

## Lissencephalic syndromes: brain and beyond

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## 1. ABSTRACT

Lissencephaly has been long maintained a malformation involving only the brain. Classic lissencephaly includes agyria and pachygyria and it is the most severe form of malformations derived from abnormal neuronal migration. It is defined as a smooth or nearly smooth cerebral surface with absence of normal sulci and gyria. It encompasses a group of syndromes which show many different clinical conditions. Four groups are actually distinguished: classic lissencephaly variants, other lissencephalies including forms with unknown pathogenesis, microlissencephaly spectrum and Cobblestone cortical malformations. Several genes and proteins are involved in this syndromic spectrum and each year new molecular data are reported in the literature: classifications in this sense are always in progress. Lissencephaly now is recognised to involve not only the brain but also several other organs and districts including eyes, face, muscles, genital organs, heart and bones. Mental retardation and different form of epilepsies usually drug-resistant are the main clinical signs. The Authors in this topic discuss on this subject, underlying the different forms of lissencephaly their wide heterogeneity and the complex involvement of several organs.

## 2. INTRODUCTION

The **development of the human cerebral cortex** is extremely complex. It can be grossly broken down into three main steps: cell proliferation; cell migration; and cortical organisation. The whole process involves a relevant number of neurons, which initially *proliferate* in the germinal zones, within and adjacent to the walls of the lateral ventricles (proliferative ventricular zones), then *migrate* - mainly radially - along various pathways to their final destination (i.e., the developing cortex) where they disengage from the guide cells (1, 2). Either during migration or after migrating into the proper cortical layer, these cells extend neurites and establish synaptic connections (*cortical organisation*) (1).

Disruption of any of these steps produce characteristic morphologic disturbances, typically abnormal sulcation and gyral patterns, that allow them to be classified into distinct entities which have been designated **malformations of cortical development (MCD)** (1). The analysis of MCD has been very useful clinically and in helping genetic counselling and has greatly aided our understanding of the process of brain development. Genetic studies have identified several of the genes associated with

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**Table 1.** Genes and proteins involved in the spectrum of lissencephalic syndromes

<i>LISI</i> gene or <i>PAFAH1B1</i> gene (alpha subunit of the intracellular 1b isoform of the platelet activating factor acetylhydrolase) - located on chromosome 17 p13.3	It is expressed predominantly on foetal and adult brain; it regulates the motor microtubular cytoplasmic protein “ <i>dynein</i> ”
<i>DCX</i> (double cortex) gene or <i>XLIS</i> gene (X-linked lissencephaly) – located on chromosome Xq22.3	It regulates polymerization and stabilization of microtubules and the motor microtubular cytoplasmic protein “ <i>dynein</i> ”
<i>TUBA1A</i> gene (Alpha tubulinic complex) – located on chromosome 12q12-q14	It causes reduction of GTP tubulin binding and of heterodimers of tubulin 2; it regulates the motor microtubular cytoplasmic protein “ <i>dynein</i> ”
<i>RELN</i> gene (Reeler mutant mouse) – located on chromosome 7p22	It encodes a large extracellular matrix protein with 3460 aminoacids that is secreted by Cajal-Retzius cells 1 in the pre-plate.
<i>VLDLR</i> gene (very low density lipo-protein receptor) -	This gene encodes for the Very Low Density Lipo-protein Receptor.
<i>ARX</i> gene (Aristaless) – located on chromosome X p22.13	It is a transcription factor expressed in forebrain which regulates proliferation and differentiation of neuronal precursor and it is involved in the tangential migration of interneurons from ventral regions to the developing cortex
<i>14-3-3e YWHAE</i> gene – located on chromosome 17p13.3	This gene belongs to the 14-3-3 family of proteins that bind phosphoserine and phosphothreonine to other proteins.

MCD which may disrupt each of the main stages of cell proliferation and specification, neuronal migration and late cortical organisation.

In this review we will focus on **Lissencephaly** (including agyria and pachygyria), which is the most severe of the known malformations from abnormal neuronal migration.

### 3. NEURONAL MIGRATION

The cortical neurons originate from neural progenitors through mitotic divisions. They are guided, in their migration process, across the cerebral walls toward the cortex by the ascending fibres of radial glial cells, which extend their axonal and dendritic prolongations from the ventricular zone to the subglial layers across the intermediate zone, the subcortical zone and finally the cortical plate, from which the two to six layers of cortical cortex are formed. The neurons migrating first will stop in the deepest cortical layers, those migrating after overpass the layers formed previously to form the more superficial cortical layers according to a migration scheme defined “inside-out”.

#### 3.1. Malformations from abnormal migration: *Lissencephaly spectrum*

In this group of malformations, neurons begin migration but are unable to complete it.

*Lissencephaly* is a rare and severe form linked to abnormal neuronal migration. Less severe defects in the same genes and developmental process result in **subcortical band heterotopia (SBH)**, a brain cortical malformation, likely due to premature arrest of neuronal migration, characterised by the presence of symmetrical and bilateral bands of heterotopic gray matter located between the ventricular wall and the cortical mantle and clearly separated from both.

One of the first descriptions of a lissencephalic patient belongs to Dr. Earl Walker, who, in 1942, reported the anomaly in a child (3). In his original description Dr Walker gave a vivid description of the phenomenon:..... “when, for some unknown reason, the human brain stops its evolution at a stage in embryonic life, it becomes possible to see certain primordial

*characteristics of the brain structure. A state in the development of human brain at which arrest is rarely seen, is represented by lissencephaly, or agyria. It is the usual condition of the adult brain of reptiles and lower animals, but is not seen in the primates, of which even the lowest representation have some evidence of fissuration of the cerebral cortex.....” (3).*

Lissencephaly is defined as a smooth or nearly smooth cerebral surface, with anomalous development of cerebral gyri (4-7). The anomaly encompasses a spectrum of different malformations: from the absence of (agyria or *complete Lissencephaly*), to few, broad, flat gyri (pachygyria, *incomplete Lissencephaly*) and merges in the *subcortical band heterotopia* (6,7).

To date, mutations of six genes have been associated with lissencephaly including *LISI*, *DCX*, *TUNA1A*, *RELN*, *VLDLR* and *ARX*, whereas co-deletion of *YWHAE* with *LISI* appears to act as a modifier locus.

In table 1 we summarised the main genes and proteins so far involved in the spectrum of the Lissencephalic syndromes.

### 4. PATHOGENESIS OF LISSENCEPHALY

The genes and the protein products summarised in Table 1 are strongly involved in the process of neuronal migration, thus an impairment of any of these genes can cause abnormalities of such process.

Infectious diseases (in particular cytomegalovirus) or ischaemic events, acting during a particular moment of neuronal migration, can also cause similar cerebral abnormalities.

Hereby we report some specific examples of migration failure due to known gene abnormalities (8-12).

The proteins coded by the *LISI*, *DCX* and *TUBA1A* genes all regulate microtubule and cytoplasmic dynein function and – at least for *LISI* – interfere with neuronal migration by blocking microtubule-directed nuclear movement in ventricular zone neuroblasts, conversion of nascent post-mitotic neurons to multipolar pre-migratory cells, and conversion of multipolar to bipolar

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**Table 2.** Main groups of lissencephalic syndromes

Lissencephaly variants
Other (AR) Lissencephalies [including forms with unknown pathogenesis]
Microlissencephaly spectrum
Cobblestone cortical malformations

migratory cells.

Abnormalities in the *RELN* gene, which encodes for a large extra-cellular matrix protein (reelin) secreted by the Cajal-Retzius from the marginal zones, hinders the younger neurones to overpass the neurons generated earlier and thus to overpass the subcortical zone. Reelin, is critical for the normal disengagement of migrating neurons from radial glial cells: as a consequence of that neurons migrated more recently will stop in their migratory process below those migrated first. The final result of the impaired process will be an inversion (with disorganisation) of the normal cortical stratification (8). Patients with *RELN* (and *VLDLR*) mutations have less cortical thickness, absence of a cell-sparse zone and profound cerebellar hypoplasia (*Lissencephaly with cerebellar hypoplasia* or **LCH**; see below).

Mutations of *ARX* are a rare cause of lissencephaly. This gene is a transcription factor expressed in the forebrain, which acts as regulator of proliferation and differentiation of neuronal progenitors and it is involved in the tangential migration of interneurons from ventral regions to the developing cortex (the severe seizures associated with less severe mutations of this gene – i.e., cryptogenic infantile spasms - are presumably related to a severe deficiency of inhibitory interneurons). Patients with *ARX* mutations have also abnormalities of the basal ganglia and absence of the corpus callosum.

Recently, Vallee and Tsai reported, on the basis of studies with neural progenitors and non-neuronal cells, that classical Lissencephaly is related to anomalies of cytoplasmic dynein function, involving not only cell migration but also division and morphogenesis (12).

## 5. CLASSIFICATION

Overall, the main clinical phenotypes associated to mutations in these six (plus one) genes (Table 1) include: (a) isolated lissencephaly sequence (**ILS**) (*DCX* in males, *LIS1* and rarely *TUBA1A*); (b) subcortical band heterotopia (**SBH**) (*DCX* in females and rare males, and *LIS1*); (c) Miller-Dieker syndrome (**MDS**) (co-deletion of *LIS1* and *YWHAE*); (d) mild lissencephaly with cerebellar hypoplasia (**LCH**) the “*disequilibrium syndrome*” (*RELN* and *VLDLR*); and (e) X-linked lissencephaly with abnormal genitalia (**XLAG**) (*ARX*).

Careful review of brain imaging and other clinical features can distinguish these syndromes and usually the causative gene (Table 1).

Following a recent classification these clinical phenotypes (including also the forms so far unclassified and the forms caused by yet unknown genes or with unknown pathogenesis) have been tentatively re-classified

in four broad clinical groups identified according to the gradient and size of the anomalies of cerebral stratification and the involvement of associated extra-cerebral structures: (a) gradient anterior versus posterior; (b) brain size; and (c) involvement of other structures beyond the brain (13). Classifications in this topic are always in progress since new forms and molecular data are frequently reported in the literature.

In Table 3 we summarised the main genes, the anatomical patterns and the clinical phenotypes involved in the clinical spectrum of lissencephalic syndromes.

In the following sections, we will focus on the main forms of Lissencephaly and lissencephalic syndromes: (classical) Lissencephaly; Other autosomal recessive Lissencephalies (including forms with unknown pathogenesis); Spectrum of Microlissencephaly; and Spectrum of Cobblestone cortical malformations.

### 5.1. Lissencephaly

#### 5.1.1. Classical Lissencephaly (LIS type 1) [the agyria-pachygyria complex or isolated lissencephaly sequence (ILS)] including Miller-Dieker syndrome (MDS) [Lissencephaly variants]

The clinical spectrum of *Classical Lissencephaly* (LIS type 1; OMIM # 607432) is characteristic. The signs and symptoms are mainly confined to the central nervous system (CNS) [the characteristic brain anomalies are the *isolated lissencephaly sequence (ILS)* or the *subcortical band heterotopia (SBH)*] (Table 3) and include mental retardation (often severe), and different forms of seizures and epileptic syndromes including West syndrome and severe partial complex seizures (14,15). Usually the age of onset, the subtype of cortical malformation (i.e., ILS or SBH) and severity of the clinical syndrome may vary depending upon the severity of the cortical malformation and the underlying genetic cause (4,16-23).

Some patients with classical (*autosomal dominant-AD*) ILS or SBH have a defect in the *LIS1* or *PAFAH1B1* gene (see Table 1 and 3), which was the first human neuronal migration gene to be cloned. It encodes the non-catalytic alpha sub-unit of the intracellular 1B isoform of platelet activating factor acetylhydrolase (PAFAH1B1), which is expressed both in foetal and adult brain and interacts with tissues to suppress microtubule dynamics.

Other patients with classical ILS or SBH (currently estimated to be about 20%) have mutations of the *DCX* gene (Table 1 and 3). These cases have been also classified as having *X-linked lissencephaly (LISX1)* or *double cortex (DC) syndrome* (OMIM # 300067), because abnormalities in the *DCX* gene, which is located on chromosome Xq22.3 q23 and is an homologous of the calcium-calmoduline dependent kinase. The anomaly causes lissencephaly in its complete form in the male while

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**Table 3.** Main genes, patterns and phenotypes involved in the lissencephalic spectrum of disorders

Classical LIS (LIS1) and Miller-Dieker syndrome (MDS) (co-deletion of LIS1 and YWHAE genes)	<i>LIS with posterior &gt; anterior gradient</i>	ILS p > a □ LCH : same as ILS with additional mild cerebellar hypoplasia □ SBH p > a [ <i>LIS1</i> gene; <i>TUBA1A</i> gene; other unknown genes]
	<i>LIS with anterior &gt; posterior gradient</i>	ILS a > p SBH a > p or no gradient Baraitser-Winter syndrome [unknown genes] [ <i>DCX</i> gene; other unknown genes]
XLAG		XLAG [ARX-related Lissencephaly] XLAG-like syndrome and eye abnormalities
LCH		LCH with severe LIS, ACC, severe CBL hypoplasia
Other (autosomal recessive) Lissencephalies		LIS with mild frontal pachygyria (AR); LCH with mild frontal pachygyria, hippocampus hypoplasia and severe cerebellar hypoplasia (caused by <i>RELN</i> and <i>VLDLR</i> gene mutations)
Severe congenital microcephaly with LIS (Microlissencephaly spectrum)		Barth microlissencephaly syndrome Norman-Roberts syndrome (NRS) : severe congenital MIC, severe LIS with normal corpus callosum, and normal cerebellum MOPD type 1, (microcephaly osteodysplastic primordial dwarfism)
Cobblestone cortical malformations		WWS; MEB; FCMD; □ [ <i>FCMD</i> , <i>FKRP</i> , <i>LARGE</i> , <i>POMGnT1</i> , <i>POMT1</i> , <i>POMT2</i> genes] □ GPR56-related bilateral fronto-parietal cobblestone-like cortical malformation □ Debré-type (AR) cutis laxa with CDG type 2 glycosylation defect and COB-like dysgenesis

LIS = lissencephaly; ILS = isolated lissencephaly sequence; LCH = lissencephaly plus cerebellar hypoplasia; p = posterior; a = anterior; MDS = Miller-Dieker syndrome; SBH = subcortical band heterotopia; XLAG = X-linked lissencephaly with abnormal genitalia; ACC = absence of corpus callosum; COB = Cobblestone lissencephaly; MOPD = microcephaly osteodysplastic primordial dwarfism; NRS = Norman Roberts syndrome; WWS = Walker Warburg syndrome; MEB = Muscle Eye Brain disease; FCMD = Fukuyama Congenital Muscular Dystrophy

in the heterozygous females result in a *double cortex*, with areas of cerebral tissue located within the white matter. This is due to the normal random inactivation of the X chromosome (*lyonisation*) occurring in females (*functional mosaicism*). The abnormal Xq22.3q23 gene (when is not compensated by its normal homologous copy because of random inactivation of the X chromosome), does not allow a normal neuronal migration: thus, the neurons harbouring the X-linked mutation in the non-inactivated X chromosome can not reach their final destination; on the contrary, the neurons containing a normal copy of the gene (whose abnormal counterpart is contained in the inactivated X chromosome) can normally migrate to the brain cortical surface (24). This “double stepped” impaired process of migration originates two bands of cortex separated by a layer of white matter (i.e., a double cortex). In males, the abnormal Xq22.3q23 is not compensated by the Y chromosome, and thus it results in a complete lissencephalic phenotype.

Rare patients with classical (autosomal dominant) ILS or SBH have been reported to have also mutations in the *TUBA1A* gene (Table 3) (also known as LIS3 or Lissencephaly 3; OMIM # 611603). These patients may also have additional brain abnormalities including thin corpus callosum, hypoplasia of the cerebellar vermis, abnormal hippocampus, and severe ventricular dilatation.

No facial dysmorphism is seen in children with mutations in the *LIS1*, *DCX* and *TUBA1* genes.

A fourth subset of the classical Lissencephaly group, harbours chromosome 17p13.3 (*LIS1* gene) and *YWHAE* gene co-deletion (*microdeletion syndrome*) (see Table 1 and 3): such individuals have characteristic facial dysmorphism consisting in microcephaly with high and prominent forehead, temporal bone receding with bitemporal hollowing, short nose with upturned nostrils,

thick lips, with edge downward and thin vermilion border of the upper lip and small jaw and are classified as having the **Miller-Dieker syndrome (MDS)** (OMIM # 247200).

Mutations of the *LIS1* (including deletions), *DCX* and *TUBA1A* genes, which account for 65%, 12% and an unknown but small percent of patients with lissencephaly, respectively, lead to the classical form of lissencephaly in which cortical thickness is increased fourfold (3.5-4 mm to 12-20 mm) and produce a recognisable gradient in which the malformation is more severe anteriorly (*DCX*) or posteriorly (*LIS1* and *TUBA1A*) (see Table 3).

The **Baraitser-Winter syndrome**, first reported in 1988, is a rare complex malformation syndrome in which *classical Lissencephaly (LIS type 1)* is associated to peculiar clinical features including microcephaly, trigonocephaly, (sometimes unilateral) coloboma of the iris (associated or not with microphthalmia and microcornea), ptosis with virtual absence of folding of the eyelids, downslanting of the palpebral fissures, hypertelorism, wide and flat nasal bridge, large mouth, postnatal growth retardation and mental retardation (25). Several patients have sensorineural hearing loss, congenital heart disease (mostly valvular defects) and musculoskeletal anomalies (including pectus excavatum and short sternum). Additional structural brain anomalies, besides LIS type 1, are focal pachygyria, lobar holoprosencephaly, generalised bilateral cerebral atrophy, thin corpus callosum, and occipital and temporal ischemic lesions.

### 5.1.2. X-linked Lissencephaly with abnormal genitalia (XLAG) (ARX-related lissencephaly) (ILS or SBH)

Berry-Kravis and Israel reported in 1994 a patient with X-linked lissencephaly with agenesis of corpus callosum and ambiguous genitalia (26). They found mutations of the *ARX* gene in this family. Now, is well known that this gene is responsible for the X-link

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**Figure 1.** (a, b, c): photos of three brothers affected by X-Linked Lissencephaly

lissencephaly with abnormal genitalia (**XLAG**). This form is also known as X-linked lissencephaly type 2 (**LISX2**; OMIM # 300215). Mutations in the **ARX** gene are also responsible for the entity known as corpus callosum agenesis (and abnormal basal ganglia) with abnormal genitalia (**ACC with abnormal genitalia** or Proud syndrome; OMIM # 300004) and for the cryptogenic infantile spasms.

The XLAG appear to be a separate type of lissencephaly. All affected patients to date have been genotypic males, and all have had normal head size at birth with severe microcephaly developing over the first months of life, intractable neonatal onset epilepsy, poor temperature regulation, chronic diarrhoea, and ambiguous and underdeveloped genitalia. Related females may have mental retardation and epilepsy, and in such cases often gave agenesis of the corpus callosum. Imaging studies show anterior pachigyria, with only a few, shallow, sulci, and posterior agyria. The cerebral cortex is usually thicker than normal (6 to 7 mm in thickness) but is thin compared to that observed in lissencephaly secondary to **LIS1** and **DCX** mutations. The corpus callosum is always completely absent and the basal ganglia are either small or dysplastic or completely absent. The brainstem and cerebellum are normal.

We are also aware of an **additional form** of **XLAG** with the same brain anomalies recorded in the classical XLAG plus eye malformation.

In 1990 one of us (**LP**) reported the first case in

the literature, of a possible case of of X-LINKED lissencephaly (27). In this family the molecular diagnosis was not performed but the clinical and anatomical picture were consistent with the diagnosis of (**LIS X1**). Briefly, in this family the parents were unrelated and lived in a small town in Sicily. Their first three pregnancies resulted in affected sons. Diagnosis was made by means of cranial computer tomography (CT) in the second child and CT coupled with autopsy findings in the third. Overall, the clinical manifestation and course were similar in all the three children. Birth weight was between the 3<sup>rd</sup> and 5<sup>th</sup> percentile; OFC was in the 25<sup>th</sup> percentile. All suffered from neonatal respiratory distress, congenital hypotonia and poor feeding. Seizures were present since between the 1<sup>st</sup> and 2<sup>nd</sup> month of life, without response to anticonvulsant treatment. The grade of lissencephaly was 3. All children died by the age of 8 months, one after the other.(Figure 1) Brain CT showed smooth cerebral surface, with scattered abortive gyri, undeveloped opercula, thick cortex and diminished white-gray interdigitations. The lateral ventricles were dilated posteriorly, consistent with a persistent foetal configuration (colpocephaly). At autopsy the third child showed cortical agyria, prevalently frontal and pachigyria posteriorly; on coronal sections, the cortex was abnormally broad with few sulci. Microscopic examination showed a typical four layered agyric cortex in the frontal and parietal regions. In the temporal and occipital regions, an unusual six-layered cortex with ganglia cells radially arrayed in columns was seen (Figure 2).

### 5.1.3. Lissencephaly Variant 2 layers

A further variant with a two-layered lissencephaly, absence of corpus callosum (ACC) and cerebellar hypoplasia has been recently reported (28).

### 5.2. Other Autosomal Recessive Lissencephalies

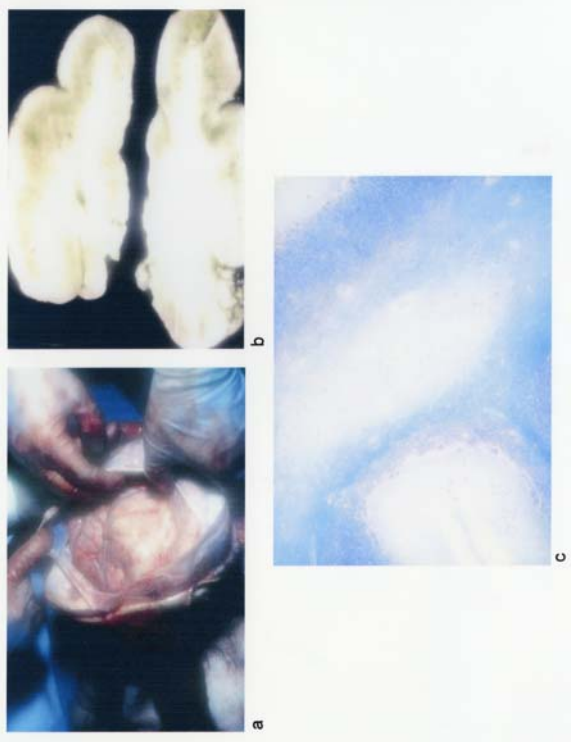
To this group belongs the entity known as *Lissencephaly with cerebellar hypoplasia (LCH)*, which is caused by mutations in the **RELN** or **VLDLR** genes (Table 3). This form encompasses the entities known as *cerebellar hypoplasia and mental retardation with or without quadrupedal locomotion (CHMRQ1; OMIM # 224050)* and the lissencephaly with cerebellar hypoplasia due to **RELN** mutations (**LCH1; OMIM # 257320**).

**VLDLR** is part of the reelin (**RELN**) signalling pathway, which guides neuroblast migration in the cerebral cortex and cerebellum. This condition appeared to represent the first example of a malformation syndrome due to a defect in a human lipoprotein receptor and the second human disease associated with a reelin pathway defect. The other is the **LCH** due to mutation in the **RELN** gene.

Affected children are usually severely compromised: hypotonic at birth with marked delay in motor and cognitive milestones, they do not sit or stand unsupported, nor they develop language. Generalised epilepsy begins at an early age; some patients have congenital limphoedema.

As a result of the defect(s) in the *reelin signalling pathway* (see also above Lissencephaly pathogenesis) the

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**Figure 2.** (a, b, c): Autopsy showing cortical agyria (a). Macroscopic (b) and microscopic (c) examination showed a typical four layered agyric cortex

normal disengagement of migrating neurons from radial glial cells is impaired and thus the cortical (and cerebellar) cortex is disorganised with layer 6 neurons closest to the molecular layer (layer 1), followed by layer 5, layer 4, etc. Imaging studies of affected children show a thickened cortex (measuring 1 cm in thickness) with too few sulci; hippocampi are incompletely rotated; the cerebellum is completely smooth, with no foliation.

### 5.3. Microlissencephaly

Microlissencephaly encompasses a group of disorders in which lissencephaly is associated to a severe reduction of head circumference (severe microcephaly) (29-30). In these patients the cranial circumference is extremely reduced (far below 2-3 SD the 3<sup>rd</sup> percentile).

The main forms of microlissencephaly are:

(a) **Barth syndrome (BS)**, a very unusual form of microlissencephaly, with severe fronto-cerebellar hypoplasia (31);

(b) **Norman-Roberts syndrome (NRS)** (also known as Lissencephaly type 2 or **LIS2**; OMIM # 257320) in which patients show a severe microcephaly, lissencephaly with normal corpus callosum and cerebellum but severe abnormalities in the hippocampus and brainstem (32). Typically, there are facial dysmorphic features (shallow face and prominent nasal bridge) not present in the MDS;

(c) A recently identified form of

microlissencephaly has been reported in which **primordial osteodysplastic dwarfism** is associated to a **severe microcephaly (MOPD type 1)** (33).

### 5.4 Cobblestone cortical malformations

The Cobblestone cortical malformations group is defined as a smooth cerebral surface with a feature similar to the stone of the Roman Cobblestone.

In Table 4 we summarised the main genes so far identified responsible of the Cobblestone phenotype; the most severe condition in this group is the **Walker-Warburg syndrome**.

#### 5.4.1. Walker-Warburg syndrome (WWS)

The Walker-Warburg phenotype is caused by abnormalities in the *POMT1* and *POMT2*, *FKTN*, *FKRP* and *LARGE* genes (34-48). About 20% of cases harbour mutations in the *POMT* genes, but probably the syndromic features are heterozygous. Individual patients have been shown to have homozygous mutations in the *FKRP* and *LARGE* genes. Some patients may have mutations in the *Fukutin (FKTN)* gene.

The syndrome is also known as **HARD +/- syndrome**, which includes hydrocephalus (**H**), agyria (**A**) and retinal dysplasia (**RD**) with (+) or without (-) encephalocele (+/- **E**) (**WWS or HARD syndrome**; OMIM # 236670).

The condition is clinically characterised by severe congenital hypotonia, ocular anomalies (including retinal detachment, persistent hypoplastic primary vitreous, retina dysplasia, congenital glaucoma, microphthalmia and optic nerve hypoplasia), testicular defects, mental retardation and drug-resistant epilepsy (49). The psychomotor developmental steps are delayed or totally absent. Affected children manifest, besides the ocular abnormalities, profound hypotonia at birth and progressive macrocephaly. In cases with the most severe neurological involvement the child usually dies within the first year of life because of severe respiratory complications.

Serum creatine kinase (CK) is usually elevated and the muscle biopsy shows changes alike congenital muscle dystrophy (**CMD**).

Brain imaging shows thickness of the cortex with few deep gyri, microphthalmia, corpus callosum hypoplasia and severe hypomyelination. The Cobblestone malformation is seen at the cortico-subcortical junction and appears irregular with several little areas of cortex migrated inside the subcortical white matter (irregular grey matter - white matter junction, reflecting the extension of bundles of disorganised cortical neurons into the underlying white matter which are separated by fibroglial vascular tissue). The characteristic of the “cobblestone” cortex may be difficult to appreciate in the hydrocephalic neonate. Besides the lissencephaly, more severe cases may have also severe pontine hypogenesis with superior and inferior collicoli and a distinctive dorsal “kink” at the mesencephalic-pontine junction, cerebellar vermis hypoplasia and dysplasia (often

**Table 4. Genes involved in the Cobblestone cortical malformations**

<p><b>FKTN</b> - located on chromosome 9q31-33 - Codifies for “<i>Fukutin</i>”, trans-membrane protein of the Golgi complex, which regulates the glycosilation of the alpha-destro-glycan carbohydrates in the skeletal muscle.</p> <p><b>FKRP</b> - located on chromosome 19 q13-32 - Codifies for a “<i>Fukutin Related Protein</i>”, which co-operates with Fukutin in the glycosilation processes of the skeletal muscle.</p> <p><b>POMTI</b> - located on chromosome 9q34 – Codifies for the “<i>protein-O-mannosyltransferase 1</i>”, which leads to the formation of the enzymes in the endoplasmatic reticule and guarantees the integrity of the muscular cell and the stability of the wall. Its absence causes defects in the myogenesis and in the structure of the muscle.</p> <p><b>POMGNTI</b> - located on chromosome 1p34 – Codifies for the “<i>protein O-linked mannose beta1,2-N-acetylglucosaminyltransferase</i>”. This protein participates in the conversion of the mannose beta 1-2 acetylalte.</p> <p><b>LARGE</b> – located on chromosome 22q12 – Codifies for the “<i>protein like-glycosyltransferase</i>”, which is implicated in the glycosilation of the alpha-destro-glycans. It is probably involved in the organization of the wall made by dysaccharides.</p>
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referred as “*cerebellar polymicrogyria*”), brainstem hypoplasia and occasionally occipital cephalocele.

From a pathogenic viewpoint the clinical features could be related to a primitive meningeal pathology, a type of *neurocristopathy*. There is evidence for two distinct developmental events: first, an early disturbance in cortex formation resulting from a disorder of radial migration and from disruption of the pial barrier; and second, a later perturbation of the organisation of the cerebral surface.

**5.4.2. Fukuyama congenital muscular dystrophy (FCMD)**

This condition is characterised by congenital muscular dystrophy (CMD) and seizures with few areas of pachygyria (FCMD; OMIM # 253800) (50-58). FCMD is an autosomal recessive condition seen primarily in children of Japanese ancestry. Its most typical CNS anomalies are of three types: (1) frontal polymicrogyria; (2) lissencephaly of the cobblestone-type; (3) temporo-occipital and cerebellar dysplasia with cysts in the cerebellar folia. In many cases, the syndrome allows a normal life with the exception of seizures.

FCMD is an autosomal recessive form of CMD caused by abnormalities in the *FKTN* gene, which encodes the protein *Fukutin*. Fukutin is a trans-membrane protein located in the Golgi complex, which regulates the glycosilation of the alpha-destro-glycan carbohydrates in the skeletal muscle. It appears that the disrupted Fukutin causes hypo-glycosilation, which abolish binding activity of destro-glycan for the ligands laminin, neurexin, and agrin and in turn affects the modification of glycosilation of *DAGI*, a cell surface protein that plays an important role in the assembly of the extracellular matrix in muscle, brain and peripheral nerves by linking the basal lamina to cytoskeletal proteins.

Histological examination of the affected muscle at various ages shows dystrophic features including fibre size variation, prominent interstitial tissue fibrosis, and adipose tissue proliferation. Inflammation, necrosis, and degeneration/regeneration of muscular fibres are less apparent. (Figure 3)

Clinically, patients with FCMD present with hypotonia and severe developmental delay; seizures develop during the first year of life in about half of affected individuals. Patients may show also ocular abnormalities including retinal dysplasia leading to myopia, nystagmus and chorioretinal degeneration to a lesser degree however

than those seen in WWS and MEB.

Brain imaging reflects the gross pathology findings: un-layered polymicrogyria, which is seen primarily in the frontal lobes, and cobblestone cortex, which is largely temporo-occipital. Most patients have also dysplasia of the cerebellar cortex with dysplastic folia and subcortical cysts usually located in the dorsal mid-portion of the cerebellar hemispheres (superior semi-lunar lobule).

**5.4.3. Muscle-eye-brain (MEB) disease**

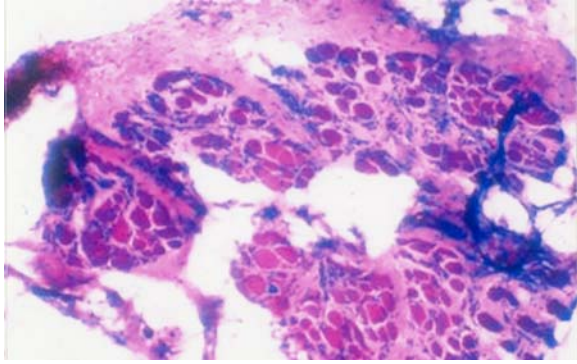
MEB disease (OMIM # 253280), originally reported by Dr Santavuori in the Finnish population, consists of a severe form of CMD, associated to retinal and other eye abnormalities and the cobblestone cortical malformation. It should be regarded as an intermediate phenotype between the WWS and the FCMD (59-62).

Brain imaging shows frontal pachygyria with less severe gyral abnormalities posteriorly and occasional agyria of the inferior occipital region. The myelinisation is delayed with irregular zones of immature myelin in the central cerebral regions. Ventricles are dilated, with brainstem hypoplasia. In 1986 one of us (LP) reported in *Neuropediatrics* with the title “Hydrocephalus, Lissencephaly, Ocular abnormalities and Congenital Muscular Dystrophy. A Warburg syndrome variant?”, a possible first reported case of MEB (62). The patient was born from unrelated parents, but three siblings were died due to severe hydrocephalus. The mother noticed that the fetal movements were feeble and polihydramnios was present. At birth, the weight, the height and the OFC were in the 90<sup>th</sup> centile. At the age of 1 month, he showed severe generalized hypotonia, hydrocephalus with CK notably elevated. At the autopsy, beyond the lissencephaly, foramen of magendie atrophy, Dandy-Walker anomaly was present. The child died at the age of 5 months.

**6. CONCLUSIONS**

In conclusion the chapter of lissencephaly is long to be ended. This anomaly is one expression with different clinical aspects involving not only the brain but others several organs. Many different genes and proteins took part in the pathologic process of this complex malformation but the role of each of these remains unsolved. The molecular defect alone can explain such a severe anomaly or other genes anomalies must be associated ? Moreover events such as infective or toxic could co-operate in causing these malformations. In the mean time new classifications of lissencephalic syndromes

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**Figure 3.** Histological examination of the affected muscle of a patient with Fukuyama congenital muscular dystrophy (FCMD). See dystrophic features including fibre size variation prominent interstitial tissue fibrosis, and adipose tissue proliferation.

are in progress following the discoveries new genes involved in the cerebral anomalies. Lissencephaly is a further example as how the morphologic defect can lead the researchers to better understand of the normal physiological process.

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**Abbreviations:** MCD: malformations of cortical development; SBH: subcortical band heterotopia; ILS: isolated lissencephaly sequence; MDS: Miller-Dieker syndrome; LCH: lissencephaly with cerebellar hypoplasia; XLAG: X-linked lissencephaly with abnormal genitalia; LIS1: Lissencephaly type 1; LIS2: Lissencephaly type 2;

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LIS3: Lissencephaly type 3; LISX1: X-linked lissencephaly; DC: double cortex; ACC: Absence of Corpus Callosum; CT: Computer Tomography; LCH: Lissencephaly with cerebellar hypoplasia; CHMRQ1: cerebellar hypoplasia and mental retardation with or without quadrupedal locomotion; LCH: lissencephaly with cerebellar hypoplasia; BS: Barth syndrome; NRS: Norman-Roberts syndrome; MOPD: microlissencephaly with primordial osteodysplastic dwarfism; WWS: Walker-Warburg syndrome; HARD: hydrocephalus, agyria and retinal dysplasia syndrome; CK: serum creatine kinase; CMD: congenital muscle dystrophy; FCMD: Fukuyama congenital muscular dystrophy; MEB: Muscle-eye-brain disease.

**Key Words:** Lissencephaly, Brain development, Neuronal migration, Review

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