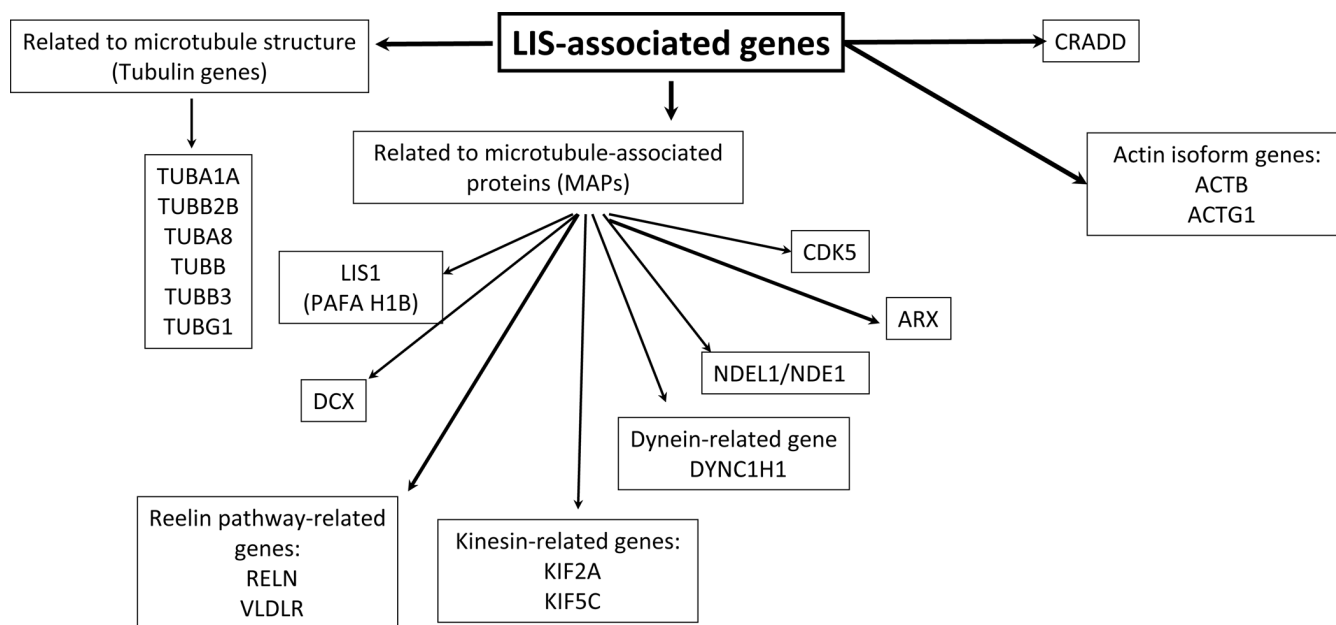


Figure 1 Lissencephaly (LIS)-associated genes, many of which are related to microtubule structural proteins (tubulin) or microtubule-associated proteins (MAPs).

ambiguous genitalia is highly suggestive of *ARX* mutation. If LIS is seen in association with macrocephaly, genetic testing for *CRADD* mutations should be considered. Several imaging features may help to narrow down the underlying genetic abnormality of LIS. These include the radiological characterization of LIS (gradient of gyral malformation and type of LIS) and associated extra-cortical findings such as malformations involving the cerebellum, basal ganglia and brainstem, as well as the presence of periventricular calcifications, ventriculomegaly and white matter signal abnormalities (Figure 2).

LIS associated-genes and their function in neuronal migration

Neuronal migration is a complex process which requires precise coordination between many gene products. Majority of LIS-related genes are related to microtubule structural proteins (tubulin) or MAPs. Their roles in association with neuronal migration are delineated in Figure 3.

LIS1 gene

LIS1-associated LIS includes isolated LIS syndrome (ILS), MDS and rarely subcortical band heterotopia (SBH).

Patients with *LIS1*-associated LIS are characterized by drug-resistant epilepsy (16). While heterozygous deletions or intragenic mutations in *LIS1* lead to ILS, variable micro deletions of chromosome 17p.13.3 including the *LIS1* and *YWHAE* genes cause MDS (17). In 2013, Classen *et al.* (18) reported a novel inverted microduplication of chromosome 17p13.3 in a child with pachygyria, profound intellectual impairment, and facial dysmorphism. Profound LIS with diffuse agyria and facial dysmorphism are features of MDS (17). *YWHAE* is crucial in the process of neuronal migration (19). Its interaction with NDEL1 (NUDEL) and dynein is also indispensable in the regulation of microtubule function (19). Isolated deletion of *YWHAE* leads to facial dysmorphism, growth retardation and structural intracranial abnormalities, including neuronal migration disorders and severe corpus callosal hypoplasia (20,21).

Approximately 60% of patients with posterior predominant classical LIS have genomic alterations of *LIS1* (22) (Figure 4). A posterior-predominant simplified gyral pattern with underlying SBH has also been associated with mosaic mutations of *LIS1* (23) (Figure 5). *LIS1*-associated SBH has also rarely been associated with germline or somatic intragenic *LIS1* pathogenic variants and, in contrast to *DCX*-related SBH, it typically presents with posterior predominant SBH (24-26). Mild

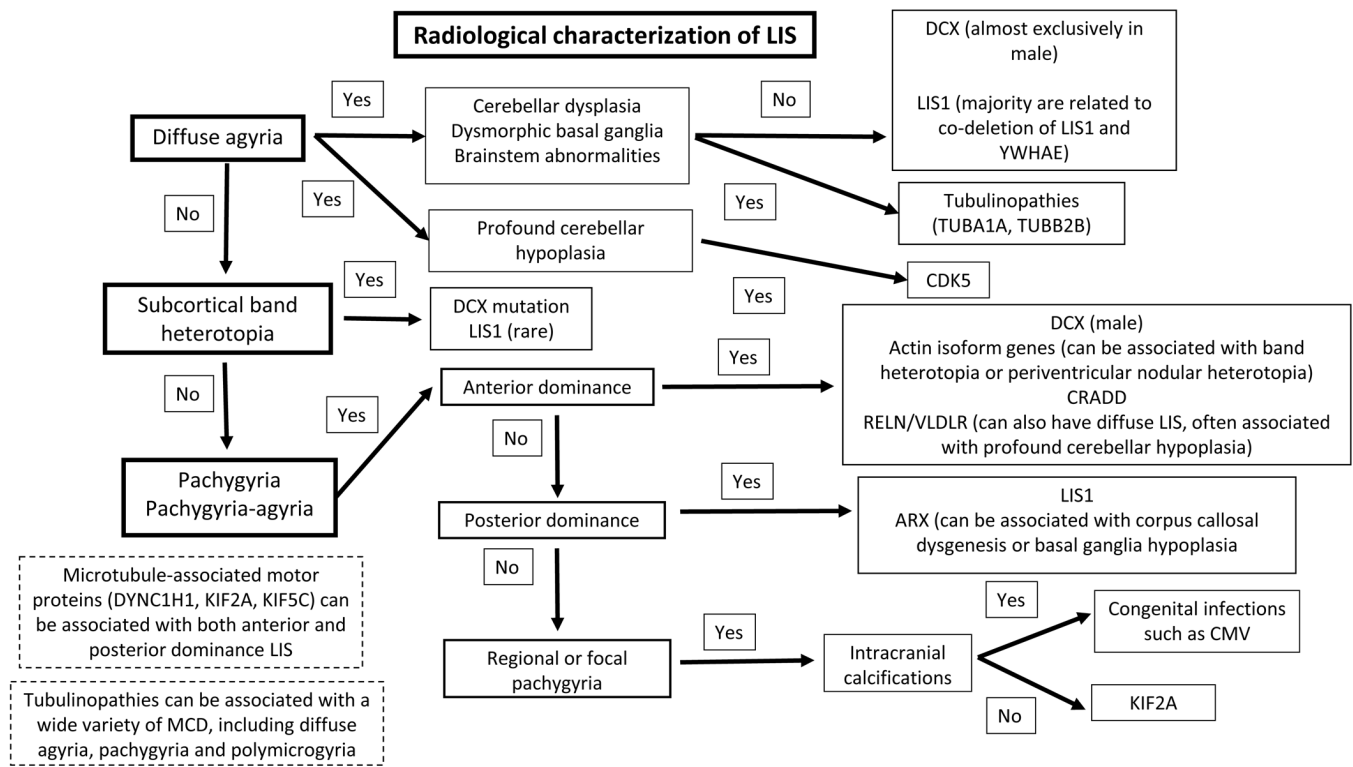


Figure 2 Radiological characterisation of LIS. Cerebellar hypoplasia/dysplasia, dysmorphic basal ganglia, thin or absent corpus callosum, ventricular dilation, and abnormalities of the hippocampus and brainstem are useful diagnostic indicators of tubulin gene involvement. Severe cerebellar/brainstem hypoplasia is also seen in association with *RELN/VLDLR* and *NDE1* mutations. In the presence of intracranial calcifications and ventriculomegaly, congenital CMV/TORCH infection needs to be excluded. LIS, lissencephaly.

ventriculomegaly, prominent perivascular spaces as well as mild hypoplasia of the corpus callosum and vermis are other reported neuro-radiological findings (27,28).

Although germline mosaicism in a parent could lead to familial recurrence, all *LIS1* pathogenic variants reported to date have been *de novo* (29). Neither the mutation type nor the location of the mutation was found to predict the severity of LIS (28).

Doublecortin (DCX) gene on chromosome Xq23

Stabilization and polymerization of microtubules are highly dependent on the *DCX* gene (30). The binding of the DCX protein to the microtubule skeleton facilitates the formation of the leading process of the migrating neuron (31).

DCX-related disorders include classical LIS, usually in males; and SBH, primarily in females. Mutations in *DCX* have been found in 80% of sporadic females and 25%

of sporadic males with SBH (32). Most cases of familial SBH are result of *DCX* mutations. Somatic or germline mosaicism was found in approximately 10% of unaffected mothers of children with *DCX*-related LIS (33,34) while the risk of transmission in a female who is heterozygous for a *DCX* pathogenic variant is approximately 50% in each pregnancy (35).

Unlike *LIS1*-related classical LIS, *DCX*-related classical LIS demonstrates an anterior predominance or may be diffuse. *DCX*-related SBH is also predominantly located in the fronto-parietal lobe. A more severe malformation that overlaps with classic LIS and SBH, is characterized by SBH in the occipital regions and pachygyria in the frontal regions, also seen in LIS associated with mutations of actin isoform genes. Other neuroimaging features described in patients with *DCX*-related LIS include prominent perivascular spaces, delayed myelination as well as ventriculomegaly (35). *DCX*-related LIS was not previously known to be associated with cerebellar hypoplasia or corpus

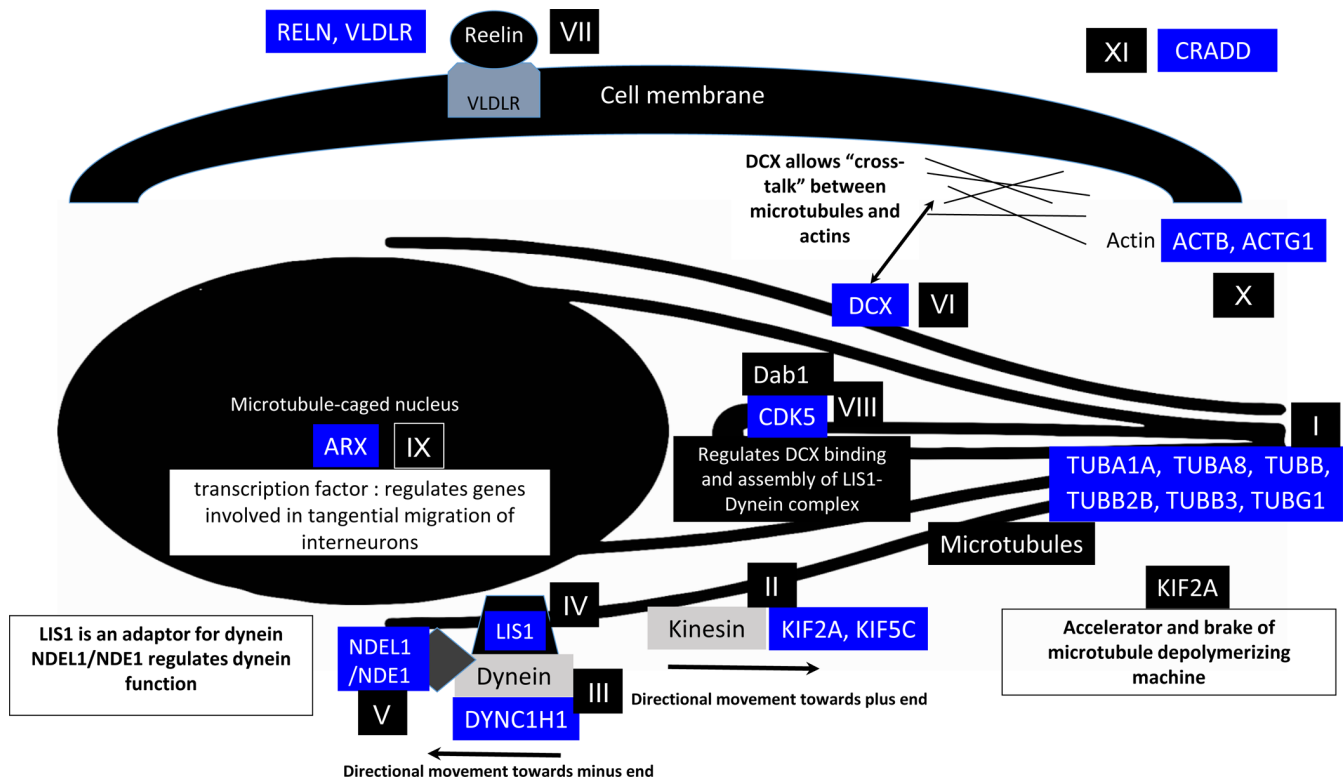


Figure 3 Roles of LIS-associated genes in association with microtubule function and neuronal migration/organization. (I) Mutations in tubulin isotypes disrupt the formation of normal heterodimers of α - and β -tubulin polypeptides, affecting the structural stability and function of microtubules; (II) kinesins and (III) dyneins are microtubule-motor proteins that power directional movement along microtubules. Lissencephaly (LIS)-related genes that encode these motor proteins include KIF2A, KIF5C and DYNC1H1; (IV) the *LIS1* gene encodes the LIS1 protein which is an adaptor for the microtubule-motor dynein that allows dynein to remain attached to microtubules for longer periods of time; (V) the mammalian NudE homologues (*NDE1* and *NDEL1*) are required for the targeting of LIS1 to the dynein complex. It also releases the blocking effect of LIS1 on cytoplasmic dynein; (VI) DCX protein binds directly to microtubules to stabilize and promote polymerization, facilitates the formation of the microtubule cage around the nucleus, as well as stabilizes microtubules in the leading process of the migrating neuron; (VII) the Reelin signalling pathway aids in the regulation of neuronal migration and positioning, generating the “inside first-outside last” configuration of the 6-layer cortex; (VIII) CDK5 regulates the binding and assembly of LIS1-dynein complex as well as the direct binding of DCX to microtubules; (IX) the *ARX* gene encodes the ARX protein (a transcription factor) which regulates genes that play crucial roles in tangential migration of GABAergic interneurons into the cortical plate; (X) *ACTB* and *ACTG1* encode β - and γ -actin. The interaction between microtubules and cytoplasmic actin plays an important role in neuronal migration. DCX protein allows “cross-talk” between microtubules and cytoplasmic actins; (XI) the *CRADD* gene is a recently discovered LIS-associated gene. Its role in neuronal migration and hence development of LIS is still unclear and needs further investigation. MCD, malformations of cortical development.

callosal dysgenesis (36). Severe hypoplasia of the corpus callosum was however observed in one of our patients with anterior predominant classical LIS (Figure 6). Mild hypoplasia of the posterior corpus callosum was also noted in another patient with *DCX*-related SBH (Figure 7). The extent of cortical abnormalities, band thickness and

ventricular enlargement are factors that predict the clinical severity of SBH (37,38).

Molecular genetic testing for *DCX* mutations should be considered in the presence of SBH, generalised or frontal predominant LIS, especially in the context of a family history compatible with X-linked inheritance.

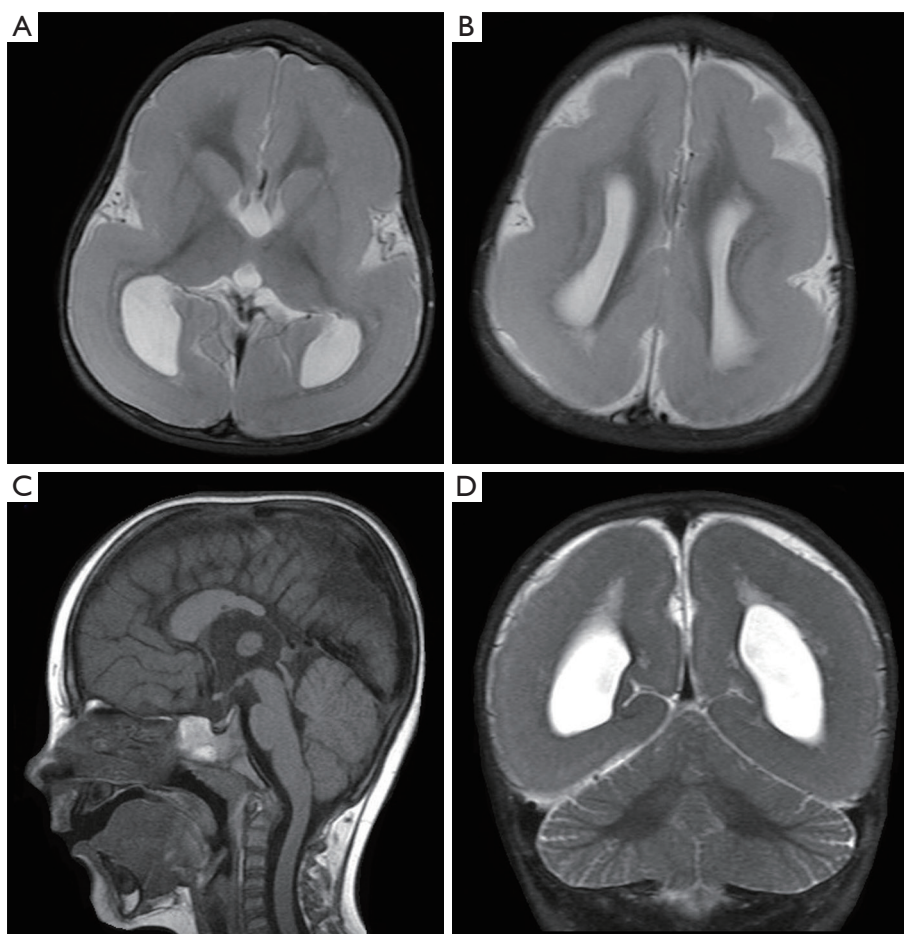


Figure 4 Classical lissencephaly in a patient with heterozygous deletion in the *LIS1* gene. (A,B) Axial T2-weighted images demonstrate the presence of posterior predominant LIS with a thick cortex. Mild ventriculomegaly is noted; (C) sagittal T1-weighted and (D) coronal T2-weighted images show normal appearances of the cerebellum and brainstem. Partial agenesis of the corpus callosum is also noted.

Tubulin genes

Microtubules are made up of alternating α - and β -tubulin polypeptides which bind to a γ -tubulin ring complex (39,40). The production of motion along microtubules is determined by a wide spectrum of MAPs. Mutations in several tubulin isotypes have been associated with various developmental brain anomalies involving the basal ganglia, cerebral cortical grey matter, commissural tracts, cerebellum and brainstem (an expression of neuronal migration and axonal guidance disorders) (39,41). Mutations in several tubulin isotypes have also been associated with hypoplastic olfactory nerves (42), diminished overall white matter volume and small, asymmetric brainstem (15,39), believed to be related to disturbances in axonal pathfinding.

TUBA1A was the first tubulin isotype to be associated with brain malformations (43) and it is the most commonly mutated tubulin gene. *TUBA1A* is highly expressed in the embryonic brain, providing more than 95% of the α -tubulin in the developing brain (44,45). Mutations to *TUBA1A* could lead to a wide variety of MCD (39,41,46-49), the core imaging phenotype of which comprise of classic LIS with or without cerebellar hypoplasia (39). In 2015, Myers *et al.* reported the presence of microphthalmia and congenital cataract in a patient with *TUBA1A* mutation (50). Congenital cataract was also seen in one of our patients with *TUBA1A* mutation (Figure 8). As the brain and eye are derived from the ectoderm, the co-occurrence of developmental anomalies of these organs is not surprising. In addition, *TUBA1A* is expressed in both the fetal brain (43) and retina (51). *TUBA1A* mutations

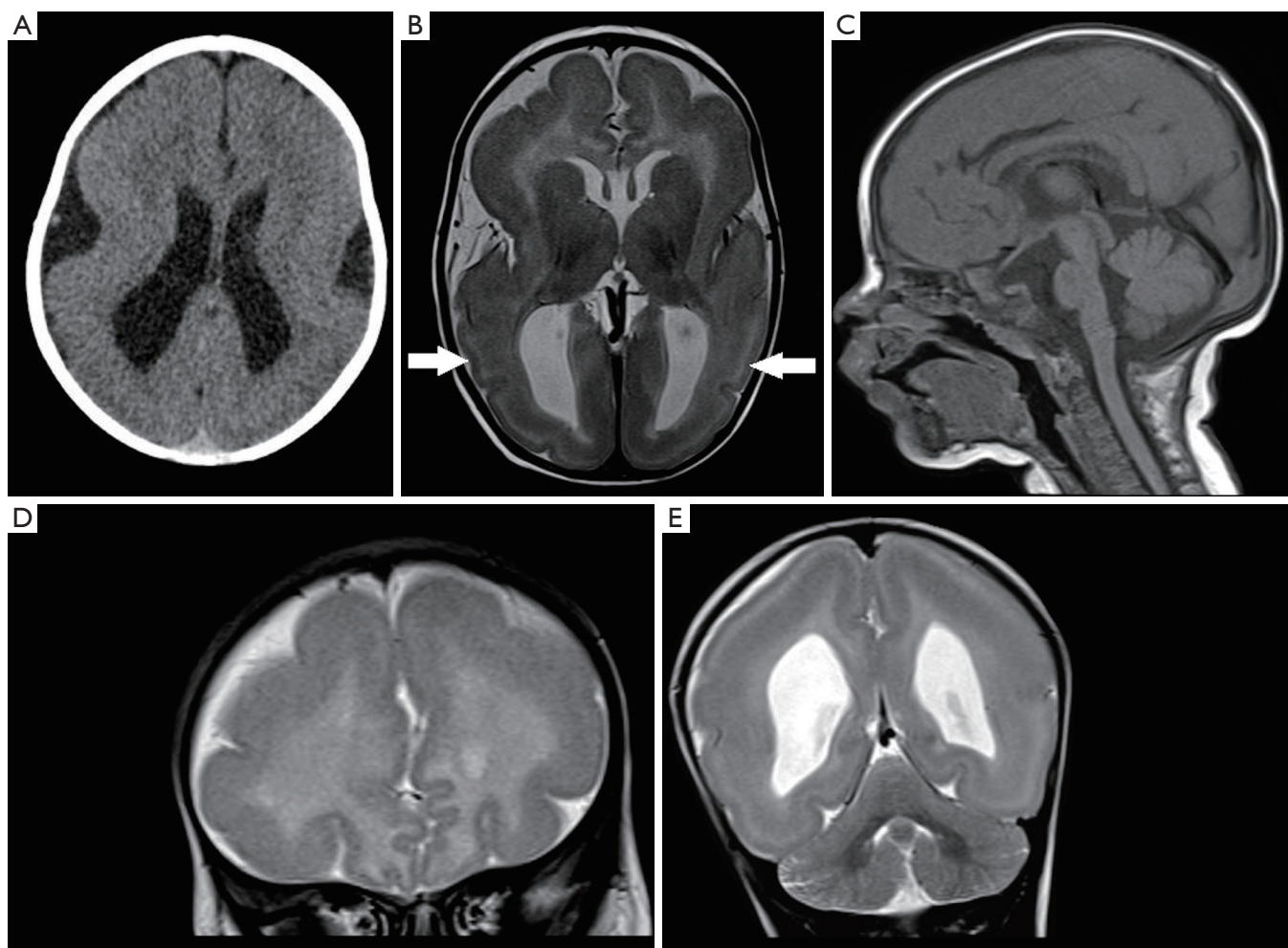


Figure 5 Posterior predominant pachygyria with underlying SBH in a patient with mosaic mutations of LIS1. (A) Axial CT image shows bilateral pachygyria with mild ventriculomegaly; (B) axial T2-weighted and (D,E) coronal T2-weighted images demonstrate the presence of bilateral pachygyria, more severe posteriorly. An underlying band of heterotopic grey matter (white arrows) is also present posteriorly; (C) sagittal T1-weighted image shows normal appearances of the cerebellum, brainstem and corpus callosum. SBH, subcortical band heterotopia.

have also been described in association with asymmetrical perisylvian polymicrogyria (PMG) (46,52,53), PMG-like cortical dysplasia (54) and microlissencephaly in foetal cases (49). Almost all reported cases of *TUBA1A*-related LIS exhibit some form of corpus callosal abnormalities, ranging from mild hypoplasia or dysmorphism to complete agenesis (55).

Mutations in several β -tubulin isotypes result in microlissencephaly, pachygyria (Figure 9), SBH and PMG. Schizencephaly (SCH), axonal dysinnervation and congenital fibrosis of extra-ocular muscles were also reported in patients with *TUBB2B* mutations (56-58).

Focal PMG associated with localized band heterotopia was also reported in a patient with *TUBB* mutation (59) while mutations in the *TUBG1* gene were identified in individuals with posterior predominant pachygyria (15).

Recently, Romaniello *et al.* proposed a term “tubulin-related cerebellar dysplasia” defined by the following characteristics: (I) consistent involvement of the hemispheres; (II) prevalent unilateral hemispheric involvement, predominantly in the supero-posterior aspect; (III) abnormal orientation of the cerebellar folia without cysts, cerebellar folial thickening or signal abnormalities. Interestingly, two of our patients with *TUBA1A* mutations

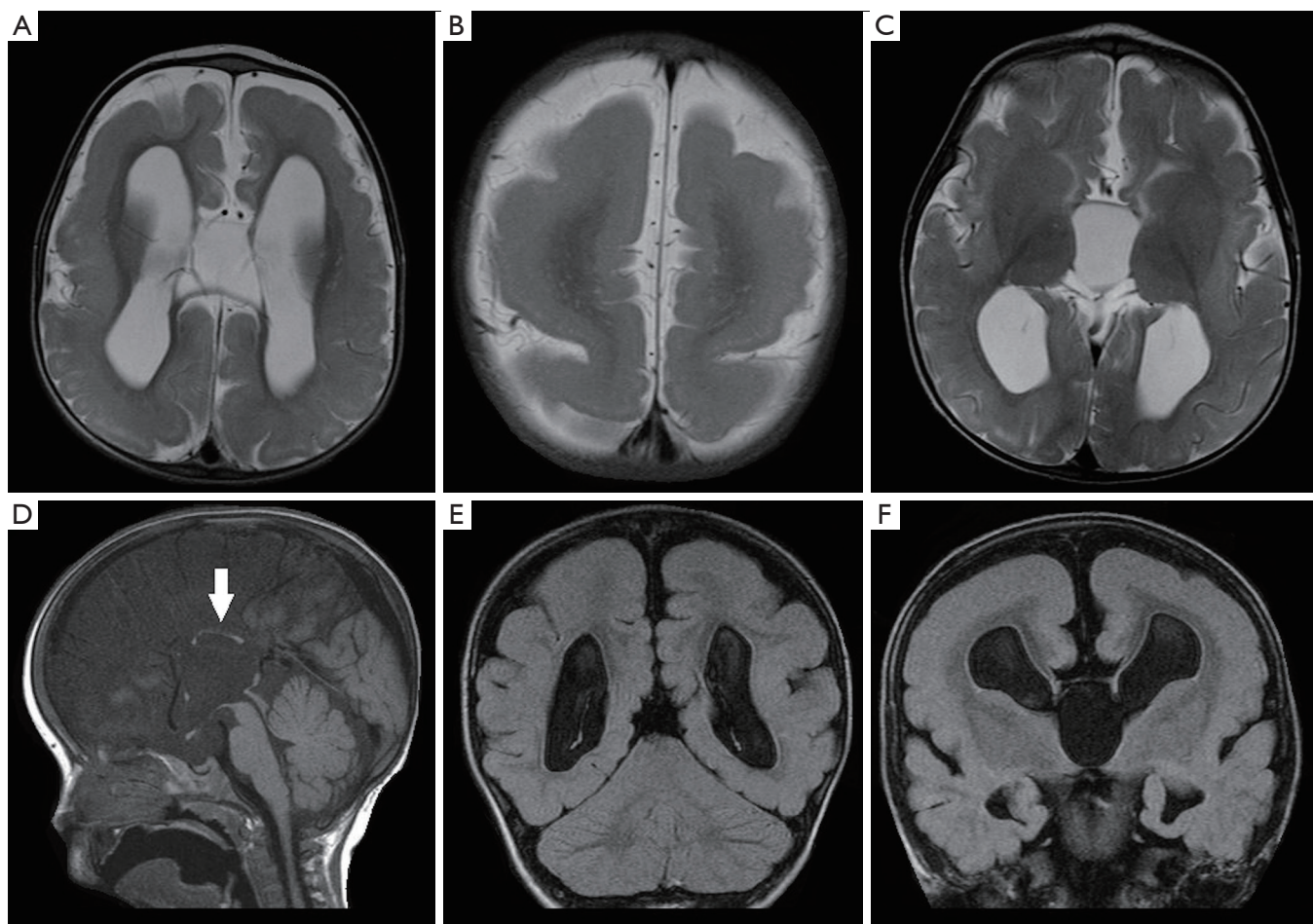


Figure 6 DCX-related lissencephaly due to a missense mutation. (A-C) Axial T2-weighted images show bilateral pachygyria with thick cortex (involving predominantly the frontoparietal lobes) and moderate ventriculomegaly. The basal ganglia is normal in appearance; (D) sagittal T1-weighted image shows severe hypoplasia of the corpus callosum (white arrow). The brainstem and vermis are normal; (E,F) coronal FLAIR images confirms the presence of morphologically normal cerebellar hemispheres and abnormal orientation of the hippocampi.

have tiny cerebellar cysts (*Figures 8,10*).

Aristaless-related homeobox (ARX)

X-linked LIS with abnormal genitalia (XLAG) is a result of *ARX* gene mutations. Gene product of the *ARX* gene plays crucial roles in neuronal proliferation, interneuronal migration, embryonic forebrain differentiation as well as testicular development (14). *ARX* mutations were described for the first time by Kitamura *et al.* in 2002 (14). Till date, at least 30 mutations involving the *ARX* gene have been associated with XLAG.

XLAG is believed to be primarily related to defects in

tangential migration of GABAergic interneurons (60). In 2005, Kato and Dobyns coined the term “interneuronopathy” to describe this pathological condition (61).

Marked disproportion between inhibitory interneurons and excitatory projection neurons result in intractable seizures in patients with XLAG (62). Hydranencephaly, LIS and early-onset epileptic encephalopathies are among the many phenotypes of *ARX* mutations (62-64). In the most severe form, profound autonomous nervous system disturbances may lead to severe morbidity or even mortality (60). Females with an *ARX* gene mutation typically exhibit a less severe phenotype. Disruption of *ARX* protein function in the pancreas results in chronic diarrhea,

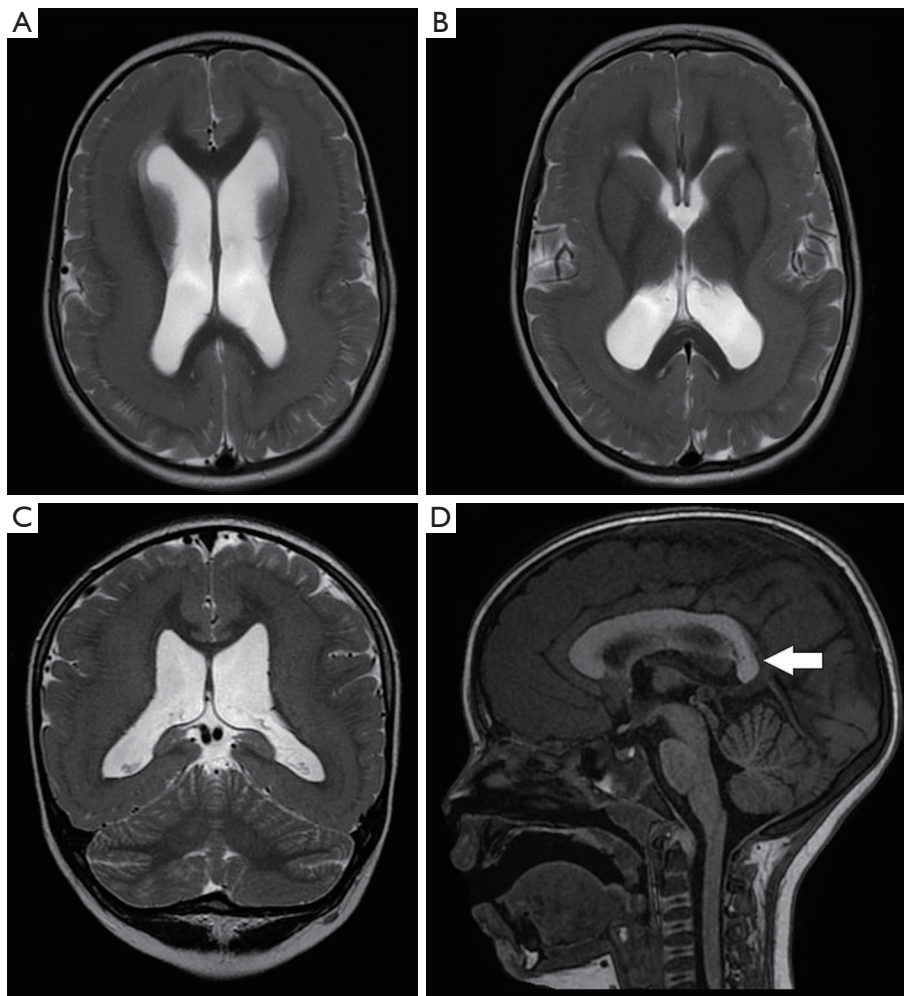


Figure 7 DCX-related SBH in a female patient. (A,B) Axial and (C) coronal T2-weighted images show bilateral SBH with ventriculomegaly and prominent perivascular spaces. The basal ganglia and cerebellum are normal; (D) sagittal T1-weighted image shows mild hypoplasia of the posterior corpus callosum with loss of the normal bulbous appearance of the splenium (white arrow). SBH, subcortical band heterotopia.

experienced by individuals with XLAG.

Posterior predominant LIS (especially anterior pachygyria and posterior agyria) with moderately increased cortical thickness, corpus callosal dysgenesis, striatal and thalamic nuclei atrophy are features described in association with XLAG (Figure 11).

Reelin pathway-related genes (RELN, VLDLR)

The *RELN* gene was first linked to cortical development by the observation of disorganized cerebral and cerebellar cortices in reeler-mutant mice (65). In humans, reelin protein (the gene product of *RELN* gene) is found in the central nervous system, especially in the cerebellum (66).

Reelin plays a key role in the organization of architectonic patterns in the cerebral cortex. *VLDLR* is an essential cell-surface receptor for reelin (67).

Mutations in *RELN* (11) and *VLDLR* (67) have been associated with anterior predominant LIS, severe hippocampal and cerebellar hypoplasia/dysplasia. However, from the authors' experience, reelin pathway-related-LIS are more commonly associated with diffuse LIS. Both *RELN* and *VLDLR* mutations are associated with profound cerebellar hypoplasia/dysplasia. The first case of *VLDLR*-related LIS with a strong cerebellar phenotype was reported in 2008 by Ozcelik *et al.* (68).

NRS is a rare form of microlissencephaly caused by a mutation in the *RELN* gene (11). It was first described

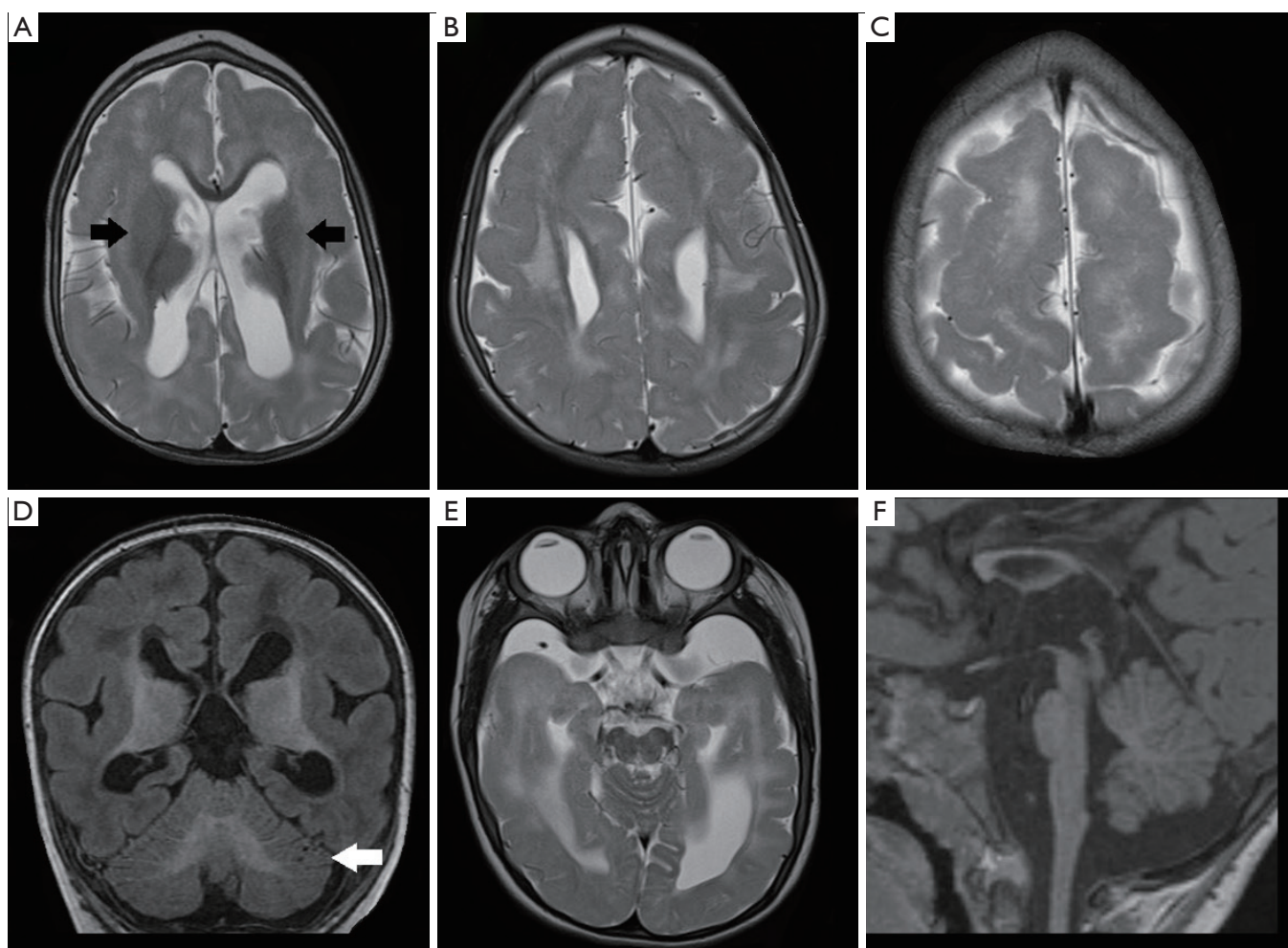


Figure 8 TUBA1A-related lissencephaly. (A-C) Axial T2-weighted images demonstrate bilateral perisylvian pachygyria-polymicrogyria with mild ventriculomegaly and signal abnormalities within the cerebral white matter. There is also absence of the anterior limb of the internal capsules with fusion of the caudate head and lentiform nucleus bilaterally (black arrow); (D) coronal T1-weighted image shows tiny cysts within the left cerebellar hemisphere (white arrow); (E) axial T2-weighted MRI image shows bilateral intra-ocular lens replacement due to congenital cataracts; (F) sagittal T1-weighted image shows partial agenesis of the corpus callosum and mild hypoplasia of the brainstem.

in two patients in 1976 by Norman *et al.* (69). In 2004, Caksen *et al.* reported two patients with NRS; one of the patients had atrial septal defect, corpus callosum agenesis and widespread intracranial calcifications while the other patient had bilateral macular cherry-red spot, persistent foramen ovale and cerebellar atrophy (70). In 2000, the autopsy findings of a male fetus with NRS was reported for the first time (71). Prenatal ultrasound at 25 weeks of gestation revealed extreme microcephaly and post-mortem examination after termination of pregnancy at 27 weeks of gestation revealed complete agyria and failure of

operculation of the insula (71). Since its first description in 1976, all reported cases share several common features; microcephaly, LIS and distinctive craniofacial features.

Cyclin-dependent kinase 5 (CDK5)

CDK5, a member of the cyclin-dependent kinases family, has profound expression in post-mitotic neurons within the central nervous system (72). It is extensively involved in signalling pathways of neuronal migration and cortical layering (73). The CDK5 protein interacts with both

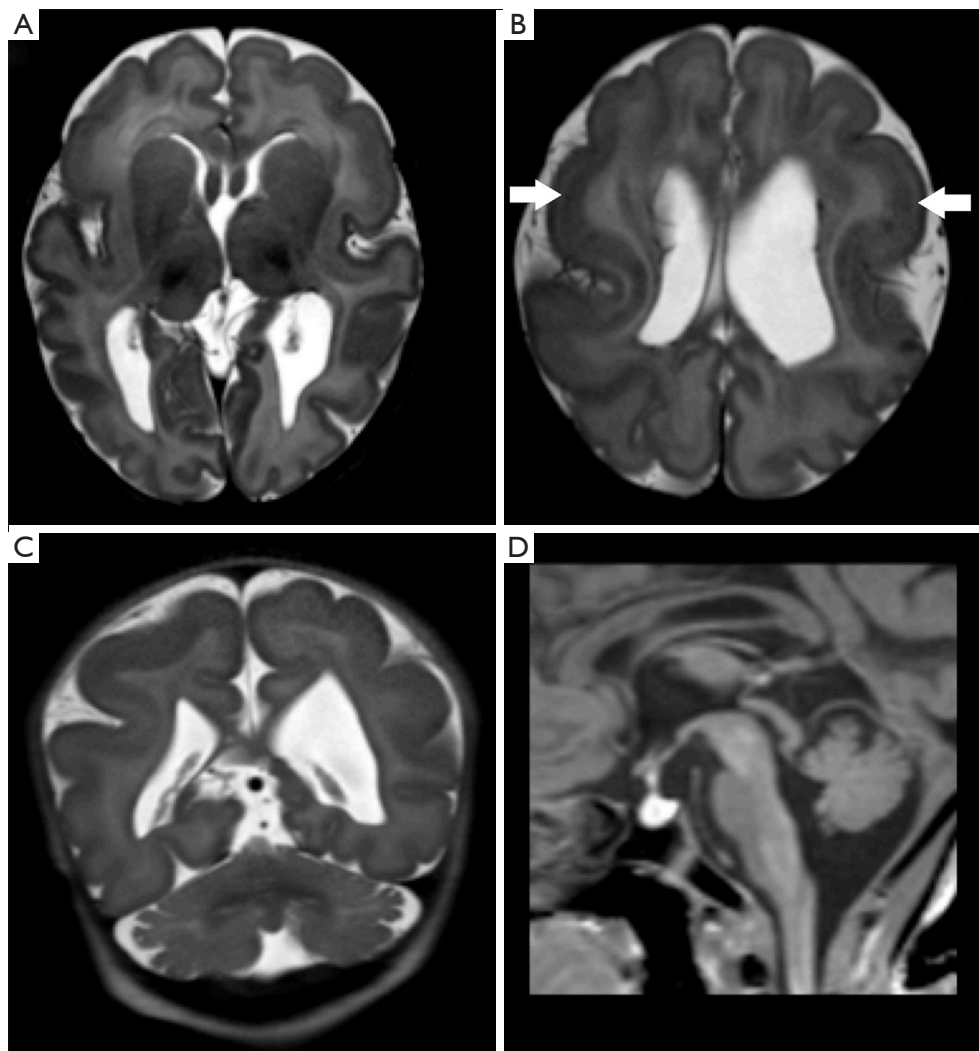


Figure 9 TUBB2B-related lissencephaly. (A,B) Axial T2-weighted images show anterior predominant pachygyria with thin cortex and underlying SBH (white arrows). There is also absence of the anterior limb of the internal capsule with fusion of the caudate head and lentiform nucleus bilaterally. The ventricles are asymmetrically enlarged; (C) coronal T2-weighted and (D) sagittal T1-weighted images show pontocerebellar hypoplasia as well as mild hypoplasia of the corpus callosum. SBH, subcortical band heterotopia.

DCX and LIS1 (74,75). Binding of DCX to microtubule is regulated by CDK5 (75). Disruption of CDK5 function results in abnormal layering of cortical and cerebellar cortices in murine models (76-78). The *CDK5*-mutant mouse exhibits an inverted cortical lamination, similar to those seen in reeler mutant mice (79). This is not surprising as CDK5 is a downstream target of the reelin signalling pathway.

In 2015, Magen *et al.* discovered a novel homozygous splice site mutation in *CDK5* which gives rise to a lethal form of LIS with cerebellar hypoplasia (72). All affected patients showed severe LIS with complete agyria, severe

cerebellar hypoplasia and corpus callosal dysgenesis (72). On histopathological examination, a combination of two-layer lamination (similar to that observed in *TUBA1A*-associated LIS) and three-layer lamination (reminiscent of *ARX*-related LIS) was seen (80).

Kinesin superfamily genes (KIF2A, KIF5C)

Kinesin uses energy released from ATP hydrolysis to power directional progression along microtubule cytoskeleton, a crucial step in neuronal migration. They are also essential in

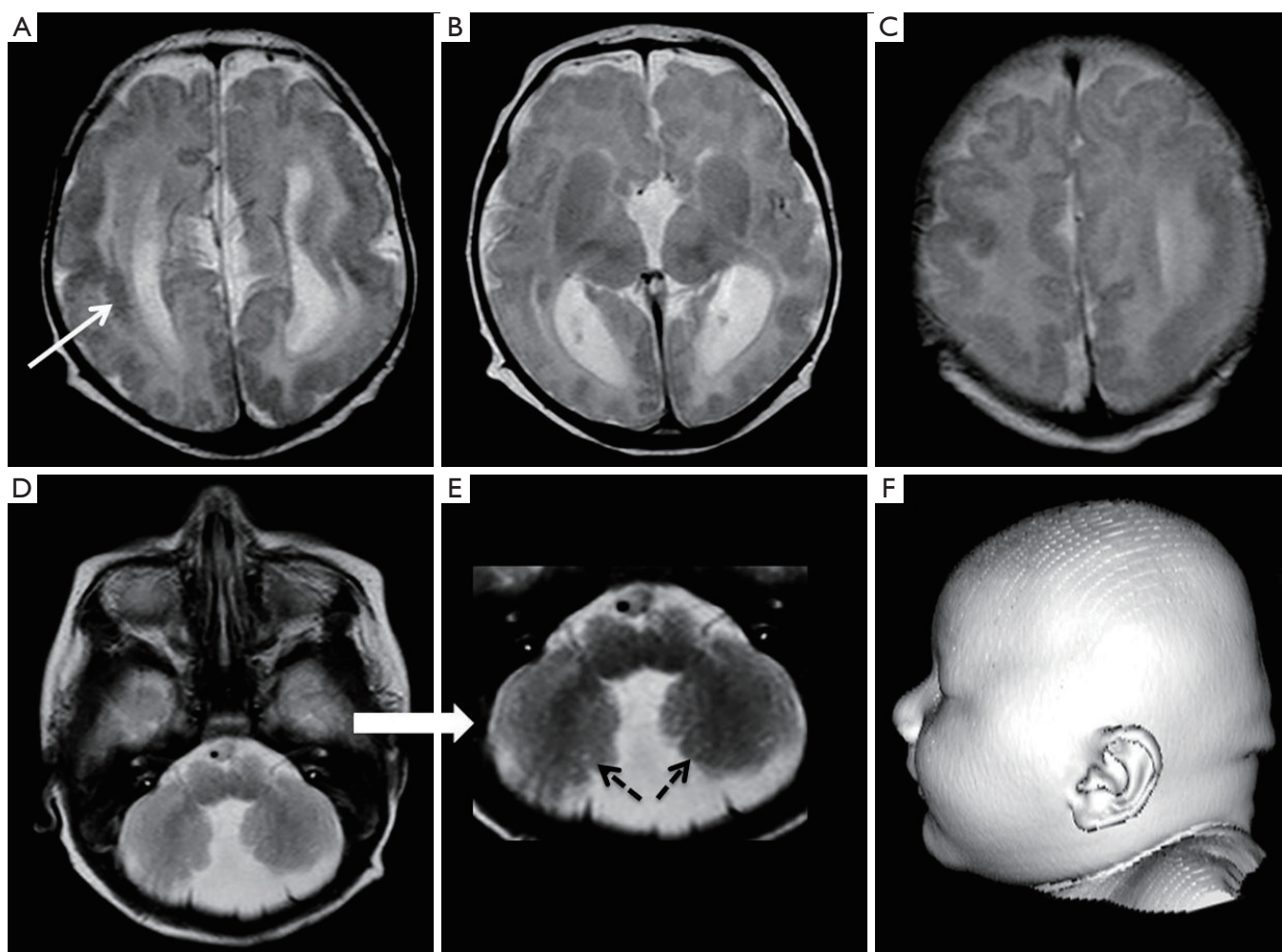


Figure 10 TUBA1A-related lissencephaly. (A-C) Axial T2-weighted images show bilateral central pachygyria-polymicrogyria with subcortical band of heterotopic grey matter (thin white arrow in A). There is also fusion of the caudate head and lentiform nucleus bilaterally due to absence of the anterior limb of the internal capsules. Complete corpus callosum agenesis is noted with colpocephaly; (D,E) axial T2-weighted image across the posterior fossa shows hypoplasia and abnormal shape of the pons. The cerebellar vermis is deficient with dysplasia of the cerebellar hemispheres and the presence of tiny cerebellar hemispheric cysts (black arrows in E); (F) 3D CT image shows severe microcephaly.

neuronal proliferation and post-migrational development. Recently, kinesin superfamily proteins were also found to play an important role as microtubule stabilizers and depolymerizers (81).

There are limited reports on kinesin-related LIS in the literature (15,82-85). Thus far, four patients with posterior predominant LIS, normal posterior fossa structures and variable degree of microcephaly were reported to harbour mutations of *KIF2A* gene involving the Ser317 and His321 residues (postulated mutation hotspots) (15,86). This pattern of LIS is similar to that related to *LIS1* gene. One

of the reported patients also has hypoplasia of the corpus callosum (15). All four reported patients have spastic tetraplegia and three out of the four patients have visual symptoms (cortical blindness and nystagmus) (86). *KIF2A*-null mice were found to have multiple brain abnormalities, including cortical lamination defects (87).

The *KIF5C* gene was recently established as a rare genetic cause of regional or focal pachygyria. Microcephaly may also be present. Thus far, only six cases were reported (15,84,85,88,89). Pathogenic variants of *KIF5C* produce kinesin proteins that are incapable of hydrolyzing ATP,

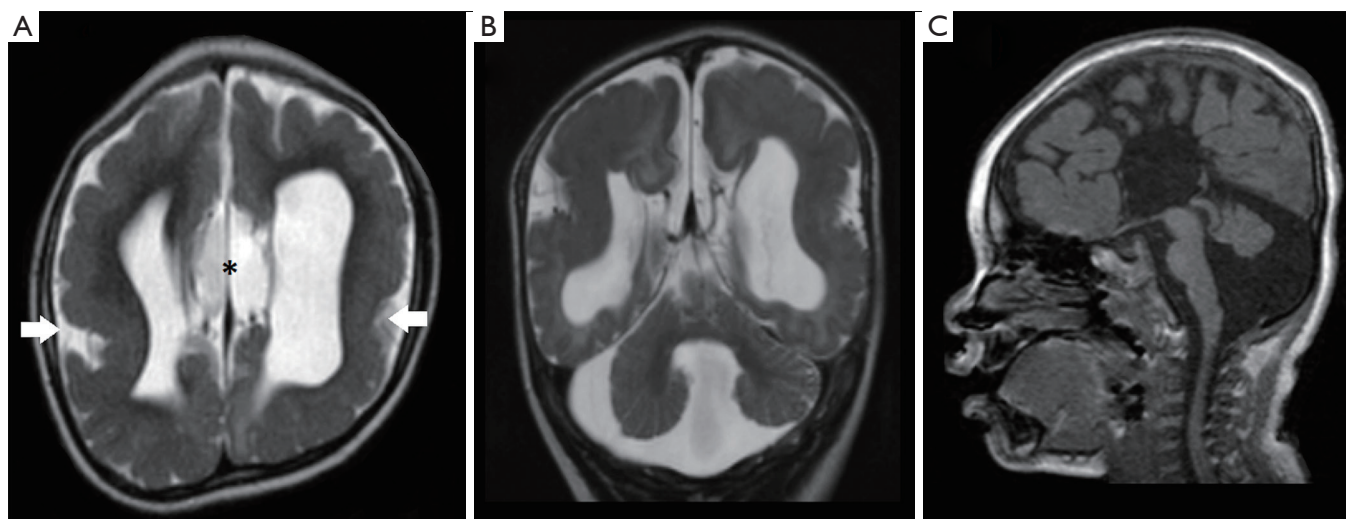


Figure 11 X-linked lissencephaly with abnormal genitalia (XLAG). This child presented with intractable seizures soon after birth and was noted to have micropenis and bilateral undescended testis on examination. (A) Axial T2-weighted; (B) coronal T2-weighted and (C) sagittal T1-weighted images show a simplified gyral pattern and perisylvian pachygyria (white arrows in A), along with hypoplasia of the brainstem, vermis and cerebellar hemispheres. There is complete agenesis of the corpus callosum with an interhemispheric cyst (*). Of note is also the presence of microcephaly.

resulting in failure of energy production crucial for directional movement along microtubules (90). Imaging revealed the presence of subtle LIS in all patients with a distinctive frontal distribution in five out of six patients (89). Only one reported patient had a posterior predominant LIS (88). Other reported MRI findings include mild ventriculomegaly and corpus callosal dysgenesis.

DYNC1H1 gene

Mutations in *DYNC1H1* have been associated with posterior-predominant pachygyria, PMG, nodular heterotopia, hypoplasia of the corpus callosum, microcephaly and basal ganglia malformation, as well as peripheral neuropathy (15).

Missense mutations in *DYNC1H1* have been reported in association with Charcot-Marie-Tooth disease (91) and spinal muscular atrophy (92,93). More recently, *de novo* missense mutations were reported in two individuals with intellectual disability and cortical malformations (93,94).

NudE homologues (*NDE1*, *NDEL1*)

LIS1 and its binding protein (*NudE* homologues) were found to have essential roles in the regulation of cytoplasmic dynein function and localization (95,96). They also play crucial roles in microtubule regulation and determination of

cell polarity (97).

Mutations of *NDE1* result in severe microcephaly with a simplified gyral pattern, agenesis of the corpus callosum, and cerebellar hypoplasia (98,99). In 2011, Bakircioglu *et al.* identified 2 different homozygous truncating mutations in the *NDE1* gene in affected members of 3 consanguineous families with LIS and extreme microcephaly (99). In the same year, Alkuraya *et al.* independently identified 2 homozygous truncating mutations in the *NDE1* gene in affected members from 2 consanguineous Saudi Arabian families with LIS (98). In two related Turkish patients with microhydranencephaly, hypoplasia of the corpus callosum, cerebellum and brainstem hypoplasia, Guven *et al.* identified a homozygous intragenic deletion in the *NDE1* gene (100). Both patients had extreme microcephaly, profound motor and mental retardation.

CRADD gene

The *CRADD* gene encodes a protein which is essential for activation of caspase-2-mediated programmed cell death (101). In 2016, Di Donato *et al.* reported six cases of mild “thin” LIS (TLIS) variant with megalencephaly and intellectual disability due to loss of *CRADD* function (10). The constellation of findings in these patients suggested reduced apoptosis as an important pathomechanism which

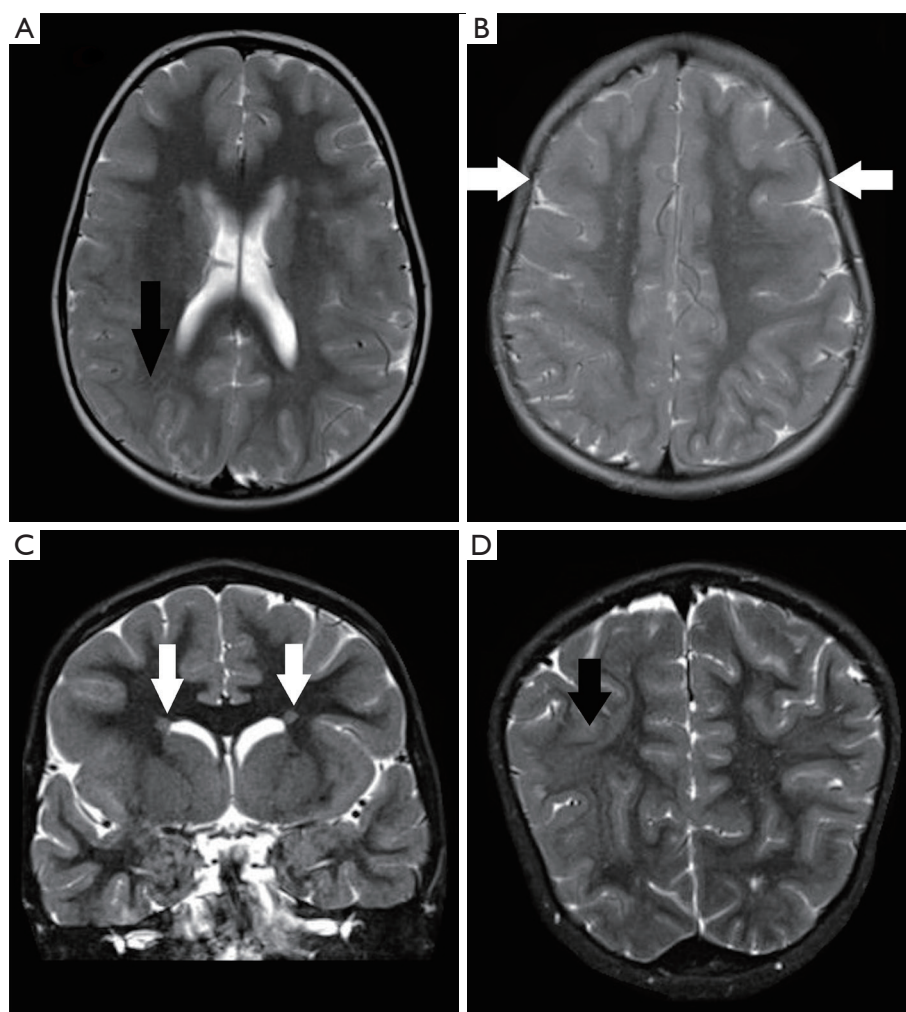


Figure 12 Actin-isoform gene-related lissencephaly. (A,B) Axial T2-weighted and (C,D) coronal T2-weighted images show subtle anterior pachygyria/simplified gyral pattern (white arrows in B) with posterior SBH (black arrows in A and D). Bilateral frontal periventricular nodular heterotopia (white arrows in C) is also observed. SBH, subcortical band heterotopia.

underlies the observed cortical malformation. The role of CRADD/caspase-2 signalling in cortical development needs further investigation and may be related to reduced synaptic elimination and decreased neuronal apoptosis.

Actin isoform genes (ACTB, ACTG1)

ACTB and *ACTG1* encode β - and γ -actin respectively, two of the six actin isoforms widely expressed in non-muscle cytoplasmic actin. In addition to microtubules, the actin cytoskeleton is also important for neuronal migration (102,103). Disruption of the actin cytoskeleton likely interferes with the shape alteration and leading process

function during neuronal migration.

Anterior predominant pachygyria is seen in majority of patients with *ACTB* and *ACTG1* mutations, reminiscent to that seen in male patients with pathogenic variants of *DCX* gene (104,105). SBH or periventricular heterotopia may also be present (105,106) (*Figures 12,13*). The lateral ventricles may be mildly prominent but the hindbrain is usually normal. The corpus callosum may be absent or appear short and thick (107). Recently, Di Donato *et al.* reported seven patients with *ACTG1* mutations. Four of these patients exhibited a highly similar imaging phenotype, characterised by frontal predominant pachygyria merging with posterior predominant band heterotopia. MRI brain of two other patients showed

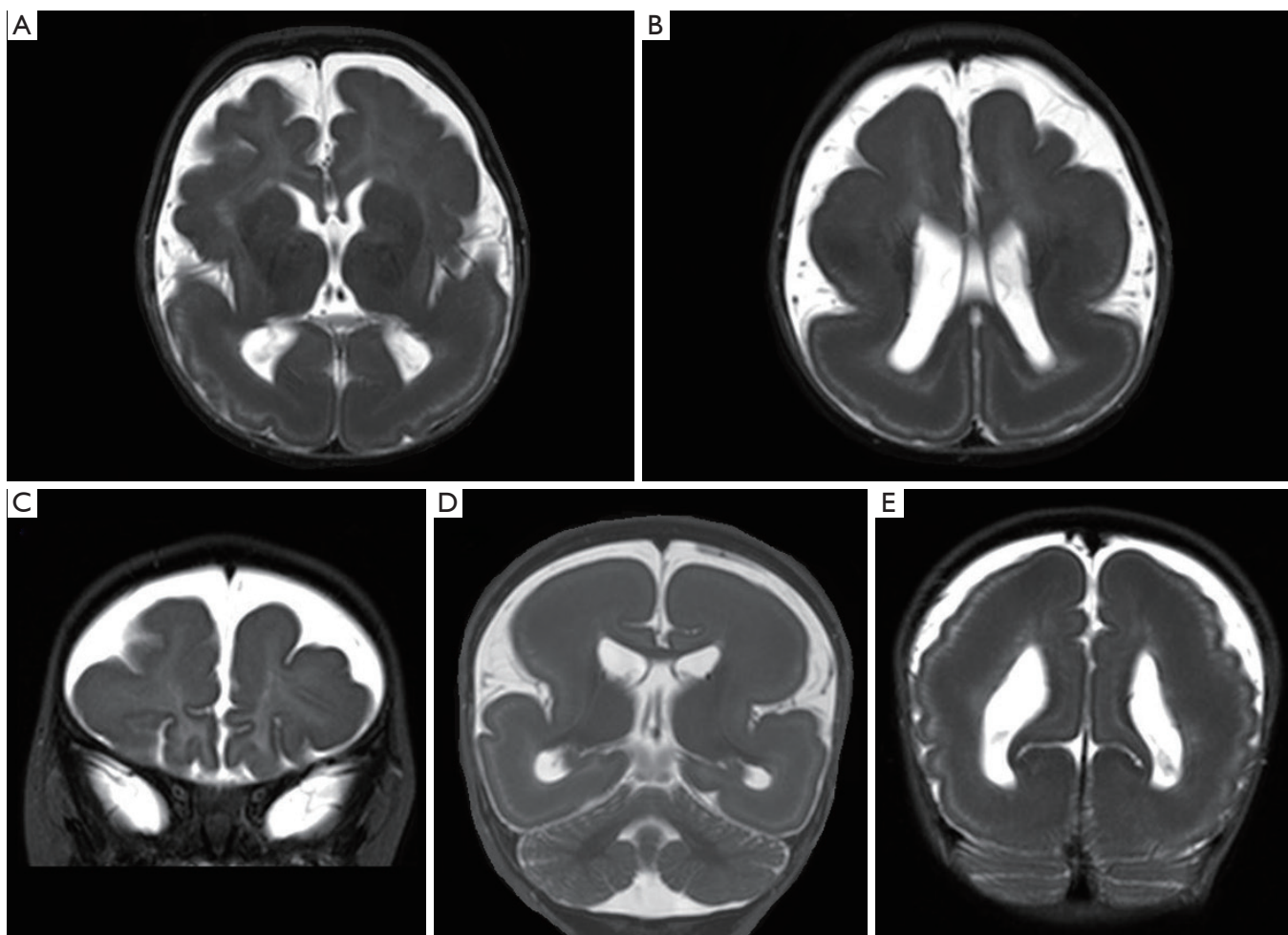


Figure 13 Actin-isoform gene-related LIS. (A,B) Axial T2-weighted and (C-E) coronal T2-weighted images demonstrate frontal predominant pachygyria merging with posterior subcortical band heterotopia. Mild ventriculomegaly is also noted. The cerebellar hemispheres are normal. LIS, lissencephaly.

bilaterally simplified gyration in the frontal lobes (108).

Gain-of-function missense mutations in *ACTB* and *ACTG1* genes are associated with BWS (109). BWS is characterized by typical craniofacial features and intellectual disability. Typical craniofacial features were reported to be more prominent in patients with *ACTB*-associated BWS, while LIS is more common in patients with *ACTG1*-associated BWS (108). Genetic testing for *ACTB* and *ACTG1* mutations should be carried out in patients with anterior predominant LIS but do not harbour *DCX* mutations.

Conclusions

Mechanisms underlying LIS map onto molecular processes/

pathways and are interdependent on one another, explaining the wide array of clinical and imaging phenotypes. The continuous advancement in the field of molecular genetics in the last decade has led to identification of at least 19 LIS-related genes, most of which are related to microtubule structural proteins (tubulin) or MAPs. We have brought together current knowledge of gene mutations associated with LIS in an attempt to provide a comprehensive genotype-phenotype correlation. This is crucial to facilitate a more targeted genetic testing in patients with LIS. Identification of an underlying genetic etiology could have important implications for the affected individual and their family. Greater understanding of the genetic basis and molecular pathways associated with LIS may also lead to

advances in diagnosis and treatment.

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Footnote

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