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Non-motile ciliopathies of the Brain

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Abstract

Non-motile ciliopathies are marked by significant clinical and genetic similarities, as well as substantial phenotypic diversity. Non-motile ciliopathies are characterized by abnormalities in hedgehog signaling, which are frequently associated with abnormalities in cerebral development. A crucial component of the treatment strategy for individuals with cilia-related illnesses is understanding the various manifestations of ciliopathies and developing screening methods for diagnosis. This review summarizes the neurological features of non-motile ciliopathies, their underlying genetics, and the functions of the proteins involved.

Keywords: Cilia, hydrocephalus, orofaciodigital, craniofacial, malformation, dysgenesis

Introduction

Ciliopathies are complicated hereditary multi-system diseases caused by aberrant motile or non-motile cilia assembly or activity. While non-motile sensory/primary cilia are present in the majority of human cells throughout development and/or in adult tissues, motile cilia are only found in certain types of cells. Non-motile ciliopathies are thus marked by significant clinical and genetic similarities, as well as substantial phenotypic diversity. Non-motile ciliopathies are characterised by abnormalities in hedgehog signalling, which are frequently associated with abnormalities in cerebral development [1, 2]. This review summarizes the neurological features of non-motile ciliopathies, their underlying genetics, and the functions of the proteins involved.

Functions of non-motile cilia in the Brain

When neuronal cells were originally shown to have primary cilia via electron microscopic studies of brain tissue samples, the significance of this discovery was not completely understood until decades later [3]. Our understanding of the role of this organelle in controlling neuronal cell fate, differentiation, migration, and signalling has significantly increased as a result of the functional analysis of ciliary genes in animal and cellular models and the analysis of the interactions between primary cilia and pathways crucial for development of brain [4].

The Shh pathway has multiple elements that are dynamically positioned inside mammalian primary cilia at various stages of system activation [5]. Primary cilia are crucial mediators of the Shh pathway in mammals. Neural tube closure deficits, hydrocephalus, and other midline

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anomalies like corpus callosum defects, occipital encephalocele, and holoprosencephaly [6] that are included in the ciliopathy spectrum are caused by dysregulation of Shh signalling resulting from mutations in genes encoding proteins of the signalling system. Additionally, cerebellar granule neuron precursors are primarily driven to proliferate by cilia-assisted Shh signalling [7, 8], and mutations or conditional disruption of specific genes involved in this pathway hypoplasia and cerebellar dysgenesis, a condition that is frequently seen in ciliopathies [9–15].

The Wnt canonical pathway, which has also been linked to cerebellar growth, was discovered to be strengthened by the ciliary protein jouberin, which is encoded by the AHI1 gene. AHI1 mutations in adult subjects cause a striking array of mid-hindbrain anomalies with cerebellar vermis hypodysplasia, the so-called "molar tooth sign" (MTS), comparable to the cerebellar vermian midline fusion defects seen in josuberin knock-out mice [16, 17]. However, other studies indicate that the Wnt pathway is negatively regulated by primary cilia [19] or even that there are no Wnt signalling faults [20], suggesting that the interaction between primary cilia and Wnt may be more intricate than generally believed and that the effect on Wnt may vary depending on the environment. Other signalling pathways associated with ciliary function besides these involve Notch, which was proven to improve cilia-mediated stimulation of the Shh pathway [22], and PDGFR, which is important in increasing directional cell migration.

The direct control of the proliferation, differentiation and directional migration, of both inhibitory and excitatory neurons in the developing cerebral cortex has also been attributed to the neuronal cilia of cortical precursor cells [23]. This is believed to be partially regulated by Shh signalling and partially by guiding cue receptors, such as PDGFR and GPCR, which are located on the interneuronal ciliary membrane [24, 25]. The cilia membrane related small GTPase ARL13B is a crucial ciliary component involved in controlling neuron migration. Its ablation impairs the tracking of certain guidance cue receptors on the cilium as well as the alignment of postmitotic interneurons, which is also accompanied by mislocalized ciliary signalling mechanism [26, 27]. It's interesting to note that Joubert syndrome [JS], a ciliopathy characterised by the MTS and related neurological disorders, is frequently caused by mutations of ARL13B. In the context of JS causing mutations, ARL13B is also involved in the regulation of membrane biosynthesis and cilia length regulation [29]. A small percentage of JS patients have been found to have explicit abnormalities of cortical genesis, like polymicrogyria [30, 31], but it is plausible that more delicate faults of cortical genesis caused by ciliary malfunction may be a factor in the cognitive deficits that are almost always present in JS patients. The absence of crossover of the pyramidal tracts and superior cerebellar peduncles seen in neuropathological and diffusion tensor imaging tractography analyses of JS patients [32, 33] has raised the possibility that the process of axonal steering is also hampered by malfunctioning primary cilia.

The development of adult neural stem cells, a population of neural precursor cells located in the hippocampus dentate gyrus and capable of producing neurons throughout postnatal life, is also

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considered to be aided by primary cilia [35]. Radial astrocyte formation in the dentate gyrus is prevented by embryonic elimination of ciliary genes or Shh pathway elements like Smo, which also prevented postnatal neuronal development [36]. The anorexigenic and orexigenic neurons in the arcuate nucleus of the hypothalamus have been found to have primary cilia, which may play a role in the metabolic control of food consumption and responsiveness to the adipocyte hormone leptin and the pancreatic hormone insulin. In fact, hyperphagia and obesity with elevated levels of leptin, insulin, and glucose were caused by the selective deletion of certain ciliary proteins in adult mice [37]. However, aberrant manipulation of Shh and Wnt signalling, both of which are involved in the control of adipocyte prliferationo, as well as leptin resistance may also be related to the obesity phenotype seen in various ciliopathies [38].

Pathology of non-motile cilia in the brain (genetic basis)

Joubert syndrome (JS)

A unique group of mid-hind brain defects describe the uncommon multisystem ciliopathy known as JS. JS is genetically diverse, involving more than 40 causative genes, just like other syndromic ciliopathies [39]. Except for JS caused by X-linked mutations in OFD1, which is autosomal recessive, the inheritance pattern of JS is autosomal recessive. Cerebellar vermis hypoplasia in conjunction with the "molar tooth sign" (a characteristic feature of JS) are two such abnormalities that can only be identified with imaging [40]. The enlarged, extended, and horizontally aligned superior cerebellar peduncles with an excessively deep interpeduncular fossa are the cause of the "molar tooth sign." On axial MRI, these characteristics may be seen most clearly near the ponto-mesencephalic junction. Extensive clinical diversity is observed in JS. All JS patients by default exhibit the typical neurological problems. A minority of the remaining JS individuals has polydactyly, retinal, liver, and kidney dysfunction in various combinations. About 25% of JS patients do not develop extra-neurological organ system disease [41]. The name "Joubert syndrome and associated diseases," which encompasses COACH and Senior-Lken syndrome (nephronophthisis and retinal degeneration), was used due to the clinical heterogeneity (colobomas, oligophrenia, ataxia, cerebellar vermis hypoplasia, and hepatic fibrosis). More lately, the name "Joubert syndrome" has been used to indicate to all patients with the "molar tooth sign," including those with COACH and Senior-Lken syndrome, for the sake of simplicity.

Majority of JS patients have hypotonia at birth. Within the initial days of life, tachypnea with or without apnea, as well as anomalies in the control of breathing, are frequently observed [39]. Developmental delays, oculomotor apraxia, speech ataxia, and truncal ataxia are additional characteristics that are identified within the first years. Oculomotor apraxia is the term used to describe the inability to move the eyes swiftly and smoothly away from the straight ahead stare, a condition sometimes remedied by head tilting [42].

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In JS, neurocognitive function ranges from normal to very low [43, 44]. A little more than two thirds of people with JS have intellectual disabilities [44]. Verbal understanding and reasoning skills are relative capabilities in JS, but visual scanning, visual discrimination and information processing speed ,are relative weaknesses [44]. The majority of JS patients profit from augmentative and assistive communication devices, occupational, physical and speech,therapy, and special education [43, 44]. Some JS patients exhibit additional neurological problems along with the molar tooth sign and cerebellar vermis hypoplasia, such as enlarged cerebellar hemispheres, an enlarged posterior fossa (similar to Dandy-Walker deformity), malformations in the brainstem, mild ventriculomegaly (which typically does not need shunting), and malrotation of the hippocampi [40]. Cerebellar vermis hypoplasia was found to be the best indicator of neurodevelopmental consequences in JS; the more serious the vermis hypoplasia, the more serious the neurocognitive defects [40]. This was determined through a systematic re-examination of the brain MRIs of more than 120 JS patients in the framework of neurocognitive activity. Less than 10% of those who have JS experience seizures [44]. Notably, diffuse background slowing in the EEG, which occurs more frequently (28%, including in seizure-free subjects), is linked to worse cognitive performance. Additionally, persons with JS have significant rates of behavioural and psychiatric issues, but these percentages are relatively low in comparison to other populations with developmental delays [44].

Up to 94% of JS cases can be explained by the identification of over 40 pathogenic genes. Some of the genes linked to the development of JS include AHI1, ARL13B, ARMC9, CEP104, KATNIP, PDE6D, and TCTN1. Other ciliopathies such as Meckel syndrome (MKS), isolated nephronophthisis (NPHP), Leber congenital amaurosis (LCA), oral-facial-digital syndromes (OFDS), Bardet-Biedl syndrome (BBS), and more have all been linked to practically all JS genes. The majority of the genes linked to JS and associated ciliopathies are found in the mother centriole, the primary cilium, the basal body, or the regulatory proteins and transcription factors that control its growth and function [45].

Meckel-Gruber syndrome (MKS)

MKS is a severe form of ciliopathy that affects around 1 in 135,000 newborns globally. Higher occurrences have been noted among Kuwaiti Bedouin groups, Tatars, Hutterites, Gujarati Indians, and Finnish people [46, 47]. MKS is often identified by the triad of postaxial polydactyly, enlarged cystic kidneys, and occipital encephalocele [47]. Another common observation is congenital hepatic fibrosis [48]. Cleft lip and/or palate, congenital heart problems, bending and shortening of long bones, and malformed male genitalia have been reported in up to 40% of cases. Situs defects, thyroid or lung cystic dysplasia, and retinal colobomas are less common abnormalities. Due to the severity of its symptoms, MKS is frequently fatal during intrauterine life. Rare cases of MKS are reported to have lived through the first several years of life, as predicted, given its allelic overlap with JS [46, 47].

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The severity of the central nervous system abnormalities in MKS varies greatly and can range from complete craniorachischisis to partial deficits of the corpus callosum. Typically, these abnormalities involve elements from one of three categories: 1) prosencephalic dysgenesis (arhinenecephaly-holoprosencephaly, microphthalmia, small optic nerves 2) Occipital exencephalocele, (extrusion through a large posterior fontanelle) 3) rhombic roof dysgenesis with varying degrees of posterior fossa abnormalities (cerebellar vermis agenesis/dysgenesis, absence of the brainstem tectum, anomalies resembling Dandy-Walker anomalies). Pachygyria and polymicrogyria are particularly prevalent [49, 50]. At least 21 distinct genes have been attributed to Meckel syndrome, and for at least 18 of these, JS also has been linked to pathogenic alterations. In certain instances, mutations anticipated to have more minor impacts on protein function are connected with JS, whereas more severe variations are linked with Meckel syndrome. There are certain families where the same pathogenic mutations can produce both JS and Meckel syndrome [51, 52, 53].

Bardet-Biedl Syndrome (BBS)

Retinal dystrophy, renal disease, obesity, cognitive impairment, postaxial polydactyly, male hypogonadotropic hypogonadism, and female genitourinary anomalies are characteristic features of this autosomal recessive ciliopathy known as Bardet-Biedl syndrome (BBS) . More than 21 genes have been linked to BBS as of now. One in 100,000 to one in 160,000 North Americans and Europeans are affected with BBS. It is more common among the Bedouin community of Kuwait and Newfoundland. Clinical characteristics are used to determine the diagnosis of BBS. Four primary features (retinal dystrophy, postaxial polydactyly, obesity, renal malformations and/or kidney dysfunction, hypogonadism, and cognitive impairment) are required. Alternatively, there must be three primary characteristics and two secondary features. Behavioral abnormalities, type 2 diabetes mellitus, oral/dental abnormalities, mild hypertonia, anosmia, brachydactyly/syndactyly, poor coordination/ataxia/imbalance, cardiovascular anomalies, developmental delay, speech abnormalities, liver disease, Hirschsprung disease, subtle craniofacial dysmorphism and eye abnormalities such as cataracts, strabismus, and astigmatism are secondary features. BBS shows both inter- and intrafamilial phenotypic diversity and varied expressivity [54, 55].

The majority of BBS patients have minor cognitive impairment [56–58]. A formal neurodevelopmental assessment of 24 BBS patients with molecular diagnoses revealed that the subjects' mean intelligence was 1.5 standard deviations below average. However, only a small percentage of individuals met the definition of "intellectual disability". Verbal fluency fell within the typical range for about half of the patients. The majority of BBS patients, however, had substantial impairments in perceptual reasoning, attentional ability, and functional independence [57].

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Through linkage analysis of extensive BBS pedigrees, the first five BBS loci were discovered. short time later, the appropriate genes were cloned. MKKS, a gene already known to cause McKusick-Kaufman syndrome, was the first gene attributed to BBS; because it did not correspond to any of the previously recognised BBS loci, it was given the label BBS6. There are now 21 known BBS genes (BBS1-BBS20 and NPHP1), and as a result of the development of exome sequencing and examination of formerly underexplored populations, their number is expected to rise. Surprisingly, all BBS genes act in cilia, either directly or indirectly through membership in BBSome, the chaperonin complex, the basal body, or other biological processes. The disruption of any of these genes results in cilia dysfunction since they appear to be non-redundant [58].

Orofaciodigital syndromes

A class of uncommon developmental abnormalities known as the oral-facial-digital syndromes (OFDS) are defined by anomalies of the face, mouth, and fingers. Additional symptoms often seen include the brain and other visceral organs, such as the kidney. The most common kind of OFD is type I, which is easily distinguished by its usual X-linked dominant male-lethal pattern of inheritance in the family. The majority of the other OFDS are sporadic occurrences and are transmitted as autosomal recessive diseases. Eleven genes that cause OFDS have been shown to be involved in recent years, enabling a clear clinical and genetic description of this diverse disorder. Based on the most recent molecular data, we can distinguish between (1) two more common types (OFDI and OFDVI), for which the causative gene has been identified, (2) four rare subtypes (OFDIII, OFDIV, OFDIX, and OFDXIV), for which the causative gene has also been identified, allowing molecular diagnosis, (3) two unclassified rare OFD subtypes whose causative genes have been identified but still need further clinical and molecular validation. Neurological manifestations include agenesis of the corpus callosum, cerebellar hypoplasia, porencephaly, hydrocephaly, cerebellar vermis hypoplasia, dandy walker malformation with cystic dilation of the iv ventricle, myoclonia, occipital encephalocele, vermis hypoplasia, sylvius aqueduct stenosis, myelomeningocele and leucoaraiosis [60–63].

In 2001, the gene for OFD type I was discovered, and for a long, it was the only known OFD gene. A variety of genes that code for additional OFDS have been discovered during the past few years, mostly using next-generation sequencing techniques. Except for DDX59 and C5ORF52, the bulk of the discovered OFD genes localise to function and development of the cilia. Functional investigations showed that OFD1 functions at the distal centriole to create distal appendages, which, however in a content-specific manner, aids in cilia development. Additionally, in vivo and in vitro research has shown that faulty Shh and Wnt signalling is present in OFD1-depleted mice. The skeletal abnormalities seen in OFDI patients may be explained in part by the disruption of Shh signalling from early on in development [62 - 67].

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Physical interaction occurs between TCTN3 and TMEM231, which are both parts of an MKS complex located near the transition zone of primary cilia. They are both necessary for ciliogenesis and Shh signalling, according to functional analyses [68, 69]. The loss of TMEM216, which is localised at the base of primary cilia affects cilio development and centrosomal docking, along with hyperactivated RhoA and Dishevelled. Both TMEM107 and the WDPCP proteins, which are involved in cilia development and planar cell polarity, are found in the transition zone and are necessary for Shh signalling [70]. Although its specific location inside cilia is unknown, TBC1D32 is a ciliary protein [71]. According to functional analyses, TBC1D32 regulates cilia shape and is necessary for the Shh pathway [72]. At centrioles, where C2CD3 co-localizes, OFD1 physically interacts with SCLT1 and C2CD3. C2CD3, SCLT1 and C2CD3 are important for mouse Hedgehog signalling and cilia development [73]. The function of C5ORF42, also known as NKAPP1, in cilia or cilia-mediated signalling is unknown, and it is inadequately understood [74]. Last but not least, DDX59 is a DEAD-box-containing RNA helicase with a still unidentified role in cilia. Functional experiments indicated that in the context of diminished Shh signalling, fibroblasts from afflicted people exhibit a typical cilia development pattern [75].

According to the evidence outlined above, centrosomal and centriolar function appear to play a significant role in the pathological mechanisms underpinning the OFD syndrome, and elements of these cilia and thier cellular compartments should be taken into consideration as candidate genes for the unexplained OFDS. How much of the phenotypic is caused by cilia failure and how much is attributable to gene activities unrelated to cilia is one of the perplexing problems in OFDS as well as in other ciliopathies. Skeletal and some neurological symptoms might be explained by Shh deficiency, which has been related to the ciliary function in several cases of OFDS. However, proteins may have distinct intracellular locations and activities, as we are discovering through omics techniques. For now we know that OFD1 is found in the nucleus and centrosome/basal body [78, 79]. Future research will explain how the OFD genes' non-ciliary actions contribute to the clinical range of these diseases.

Acrocallosal syndrome

Agenesis of the corpus callosum, macrocephaly, hallux duplication, polydactyly, minor craniofacial deformities, and severe psychomotor impairment are all features of the recessive disorder known as acrocallosal syndrome (ACLS). KIF7 mutations have been linked to either an ACLS, JS, or Hydrolethalus syndrome, which is typically a fatal disorder accompanied with midline brain malformations including hydrocephalus or anencephaly, suggesting that these conditions are allelic [80, 81].

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Hydrolethalus syndrome

A research of Meckel syndrome in Finland led to the initial discovery of Hydrolethalus (HLS) syndrome, an autosomal recessive lethal disease with a severe brain deformity. Lethality, polyhydramnios, and hydrocephalus are all referred to as hydrolethalus. The majority of face malformations, congenital heart defects, anomalies of the respiratory system, bifid uterus, and other genital deformities are present in the patients that have been recorded. Micrognathia, polydactyly, and improper lung lobation are additonal common abnormalities. A missense mutation in the HYLS1 gene situated on chromosome 11 is known to cause hydrolethalus syndrome [82].

HYLS1 was initially identified as the gene responsible for HLS, a rare recessive fatal hereditary condition that causes significant problems in foetal development resulting in birth defects [83]. First, C. elegans was used as a model organism to thoroughly investigate its function. According to research by Dammermann et al., the centriole protein HYLS1 is attracted to the outer centriole wall through an interaction with the central centriolar protein SAS-4/CPAP. Surprisingly, while HYLS1 is primarily implicated in cilia development in C. elegans, it is dispensable for cell division, embryonic viability and centriole assembly in worms. Then, by controlling the development of the ciliary gate, showing that HYLS1 is essential for attracting the TF protein FBF1, and showing that it controls ciliogenesis, and plays a small role in TZ assembly [84].

Greig cephalopolysyndactyly syndrome

Gli3 has a significant role in the structuring of the forebrain in both mice and humans, according to genetic data. Greig cephalopolysyndactyly syndrome and Pallister-Hall syndrome are the two primary syndromes associated with brain abnormalities in humans and are connected to heterozygous mutations in GLI3. Greig cephalopolysyndactyly involves macrocephaly with frontal bossing, hypertelorism linked with polysyndactyly, and may be related to various mutations within the GLI3 gene, including complete gene deletions [86]. Gli3 is a crucial component of the telencephalic development in mice. The mouse extra-toes mutant, which is a null Gli3 mutant, has an enlarged subpallium, particularly in the most anterior area, a drastically diminished dorsomedial telencephalon as well as lacks olfactory bulbs [87, 88]. Additionally, Gli3 regulates the transition of cortical radial glial cells from symmetric proliferative to asymmetric neurogenic cell replication [89]. Compelling evidence suggest that Gli3 functions primarily as a repressor comes from the fact that the dorsal telencephalon primarily develops Gli3R and twin embryos partially restore telencephalic patterning [90]. Gli3 has a role in the development of the hypothalamus, diencephalon, and eyes as well [91, 92]. While mouse Gli3 mutants have symptoms like Greig cephalopolysyndactyly, the Gli3Δ699 mouse mutant exhibits constitutive repressor activity and resembles PSH [93]

Pallister–Hall syndrome

The GLI3 gene, a zinc finger transcription factor gene located on chromosome 7p14.1, is the source of the heterozygous mutation that leads to Pallister-Hall syndrome (PHS), a rare

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autosomal dominant disease with unknown prevalence [94]. A transcription factor called GLI3 is recognised as a mediator in ciliary signalling. Congenital hypothalamic hamartoblastoma syndrome, often known as PHS, was named in 1980 [95]. Indeed, the presence of hypothalamic hamartomas (HHs) is the key characteristic of PHS. usually located at the base of the brain, on the third ventricle floor, close to the tuber cinereum and the mammillary bodies, HHs are typically small, 0.5-2 cm in diameter, slowly-growing abnormalities of grey matter made of hyperplastic neurons. "Giant HHs" are defined as HHs with a dimension less than 40 mm[96]. As HHs develop over time, seizures, panhypopituitarism, and visual impairment may appear due to their position in such an expressive part of the brain [97]. Additionally seen in PHS were central polydactyly and pituitary dysfunction. The majority of the GLI3 gene's mutations that cause Pallister-Hall syndrome occur close to its centre and result in a shortened Gli protein with constitutive repressor activity [98]. In occasional instances of hypothalamic hamartomas with gelastic epilepsy, somatic mutations in GLI3 and the PRKACA gene, which codes for a PKA subunit implicated in the synthesis of Gli3R, have been identified [99].

Conclusion

A crucial component of the treatment strategy for individuals with cilia-related illnesses is understanding the various manifestations of ciliopathies and developing screening methods for diagnosis. Specific ciliopathies are being treated with targeted medications and gene-based treatments such as gene substitution, exon skipping and gene editing.

S.No.	Ciliopathy	Neurological manifestation
1	Joubert syndrome	Cerebellar vermis hypoplasia Molar tooth sign Hypotonia Developmental delay Speech ataxia Truncal ataxia Oculomotor apraxia Neurocognitive deficit
2	Meckel-Gruber syndrome	Occipital encephalocele prosencephalic dysgenesis Occipital exencephalocele Rhombic roof dysgenesis Cerebellar vermis agenesis/dysgenesis Absence of the brainstem tectum Anomalies resembling Dandy-Walker anomalies Pachygyria Polymicrogyria

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3	Bardet-Biedl Syndrome	Behavioral abnormalities Mild hypertonia Poor coordination/ ataxia/ imbalance Developmental delay Subtle craniofacial dysmorphism
4	Orofaciodigital syndromes	Agenesis of the corpus callosum Cerebellar hypoplasia Porencephaly Hydrocephaly Cerebellar vermis hypoplasia Dandy walker malformation with cystic dilation of the iv ventricle Myoclonia Occipital encephalocele Vermis hypoplasia Sylvius aqueduct stenosis Myelomeningocele Leucoaraiosis
5	Acrocallosal syndrome	Agenesis of the corpus callosum Macrocephaly Minor craniofacial deformities Severe psychomotor impairment
6	Hydrolethalus syndrome	Hydrocephalus Keyhole foramen magnum Craniofacial malformations
7	Greig cephalopolysyndactyly syndrome	Macrocephaly with frontal bossing Seizures Mental retardation Developmental delay Subtle craniofacial dysmorphic features
8	Pallister–Hall syndrome	Hypothalamic hamartoblastoma Craniofacial malformations Developmental and postnatal retardation Holoprosencephaly Pituitary agenesis/dysgenesis with hormone dysfunction

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