Clinical genetics and pathobiology of ciliary chondrodysplasias

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Abstract Ciliary chondrodysplasias represent a heterogeneous group of rare, nearly exclusively autosomal recessively inherited developmental conditions. While the skeletal phenotype, mainly affecting limbs, ribs and sometimes the craniofacial skeleton, is predominant, extraskeletal disease affecting the kidneys, liver, heart, eyes and other organs and tissues is observed inconsistently. Significant lethality, resulting from cardiorespiratory failure due to thoracic constriction as well as from renal and hepatic insufficiency or primary cardiac failure due to congenital heart disease, is observed with these conditions. The underlying genetic defects as well as developmental biology and cell biology work undertaken using animal model systems, suggest that these rare conditions result from ciliary malfunction. The skeletal phenotype is believed to result from imbalances in the hedgehog signaling pathway that normally occurs in functional cilia in chondrocytes. Although phenotypes have been historically distinguished based on clinical features into short-rib polydactyly syndrome, Jeune asphyxiating thoracic dystrophy, Mainzer-Saldino syndrome, Sensenbrenner syndrome (cranioectodermal dysplasia), oral-facial-digital syndrome and Ellis-van Creveld syndrome, recent research suggests that there is significant genetic as well as phenotypic overlap between the conditions. This review discusses ciliary chondrodysplasias from phenotypic hallmarks to clinical management and summarizes progress in identification of the underlying molecular mechanisms as well as potential future therapeutic perspectives.

Keywords: Cilia, chondrodysplasia, Jeune syndrome, short-rib polydactyly syndrome, Sensenbrenner syndrome

1. Introduction

The term “ciliary chondrodysplasias” summarizes inherited conditions resulting from cilia malfunction affecting skeletal development in mammals. Estimated disease frequencies are 1 in 200,000 [1] to more than 1,000,000 in western populations [2], but can be higher in genetically isolated populations [3]. However, as no large patient studies have been performed, no exact numbers are available.

Cilia are hair-like organelles projecting from the surface of cells and can be divided into two main subgroups: motile cilia, occurring in bundles of hundreds and single non-motile (primary) cilia. While the presence of motile cilia is restricted to highly specialized tissues such as the respiratory tract, brain ventricles, reproductive tract and embryonic node in mammals, primary cilia can be found on nearly every cell throughout the organism. Each cilium contains nine pairs of microtubules (9 + 0 structure) and a 10th pair, the so-called central pair, is additionally present in motile cilia (9 + 2 structure). These motile cilia also contain other proteins necessary for the motile apparatus such as dynein arms and radial spokes not
Ciliary chondrodysplasias represent a group of phenotypically and genetically related disorders inherited in an autosomal recessive fashion including short-rib polydactyly syndromes, which are also referred to as short-rib thoracic dystrophy (SRPS; MIM 611263, MIM 613091, MIM 263520, MIM 269860, MIM 614091), Jeune asphyxiating thoracic dystrophy or Jeune syndrome (JATD; MIM 208500), Mainzer-Saldino syndrome (MIM 266920), Soguren syndrome or cranio-ectodermal dysplasia (CED; MIM 218330), oral-facial-digital syndrome 4 (OFD4; MIM 258860) and Ellis-van Creveld syndrome (EVC; MIM 225500). An exception from this inheritance pattern is Weyers acrodental dysostosis (WAD; MIM 193530), which is caused by heterozygous mutations in the EVC genes. Recently, ciliary chondrodysplasias with narrow thorax and polydactyly such as SRPS and JATD have also been summarized under the term short-rib thoracic dystrophy (SRTD). However, the current SRTD classification in MIM takes only into account the underlying genetic cause while the former SRPS and JATD classification was based on phenotypic features. This can be confusing, therefore in this review I will relate to the previous established clinical classification of ciliary chondrodysplasias. Clinical hallmarks of the ciliary chondrodysplasia group include shortened limbs and ribs, polydactyly and sometimes craniofacial

observed in primary cilia. Figure 1 depicts a simplified schematic of the ciliary ultrastructure. The main function of motile cilia is fluid movement and mucociliary clearance. Defects in genes encoding for proteins of the motile apparatus lead to a cystic fibrosis-like disease named primary ciliary dyskinesia (PCD; MIM 244400). Roughly, half of individuals affected by PCD present with laterality defects, which are due to impaired motile ciliary function in the embryonic node [4]. Laterality defects can also occur in non-motile ciliopathies, usually in combination with many other features. Over the past two decades, an increasing number of human genetic conditions have been linked to malfunction of primary cilia, such as polycystic kidney disease (MIM 173900, MIM 613095, MIM 236200), nephromegaly (NPHP; MIM 256100), Joubert syndrome (MIM 213300), Bardet-Biedl syndrome (MIM 209900), Alstrom syndrome (MIM 203800) and the ciliary chondrodysplasias, which are highlighted in this review [5].

Fig. 1. Schematic of the ciliary ultrastructure. Primary cilia consist of nine pairs of microtubules, while motile cilia display an additional central pair as shown in the cross-sections. The ciliary axoneme extends from the basal body, the former mother centriole of the cell, and is covered by ciliary membrane. Transition zone fibers connect ciliary membrane with the cilium and are thought to form a barrier towards the cellular cytoplasm. The ciliary pocket has been identified as a hub for cell signaling pathways and it is thought that proteins produced within the cell body are transported to the ciliary pocket within vesicles.
malformations such as craniosynostosis. Renal, liver, eye, heart and other organ involvement may be additionally present and phenotype severity varies significantly between the different conditions, but also between patients with the same condition [6]. The most severe thoracic constriction is usually seen in SRPS and JATD. The thoracic phenotype in SRPS is not compatible with life beyond the early neonatal age due to cardiorespiratory failure, while approximately 40% of affected individuals with JATD survive into adulthood after a period of intensive care and threat of cardiopulmonary arrest during infancy [7]. In contrast to SRPS and JATD, individuals with MZSDS and CED usually display a much milder rib phenotype, but frequently develop extraskeletal symptoms such as dysplastic finger and toenails, hair and teeth abnormalities [8]. Finally, EVC is frequently associated with congenital heart anomalies such as primary atrial septation defects [10, 11]. A complete overview of ciliary chondrodysplasias is shown in Table 1.

2. Clinical features of ciliary chondrodysplasias

As briefly described above, extensive phenotypic overlap is observed between different conditions of the ciliary chondrodysplasias disease spectrum, so that clinical diagnosis can be difficult to make, especially in fetal cases. Radiographs of the skeleton play a crucial role, but even for experts it may be difficult to distinguish between the different forms [12]. This might appear arbitrary, however, making a precise diagnosis may help to predict the clinical course: SRPS are always lethal [6], MZSDS and CED have a milder rib phenotype but higher rate of renal, retinal and liver disease than classical JATD [8, 13–15] while in EVC, severe heart defects are most frequent [10, 16]. Nevertheless, knowing the underlying genetic defect might represent a more suitable prediction tool for disease severity and phenotypic features than applying a clinical disease term. Further, identification of the causative gene improves opportunities for genetic counseling.

2.1. Phenotypic spectrum of perinatal lethal SPRS

The phenotypic SRPS disease group consists of SRPS I-V, but JATD could be considered as the mild end of the spectrum: while polydactyly is a consistent feature of SRPS, it is rarely observed in JATD and the rib phenotype is usually milder in JATD accounting for reduced lethality compared to SRPS. Further, while extraskeletal malformations of the brain, heart, kidneys, liver and pancreas can be frequently observed in SRPS in prenatal ultrasound examinations, this is usually not the case for JATD. Five subtypes of SRPS are phenotypically distinguished: SRPS-I (Saldino-Noonan type; MIM 613091 [17]), SRPS-II (Majewski type; MIM 263520 [18]), SRPS-III (Verma-Naumoff type; MIM 613091 [19]), SRPS-IV (Beemer-Langer type; MIM 269860 [20]) and SRPS-V (MIM 614091 [21]). Typical clinical SRPS features are displayed in Fig. 2.

2.1.1. SRPS-I and SRPS-III

Similar to SRPS-II and IV, polydactyly, hydroropic appearance and small thorax with short horizontal ribs causing cardiorespiratory lethality, is observed in SRPS-I. However, the typical hallmark of SRPS-I is extreme micromelia resulting in ‘flipper-like’ limbs [17]. Ossification defects of the vertebrae, pelvis, as well as of the bones of the hands and feet are also frequently observed. Pelvic anomalies include small ilia with flattened acetabular roofs with ossified spurs, resembling the pelvis configuration in EVC and JATD. Polycystic kidneys, transposition of the great vessels as well as atrietic lesions of the gastrointestinal and genitourinary systems are reported extraskeletal features [22–24]. SRPS-III shares the typical features of SRPS such as hydroropic appearance at birth, short long bones, short horizontal ribs, narrow thorax and protuberant abdomen, but is additionally characterized by a short cranial base, bulging forehead, depressed nasal bridge and flat occiput [19]. Radiologically, the long tubular bones show a corticomediullary demarcation, slightly widened metaphyses and marked longitudinal

M. Schmidts / Ciliary chondrodysplasias
| Condition | Inheritance | Skeletal phenotype | Renal phenotype | Retinopathy | Liver phenotype | Obesity | Developmental delay | Situs inversus | Other | Gene |
|-----------|-------------|--------------------|----------------|-------------|----------------|--------|----------------------|---------------|-------|------|
| SRPS      | Autosomal recessive | Most often polydactyly, short ribs, shortened long bones, brachy-dactyly, abnormal pelvis configuration, sometimes orofacial clefts | Often, NPHP-like or polycystic | Not evident at or near birth | Cysts and fibrosis may occur | Not applicable (early lethality) | Rarely | Always lethal perinatal due to cardio-respiratory insufficiency resulting from severe thoracic constriction. Heart defects and gastro-intestinal anomalies occur | | DYNC2H1, NEK1, WDR60, WDR35, WDR34 |
| OFD1      | Autosomal recessive | Variable rib shortening, often polydactyly, micrognathia, orofacial clefts, disproportional small and oval tibia | Cystic-dysplastic | | Cysts and fibrosis may occur | Brain defects | – | Lateralized tongue, coloboma, ambiguous genitalia, anal atresia, deafness have been observed | | TCTN3 |
| JNTD      | Autosomal recessive | Short ribs, shortened long bones, polydactyly, abnormal pelvis configuration, scoliosis, orofacial clefts | Rarely | Frequently elevated liver enzymes but rarely progression into liver failure | | – | Not described | Often severe cardio-respiratory distress with ∼40% lethality | DYNC2H1, WDR60, IFT100, IFT112, IFT140, WDR34, TTC21B, CSPP1 |
| MZSDS     | Autosomal recessive | Usually, mainly NPHP-like, rarely cystic | Always | Cholestasis and hepatic fibrosis | | – | Not described | Mild thorax phenotype, usually no cardiorespiratory lethality | JFT140, IFT172 |

**Table 1**
Clinical hallmarks and underlying gene defects of ciliary chondrodysplasias
| Condition       | Inheritance | Skeletal phenotype                                      | Renal phenotype | Retinopathy | Liver phenotype | Obesity | Developmental delay | Situs inversus | Other                                      | Gene                  |
|-----------------|-------------|--------------------------------------------------------|-----------------|-------------|-----------------|---------|---------------------|---------------|-------------------------------------------|-----------------------|
| CED             | Autosomal recessive | Mildly short ribs, brachydactyly, craniosynostosis leading to dolichocephalus | Very often, mainly NPHP-like | Sometimes | Inconsistent hepatic cysts and thrombosis, ductal plate malformation | Sometimes | Usually not | Facial dysmorphism with telecanthus/epicanthus, high forehead, broad nasal bridge, low-set prominent ears, thin and sparse growing hair, nail dysplasia, teeth abnormalities, heart defects; usually mild thorax phenotype and no cardiorespiratory lethality | IFT122, WDR19, IFT43, MKDA5 |
| EVC             | Autosomal recessive | Short ribs and long bones, abnormal pelvic configuration, polydactyly of the hands | –                | –           | –               | –       | –                   | –             | Hypoplastic nails, teeth abnormalities, heart defects | EVC, EVC2             |
| Weyers acrodental dysostosis | Autosomal dominant | Short stature, short extremities, polydactyly of the hands | –                | –           | –               | –       | –                   | –             | Hypoplastic nails, teeth abnormalities | EVC, EVC2             |

SRPS = Short-rib polydactyly syndrome; OFD4 = Oral-facial-digital syndrome 4; JATD = Jeune asphyxiating thoracic dystrophy; MZSDS = Mainzer-Saldino syndrome; CED = Cranio-ectodermal dysplasia; EVC = Ellis-van Creveld syndrome; NPHP = Nephronophthisis.
Fig. 2. Phenotypic features of short-rib thoracic dystrophy, oral-facial-digital syndrome 4 and Jeune asphyxiating thoracic dystrophy. Radiological hallmarks of short-rib polydactyly syndrome (A) and oral-facial-digital syndrome 4 (B, C) including shortened long bones and short horizontal ribs, small thorax, protruding abdomen and polydactyly. (D–I) Clinical features of Jeune asphyxiating thoracic dystrophy: narrow thorax (D, G, H), horizontal short ribs and handlebar clavicles (D), acetabular spurs (F) and cone-shaped epiphyses of the phalanges (E). Polydactyly is rarely observed (I). Reprinted with permission from El Hokayem et al. NEK1 and DYNC2H1 are both involved in short-rib polydactyly syndrome. J Med Genet 2012;49(4):227-33. Copyright 2012 J Med Genet. (Picture A); Thomas et al. TCTN3 mutations cause Mohr-Majewski syndrome. Am J Hum Genet 2012;91(2):372-8. Copyright 2012 Am J Hum Genet (pictures B and C); Halbritter et al. Defects in the IFT-B component IFT172 cause Jeune and Manizer Saldino syndromes in humans. Am J Hum Genet. 2013; 93(5):915-25. Copyright 2013 Am J Hum Genet. (pictures D, G and I); Schmidts et al. Combined NGS approaches identify mutations in the intraflagellar transport gene IFT140 in skeletal ciliopathies with early progressive kidney disease. Hum Mut 2013; 34(5):7714-24. Copyright 2013 Hum Mut (picture E).

The structure of the pelvis in SRPS-III resembles the pelvis configuration observed in SRPS-I, EVC and JATD. Although commonly observed, polydactyly is not completely penetrant. Cleft lip and palate are reported as well as malformation of the larynx and epiglottis [25, 26]. In contrast to SRPS-I, where developmental urogenital defects seem common, those are rarely observed in SRPS-III [27].
2.1.2. SRPS-II, SRPS-IV and OFD4

The clinical picture in SRPS-II and SRPS-IV is quite similar with hydropic appearance at birth, short long bones, small and narrow thorax with horizontal ribs and protuberant abdomen [18], but in contrast to SRPS-II, polydactyly is often absent in SRPS-IV. Also, disproportional short tibia (the tibia is shorter than the fibula), a hallmark of SRPS-II, is not observed in SRPS-IV [23]. However, dysplastic tibia also occur in OFD4 (Mohr-Majewski syndrome, Baraitser-Burn syndrome; MIM 258860), presenting with variable thoracic constriction, pre- and postaxial polydactyly of hands and feet, cleft and pseudo-cleft of the lip and/or palate, lobulated tongue, cystic dysplastic kidney and liver involvement, brain malformations [28], severe bilateral deafness [29] and coloboma of the eye [30]. Orofacial clefts, cerebral malformations and renal involvement are also observed in SRPS-II [23, 31], and SRPS-IV [3, 20, 32, 33].

2.1.3. SRPS-V

SRPS-V was only recently described and the underlying genetic defect identified in two consecutively affected pregnancies of a mother from Maori descent from New Zealand. Hydrops, narrow chest and severely shortened and bowed long bones displaying lack of ossification, hypoplastic scapulae, and peritoneal calcifications, postaxial poly-syndactyly and cleft palate were reported. Extraskeletal findings include bilateral cystic hygroma, hypospadias, mainly glomerular kidney cysts and intestinal malrotation. Acromesomelic hypomineralization and campomelia distinguish SRPS-V from SRPS subtypes I-III [21, 34].

2.2. Phenotypic spectrum of childhood chondrodysplasias

There are a number of ciliary chondrodysplasias that have significant overlap with the SRPS, but that are less severe and occur in childhood and therefore have been summarized with SRPS under the term SRTD. These include JATD, MZDS, CED, and EVC. WAD in contrast does not affect the thorax.

2.2.1. JATD

JATD is characterized by a narrow, sometimes bell-shaped thorax due to shortening of the ribs, which restricts pulmonary development and may cause severe respiratory distress during the first two years of life, but compared to SRPS, the phenotype is less severe (Fig. 2). Respiratory problems account for most of the mortality in JATD ranging from 20-60% [1, 7, 35], but patients seem to somewhat “grow out” of the respiratory phenotype [7, 35, 36]. Other skeletal hallmarks include pelvis abnormalities similar to those observed in SRPS-I, III and EVC, cone-shaped epiphyses and infrequently polydactyly (Fig. 2). End-stage renal disease in childhood due to NPHP-like (and rarely cystic) kidney involvement affects probably less than 20% of all individuals with JATD, and seems to depend mainly on the underlying genetic defect with mutations in IFT140 and IFT172 predicting this phenotype with nearly 100% probability [8, 13, 14]. Patients with mutations in one of those two genes also develop retinal degeneration, while this phenotype has been described as “rare” in literature [37, 38]. However, Baujat et al. [35] observed electroretinogram (ERG) abnormalities in up to 50% of JATD patients with DYNC2H1 mutations but it is not clear to date how many of these patients will develop clinically relevant retinal disease later on. Pancreatic lesions [39], elevated liver enzymes [13, 40] and brain malformations [13, 41, 42] can also occur in JATD. The latter are rare in JATD, but common in Joubert syndrome and can be imaged as a so-called molar tooth sign on magnetic resonance imaging.

2.2.2. MZDS

Like JATD, MZDS is described as “cono-renal syndrome” due to cone-shaped epiphyses observed radiologically after the first year of life (Fig. 3). This phenotype occurs in association with impaired renal function (due to both polycystic disease and NPHP) and retinal degeneration. Similar as in JATD, the thorax of MZDS patients is often narrow but to a milder degree [23, 43–45] (Fig. 3). JATD and MZDS diseases are considered allelic disorders [8, 13, 14]. Like in JATD, age of onset and speed of progression for renal and retinal disease vary between and even within families and complicates accurate prognosis for these patients. Additionally, the information that is currently available about retinal disease relies on different tests (ERG, fundoscopy) that are not equally sensitive, e.g. fundoscopy may appear normal in case of retinal degeneration without pigmentary deposits and although ERG is very informative, it is difficult to obtain reliable ERG results in non-cooperative young children. In summary, accurate conclusions cannot be drawn at the moment but childhood onset for renal
Fig. 3. Clinical hallmarks of Mainzer-Saldino syndrome and Sensenbrenner syndrome. Mildly narrowed thorax (A, B) and brachydactyly with cone-shaped epiphyses of the phalanges (C) define the skeletal phenotype in Mainzer-Saldino syndrome. Reprinted with permission from Perrault et al. Mainzer-Saldino Syndrome is a ciliopathy caused by IFT140 mutations. Am J Hum Genet 2012;90(5):864-70. Copyright 2012 Am J Hum Genet. (picture A); Schmidts et al. Combined NGS approaches identify mutations in the intraflagellar transport gene IFT140 in skeletal ciliopathies with early progressive kidney disease. Hum Mut 2013; 34(5):7714-24. Copyright 2013 Hum Mut (picture c); reprinted with permission from Walczak-Sztulpa et al. Cranioectodermal dysplasia, Sensenbrenner syndrome, is a ciliopathy caused by mutations in the IFT122 gene. Am J Hum Genet 2010; 86(6):949-56. Copyright 2010 Am J Hum Mut and from Bedrup et al. Ciliopathies with skeletal anomalies and renal insufficiency due to mutations in the IFT-A gene WDR19. J Med Genet 2011; 48(5):434-43. Copyright 2011 J Med Genet.

and retinal disease seems common for patients with IFT140 and IFT172 mutations [8, 13, 14]. Hepatic involvement with cholestasis and fibrosis has also been observed in some cases [8, 13]. Last, Mainzer et al. [43] and Giedion [46] described some of their MZSDS patients with ataxia, a finding not confirmed in later studies [8, 13].

2.2.3. Sensenbrenner syndrome

In contrast to JATD and MZSDS subjects, patients with CED present characteristic facial dysmorphic features and ectodermal defects including nail, hair and teeth abnormalities (Fig. 3). Common skeletal features are rhizomelic micromelia and brachydactyly as well as variable narrowing of the thorax, which is usually milder than what is observed in JATD or SRPS (Fig. 3) [9, 15]. However, dolichocephalus resulting from craniosynostosis of the sutura sagittalis [47], can be helpful to distinguish CED from other ciliopathies [48]. In contrast to JATD and MZSDS, developmental delay and skin laxity, potentially increasing the risk of hernias, can be additional features. Visceral manifestations frequently occur and often include progressive renal failure due to a NPHP-like renal phenotype with small hyperechogenic kidneys, the histological picture of tubulointerstitial nephritis and microscopic
Fig. 4. Schematic presentation of intraflagellar transport. Ciliary proteins are thought to be transported to the cilium within vesicles that merge with the ciliary membrane in the ciliary pocket area. Anterograde intraflagellar transport (IFT) from the ciliary base to the tip is facilitated by IFT complex B, while retrograde transport back to the base requires IFT complex A. Most genes found to be involved in ciliary chondrodysplasias encode for proteins of complex A and the associated motor complex, cytoplasmic dynein-2. However, EVC/EVC2, CSPP1 and NEK1 localize to the base of the cilium and TCTN3 is found at the ciliary transition zone. To date, no human mutations have been identified in the motor for complex B, kinesin-2. Hedgehog (Hh) signaling is essential to maintain a balance between proliferation and cellular differentiation at the growth plates. In Hh signaling, activated GLI proteins finally translocate to the nucleus where they influence gene expression. IFT mutant mice as well as mice lacking Evc function show abnormal hedgehog signaling, potentially due to disturbed localization of the hedgehog receptor smoothened to the cilium.

glomerular and tubular cysts [49, 50]. Hepatic cysts, fibrosis and ductal plate malformation are also common [51–53], while heart defects and retinal dystrophy are less frequent [15].

2.2.4. EVC syndrome
EVC was first recognized in 1940 by Ellis and van Creveld [54], and McKusick et al. [55] described a large consanguineous Amish pedigree in Pennsylvania in 1964. Acromelic dwarfism, polydactyly of the hands (but not feet), ectodermal defects such as dysplastic nails and teeth abnormalities (prenatal eruption of teeth, hypodontia and malformed teeth) and cardiac defects are classical hallmarks; EVC is therefore referred to as “six finger dwarfism”. The heart defects mainly represent primary atrial septal defects [11, 55] affecting approximately half of all patients. Hydrocephalus due to a Dandy-Walker malformation has also been described [56]. Radiological features in EVC, including brachydactyly, polydactyly, short ribs and trident acetabulum with spurs, can make this condition difficult to distinguish from JATD, however, cardiac and ectodermal defects are common in EVC and not a feature of JATD, while JATD patients may rather present with additional renal, liver, and retinal disease not usually observed in EVC [2].

2.2.5. Weyers acrodental dysostosis (WAD)
WAD or Curry-Hall syndrome was first described by Weyers [57], and is allelic to EVC, however inherited in an autosomal dominant pattern. Patients present with a milder phenotype consisting of polydactyly of the hands, dentition anomalies such as abnormal shape and number of teeth, and dystrophic nails as well as short stature with short extremities. In contrast to EVC, thoracic constriction and/or visceral involvement is usually not observed [57–60].
3. Progress in gene identification

Except WAD, ciliary chondrodysplasias are inherited autosomally recessively. Genetic heterogeneity is significant, especially for JATD and CED and genetic overlap is observed between different SRPS types as well as between SRPS, IATD, MZSDS and CED (Fig. 4). Similar to other (genetically heterogeneous) ciliopathies, ciliary chondrodysplasias have hugely benefited from the introduction of next-generation sequencing (NGS) which is currently revolutionising patient genotyping and gene discovery in the research setting in form of gene panel sequencing and whole exome and genome sequencing. This has led to the identification of many new human disease associated genes over the last years, mostly encoding intraflagellar transport (IFT) proteins (IFT172 [13], WDR19 [61], TTC21B [62], IFT40 [8, 14], IFT122 [52], IFT80 [63, 64], IFT43 [65], and WDR55 [21, 66]) or components of the retrograde IFT motor complex dynein-2 (i.e. DYNC2H1 [67–69], WDR34 [70–73], and WDR60 [74, 75]). Further, proteins localizing to the base of the cilium (basal body, peri-basal body region or pericentriolar matrix) seem to play a role as indicated by mutations in genes encoding NEK1 [69, 76], CSPP1 [42] and EVC/EVC2 [77, 78], TCTN3, mutated in OFD4, localizes to the ciliary transition zone that forms a barrier between the ciliary and cytoplasmic compartments [79]. The proportion of cases caused by mutations in currently known disease causing genes varies between the different conditions: while the vast majority of EVC cases occurs due to mutations in EVC and EVC2 [80] and causative mutations in NEK1 and DYNC2H1 are found in over 2/3 of all SRPS-II cases [69], the majority of all MZSDS are caused by IFT40 and IFT172 mutations [8, 13], and every other OFD4 case appears to result from mutations in TCTN3 [79]. JATD is genetically more heterogeneous. Most cases are caused by mutations in DYNC2H1 (approximately 50%) [7, 35], followed by mutations in WDR34 (approximately 10%) [70, 71], and currently more than 70% of all patients harboring mutations in known genes. Similarly, multiple genes have been found to cause CED and the frequency of WDR19, IFT122 and WDR35 mutations seems fairly equally distributed, whereas mutations in IFT43 are less commonly identified. The total number of cases reported to date is, however, too small to draw final conclusions in this respect [15].

First genotype-phenotype correlations especially in JATD and MZSDS and the phenotypic spectrum of CED further suggest that mutations in IFT complex A components lead to a rather mild rib phenotype but often cause significant extraskeletal symptoms such as renal, hepatic and retinal disease [8,13–15], while DYNC2H1 mutations are associated with a very severe thorax phenotype but infrequent clinically relevant renal or eye involvement in affected children [7, 35].

Digenic inheritance of heterozygous mutations in two different genes has been reported in a single case of SRPS-II with a heterozygous mutation in NEK1 as well as DYNC2H1 [76]. So-called “triallelic inheritance”, previously described in other ciliopathies such as Bardet-Biedl syndrome [81] has not been described in ciliary dysplasias to date. However, there are indications that “mutational load” (the total of mutations in genes known to cause the disease), could potentially play a role in ciliary chondrodysplasias [14].

4. Molecular mechanisms

Many genes implicated in ciliary chondrodysplasias to date encode for proteins involved in IFT, mostly components of the IFT complex A (retrograde transport) [8, 14, 21, 52, 61, 62, 65, 66], but also two components of IFT complex B (anterograde transport) [13, 63] as well as the dynein-2 complex representing the motor for IFT-A [67, 68, 70, 71, 74]. EVC and EVC2 are found at the ciliary base [82], but do not seem to be involved in IFT, while NEK1 encodes a serine/threonine kinase involved in the control of cell-cycle dependent ciliogenesis [76]. CSPP1 also localizes to the base of the cilium but its function there has not been elucidated to date [42, 83, 84]. Last, TCTN3 is found in a complex with TCTN1 and TCTN2 at the ciliary transition zone [79] (Fig. 4).

Because the cilium does not have a protein synthesis machinery, all required proteins are produced within the cell body and transported to the base of the cilium where they are subsequently loaded onto IFT particles, which facilitate transport along the ciliary axoneme towards the cilium tip (anterograde IFT complex B, powered by the dynein-2 complex) [85–87]. Dysfunctional IFT therefore leads to transport defects along the ciliary axoneme, causing ciliogenesis defects with absent or very short cilia in extreme cases [4]. Mild forms of
such defects have been described for patient’s fibroblasts with mutations in DYNC2H1, NEK1, WDR19 and WDR60 [61, 68, 74, 76]. However, in other patients with mutations in genes encoding for retrograde IFT motors or the retrograde motor protein DYNC2H1, cilia seem to be present on skin fibroblasts in normal numbers and reach normal length, but accumulation of IFT-B components at the ciliary tip can be observed [7, 65]. While the Dynein2h1 knockout mice display a severe ciliogenesis defect [88], the milder cellular human phenotype presumably results from hypomorphic missense mutations found in human patients [7].

Further, as expected, mutations in IFT172, impairing anterograde transport, result in reduced incorporation of ciliary proteins such as adenylate cyclase III and IFT molecules into the ciliary axoneme [13]. As the cilium transmits signals from outside the cell to the inside (serving as an “antenna”) and also processes signals from within the cell [89–92], lack of primary cilia or impaired IFT resulting in accumulation of lack of signal transduction particles critically interrupts the flow of cellular signaling information causing severe developmental defects [93, 94]. Cartilagelike bone development and growth is influenced by many fundamental cell signaling pathways, but the hedgehog signaling pathway has been identified as crucially influencing chondrogenic (and subsequently osteogenic) proliferation and differentiation [95]. Mouse models for Evc, Dynein2h1 and Ift80 indicate that IFT defects indeed lead to imbalances in the hedgehog signaling pathway causing a premature stop of chondrogenic proliferation and induction of chondrogenic differentiation at the growth plates severely slowing down bone growth [82, 96]. IFT-A mouse mutants seem to display ligand independent expansion of hedgehog signaling resulting in abnormal digit numbers and oro-facial clefts [88] (Fig. 4).

Renal and retinal disease are frequent ciliopathy symptoms in ciliary chondrodysplasias [6] and seem to mainly result from mutations in IFT-A genes [8, 14, 15] and the IFT-B component encoded by IFT172 [13], while these traits are less frequently observed in surviving patients with DYNC2H1 [7, 35] or IFT80 [63] mutations. The underlying pathophysiological mechanism remains to be defined. Cells in the kidney tubules exhibit primary cilia, and loss of the physical structure of the cilium as well as loss of ciliary proteins has been shown to lead to renal cyst formation in mice [97–99]. While hypomorphic Ift80 knockout mice do not exhibit any renal phenotype [96], loss of Ift140, or Ift172 in mice produces an early onset kidney phenotype [100, 101], resembling human phenotype. Ift140 knockout mice show normally orientated mitotic spindle axis, but hyper-proliferation of renal tubular cells was noted in the pre-cystic epithelium, while increased canonical Wnt and hedgehog signaling was only observed in cystic tissue [100]. Unbalances between the canonical and non-canonical Wnt pathways with loss of non-canonical and increased canonical signaling have been previously associated with dysfunction of genes causing NPHP when disrupted. The best known example concerns the INVS gene encoding inversin: loss of function causes situs inversus and NPHP in humans and mice, and inversin was shown to facilitate a switch from canonical to noncanonical Wnt signaling in vitro, as well as in vivo, probably by targeting cytoplasmic disheveled for ubiquitin-dependent degradation and thereby reducing canonical Wnt signaling and promoting non-canonical Wnt or planar cell polarity (PCP) signaling [102, 103]. Neither disturbances in hedgehog nor Wnt signaling seem to initiate cyst formation in Ift140 knockout mice but might contribute to cyst progression. How this relates to the human pathophysiology remains to be defined.

Retinal photoreceptors consist of two parts crucial for light processing: the inner and outer segment. These segments are connected via a narrow bridge, the so-called “connecting cilium” which shares similarities with the transition zone of a classical cilium. The connecting cilium is essential for IFT-molecule dependent rhodopsin transport between the segments and impaired transport results in accumulation of rhodopsin causing photoreceptor death [72,104–106]. In contrast to the primarily developmental skeletal phenotype resulting from IFT mutations, the retinal phenotype therefore appears to be a degenerative process. Like the renal phenotype, retinal degeneration seems to be associated with mutations in IFT-A genes and IFT172 [8,13–15], while it appears less common in subjects with DYNC2H1 mutations [7, 35].

5. Clinical management and future perspectives

Ciliary chondrodysplasias are rare diseases and no large long-term follow-up studies have been performed to date. Curative therapies are not currently available and treatment is therefore symptomatic. For SRPS subtypes I–V, only short-term palliative care is possible and therefore interruption of the pregnancy is usually
5. Skeleton

Lethality in ciliary chondrodysplasias is mainly thought to be a result of cardiorespiratory failure due to lung hypoplasia secondary to the constricted ribcage (this does not occur in WAD). The majority of fatalities occur in JATD and are observed perinatally and up to the second birthday. Mechanical ventilation, continuous positive airway pressure ventilation or oxygen supply can be necessary for a long time. However, as many patients seem to “grow out” of the thoracic phenotype, invasive therapy is rarely required later in life [2, 6, 7, 35, 36]. Thoracic expansion surgery may be offered in cases where conservative treatment is insufficient in a handful of highly specialized centers worldwide, however, this treatment imposes a significant risk [36, 107–111]. Pulmonary function should be assessed by spirometry and volume measurements as well as polygraphic sleep studies; these assays should be performed every one to two years [35].

If ciliary chondrodysplasias cause secondary and/or degenerative skeletal health issues later in life is not clear to date due to lack of larger long-term follow-up studies, but scoliosis appears to be a frequent feature in JATD [7, 35]. While for subjects with EVC body length ranges from 119 cm to 167 cm have been reported [2, 112, 113], many JATD patients reach normal adult height [7, 35] with the exception of patients with impaired renal function [14]. Growth hormone treatment is currently not recommended for patients with ciliary chondrodysplasias [2]. Extra fingers, neonatal teeth and craniosynostosis might require surgical correction in the first 1–2 yr of life and additional orthodontic corrections may be required later on.

5.2. Extraskeletal disease

Yearly monitoring of renal- and hepatic blood markers as well as ultrasound examination should be performed, especially for patients with MZSDS and CED as well as JATD individuals with WDR19, IFT140 or IFT172 mutations [8, 13–15]. JATD patients with IFT80 and DYNC2H1 mutations seem at a lower risk [7, 35, 63]. Supportive therapy includes dialysis and/or renal/liver transplantation. The limited available data suggests that most JATD and CED patients exhibit mild liver disease [35, 36] with only a handful of cases progressing into liver failure reported [13, 40, 114]. Elevated liver enzymes in JATD seem to respond to ursodeoxycholic acid treatment [35, 115]. Liver disease is not associated with EVC and is infrequent in MZSDS [2, 8, 13].

Patients with CED, MZSDS as well as JATD patients with WDR19, IFT140 or IFT172 mutations are at significant risk of developing retinal degeneration, mainly with childhood onset [8, 13, 14]. As ERG changes precede pathological findings in fundoscopy and clinical manifestation of retinal dystrophy, eye monitoring should always include ERG [116]. That said, it may be difficult to obtain reliable ERG results in young children. Clinically relevant sight loss seems to occur less in young individuals with DYNC2H1 mutations [7]. Nevertheless, these patients also require monitoring as ERG abnormalities were noted in up to 50% of cases [35]. Clinically relevant heart defects should be treated according to cardiological guidelines, however, heart defects can shorten life expectancy depending on the defect and depending on if surgery is needed and what kind of operation is required [2, 117]. Postoperative mortality was reported as high as 44% in a small Amish cohort with EVC [16].

Although most CED, JATD and MZSDS patients develop normally, clinical and radiological features of Joubert syndrome have been observed in a few JATD and CED patients [41, 42] and some MZSDS patients with ataxia [43, 46]. Evaluation by pediatric neurology specialist should be undertaken for cases with neurological symptoms and/or developmental delay.

Therapy in ciliary chondrodysplasias is currently symptomatic and supportive only. It will be challenging to attempt to therapeutically influence the skeletal phenotype; first because one would have to start treatment at birth or even in utero, and second because the developing skeleton is not as easily accessible, e.g. the respiratory tract, in case one would want to develop gene therapy. The size of some of the genes involved (e.g. DYNC2H1 and IFT172) represents an additional hurdle. As most mutations are missense changes, read-through drugs such as PTC124/ataluren will not be applicable to many patients.

5.3. Psychological and genetic counseling

As ciliary chondrodysplasias have significant psychological impact on affected families due to (often late) interruptions of pregnancies, loss of children in
the neonatal period or infancy, and chronic disease with potential life-threatening complications, psychological counseling should be offered. Genetic counseling is recommended for all ciliary chondrodysplasias as the recurrence risk is 25% for subsequent pregnancies, except for WAD with a risk of 50%. Prenatal genetic testing should be offered to families where the causative mutation is known and families should be informed about the possibility of pre-implantation diagnostics as well as sperm or egg cell donation. That said, significant variability of the phenotype severity is observed between patients from different families with mutations in the same gene as well as between siblings carrying the same mutations [7, 74] can make it difficult to predict the exact phenotype for subsequent pregnancies based on genetic findings.

In the past, extensive genetic- and phenotypical heterogeneity as well as overlap between the different disease entities have made it difficult to establish a molecular diagnosis. However, the introduction of NGS has significantly facilitated genetic diagnostics, either in form of specific gene panels or whole-exome sequencing. Single gene analysis still has a fairly high success rate in EVC sequencing. Single gene analysis still has a fairly high success rate in EVC sequencing. However, the introduction of NGS has significantly facilitated genetic diagnostics; either in form of specific gene panels or whole-exome sequencing. Single gene analysis still has a fairly high success rate in EVC sequencing. Single gene analysis still has a fairly high success rate in EVC sequencing. In patients without any causative mutation can be identified using targeted NGS panel approach, whole-exome and/or whole-genome analysis might reveal the underlying genetic defect. Copy number variant analysis of NGS data, especially in exome- and whole-genome data, is highly recommended [7].

In summary, ciliary chondrodysplasias require multidisciplinary long-term clinical management coordinated by the discipline most closely involved with the patient. This can be best achieved in a centre with experience with ciliary chondrodysplasias and all disciplines located within this centre.

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References

[1] Onerkalaid F, Danks DM, Mayer V, Campbell P. Asphyxiating thoracic dysplasia. Clinical, radiological, and pathological information on 10 patients. Arch Dis Child 1977;52(10):758-65.
[2] Baust J, Le Meur M. Ellis-van Creveld syndrome. Orphanet J Rare Dis 2007;2:27.
[3] Kovics N, Sárkány I, Mihay G, Adamovich K, Ent I, Kozutshny G, et al. High incidence of short rib-polydactyly syndrome type IV in a Hungarian Roma subpopulation. Am J Med Genet A 2006;140(24):2816-8.
[4] Elsegard M, Benzing T, Ousman H. When cilia go bad: Cilia defects and ciliopathies. Nat Rev Mol Cell Biol 2007;8(11):888-93.
[5] Baker K, Reales PL. Making sense of cilia in disease: The human ciliopathies. Am J Med Genet C Semin Med Genet 2009;156C:284-95.
[6] Huber C, Cermenis-Darre V. Ciliary disorder of the skeleton. Am J Med Genet C Semin Med Genet 2012;160C(3):165-74.
[7] Schmidts M, Aris IH, Bongers EM, Top J, Oud MM, Antony D, et al. Exome sequencing identifies DYNC2H1 mutations in ciliopathy caused by IFT440 mutations. Am J Hum Genet 2012;90(5):664-70.
[8] Perrault J, Suarmer S, Hanin S, Filhol E, Bizié AA, Collins F, et al. Mutzer-Saldino syndrome is a ciliopathy caused by BBS6 mutations. Hum Genet 2013;132(6):977-82.
[9] Levin LS, Perrin JC, Ose L, Doris JP, Miller JD, McKusick VA. A heritable syndrome of craniosynostosis, short thin hair, dental abnormalities, and short limbs: Cranioscrotal dysplasia. J Pediatr 1977;90(1):55-64.
[10] Bills CR, Kuchichia L, Schianni LA, Moller JH. Ellis-van Creveld syndrome and congenital heart defects. Presentation of an additional 32 cases. Pediatr Cardiol 2011;32(7):977-82.
[11] Blackburn MG, Belliveau RE. Ellis-van Creveld syndrome. A report of previously undescribed anomalies in two siblings. Am J Dis Child 1971;122(3):267-70.
[12] Elsstell NH, Hall CM. Diagnostic dilemmas in the short rib-polydactyly syndrome group. Am J Med Genet 2002;114B(2):392-400.
[13] Halbritter J, Bizié AA, Schmidts M, Parabé KD, Fottea DA, Gehr HY, et al. Defects in the IFT-B component IFT172 cause Jeune and Mainzer-Saldino syndromes in humans. Am J Hum Genet 2013;93(5):915-23.
[14] Schmidts M, Frank V, Eisendenger T, Al Turk S, Bizié AA, Antony D, et al. Combined NGS approaches identify mutations in the intraflagellar transport gene IFT140 in skeletal ciliopathies with early progressive kidney disease. Hum Mutat 2013;34(5):714-24.
[15] Le AE, Traum AZ, Sakai J, Keppler-Noreuil K, Kukolich MK, Adam MP, et al. Sensenbrenner syndrome (Cranioscrotal dysplasia): Clinical and molecular analyses of 39
patients including two new patients. Am J Med Genet A 2013;161A(11):2782-76.

[16] O'Connor ME, Collins MF. 2nd. Ellis-van Creveld syndrome and congenital heart defects: Presentation of an additional 31 cases. Birth Defects 1972;8:491-501.

[17] Salton RM, Noonan CD. Severe thoracic dystrophy with striking microsomia, abnormal osseous development, including the spine, and multiple visceral anomalies. Am J Roentgen Radium Ther Nucl Med 1972;114(2):257-63.

[18] Majewski F, Pfeiffer RA, Lerza W, Muller R, Feil G, Seiler R. Polydactyly, short limbs, and genital malformations - a new syndrome? Z Kinderheilkunde 1971;111(2):118-38 (in German).

[19] Verma IC, Bhargava S, Agarwal S. An autosomal recessive form of lethal chondrodysplasia with severe thoracic narrowing, thoracoscopic type of microsomia, polydactyly and genital anomalies. Birth Defects Orig Artic Ser 1975;11(1b):185-7.

[20] Bremer PA, Langer LO Jr, Klop-de Pater JM, Hennens AM, Byloma JB, Paoli RM, et al. A new short rib syndrome: Report of two cases. Am J Med Genet 1983;14:115-23.

[21] Mill P, Lochbart P, Finzi-Patrick E, Mountfound HS, Hall EA, Rejmi MA, et al. Human and mouse mutations in WDR5 cause short-rib polydactyly syndromes due to abnormal cilogenesis. Am J Hum Genet 2011;88:4:508-15.

[22] Spranger J, Gimmi B, Weller M, Weissenbacher G, Hermann J, Gilbey E, et al. Short rib-polydactyly (SRP) syndromes, types Majewski and Salton-Noonan. Z Kinderheilkunde 1974;114(2):73-94 (in German).

[23] Spranger J, Langer LO, Weller MH, Hermann J. Short rib-polydactyly syndromes and related conditions. Birth Defects Orig Artic Ser 1974;10(9):117-23.

[24] Le Marc P, Passegue E, Dellenbach P, Kersjorg I, Ferrand B, et al. Lethal neonatal forms of chondroectodermal dysplasia. Apropos of 5 cases. Ann Radiol (Paris) 1976;19(4):309-18 (in French).

[25] Naumoff P, Young LW, Mazer J, Amortegui AJ. Short rib-polydactyly syndrome type 3. Radiology 1977;122(2):443-7.

[26] Bernstein R, Isabella C, Minot H, Attouni AJ. Short rib-polydactyly syndrome type 3. Radiology 1977;122(2):443-7.

[27] Bernstein R, Isida E, Poln H, Duttill Zauzeman J, Jenkins T. Short rib-polydactyly syndrome: A single or heterogeneous entity? A re-evaluation prompted by four new cases. J Med Genet 1985;22(1):46-53.

[28] Yang SS, Langer LO Jr, Cacciarelli A, Dahms BB, Unger ER, Roskamp J, et al. Three conditions in neonatal asphyxia: Report of a patient. Am J Med Genet 1989;32(2):151-4.

[29] Yang SS, Langer LO Jr, Cacciarelli A, Dahms BB, Unger ER, Roskamp J, et al. Three conditions in neonatal asphyxia: Report of a patient. Am J Med Genet 1989;32(2):151-4.

[30] Bajuk G, Hutter C, El Hokayem J, Caumes R, Du Nippe Thaum C, Daval A, et al. Asphyxiating thoracic dysplasia: Clinical and molecular review of 39 families. J Med Genet 2013;50(2):91-8.

[31] de Vries J, Yntema JL, van Der CE, Crama N, Cornuils-SEM EA, Hamel BC. Jeune syndrome: Description of 13 cases and a proposal for follow-up protocol. Eur J Pediatr 2010;169 (1):77-88.

[32] Allen AW Jr, Moon JB, Howland KR, Minckley DS. Occu- lar findings in thoracic-pelvis-phalangeal dysplasia. Arch Ophthalmol 1967;75(3):489-92.

[33] Bard LA, Bard PA, Owens GW, Hall BD. Retinal involvement in thoracic-pelvis-phalangeal dysplasia. Arch Ophthalmol 1978;96(2):278-81.

[34] Hoppe MS, Bosselie JE, Watson AR. Polyhydromydinos associated with congenital pancreatic cysts and asphyxiating thoracic dysplasia. A case report. S Afr Med J 1975;56(4):32-3.

[35] Leyman LM, Brady L, Hart J. Hepatic manifestations of Jeune syndrome (asphyxiating thoracic dysplasia). Semin Liver Dis 2003;23(2):195-200.

[36] Lehmann AM, Eyestone P, Doherty D, Glass IA, Chitayat D, Chung BV, et al. Co-occurrence of Juibert syndrome and Jeune asphyxiating thoracic dysplasia. Am J Med Genet A 2010;152A(6):1411-9.

[37] Tut K, Brachmann-Gaymuc R, O’Day DR, Hara K, Isabella CR, Phillips JG, et al. Mutations in CDSPP1 cause primary cilia abnormalities and Juibert syndrome with or without Jeune asphyxiating thoracic dysplasia. Am J Hum Genet A 2014;94(1):62-72.

[38] Musterer F, Salton RM, Ostrom MB, Minagi H. Familial nephropathy associated with retinitis pigmentosa, cere- bellar ataxia, and skeletal abnormalities. Am J Med 1970;49(4):556-62.

[39] Popovic-Radonic M, Calco-Peccini, N, Benjangack G, Ngor- avicic: D. Jeune nephropathy associated with retinal pigmentary dystrophy, cerebellar ataxia, and skeletal abnor- malities. Arch Dis Child 1976;51(10):801-3.

[40] Robins DG, French TA, Chakera TM. Jeune nephropathies associated with skeletal abnormalities and hepatic fibrosis. Arch Dis Child 1976;51(10):799-801.

[41] Girdon A, Philangal corne sheets epifhys of the (Phil‿SEH) and chronic renal disease–the conorenal syn- dromes. Proced Radiat 1979;8(1):32-8.

[42] Amr MJ, Simper HR, Kourteff MG. Expanded phenotype of jeune (pheli-sense allied type of the pheli-sense) syndrome. Am J Med Genet 1997;79(4):349-52.

[43] Amer H, Knowl N. Cranioectodermal dysplasia. In: Pagon RA, Adam MP, Ardinger HH, Bird TD, Dolan CR, Fong CT, Smith RJH, Stephens K, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, 1993-2014. Avail-
able at: http://www.ncbi.nlm.nih.gov/books/NBK154503/
Accessed September 12, 2013.
[49] Law GD, Young ID. Cranioscutodental dysplasia in utero. J Med Genet 1951;28(4):424.
[50] Ekl T, Woodard G, Young ID. A new occulodental syndrome: Retinal dystrophy and tubulointestinal nephropathy in cranioscutodental dysplasia. In: Hipppolito 1996;38(5):491-9.
[51] Zaffaroni M, type III. Am J Hum Genet 2009;85(2):388-91.
[52] Callea F, Emma F, Sensenbrenner syndrome: A new member of the hepatoportal fibrocystic family. Am J Med Genet A 2006;140(21):2360-40.
[53] Walczak-Stojak J, Eggenschwiler J, Osborn D, Brown DA, Emma F, Klingberg C, et al. Cranioscutodental dysplasia, Sensenbrenner syndrome, is a ciliopathy caused by mutations in the IFT22 gene. Am J Hum Genet 2010;86(6):949-56.
[54] Konstantinidou AE, Fryssira H, Sifakis S, Karadimas C, Kaminopoulos P, Agropoulou G, et al. Cranioscutodental dysplasia: A probable ciliopathy, Am J Med Genet A 2009;149A(10):2206-11.
[55] Ellis RW, van Creveld S. A syndrome characterized by ectodermal dysplasia, polydactyly, chondro-dysplasia and congenital muscular contractures. Report of three cases. Arch Dis Child 1940,15(2):65-84.
[56] McKinley VA, Elbrügge R, Horshttel JE, Englund JA. Dwarfism in the Amish. Trans Assoc Am Physicians 1964;77:151-68.
[57] Zannoull KM, Boal DK, Ladda RL. Dandy-Walker malformation in Ellis-van Creveld syndrome. Am J Med Genet 1980;13(1):123-9.
[58] Weyers H. A correlational abnormality of the mandible and extrornitine dysostosis (acrofacialis). Fortsch Rheumat 1952;77:5-5 (in German).
[59] Roukhch M, Spranger J. Weyers congenital dysostosis in a family. Clin Genet 1984;26(6):587-90.
[60] Roukhch M, Spranger J. Syndrome of polydactyly, conical teeth and nail dysplasia. Am J Hum Genet 1985;20(1):205-7.
[61] Curry CI, Hall BD. Polydactyly, conical teeth, nail dysplasia, and short limbs: A new autosomal dominant malformation syndrome. Birth Defects Orig Artic Ser 1979;15(5B):253-63.
[62] Breuer C, Saumier S, Oud MM, Fokkerstra T, Huischot A, Bruckman D, et al. Cleftpalhes with skeletal anomalies and renal insufficiency due to mutations in the IFT-A gene. Hum Genet 2010;127(6):634-43.
[63] Davis EE, Zhang Q, Liu Q, Deplas BH, Davry L.M, Hartley J, et al. TCTBP1 contributes both causal and modifying alleles across the ciliopathy spectrum. Nat Genet 2011;43(9):969-72.
[64] Beales PL, Blund E, Tobin B., Bucchel C, Tyanov B, Hill J, et al. IFT80, which encodes a conserved intraflagellar transport protein, is mutated in Jeune-Verma-Naumoff dysplasia spectrum. J Med Genet 2011;48(2):88-92.
[65] Arts HH, Bongers EM, Mans DA, van Beersum SE, Oud MM, Boeltj J, et al. IFT80(IFT43) is mutated in Sensenbrenner syndrome. J Med Genet 2011;48(6):390-5.
[66] Gilissen C, Arts HH, Hoischen A, Spruijt L, Mans DA, Arts P, et al. Exome sequencing identifies WDR45 variants involved in Sensenbrenner syndrome. Am J Med Genet 2010;48(7):3-118-8.
[67] Deiterman N, Gelot M, Gonzalez J, Martinovic J, Smithson S, et al. DYNC2H1 mutations cause axonopathetic hypothalamic dysfunction and short rib polydactyly syndrome, type III. Am J Hum Genet 2011;88(1):106-14.
[68] Merrill AE, Merriman B, Farrington-Rock C, Camacho J, Smithson S, et al. NEK1 mutations cause short rib polydactyly Majewski type but not in Beemer Longer cases. J Med Genet 2012;49(4):227-33.
[69] Schmidts M, Voedopijatz J, Christos-Savanis S, Cortes CR, McInerney-Leo AM, Emers BD, et al. Mutations in the gene encoding IFT dynein complex component WDR35 cause Jeune axonopathetic dystrophic syndrome. Am J Med Genet 2013;163(5):152-4.
[70] Huber C, Wu S, Kim AS, Signauly S, Sarikhanov A, Serre Y, et al. WDR45 mutations that cause short rib polydactyly syndrome type III/severe axonopathetic dystrophic syndrome reveal a role for the NE-IF-kappaB pathway in cilia. Am J Med Genet 2011;159A(5):526-31.
[71] Weyers H. A correlational abnormality of the mandible and extrornitine dysostosis (acrofacialis). Fortsch Rheumat 1952;77:5-5 (in German).
[72] Rondolos P, Pedersen LB, Patil-King RS, King SM. Chylidodystromas FAP133 is a dynen intermediate chain associated with the retrograde intraflagellar transport motor. J Cell Sci 2007;120(Pt 20):3653-65.
[73] McInerney-Leo AM, Schmidts M, Cortes CR, Lave J, et al. Short rib polydactyly and Jeune syndromes are caused by mutations in WDR60. Am J Hum Genet 2013;93(3):515-23.
[74] Patil-King RS, Gilbert HM, Emers FS, King SM. Chylidodystromas FAP133 is a dynen intermediate chain required for retrograde intraflagellar transport in cilia Mol Biol Cell 2013;24(17):2666-71.
[75] Thiel C, Kesler K, Giebel A, Dimmel A, Shelay SA, von der Heur K, et al. NEK1 mutations cause short-rib polydactyly syndrome type Majewski. Am J Hum Genet 2011;88(1):106-14.
[76] Ruiz-Perez VL, Idac SE, Storm TM, Lorentz B, Wilson D, Woods K, et al. Mutations in a new gene in Ellis-van Creveld syndrome and Weyers acrofacial dysostosis. Nat Genet 2000;24(3):283-6.
[77] Thompson SW, Ruiz-Perez VL, Blue HD, Barton S, Navarro V, Rockon JL, et al. Sequencing EVC and EVC2 identifies mutations in two-thirds of Ellis-van Creveld syndrome patients. Hum Genet 2007;120(5):663-70.
[78] Thomas S, Legendre M, Saunier S, Bessieres B, Alby C, Bonneree M, et al. TCTBP3 mutations cause Moeb-Majewski syndrome. Am J Hum Genet 2012;90(2):372-8.
[79] D’Aspia MC, Torroni L, Consolo F, Ferre R, Magliozzi M, Bernardini L, et al. Novel and recurrent EVC and EVC2 mutations in Ellis-van Creveld syndrome and Weyers acrofacial dysostosis. Eur J Med Genet 2013;56(2):60-7.
[91] Davenport JR, Watts AJ, Roper VC, Croyle MJ, van Groen M, Moyer JH, Lee-Tischler MJ, Kwon HY, Schrick JJ, Avner R, Rix S, Calmont A, Scambler PJ, Beales PL. An Ift80 mouse disease. Curr Biol 2007;17(18):1586-94.

[92] Satir P, Pedersen LB, Christensen ST. The primary cilium in development, homeostasis, and disease. Cell 2010;11(5):331-44.

[93] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[94] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[95] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[96] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[97] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[98] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[99] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[100] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[101] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[102] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[103] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[104] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[105] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[106] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[107] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[108] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[109] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[110] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[111] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.

[112] Todd DW, Tingulj SY, Norberg WJ. A thoracic expansion technique for Jeune’s asphyxiating thoracic dystrophy. J Pediatr Surg 1998;33(10):1578-81.