Review
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Genetic Causes, Clinical Manifestations and Diagnosis of Central Nervous System Malformations with Emphasis on Corpus Callosum

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Abstract
The pathological processes of the central nervous system, intrinsic or extrinsic, occurring during the embryonic period are the most common cause of pregnancy termination. The defects of the neural tube which is primitive form of brain and spinal cord are the most common central nervous system (CNS) malformations. In some defects the fetus continues to develop and results in the birth of a child with sever mental and physical deficiencies. The corpus callosum is the largest white matter tract connecting the two cerebral hemispheres and permits the transfer of information between the two cerebral hemispheres. Its partial or complete agenesis is caused by abnormalities during embryonic development. The severity of symptoms varies widely depending on the degree of dysgenesis. Hypotonia, visual impairment, seizures, spasticity, motor co-ordination issues, and atypical facial features are common symptoms. In this review we focus on genetic causes, clinical manifestations and diagnosis of various malformations of central nervous system with special emphasis on corpus callosum.
Keywords: Central nervous system, corpus callosum, diagnosis

Introduction

Malformations result from pathological processes occurring during the embryonic period. These pathological processes could be intrinsic or extrinsic. Fetal brain malformations occur at a rate of 2–3 per 1000 pregnancies and are considered the most common cause of pregnancy termination.[1] The fetal brain begins to develop shortly after conception and continues to grow throughout pregnancy. The symptoms and prognosis of congenital brain malformations vary, depending on the type and severity. Neural tube defects (NTDs) are the most common central nervous system (CNS) malformations. The neural tube closure takes place at the fourth week post conception. The prevalence of NTDs at birth has decreased over the past few years due to the introduction of antenatal folic acid use, especially during the 1st trimester.[2]

The brain develops from the cranial part (rostral part) of the neural tube. By the end of the fourth-week of gestation three primary cerebral vesicles are differentiated from the neural tube; namely the prosencephalon (forebrain), mesencephalon (midbrain), rhombencephalon (hindbrain).[3] By the fifth week of gestation, the three primary vesicles further subdivide into five secondary vesicles; **telencephalon**, that differentiates to the cerebral hemispheres; **diencephalon**, that differentiates to thalamus, hypothalamus, posterior pituitary and the optic vesicles; **mesencephalon**, that forms the midbrain; **metencephalon,** that forms pons and cerebellum; and **myelencephalon,** that differentiates to medulla oblongata.[4] Primary and secondary cerebral vesicles in early embryonic development are illustrated in Figure 1.

Epigenetic and epigenomic focus on mechanisms governing brain and behavior development, genetic evolution, neural resilience and homeostasis. Epigenetic studies tackle the etiology of neurological conditions in addition to normal neural processes.[5] The four main epigenetic mechanisms involved in the dynamic identification of nuclear structure and genomic landscape are DNA methylation, chromatin modification, non-coding RNA editing of nuclear acids, and modification of histones.

Environmental epigenomic science explores the environmental determinants that modulate the initiation and progression of certain neurological conditions in addition to the identification of response of treatment interventions.[6] Furthermore, pharmaco-epigenomics is a new science that is interested in therapies improving recovery of cognitive, behavioral, and senso-motor functions.[7]

DNA methylation is the most common mechanism which is catalyzed by DNA methyltransferase (DNMTs) that transfers a methyl group to DNA sequence and suppresses gene-transcription. A Similar RNA counterpart (DMT2) is responsible for gene-silencing in the developmental process. The DNA methylation shows interactions with various items of epigenetic machinery and contributes to the expression of epigenetic marks essential for multigenerational inheritance.[9]

Many studies found that individual-specific DNA methylation is related to neuronal identity and specific functional development. The *De novo* methylation of DNA was found associated with the prevention of early premature development of stem cell neurons. Moreover, DNMT level is high in the nervous system of the embryo to preserve DNA methylation during the division of neural precursors. Different forms of DNMT are found in the adult brain where they enhance brain cell repair and improve cell turnover. DNA methylation organizes the time of astrocyte development by mediating the

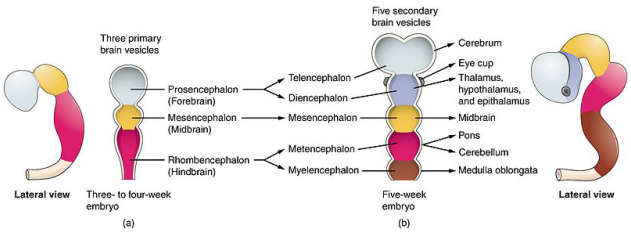

Fig. 1 **Primary and secondary cerebral vesicles (a) Three primary brain vesicles in 3–4 weeks embryo and (b) Five secondary brain vesicles in 5th-week embryo. Printed with permission.[8]**

methylenation of certain factors in the process of glial maturational genes.[10]

Epigenetics plays an important role in the identification of neural dysfunction associated with some conditions such as Rett Syndrome where the study of Mecp2 mutant mice provides substantial insight into the pathological mechanisms of the syndrome.[11]

Dynamic remodeling of the chromatin network is mediated by many enzymes and signal transportation pathways. Chromatin is formed of DNA units with proteins, histone and non-histone, responsible for 3D folding of DNA and functional regulation of the nucleus. Furthermore, the nucleus contains molecular platforms for organizing genome-wide chromatin remodeling. Histone alteration and chromatin remodeling are related to neural stem cells repair which have been linked to many cognitive and behavioral disorders.[12]

In the eukaryotic nucleus, the areas of non-protein-coding have been remarkably increased, which reflected the functional development during evolution. However, the quantity of protein-coded areas has been unchanged. Human accelerated genes (HARs) which are responsible for the evolution of humans from ancestors are identified in non-protein-coding regions of the genome, most of them adjacent to the essential neurodevelopmental genes. The most important genetic loci are HAR1, which is expressed with reelin, which participate in cortical neurons development.[13]

Two sub-types of RNA editing enzymes can modify the magnitude of expression and the functional differentiation of RNA. During neural development, RNA editing enzyme expressed changing subcellular localization within neurological development. The RNA editing can change biogenesis, maturation properties, immense gene products which play a broad variety of neurodevelopmental functions enhancing adult neural homeostasis.[14] Animal studies showed that RNA editing is important for cognitive and behavioral responses of the nervous system. Many neurological diseases as well as brain cancer were associated with deregulation of RNA editing.[15]

Several neurodevelopmental disorders, such as autism spectrum disorders (ASDs), are linked to defects in epigenetic mechanisms. Epigenetic defects such as DNA methylation at certain imprinted gene loci were found associated with neurological disorders like Prader-Willi and Angelman Syndromes.[16]

There is a considerable amount of evidence about the relation between neurodegenerative diseases and abnormalities in epigenetic mechanisms. The evidence suggested the lack of a simple Mendelian inherited pattern, dysregulation of transcriptional mechanisms as well as many pathological RNA alterations. Mechanisms such as microsatellite sequence were found important in regulating cognitive functions, circadian rhythm, and social skills.[12]

Cancer was found related to some genomes-wide epigenetic changes that enhance tumor induction, progression, invisibility, metastatic ability, and response to the treatment. Cancer epigenetic etiology is a result of multiple inter-related mechanisms such as DNA methylation, non-gene protein-coding, chromatin modifications, and editing of nucleic acids. The abnormalities in these epigenetic mechanisms enhance the silencing of tumor-suppressing genes and the activation of oncogenes. Some CNS cancers such as glioblastomas were found significantly associated with alteration in gene expression profiles that inhibit tumor-suppressing genes.[17] In this review, we highlight the genetic causes, clinical manifestations and diagnosis of different CNS malformations.

Agenesis of Corpus Callosum (ACC)

The corpus callosum (CC) is the largest white matter tract connecting the two cerebral hemispheres. It comprises 4190 million topographically organized axons. Functionally, it permits the transfer of information between the two cerebral hemispheres, and inhibits any concurrent activity in the contralateral hemisphere.[18] It contributes to cognition and behavior. Thickness of CC, fiber cross-section and bundle size increases through childhood and adolescence with slight differences among sexes. Fetal development of CC may be affected by various genetic factors and maternal alcohol abuse. Figure 2 illustrates the normal appearance of the corpus callosum in the mid-sagittal. The CC starts to develop at sixth week of gestation, and continues to differentiate to attain its shape by the eighteenth to twentieth weeks of gestation; therefore imaging of this structure before 20 weeks may not be optimal (Figure 3).[19]

In mid-sagittal views of the fetal brain (two-dimensional (2D) ultrasound) the CC appears as a thin anechoic space, lined superiorly and inferiorly by two echogenic lines. Sonographic demonstration of the CC requires careful imaging in a center with a high level of expertise to make a full assessment and exclude co-existing brain abnormalities.[20]

Among infants, 2–3% will have major CC malformations that will be detected at birth or a few weeks after birth. Agenesis of corpus callosum (ACC) is the most common abnormality affecting the CC. It can be partial or complete, isolated or complex (associated with other malformations).[21] Other abnormalities of CC are hypoplasia of CC (thinning of CC) and hyperplasia of CC (thickening of CC).[20]

The most common causes of ACC are gene mutations.[22] The overall incidence of ACC is 0.5–70 in 10,000 livebirths.[19] Generally, the outcome of isolated ACC is favorable. Patients showed normal intelligence and neuropsychological

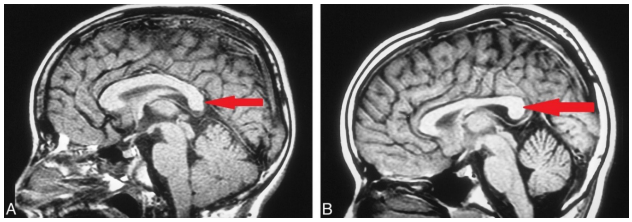

Fig. 2 **Brain magnetic resonance imaging (MRI) T_1 weighted mid-sagittal view showing the normal appearance of corpus callosum (red arrow).**

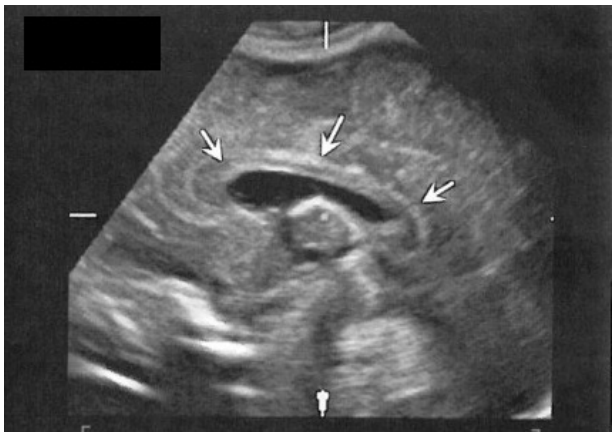

Fig. 3 **Prenatal ultrasound of fetal brain midsagittal view showing the normal appearance of corpus callosum at 20 weeks of gestation.**[20]

development in up to 70% of cases.[23] In the other individuals, deficits in language comprehension, humor, theory of mind and social reasoning are noted. The overall rate of chromosomal abnormality in fetuses with ACC is 18%. Careful imaging in a center with a high level of expertise is required to make a full assessment and to exclude coexisting abnormalities.

A wide range of neurological disorders and tumors were associated with epigenetic abnormalities. Defects in chromatin remodeling have been linked to agenesis of the corpus callosum, mainly chr.22q11.2 microdeletion or duplication. A little data is available about the effect of nuclear signaling and cellular mechanisms in disorders associated with commissural phenotypes such as callosal agenesis. However, a lack of C11orf46 in reference to microdeletion of ch.11p13-14.1 is strongly linked to neurodevelopmental abnormalities which are related to agenesis of the corpus callosum.[24]

The C11orf46 is a nuclear protein that is expressed in an age-related pattern with a larger amount expressed at pre and post-natal periods in comparison to adulthood. The cellular expression pattern of C11orf46 in the developmental stage of the brain is a nuclear punctate type in NeuroD2-positive cells. The role of C11orf46 in cortical development was demonstrated in animal studies where knockdown of C11orf46 lead to a reduction in corpus callosum thickness. Inhibition of C11orf46 reduced callosal development and commissural connection between cerebral hemispheres.[25]

The C11orf46 plays an important role in axonal connectivity and it is linked to regulators repressive chromatin which is related to trans-callosal connectivity. Moreover, C11orf46 affinity to KMT-RC is a determinant to orderly brain development. An epigenomic editing trial, working on HEK293 cells, found that C11orf46 could effectively suppress the genes responsible for corpus callosum development.[26]

Genetic defect: Genetic causes of ACC are heterogeneous. It could be a part of monogenic syndromes or complex chromosomal abnormalities.[19] The overall rate of chromosomal abnormalities in fetuses with ACC is 18%; nevertheless, recent studies suggest that chromosomal abnormalities are rare in isolated cases.[20] The increased use and resolution of comparative genomic hybridization (CGH) have implicated many more genes and genomic loci in corpus callosum development,[27] and have revealed a great diversity of genetic causes for ACC syndromes (Table 1A–1C). At present, however, the

Table 1A. **Different autosomal dominant gene syndromes and their responsible genes that may be associated with ACC**

Syndromes	Gene	Gene Locus
Apert Syndrome	FGFR2	10q26
Greig Cephalopolysyndaktyly Syndrome	GLI3	7p14.1
Miller–Dieker Syndrome	Microdeletion	17p13.3
Mowat–Wilson Syndrome	ZEB2	2q22
Opitz gbbb Syndrome	Microdeletion	22q11.2
Coffin-Siris / Fifth Digit Syndrome	ARID1A	1p36.11
	ARID1B	6q25.3
	SMARCA4	19p13.2
	SMARCB1	22q11.23
	SMARCE1	17q21.2
	SOX11	2p25.2
Rubinstein–Taybi Syndrome	Microdeletion	16p13.3
	EP300	22q12
Basal cell Nevus Syndrome	PTCH	9q22.3
	SUFU	10q24.32

Table 1B. **Different autosomal recessive gene syndromes and their responsible genes that may be associated with ACC**

Syndrome	Gene	Gene Locus
Acrocallosal Syndrome	KIF7	15q26.1
	GLI3	7p13
Andermann Syndrome	SLC12A6	15q13-q14
Dincsoy Syndrome		
Fryns Syndrome	PIGN	18q21.33
Fukuyama Congenital Muscular Dystrophy	FKTN	9q31.2
Hydrolethalus Syndrome	KIF7	15q26.1
Joubert Syndrome	33 autosomal recessive genes	
Lowry Wood Syndrome	RNU4ATAC	2q14.2
Meckel-gruber Syndrome	11 autosomal recessive genes	
Microcephalic Osteodysplastic Primordial dwarfism type (mopd) i/iii	RNU4ATAC	2q14.2
Muscle Eye Brain Disease		
Neu-laxova Syndrome	PHGDH	1p12
	PSAT1	9q21.2
	PSPH	7p11.2
Peters-plus Syndrome	B3GLCT	13q12.3
Septo-optic Dysplasia		
Toriello-carey Syndrome		
Vici Syndrome	EPG5	18q12.3-q21.1
Walker-warburg Syndrome	POMT1	
	POMT2	
	FKTN	9q31.2
Warburg-mikro Syndrome		

Table 1C. **Different X-linked gene syndromes and their responsible genes that may be associated with ACC**

Syndrome	Gene	Gene Locus
Aicardi Syndrome	Not known	Xp22
Atr-x Syndrome		
Cranial Frontonasal Syndrome	EFNB1	Xq13.1
FG Syndrome	CASK	Xp11.4
Hydrocephalus Masa Syndrome		
Lujan-fryns Syndrome		
MLS Syndrome		
Oral-facial Digital Syndrome Type 1 proud syndrome		
Proud Syndrome		
X-linked Lissencephaly		

cause of 55–70% of cases with ACC cannot be identified by clinical evaluation.[28,19] Non-genetic causes of ACC include maternal alcohol use during pregnancy[29] or maternal phenylketonuria.[30]

Apert Syndrome

Apert syndrome is characterized by the presence of multi-suture craniosynostosis and syndactyly of the hands (fusion of the digits and nails) (Figure 4). Affected individuals have large anteriorly displaced "Anterior Fontanelle" and cloverleaf skull. The ocular abnormalities, hearing loss, and nonprogressive ventriculomegaly had been reported in most cases. Cervical vertebral fusions are found in 68% of affected individuals. Most individuals with Apert syndrome have normal intelligence or mild intellectual disability. Abnormalities of the corpus callosum; namely ACC, were described in 23% of cases.

Genetic defect: Fibroblast Growth Factor Receptor (*FGFR2)* gene mutations are linked to many genetic disorders, one of them is Apert syndrome. Heterozygous mutation in *FGFR2* mostly reported small intragenic deletions/insertions finally resulting in replacement of serine amino acid with tryptophan amino acid at protein position 252 (written as Ser252Trp). Another mutation replaces proline amino acid with arginine amino acid at position 253 (written as Pro253Arg). These changes are described as "gain-of-function" because they increase the activity of the resultant protein, leading to stronger signaling.[31,32]

Greig Cephalopolysyndaktyly Syndrome (GCPS)

It is a rare genetic disorder characterized by macrocephaly, widely spaced eyes, preaxial polydactyly, and cutaneous syndactyly. Affected individuals have developmental delay, intellectual disability, and/or seizures. Approximately 200 cases are reported worldwide.[34] The ACC is reported in approximately 20% of affected individuals.[35]

Genetic defect: The GCPS is caused by heterozygous mutation in GLI family zinc finger 3 *(GLI3)* in 80% of cases, whereas 20% of cases are caused by deletion of the short arm of chromosome 7 (7p14.1) in the area involving *GLI3* gene.[36] Reported mutations causing GCPS were large deletions,

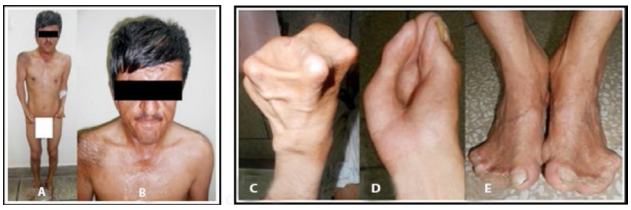

Fig. 4 **A = A patient with Apert syndrome, B = Face, C = hoof-shaped hand, D = Syndactyly shape of a rosebud, and E = Syndactyly of feet (printed with permission from Rathore et al.,[33] 2017).**

exonic deletions and duplications, small in-frame deletions, and missense, frameshift/nonsense, and splicing mutations in *GLI3* gene.[37] *Debeer et al.*[38] *2003* found a missense mutation in the GLI3 gene resulting in the replacement of arginine amino acid with tryptophan at position 625 of the resultant protein; arg625trp (R625W). This mutation was partially penetrant. Another mutation reported by Kalff-Suske et al.,[39] 1999 was G-to-T transversion at nucleotide 1627 of the GLI3 gene, resulting in a glu543-to-ter mutation. The *GLI3* gene mutations may result in another genetic syndrome called Pallister-Hall Syndrome (PHS); but the site and type of mutation totally different from that occurring in GCPS cases. Mutations typically involve exons spanning nucleotides 1813-2103 of the *GLI3* cDNA; and most of them were deletions resulting in a frameshift and premature protein termination codon with the final production of truncated proteins.[40]

Miller–Dieker Syndrome (MDS)

It is a rare genetic disorder that comprises severe lissencephaly (smooth brain) and characteristic facial features; including a high and prominent forehead, bitemporal narrowing, short upturned nares, protuberant upper lip with downturned vermilion border, and small jaw (Figure 5). Manifestations include hypotonia and feeding difficulties. Affected individuals suffer from severe mental retardation, seizures, and developmental delay. Other malformations reported in these individuals include omphalocele and congenital heart defects.[41] Hypoplasia or complete agenesis of CC is described in most cases of MDS.[42]

Genetic defect: Approximately 80% of individuals with MDS have a *de novo* deletion involving the short arm of chromosome 17 (17p13.3) in the area involving *PAFAH1B1* gene (formerly *LIS1*); whereas 20% have inherited a deletion from a parent who carries a balanced chromosome rearrangement.[43] Most deletions are microdeletions that can be detected in 70% of cases by either high resolution karyotyping or FISH technique (Flourescent in situ hybridization).[43]

PAFAH1B1 gene Abnormalities may cause MDS, isolated lissencephaly or subcortical band heterotopia (SBH).[45]

Mowat–Wilson Syndrome (MWS)

It is a very rare disorder that its prevalence has been estimated to be 1:50,000 – 1:70,000 live births.[46] The MWS is characterized by distinctive facial features (widely spaced eyes, broad eyebrows with a medial flare, low-hanging columella, prominent chin, and uplifted earlobes with a central depression (Figure 6). The facial features evolve and become more pronounced with age.[47] Hirschsprung disease (in 44% of cases) or chronic constipation (in 30% of cases) had been described

with MWS.[48] Congenital heart defects; with a predilection for abnormalities of the pulmonary arteries and/or valves, and genitourinary anomalies (particularly hypospadias and cryptorchidism in males) are frequently described manifestations with MWS.[48] Hypoplasia or complete agenesis of CC is described in most cases of MWS.[48]

Genetic defect: MWS is caused by hetero-zygous mutation in *ZEB2* gene in 84% of affected individuals.[50] 15% of MWS patients are caused by deletions in *ZEB2* gene.[51] 1% of cases are caused by chromosome rearrangements at the long arm of chromosome 2; which disrupt ZEB2 gene[51] Missense, splice site, or in-frame variants in *ZEB2* represent fewer than 2% of cases with typical MWS.[49] Yoneda et al.[52] 2002, reported 3-bp in-frame deletion affecting *ZEB2* in an adult with mild intellectual disability, atypical facial features, and megacolon. Zweier et al.[53] 2006, found a novel splice site variant in the UTR in a patient with facial features and speech delay.

Opitz GBBB Syndrome

It is a genetic disorder that affects structures along the midline of the body. Patients have characteristic facial features including widely spaced eyes and a cleft lip. Other manifestations include laryngotracheoesophageal abnormalities causing breathing problems and difficulty swallowing. Affected individuals usually suffer from intellectual disability, heart defects, and/or imperforate anus.[54] ACC and/or cerebellar vermis and Dandy-Walker malformations were identified in 50% of affected individuals.[54]

Genetic defect: Opitz GBBB syndrome has two genetic forms one is autosomal dominant (ADOS; type II) and the other is X-linked (OSX; type I) form.[55] The autosomal dominant form is caused by microdeletion (submicroscopic) at the long arm of chromosome 22 (22q11.2).

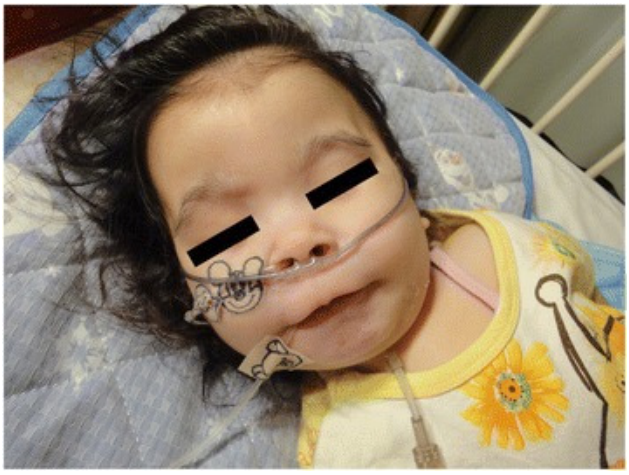

Fig. 5 **Typical facial features of Miller–Dieker syndrome (MDS), including a prominent forehead, bitemporal hollowing, short nose with upturned nares, prominent upper lip, and micrognathia. (printed with permission from Kim et al.,[44] 2011).**

Coffin-Siris Syndrome (CSS)/Fifth Digit Syndrome

It is a rare genetic disorder characterized by aplasia or hypoplasia of the distal phalanx/nail of the fifth and additional digits, developmental delay, intellectual disability, distinctive facial features, hypotonia, hypertrichosis, and hearing impairment. Congenital anomalies were also reported in individuals affected including malformations of the heart, gastrointestinal, genitourinary, and central nervous systems.[56]

Genetic defect: CSS is caused by a heterozygous pathogenic variant in one of the genes listed in Table 2.

Rubinstein–Taybi Syndrome (RSTS) (Broad Thumb-allux Syndrome)

The RSTS is characterized by distinctive facial features, broad and often angulated thumbs and halluces, short stature, and moderate-to-severe intellectual disability. The characteristic facial features include downward slanting of palpebral fissures, high palate, grimacing smile, and talon cusps. Additional features include ocular abnormalities, hearing loss, respiratory difficulties, congenital heart defects, renal abnormalities, cryptorchidism, feeding problems, recurrent infections, and severe constipation.[58] Rarely, RSTS is associated with ACC;[59] however, it had been reported in some cases.[60]

Genetic defect: The RSTS is caused by heterozygous mutations in either *CREBBP* gene (50%-60% of cases)[61] or *EP300* gene (8%-10% of cases).[62] Rusconi et al.[63] 2015, described 14 patients with RSTS having *CREBBP* deletions of different sizes; ranging from single exons to whole gene deletions, showing no difference in their phenotype. Somatic mosaicism and mosaic microdeletions have been noted in some individuals with RSTS. They tend to have a mild phenotype.[64]

Table 2. **Genes and Percentage of CSS caused by a pathogenic variant**

Gene	Gene locus	Percentage of CSS caused by pathogenic variants in this gene
ARID1A	1p36.11	5%
ARID1B	6q25.3,	37%
SMARCA2	9p24.3	2%
SMARCA4	19p13.2	7%
SMARCB1	22q11.23	7%
SMARCE1	17q21.2	2%
SOX11	2p25.2	2%
Unknown		40%

Fig. 6 **Main common features of the Mowat-Wilson Syndrome: large eyebrows, medially flaring and sparse in the middle part, and widely spaced eyes (printed with permission from Garavelli et al.,[57] 2007).**

Basal Cell Nevus Syndrome (BCNS)/ Nevoid Basal Cell Carcinoma Syndrome (NBCCS)/ (Gorlin Syndrome)

BCNS is a rare autosomal dominant disorder characterized by the development of multiple jaw keratocysts, and/or basal cell carcinomas; manifesting from the third decade onward, skeletal anomalies, and ectopic calcifications (especially the falx).[65,66] Only 5% of children with BCNS develop medulloblastoma with a peak incidence at one to two years of age.[67] More than 100 clinical features that are variable within and among families have been associated with BCNS [68] The prevalence of BCNS had been reported in some studies to be 1:30,827.[69] The ACC in cases with BCNS was estimated in some studies to be 10%.[66]

Genetic defect: Identification of a heterozygous germline pathogenic variant in either *PTCH1* gene or *SUFU* gene establishes the diagnosis of BCNS. The *PTCH1* gene is located on the short arm of chromosome 9 (9q22.3). The PTCH1 gene provides instructions for producing a protein (Patched-1), which functions as a receptor for Sonic Hedgehog protein. Together, Patched-1 and Sonic Hedgehog trigger signals that affect cell development and function that is essential for early development.[70] The PTCH1 is seen as a tumor suppressor gene.[71]

Sim et al.,[72] *2018,* reported frameshift mutations in PTCH1 gene (c.817_818ins(T), c.1226_1227ins(A), and c.2748del(C)), splicing (c.1504-2A>T), and missense (c.385T>C) mutation. Mutations were found in exon 1, 6, 9, 17, and intron 10. The SUFU-related BCNS is associated with a high risk for medulloblastoma of up to 33% compared to that in PTCH1-related BCNS which was less than 2%.[65]

Acrocallosal Syndrome (ACLS)

ACLS is a rare autosomal recessive disorder characterized by pre- or postaxial polydactyly, cutaneous syndactyly, hallux duplication, agenesis of the corpus callosum, widely spaced eyes, macrocephaly, moderate-to-severe ID, intracerebral cysts, seizures, umbilical & inguinal hernias.[73]

Genetic defect: The ACLS is caused by homozygous mutations (or compound heterozygous) in *KIF7* gene. *KIF7* is located on the long arm of chromosome 15 (15q26.1) and comprise 19 exons. *KIF7* is a 1343 amino acid protein with a kinesin motor, coiled coil, and Gli-binding domains. The ACLS may also result from a heterozygous mutation in *GLI3* (7p14.1); the causative gene for Greig cephalopolysyndactyly syndrome (GCPS). The clinical manifestations of ACLS and GCPS overlap significantly; that's why ACLS is considered the severe form of GCPS.[73] The proteins produced from the *KIF7* and *GLI3* gene are part of the Sonic Hedgehog (SHH) signaling pathway (Figure 7). This pathway is involved in cell growth, cell specialization, and the regulation of microtubular dynamics necessary for the proper function of the primary

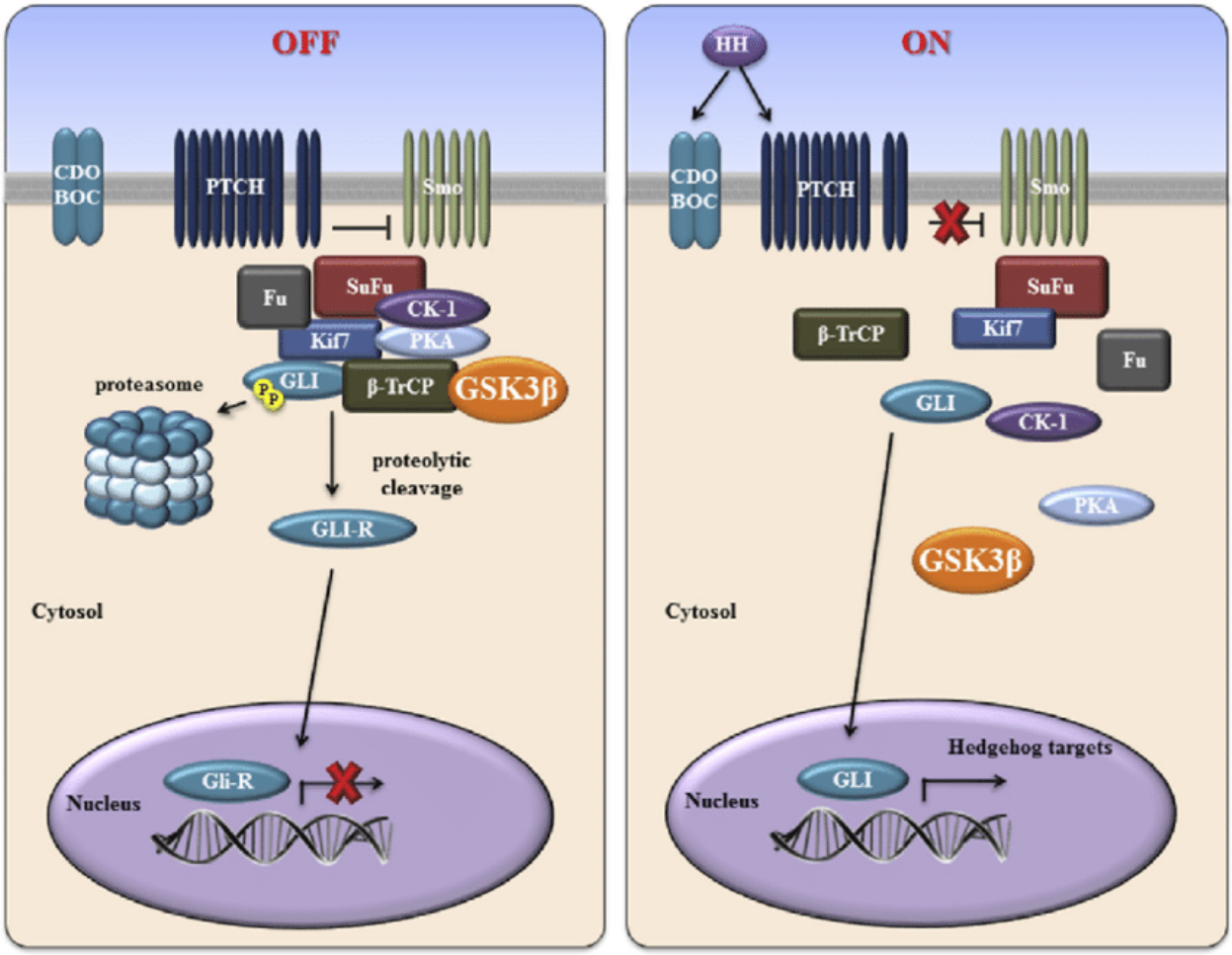

Fig. 7 **Schematic overview of Sonic Hedgehog signaling pathway (*Cervello et al.,*[80] *2017*).**

cilia, and hence genetic disorders involving genes regulating this pathway are called ciliopathies. The resultant proteins in SHH signaling pathway are responsible for patterning of the brain and limbs.[74] The *KIF7* gene mutations had been linked also to Joubert syndrome, a rare genetic disorder characterized by cerebellar hypoplasia, ataxia, psychomotor delay, and an altered respiratory pattern in the neonatal period. Retinal degeneration, renal cysts, liver fibrosis, and skeletal involvement were also described with Joubert syndrome.[75] Pathogenic variants in *KIF7* reported with ACLS include; in-frame deletion mutation (p.218-221del),[76] nonsense, missense, and splice site mutations were also described. *Ibisler et al,.[77] 2015* reported a nonsense mutation in exon 11 of the KIF7 gene (c.2335G>T, p.Glu779).

Left side: In the absence of HH ligand, PTCH inhibits Smo allowing GLI to form a complex with Kif7 and SuFu, promoting GLI phosphorylation by PKA, CK-1, and GSK-3b. Upon phosphorylation, GLI proteins are processed into transcriptional repressors (GLI-R) or are targeted to the proteasome.

Right side: The HH ligand binding to PTCH and to co-receptors CDON and BOC and relieves repression of Smo, triggering its interaction with Kif7. This facilitates the release of GLI from SuFu/Fu complex, bypassing proteolytic cleavage. Full-length GLI factors lead to the expression of HH target genes.

Andermann Syndrome/Agenesis of Corpus Callosum with Peripheral Neuropathy (ACCPN)

It is an autosomal recessive disorder characterized by progressive sensorimotor neuropathy with areflexia, developmental delay.[78] Sensory nerve action potentials cannot be recorded at the median, ulnar, or sural nerves as early as the first year of life. The 86% of affected individuals develop scoliosis.[79] The ACC is present in 60% of affected individuals.

Genetic defect: The ACCPN is caused by biallelic pathogenic variants in *SLC12A6*. The *SLC12A6* gene provides instructions for making a protein called K-Cl cotransporter (Electroneutral cotransporter); which is critical for the development and maintenance of nerve tissue. The *SLC12A6* gene is located on the long arm of chromosome 15 (15q13-q14). Small intragenic deletions/insertions and missense, nonsense, and splice-site variants in *SLC12A6* were reported in cases with ACCPN. *Howard et al.[81] 2002*, identified 4 truncating mutations in the *SLC12A6* gene.

Fryns Syndrome

It is a rare autosomal recessive genetic disorder characterized by diaphragmatic defects including diaphragmatic hernia, characteristic facial features, short distal phalanges of the fingers and toes, pulmonary hypoplasia, microphthalmia, brain malformations including agenesis of the corpus callosum, and cardiovascular anomalies.[82] The prognosis in Fryns syndrome is influenced by the malformations present. Survival beyond the neonatal period is rare.[83]

Genetic defect: The molecular diagnosis of Fryns syndrome is established when biallelic pathogenic variants (homozygous/compound heterozygous mutations) in *PIGN* gene are present in a proband with suggestive clinical findings i.e. diaphragmatic hernia.[84] The *PIGN* gene is located on the long arm of chromosome 18 (18q21.33*)*. This gene encodes glycosylphosphatidylinositol (GPI) ethanolamine phosphate transferase-1, an enzyme responsible for GPI anchor to cell surface proteins. *Maydan et al.[85] 2011* determined that the PIGN gene contains 31 exons spanning 142.8 kb. Missense, nonsense, and splice-site variants had been associated with *PIGN* associated Fryns syndrome e.g. c.2620-1G>A.[86]

Fukuyama Congenital Muscular Dystrophy (FCMD)

FCMD is a rare autosomal recessive congenital muscular dystrophy characterized by early-infantile hypotonia and weakness with contractures of the joints. Affected individuals suffer from intellectual disability and speech delays. The condition is seen primarily in children of Japanese ancestry.[87] Ophthalmologic abnormalities, including visual impairment in 53% and retinal abnormalities in 32% were also reported in patients suffering from FCMD.[88] Cobblestone lissencephaly and white matter abnormalities can be detected in the MRI images of the brain of individuals with FCMD[89] (Figure 8). Cobblestone

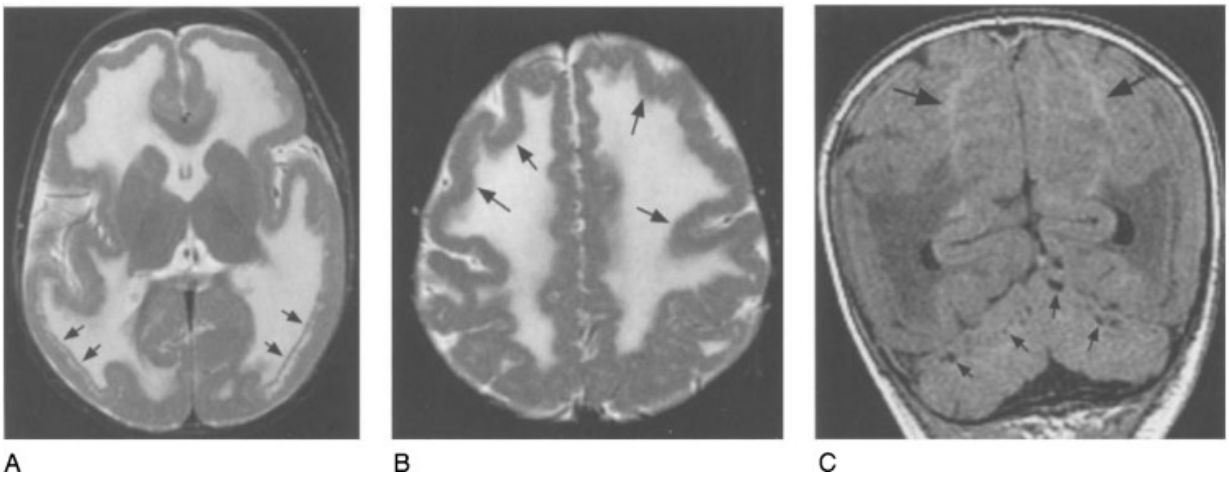

Fig. 8 **Cobblestone lissencephaly in FCMD (*Barkovich,[90] 2005*). (A) Axial T_2-weighted image showing occipital cobblestone with a thick cortex and smooth outer surface (B) Axial T2-weighted image at a higher level showing polymicrogyria of the frontal lobes. (C) Coronal T_1-weighted image showing the characteristic cortical cysts in the cerebellar hemispheres (smaller arrows).**

cerebral cortex malformations are associated with congenital muscular dystrophies as in FCMD, Walker–Warburg syndrome, and muscle–eye–disease of Santavuori.[90]

The elevated serum creatinine and interstitial fibrosis without muscle degeneration and regeneration seen on histopathological examination of muscle biopsies are consistent features of FCMD.[91]

Genetic defect: The molecular diagnosis of FCMD is confirmed when biallelic pathogenic variants in *FKTN* gene are detected in a proband with clinical findings suggestive of FCMD. The *FKTN* gene is located on the long arm of chromosome 9 (9q31.2). *This* gene encodes for a 461-amino acid fukutin protein, which is expressed in various tissues in normal individuals. It is believed that fukutin play an important role in neuronal migration and glycosylation of Alpha-dystroglycan (DAG1) of skeletal and cardiac muscle fibers.[92,93]

Kobayashi et al.[87] *2017*, analyzed *FKTN* gene in 107 affected individuals that showed the prevalence of the homozygous Japanese founder variant (c.*4392_*4393insAB185332.1) among patients; where there is insertion of retrotransposal sequence into 3'-UTR (untranslated region) of *FKTN*. The second common mutation in *FKTN* gene associated with FCMD reported in Korea by *Lim et al.*,[94] *2010* is (c.647+2084G>T) (p.Arg216SerfsTer10); an intronic mutation that activates a pseudoexon between exons 5 and 6 resulting in a truncated fukutin protein.

Saredi et al.[95] *2009*, found 1 bp deletion mutation in *FKTN* gene in an Italian patient with muscular dystrophy. The mutation (c.42del) (p.Thr14_Leu15insTer) results in a premature termination of protein synthesis producing a truncated protein with loss of its function.

Joubert Syndrome (JBTS) and Joubert Syndrome and Related Disorders (JSRD)

JBTS is characterized by three primary findings: (1) A distinctive cerebellar and brain stem malformation called the molar tooth sign (MTS) (Figure 9), (2) Hypotonia and (3) Developmental delays.

Affected individuals may also suffer from breathing abnormalities (tachypnea or apnea), abnormal eye movements, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis or polydactyly.[96,97]

The ACC is common in 80% of individuals with JBTS.[98] Callosal abnormalities are relatively frequent in those with biallelic KIF7 pathogenic variants suggesting overlap with acrocallosal syndrome.[99]

Genetic defect: The JBTS is diagnosed genetically by the presence of biallelic pathogenic variants in one of the 33 autosomal recessive JS-related genes or heterozygous mutation in one X-linked gene. Table 3A and 3B show JS related genes and examples of the most common pathologic variants occurring in each gene.

15. Lowry Wood Syndrome (LWS)

A rare genetic disorder characterized by epiphyseal dysplasia, short stature, microcephaly and retinal dystrophy.[100] Other skeletal manifestations of this disorder included a bilateral absence of radial heads, lateral dislocation of both patellae, and dislocation of both hips.[120] Clinical features of microcephalic osteodysplastic primordial dwarfism type I (MOPD1)

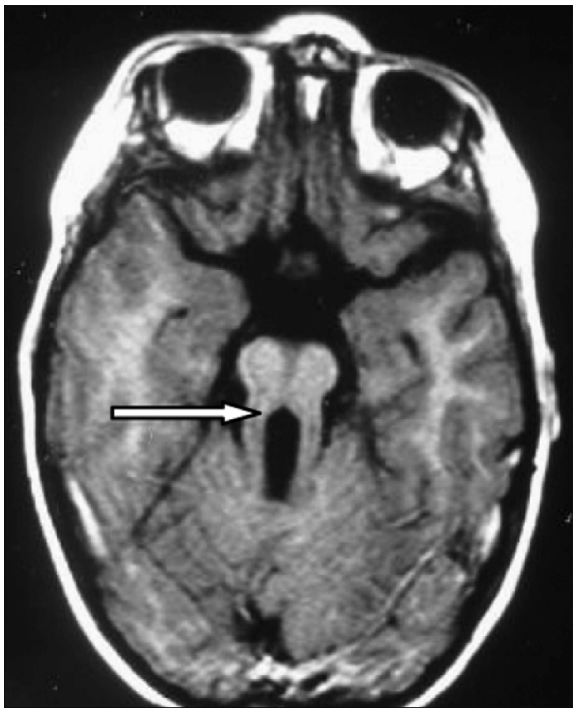

Fig. 9 **Brain MRI T_1 weighted axial view showing "Molar tooth" sign shown by the arrow in a patient with JBTS (*Embiruçu et al.*,[101] *2009*)**

overlap with those of Lowry Wood Syndrome; which is also caused by a biallelic mutation in the *RNU4ATAC* gene.

Genetic defect: The LWS is caused by biallelic pathologic variants in the *RNU4ATAC* gene encoding a small nuclear RNA (snRNA); located on the long arm of chromosome 2 (2q14.2).[100] *Shelihan et al.*[121] *2018*, identified compound heterozygosity in the RNU4ATAC gene, one was for an r.53C-T transition and the other r.8C-A transversion. Other mutations that had been associated with *RNU4ATAC* gene in cases of Lowry Wood Syndrome were n.46G>A transition, r.5A-C transversion,[100] r.120T-G transversion, and r.114G-C transversion.[121]

Meckel-Gruber Syndrome (MKS)/ Dysencephalia Splanchnocystica

The MKS is a rare autosomal recessive lethal ciliopathy characterized by bilateral polycystic kidneys, occipital encephalocele and postaxial polydactyly[122] (Figure 10). Other abnormalities that could be found in MKS are cleft lip and palate, congenital heart defects, and pulmonary hypoplasia.[123]

The worldwide incidence of MKS has been estimated to be 1 in 135,000 live births,[124] however, it has a higher incidence in some populations where the consanguineous marriage rate is high, for example, Hutterites,[125] Finland,[126] Kuwaiti Bedouin tribes,[127] and in Saudi Arabia.[128] The MKS phenotype overlap with other ciliopathies such as Joubert Syndrome (JBTS), COACH Syndrome (cerebellar vermis hypo/aplasia, oligophrenia, congenital ataxia, ocular coloboma, and hepatic fibrosis), Oro-facio-Digital Syndrome (OFD), nephronophthisis (NPHP), and Bardet–Biedl Syndrome (BBS); that forms a challenge in the diagnosis of MKS.[109,129,130]

Genetic defect: The molecular diagnosis of MKS is established when biallelic pathologic variants are found in one of the MKS causing genes. To date, there are 11 autosomal

Table 3A. **Joubert Syndrome related Genes and Pathogenic variants**

Gene	Gene locus	Pathogenic variants	Phenotypic variant (other than molar tooth sign)	Ethnic group	References
1-AHI1	6q23.3	Missense and frameshift mutations c.2988del (p.Val997fs)	Retinal dystrophy, renal disease		*Bachmann-Gagescu et al., 2015a*[99]
2-CPLANE1	5p13.2	p.Arg2904Ter	Tongue hamartomas +/- cleft lip/palate +/- polydactyly	Dutch, French Canadian	*Vilboux et al., 2017*[102]
3-CC2D2A	4p15.32	c.100C>T (p.Arg34Ter)	Renal disease, hepatic disease	French Canadian	*Doherty et al., 2010*[103]
4-CEP290	12q21.32	c.6012-12T>A	Retinal dystrophy, renal disease, hepatic disease	Japanese population	*Suzuki et al., 2016*[104]
5-CSPP1	8q13.1-q13.2	c.363_364delTA	Skeletal dysplasia	Hutterite	*Tuz et al., 2014*[105]
6-INPP5E	9q34.3	Missense and frameshift mutations c.1897_1898del (p.Gln633fs)	Retinal dystrophy, hepatic disease		*Vilboux et al., 2017*[102]
7-KIAA0586	14q23.1	c.392del (p.Arg131fs)	Skeletal dysplasia		*Alby et al., 2015*[106]
8-MKS1	17q22		Retinal dystrophy		*Slaats et al., 2016*[107]
9-NPHP1	2q13		Renal disease	French Canadian	*Vilboux et al., 2017*[102]
10-RPGRIP1L	16q12.2		Renal disease, hepatic disease		*Delous et al., 2007*[108]
11-TCTN2	12q24.31		Tongue hamartomas +/- cleft lip/palate +/- polydactyly		*Bachmann-Gagescu et al., 2015a*[99]
12-TMEM67	8q22.1		Hepatic disease		*Brancati et al., 2009*[109]
13-TMEM216	11q12.2	p.Arg73Leu	Retinal dystrophy, renal disease, tongue hamartomas +/- cleft lip/palate +/- polydactyly	Ashkenazi Jewish	*Valente et al., 2010*[110]
14-ARL13B	3q11.1-q11.2				*Cantagrel et al., 2008*[111]
15-B9D1	17p11.2				*Romani et al., 2014*[112]
16-B9D2	19q13.2		Tongue hamartomas +/- cleft lip/palate +/- polydactyly		*Bachmann-Gagescu et al., 2015a*[99]
17-C2CD3	11q13.4		Tongue hamartomas +/- cleft lip/palate +/- polydactyly		*Bachmann-Gagescu et al., 2015a*[99]
18-CEP41	7q32.2		Retinal dystrophy		*Lee et al., 2012a*[113]

Table 3B. **Joubert Syndrome related Genes and Pathogenic variants**

Gene	Gene locus	Pathogenic variants	Phenotypic variant (other than molar tooth sign)	Ethnic group	References
19-CEP104	1p36.32				*Srour et al., 2015*[114]
20-CEP120	5q23.2		Tongue hamartomas +/- cleft lip/palate +/- polydactyly 2-Skeletal dysplasia		*Shaheen et al., 2015b*[115]
21-IFT172	2p23.3		Skeletal dysplasia		*Halbritter et al., 2013*[116]
22-KATNIP (KIAA0556)	16p12.1				*Sanders et al., 2015*[117]
23-KIF7	15q26.1		Tongue hamartomas +/- cleft lip/palate +/- polydactyly, acrocallosal syndrome		*Dafinger et al., 2011*[75]
24-OFD1	Xp22.2		Renal disease, tongue hamartomas +/- cleft lip/palate +/- polydactyly		*Coene et al., 2009*[118]
25-PDE6D	2q37.1				*Thomas et al., 2014*[119]
26-POC1B	12q21.33				
27-TCTN1	12q24.11				
28-TCTN3	10q24.1		Tongue hamartomas +/- cleft lip/palate +/- polydactyly		

(Continued)

Table 3B. **Joubert Syndrome related Genes and Pathogenic variants—Continued**

Gene	Gene locus	Pathogenic variants	Phenotypic variant (other than molar tooth sign)	Ethnic group	References
29-TMEM107	17p13.1		Retinal dystrophy, tongue hamartomas +/- cleft lip/palate +/- polydactyly		
30-TMEM138	11q12.2		Retinal dystrophy, renal disease		
31-TMEM231	16q23.1			French Canadian	*Srour et al., 2015*[114]
32-TMEM237	2q33.1	p.Arg18Ter	Renal disease	Hutterite	
33-TTC21B	2q24.3				
34-ZNF423	16q12.1		Renal disease		

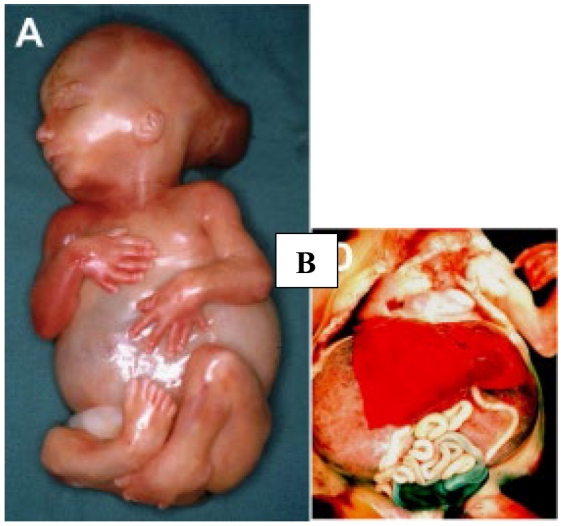

Fig. 10 **Showing a fetus aged 16 weeks gestational age (A) Occipital encephalocele and bilateral postaxial polydactyly and (B) Bilateral polycystic kidneys (*Hartill et al.,* [131] *2017*).**

recessive genes associated with MKS. Table 4 shows the 11 MKS causative genes with examples of the most common pathologic variant occurring in each gene.

The MKS1 gene (609883) is located on the long arm of chromosome 17 (17q22). The MKS1 gene encodes a protein responsible for centriole migration to the apical membrane and the formation of the primary cilium during embryonic life. It is 21,170 bp in length, comprises 18 exons, and encodes a 559-amino acid protein.[132] *Kyttala et al.*[133] *2006*; identified a 29-bp deletion in intron 15 of MKS1 gene (c.1408-35_1408-7del29) (609883.0001) in 3 Finnish families. The same intronic deletion was found in other Finnish families and families of European descent; it was then denoted as the Finnish founder variant (Campomelic variant).[124]

Microcephalic Osteodysplastic Primordial Dwarfism Type (MOPD) I/III

The MOPD is a rare autosomal recessive developmental disorder characterized by extreme intrauterine growth retardation, severe microcephaly, central nervous system abnormalities, dysmorphic facial features, skin abnormalities, skeletal changes, limb deformations[144] (Figure 11). The syndrome was characterized by Majewski as MOPD types I and III; which were considered parts of the same clinical spectrum and since that time they are combined and denoted as the same disorder.[146]

The ACC had been reported in patients with MOPD I, whether partial or complete.[147,148]

Genetic defect: The MOPD I is caused by homozygous or compound heterozygous mutation in the RNU4ATAC gene (601428); the gene that is also associated with Lowry Wood Syndrome. This gene as mentioned above is located on the long arm of chromosome 2 (2q14.2); and is responsible for the production of small nuclear RNA (snRNA) U4atac (a nonprotein-coding gene); which is a component of the minor spliceosome.[149]

The spliceosome is a large ribonucleoprotein (RNP) complex that catalyzes the removal of introns from a transcribed pre-mRNA, and the ligation of the flanking exons.[150] Spliceosomes are either major or minor that differ in their splicing processes and snRNA components. The minor spliceosome is assembled within the nucleus from 5 subunits; U11, U12, U4atac, and U6atac, together with U5. This type of Spliceosome splices a rare class of pre-mRNA introns, denoted U12-type. Figure 12 shows the detailed structure of the minor spliceosome.[151]

He et al.[149] *2011*, identified 4 different mutations in the RNU4ATAC gene associated with MOPD I, all these mutations ended up in defective U12-dependent splicing (reduced by greater than 90% compared to wildtype U4atac). The mutations were genomic 51G-A, genomic 55G-A, genomic 30G-A, 111G-A. *Edery et al.*[152] *2011*, identified another mutation in RNU4ATAC gene; 51G-A. *Abdel-Salam et al.*[153] *2012*, identified a homozygous mutation for the genomic 55G-A in RNU-4ATAC gene (previously reported by *He et al.* [149] *2011*), in 2 sibs with mild MOPD1 phenotype.

Vici Syndrome

Vici Syndrome (OMIM242840) is an autosomal recessive disorder characterized by agenesis of the corpus callosum, cataracts, oculocutaneous hypopigmentation, progressive cardiomyopathy, and combined immunodeficiency[154] (Figure 13). Affected individuals suffer also from severe developmental delay, intellectual disability and acquired microcephaly.[155] An additional finding is muscle myopathy manifested as progressive hypotonia and elevated serum creatinine kinase. Histopathological examination of skeletal muscle fibers by light microscopy reveals wide variation in fiber size, centralized nuclei, and small fibers with high glycogen content.[156]

Table 4. **MKS causative genes and the most common pathologic variant**

Gene	Gene Locus	Pathogenic variant	References
MKS1	17q22	Finnish c.1408-35_1408-7del29	*Kyttälä et al., 2006*[133]
MKS2 (TMEM216)	11q12.2	Ashkenazi c.218G > T (p.R73L)	*Edvardson et al., 2010*[134]
MKS3 (TMEM67)	8q22.1	Pakistani c.1575 + 1G > A	*Smith et al., 2006*[135]
MKS4 (CEP290)	12q21.32	4-BP Del, c.384_387TAGA, (p.Asp128GlufsTer34)	*Baala et al., 2007b*[136]
MKS5 (RPGRIP1L)	16q12.2	European c.1843A > C (p.T625P)	*Arts et al., 2007*[137]
MKS6 (CC2D2A)	4p15.32	Finnish c.1762C > T (p.?)	*Tallila et al., 2008*[138]
MKS7 (NPHP3)	3q22.1	IVS19AS, 2-BP Del, (c.2694-1_2 del)	*Bergmann et al., 2008*[139]
MKS8 (TCTN2)	12q24.31	IVS13AS, A-G, -2	*Shaheen et al., 2011*[140]
MKS9 (B9D1)	17p11.2	505, T-C, +2, (p.Thr82CysfsTer44), splice site donor mutation)	*Hopp et al., 2011*[141]
MKS10 (B9D2)	19q13.2	301A-C transversion, (p. Ser101Arg)	*Dowdle et al., 2011*[142]
MKS11 (TMEM231)	16q23.1	c.751G-A transition, (p.Val251SerfsTer9)	*Shaheen et al., 2013*[143]

Fig 11. **A photo of a patient diagnosed with MOPD I at 4 weeks (left) and 6 months of age (right). Note typical facial features with sloping forehead, beaked nose with downturned nasal tip, small low-set ears, sparse hair and joint contractures (both wrists, both elbows, and both knees) (*Nagy et al.,*[145] *2012*).**

Patients with Vici Syndrome may develop by time progressive reduction of absolute lymphocyte count and immunoglobulin level that may necessitate intravenous immunoglobulin (IVIG) therapy.[154] Patients usually present with recurrent chest infections, particularly pseudomonas and klebsiella associated with lymphopenia.[157]

Genetic defect: Vici Syndrome is caused by a biallelic pathogenic variant in *EPG5* gene that is located on the long arm of chromosome 18 (18q12.3-q21.1). *EPG5* gene encodes a protein that has a role in the autophagy pathway (a conserved lysosomal degradation pathway).[158] *Cullup et al.*[158] *2013*, identified compound heterozygosity (2 different mutations in the same patient) in the *EPG5* gene: One was (4588C-T transition), resulting in a (gln1530-to-ter; 615068.0001), and the other one was 1-bp duplication (5704dupT), resulting in a frameshift and premature termination (Tyr1902LeufsTer2; 615068.0002). *Ehmke et al.*[159] *2014*, identified a homozygous mutation (2 similar mutations in the same patient) in exon 43 of the *EPG5* gene; which was (c.7447C-T transition) resulting in an (arg2483-to-ter; 615068.0006). *Maillard et al.*[155] *2017*, identified compound heterozygosity in the EPG5 gene; One was a (c.4007G-A transition), resulting in a (gly1336-to-glu substitution; 615068.0007), and the other one was 1-bp insertion (c.2352_2353insG), resulting in a frameshift and premature termination (Ala785GlyfsTer20; 615068.0008).

Primary Microcephaly with or without Cortical Malformation (MCPH)

The MCPH is an autosomal recessive neurodevelopmental disorder in which an individual has a head circumference more than 3 standard deviations (SD) below the age- and sex-matched population mean.[161] Motor development may be normal or delayed, whereas mental retardation may vary from mild to severely delayed speech acquisition.[162,163]

At least 17 genetic loci (MCPH1–17) have been implicated in MCPH, all of which have now been connected to single genes: *MCPH1*, *WDR62*, *CDK5RAP2*, *KNL1*, *ASPM*, *CENPJ*, *STIL*, *CEP135*, *CEP152*, *ZNF335*, *PHC1*, *CDK6*, *CENPE*, *SASS6*, *MFSD2A*, *ANKLE2*, and *CIT*.[164] Mutations in *WDR62*, encoding WD repeat-containing protein 62, are responsible for MCPH2, which is the second most frequent form of MCPH after MCPH5 caused by *ASPM* mutations. Over 40 pathogenic mutations in WDR62 have already been reported. Cortical malformations may be associated in addition to microcephaly in these patients.[165,166]

Genetic defect: The MCPH2 is caused by homozygous or compound heterozygous mutation in *WDR62* gene (MIM 613583). The *WDR62* gene is located on the long arm of chromosome 19 (19q13.12). *WDR62* gene contains 32 exons and encodes a 1,523-amino acid protein.[167] These researchers identified a homozygous mutation in exon 31 of the *WDR62* gene in 2 Turkish sibs affected with MCPH2. The mutation was a 4-basepair deletion (TGCC) that resulted in a frameshift and premature termination of the protein (Val1402GlyfsTer12; 613583.0001). *Nicholas et al.*[163] *2010*, identified a homozygous 1313G-A transition in exon 10 of the WDR62 gene in 2 Pakistani patients, resulting in an (arg438-to-his substitution; 613583.0006) at a highly conserved residue. *Zombor et al.*,[168] *2019*, identified a homozygous missense mutation in exon 6 of the *WDR62* gene, c.668T>C, p.Phe223Ser. Mutations were detected by whole exome sequencing (WES).

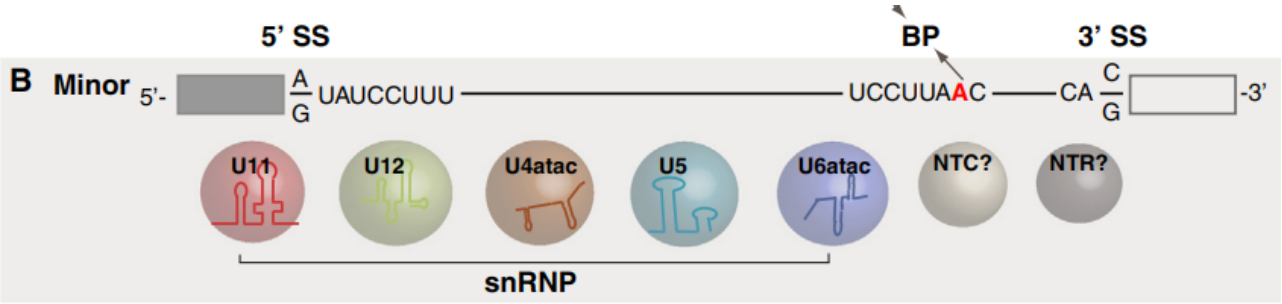

Fig. 12 **The structure of the minor spliceosome *(Chen and Moore, 2015).*[151]**

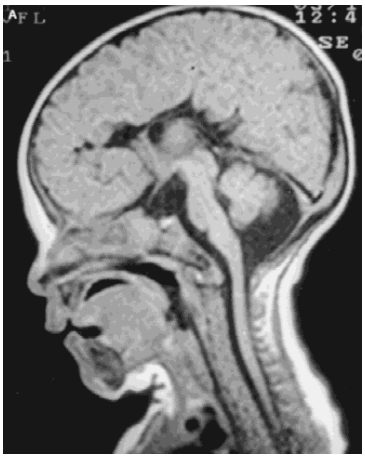

Fig. 13 **Brain MRI T_1 weighted mid-sagittal view showing complete agenesis of the corpus callosum at the age of 2 months in a patient diagnosed with Vici syndrome (*del Campo et al.,*[160] *1999*).**

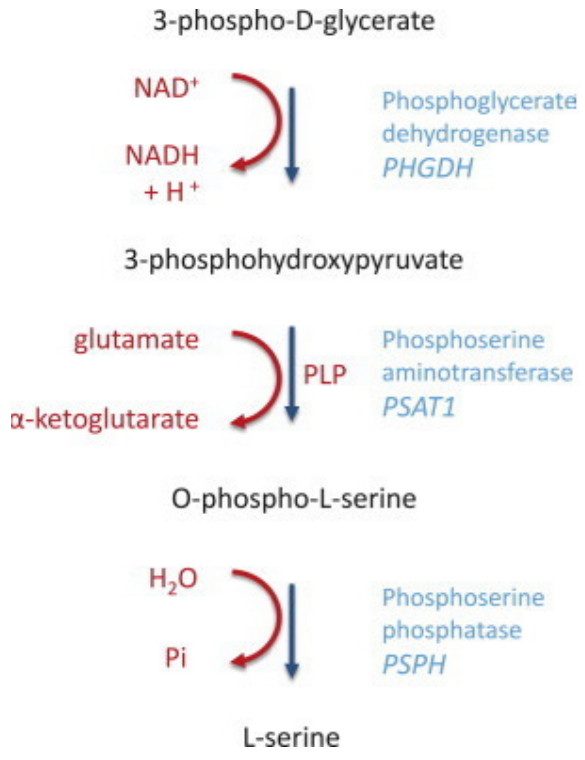

Fig. 14 **L-Serine Biosynthesis Pathway. The first and limiting step of this pathway is the conversion of 3-phosphoglycerate to 3-phosphohydroxypyruvate by PHGDH (*Acuna-Hidalgo et al.,*[172] *2014*).**

Neu-Laxova Syndrome (NLS)

The NLS is a rare autosomal-recessive disorder characterized by characteristic facial features with shortened eyelids, proptosis, round gaping mouth, microcephaly, intrauterine growth restriction (IUGR), ichthyosis (skin hyperkeratosis), and flexion deformities[169] (Figure 14). The CNS malformations reported with NLS were variable such as abnormal gyration, lissencephaly, agenesis of the corpus callosum, Dandy-Walker anomaly, choroid plexus cysts, or neural-tube defects.[170-172] The NLS is caused by mutations in the genes encoding enzymes required for the L-serine biosynthesis pathway; hence it is considered also an inborn error of metabolism (IEM).[173]

Genetic defect: The molecular diagnosis of NLS is confirmed by the identification of biallelic pathogenic variants in one of the 3 causative genes; *PHGDH* gene (phosphoglycerate dehydrogenase gene [MIM 606879]), *PSAT1* gene (phosphoserine aminotransferase 1 gene [MIM 610936]), or *PSPH* gene (phosphoserine phosphatase gene [MIM 172480]).

The *PHGDH* gene is located on the short arm of chromosome 1 (1p12); and encodes 3-phosphoglycerate dehydrogenase enzyme (the first and rate-limiting enzyme in the L-serine biosynthesis pathway). *Shaheen et al.*[174] *2014*, identified 2 mutations in the *PHGDH* gene in Saudi patients clinically diagnosed with NLS. Both mutations were at a region of highly conserved residue within the NAD(P)-binding domain and at the PHGDH dimer interface. The first mutation was c.418G-A transition resulting in a gly140-to-arg substitution; 606879.0007. The second mutation reported by *Shaheen et al.*[174] *2014*, was c.488G-A transition resulting in a arg163-to-gln substitution; 606879.0008. Both mutations were detected by a combination of autozygosity mapping and exome sequencing and confirmed by Sanger sequencing.

The *PSAT1* gene is located on the long arm of chromosome 9 (9q21.2); and encodes phosphoserine aminotransferase enzyme, the second enzyme in L-serine biosynthesis pathway. The *PSAT* gene contains 9 exons and spans 56 kb.[175] *Acuna-Hidalgo et al.*[173] *(2014)* identified a homozygous complex insertion/deletion mutation in the last exon of the *PSAT1* gene in a fetus with Neu-Laxova Syndrome; (c.1023_1027delinsAGACCT) resulting in a frameshift and premature termination (Arg342AspfsTer6; 610936.0003). The mutation was detected by detailed reanalysis of exome sequencing. *Acuna-Hidalgo et al.*[173] *(2014)*, identified another mutation in the highly conserved residue of the *PSAT1* gene in 2 stillborn fetuses and a preterm newborn who died within the first week

of life, who were all affected by NLS. The mutation was c.296C-T transition resulting in an ala99-to-val substitution; 610936.0004.

Conclusion

Many malformations of the central nervous system can occur during fetal development. The prevalence of neural tube defects has decreased over the past few years due to the introduction of antenatal folic acid use, especially during the first trimester. In this review we enlisted many malformations with genetic links. With advancement in the prenatal genetic testing, these abnormalities can be detected using pre-implantation genetic testing on the day-5 embryo or via non-invasive prenatal genetic testing of pregnant women to avoid devastating lifelong sufferings.

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