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## REVIEW

# 'Kinesinopathies': emerging role of the kinesin family member genes in birth defects

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**ABSTRACT**

Motor kinesins are a family of evolutionary conserved proteins involved in intracellular trafficking of various cargoes, first described in the context of axonal transport. They were discovered to have a key importance in cell-cycle dynamics and progression, including chromosomal condensation and alignment, spindle formation and cytokinesis, as well as ciliogenesis and cilia function. Recent evidence suggests that impairment of kinesins is associated with a variety of human diseases consistent with their functions and evolutionary conservation. Through the advent of gene identification using genome-wide sequencing approaches, their role in monogenic disorders now emerges, particularly for birth defects, in isolated as well as multiple congenital anomalies. We can observe recurrent phenotypical themes such as microcephaly, certain brain anomalies, and anomalies of the kidney and urinary tract, as well as syndromic phenotypes reminiscent of ciliopathies. Together with the molecular and functional data, we suggest understanding these 'kinesinopathies' as a recognisable entity with potential value for research approaches and clinical care.

**INTRODUCTION**

The mammalian kinesin superfamily proteins (KIFs) are microtubule and ATP-dependent molecular motors, which were first identified in 1985 as axonal transporters in squid and bovine brains.<sup>1</sup> Forty-five different kinesin family member (KIF) genes were identified in the mouse genome so far, 44 of which are present in the human genome. Phylogenetic analysis based on sequence homology between the human and the mouse genome led to the classification of KIF genes into 16 families, from kinesin-1 to kinesin-14B (figure 1).<sup>2</sup> The first kinesins discovered belong to the kinesin-1 family (KIF5A, KIF5B and KIF5C), and they form a heterotetramer of two heavy chains and two light chains (KLC1-4).<sup>2</sup> KIF genes encode KIFs, a specific class of motor proteins generating intracellular motility by driving directional transport of various cargoes such as organelles, protein complexes and mRNAs along the microtubule system.<sup>2</sup> Studies using knockout mouse models by Hirokawa and colleagues significantly contributed to elucidate the roles of kinesins in mammalian physiology. Their role in transport is fundamental to cellular logistics and performance, and the molecular motors are not only effectors of signal transduction cascades but also transport and/or bind to important signal transduction molecules to actively modulate their function.<sup>3</sup>

The first kinesins were observed in the context of axonal transport in neurons, and a novel disease entity of 'motor-proteinopathy' was proposed for the pathogenesis of axonal neuropathies in 2001.<sup>4</sup> Due to their role in cellular membrane trafficking, however, kinesins are essential for the functioning of many polar cell types, such as neurons, epithelial cells, sperm cells or stem cells during organogenesis. Kinesins also play a fundamental role in cell-cycle dynamics, both during mitotic and meiotic processes. They regulate chromosomal condensation and alignment, spindle formation, cytokinesis and cell-cycle progression.<sup>5</sup> It is estimated that about a dozen kinesins are involved in the cell cycle. Among these, there is a specific subclass of chromokinesins (kinesin 4 and kinesin 10 family) which are able to bind chromosomes.<sup>6</sup> Recently, KIFs were discovered to act as microtubule stabilisers (KIF26A and KIF21A) and depolymerisers (KIF2A and KIF2C), activities which are important for both cellular morphogenesis and mammalian development, playing a role in neuronal and axonal morphology and ciliogenesis.<sup>7</sup>

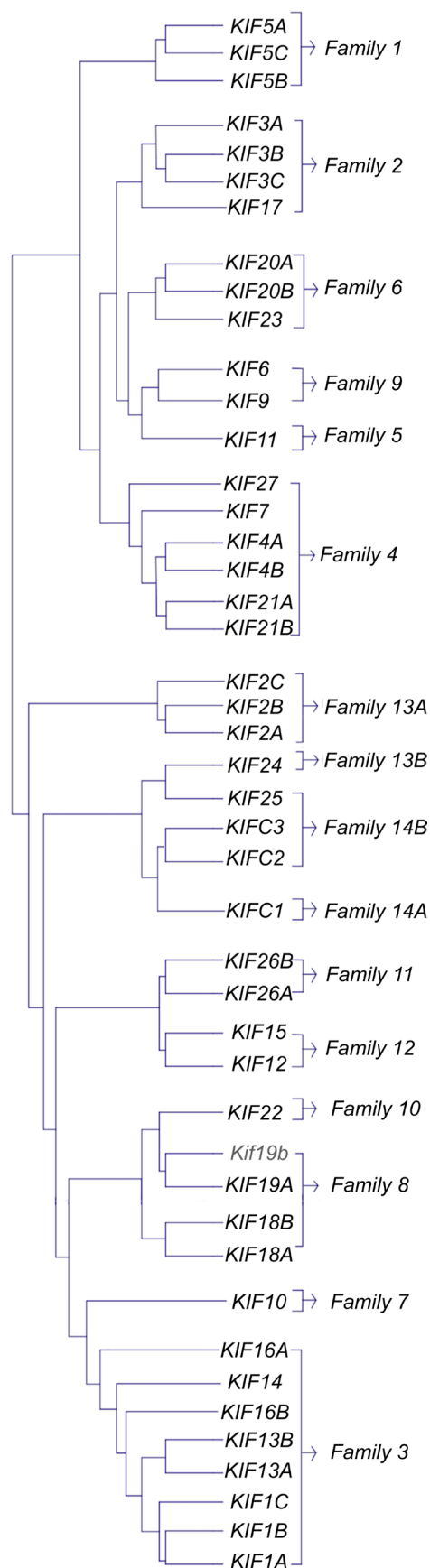
Alterations in motor kinesins are leading to human disease by various pathological mechanisms, including cancer and multifactorial and monogenic disorders. Variants in 18 out of the 44 human KIF genes were identified to cause monogenic disorders, following different modes of Mendelian inheritance and associated with a wide spectrum of clinical signs. These range from lethal and multiple to isolated congenital anomalies—including birth defects potentially detectable in the foetal period by current prenatal imaging studies—to postnatally apparent neurodevelopmental disorders, intellectual disability and neurological conditions.

We will review the current state of knowledge of the biological processes kinesins are involved in and discuss their emerging role in human disease, particularly in birth defects and congenital anomaly syndromes. Birth defects remain a leading cause of perinatal lethality in industrialised countries.<sup>8</sup> Structural anomalies are recognised with increasing reliability during early pregnancy by the use of high-resolution ultrasound technologies, thus raising questions about diagnosis, aetiology, prognosis and recurrence risk, particularly in the presence of more than one anomaly, which most likely indicates a genetic aetiology. We identify recurrent phenotype patterns caused by alterations in KIF genes, and we outline the complexity of phenotype-genotype correlations mirroring the processes of intracellular microtubule-mediated transport and movement, in which kinesins play a fundamental role. There are



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**Figure 1** Phylogenetic tree of mammalian kinesin superfamily genes identified in the human (and mouse) genome and classified in 16 subfamilies (from kinesin 1 to 14B) (adapted from Hirokawa *et al*<sup>3</sup>).

likely many more relationships between the clinical signs and the genetic variants to be identified in the future, and the functional network of kinesins and their role in human disease need to be further elucidated. We propose to introduce the term ‘kinesinopathies’ for this group of conditions, which are phenotypically and genetically overlapping and characterised by the functional impairment of a specific group of molecular motors. We hope that their systematic approach leads to a better recognition in clinical practice, as well as in genome-wide sequencing for diagnosis and research, and opens strategies for the future development of molecular therapies.

### KIF STRUCTURE

All KIFs have a phylogenetically well-conserved motor domain head, consisting of an ATP-binding motif and a microtubule-binding domain. Depending on the position of the motor domain, kinesins can be subdivided into N-kinesins (amino-terminal motor domain), M-kinesins (middle-region motor domain) and C-kinesins (carboxy-terminal motor domain).<sup>2</sup> Most kinesins belong to the N-kinesin subgroup, but members of the kinesin 13A family (figure 1) belong to the M-kinesin subtype, while KIF1C, KIF2C and KIF3C belong to the C- kinesin subfamily.<sup>3</sup> Both N-kinesins and C-kinesins are responsible for plus end and minus end-directed motility, M-kinesins for depolymerisation of microtubules in tubulin molecules. However, there are a few exceptions to this categorisation.<sup>9</sup> The motor domain head attaches to the neck, the coiled coil stalk and the tail. The kinesins’ neck is family-specific and responsible for the direction of motility or regulation of activity. The coiled coil stalk and tail are involved in kinesin dimerisation and/or interactions with cargoes. Kinesins typically use scaffold proteins and adaptor proteins to bind their cargoes but can sometimes bind the cargo directly. Scaffolds and adaptors might also have regulatory roles in kinesin-driven intracellular transport, that is, recognising specific cargoes and regulating their loading and unloading.<sup>3</sup>

### ROLE OF KIFs IN PHYSIOLOGY AND DISEASE

The application of genome-wide sequencing for gene identification in research or for clinical diagnostic purposes significantly contributes to the identification of *KIF* candidate genes. Genotype–phenotype correlations in *KIF* gene-related disorders, together with functional and animal studies, continue to elucidate the complex involvement of KIFs in human developmental pathways and disease. Table 1 summarises the monogenic conditions caused by variants affecting the function of *KIF* genes.

The kinesins’ functions in physiological processes, however, are complex and still incompletely understood, but their role in cell-cycle progression and regulation, including both meiosis and mitosis, in intracellular trafficking, axonal transport, microtubule activity and ciliogenesis, is increasingly studied. Figure 2 summarises the clustering of *KIF* genes according to their functional roles and the phenotypical consequences as identified to date in 32 out of the 44 human kinesin genes.

Kinesins play a pivotal role during early development and organogenesis. Microcephaly is one of the most frequently associated clinical signs, mirroring a defect in the regulation of the final number of neurons during development.<sup>10</sup>

KIF4A is a motor protein that translocates PRC1, a cytokinesis protein, to the ends of the spindle microtubules during mitosis, regulates the PARP1 activity in brain development and the survival of neurons, and is a member of the L1CAM recycling pathway. Variants in *L1CAM* cause X-linked isolated and

**Table 1** Specific monogenic disorders caused by variants affecting the function of *KIF* genes

Kinesin family	KIF gene	Associated phenotypes, OMIM	Clinical description	Cytogenetic location	Inheritance	Variant type
Kinesin 1	<i>KIF5A</i>	Spastic paraplegia type 10, #604 187	Gait abnormalities, lower limb hyper-reflexia, spasticity and weakness; upper limb spasticity and bladder dysfunction frequent; sensory disturbances common; variable phenotype, also including intellectual disability	12q13.3	AD	Missense variants Motor domain
		Neonatal intractable myoclonus, #617 235	Nystagmus, optic nerve pallor, myoclonus seizures, clonic seizures, developmental arrest, delayed myelination, athetoid and choreiform movements	12q13.3	AD	Stop-loss frameshift variants Cargo-binding domain
	<i>KIF5C</i>	Cortical dysplasia, complex, with other brain malformations 2, #615 282	Delayed psychomotor development, foetal akinesia, spastic tetraplegia, seizures, malformations of cortical development and arthrogryposis	2q23.1-q23.2	AD	Missense variants Microtubule-binding domain
	<i>KLC2</i>	Spastic paraplegia, optic atrophy, and neuropathy, #609 541	Congenital optic atrophy, early-onset progressive spastic paraplegia, hyper-reflexia, dysarthria, distal axonal motor and sensory peripheral neuropathy	11q13.2	AR	Missense variants Motor domain
Kinesin 2	<i>KIF3C</i>	Sporadic infantile spasm syndrome <sup>58</sup>	Clinical spasms with ictal electrodecrement, usually occurring before the age of 1 year and frequently associated with cognitive impairment	2p23.3	Candidate gene/AD	Missense variant Coiled-coil region
Kinesin 3	<i>KIF1A</i>	Hereditary sensory neuropathy type IIC, #614 213	Progressive sensory neuropathy, areflexia, hyporeflexia and developmental delay	2q37.3	AR	Truncating variants
		Mental retardation, autosomal dominant 9, #614 255	Developmental delay, intellectual disability, microcephaly, cerebellar atrophy, spasticity, possible seizures, hypotonia and clubfoot	2q37.3	AD	Missense variants Motor domain
		Spastic paraplegia type 30, #610 357	Lower limb spasticity, spastic gait, hyper-reflexia, lower limb muscle atrophy and weakness	2q37.3	AR	Missense variants Motor domain
	<i>KIF1B</i>	Charcot-Marie-Tooth disease, axonal, type 2a1, #118 210	Distal limb weakness and atrophy due to peripheral neuropathy, foot drop, hyporeflexia, areflexia, pes cavus and hammer toes; childhood onset of the disease	1p36.22	AD	Loss-of-function variants Motor domain
	<i>KIF1BP / KIAA1279</i>	Goldberg-Shprintzen megacolon syndrome, #609 460	Intellectual disability, microcephaly and dysmorphic facial features; Hirschsprung disease and/or gyral abnormalities of the brain in most patients; megalocornea or urogenital anomalies may also be present	10q22.1	AR	Nonsense variants
	<i>KIF1C</i>	Spastic ataxia type 2, #611 302	Dysarthria, cerebellar gait ataxia, dysmetria, tremor, spasticity of the lower limbs, hyper-reflexia and distal muscle atrophy; onset in teenage years	17p13.2	AR	Nonsense/truncating variants/whole-gene deletion
	<i>KIF14</i>	Meckel syndrome 12, #616 258	IUGR, corpus callosum agenesis, cerebral and cerebellar hypoplasia, flexion arthrogryposis, renal agenesis and microcephaly	1q32.1	AR	Truncating variants
	<i>KIF16B</i>	Primary microcephaly type 20, #617 914	Microcephaly, ID, autistic features; highly variable severity	1q32.1	AR	See table 2 for details.
Kinesin 4	<i>KIF7</i>	Acrocallosal syndrome, #200 990	Severe intellectual disability, postaxial polydactyly, hallux duplication, macrocephaly and absence of the corpus callosum	15q26.1	AR	Frameshift/nonsense variants Throughout the gene
		Joubert syndrome 12, #200 990	ID, molar tooth sign on brain MRI, ataxia, agenesis of the corpus callosum, hypertelorism, triangular mouth, downslanting palpebral fissures, low-set ears, prominent forehead and polydactyly	15q26.1	AR	Truncating variants/non-sense mediated decay
		Al-Gazali-Bakalinova syndrome, #607 131	Macrocephaly, frontal bossing, hypertelorism, flattening of the malar region, low-set ears, pectus excavatum and carinatum, spindle-shaped fingers with interdigital soft-tissue webbing, clinodactyly, genu valgum, swelling of the joints, dysplasia of the epiphyses of the long bones, agenesis of the corpus callosum and frontotemporal brain atrophy	15q26.1	AR	Missense variants Structural maintenance of chromosomes domain
		Hydrolethalus syndrome 2, # 614 120	Lethal developmental disorder: hydrocephaly, arhinencephaly, upper limb postaxial polydactyly, hallux duplication and molar tooth sign on MRI	15q26.1	AR	Microdeletion Coiled-coil region
	<i>KIF4A</i>	Mental retardation, X-linked 100, #300 922	Intellectual disability, seizures and mild facial dysmorphisms	Xq13.1	XLR	In-frame deletion, splicing affected
		Isolated hydrocephalus <sup>11</sup>	Hydrocephalus internus at 22 weeks of gestation	Xq13.1	Candidate gene/ XLR	Missense variant Coiled-coil domain
	<i>KIF21A</i>	Fibrosis of extraocular muscles, congenital 1, #135 700	Ptosis, hypotropic strabismus, fibrosis of extraocular muscles and compensatory backward tilt to the head	12q12	AD	Missense variants Stalk domain
		Fibrosis of extraocular muscles, congenital, 3B, #135 700	Eyes in neutral primary position, residual upgaze and absence of ptosis	12q12	AD	Missense variants Stalk domain
Kinesin 5	<i>KIF11</i>	Microcephaly with or without chorioretinopathy, lymphoedema or mental retardation, #152 950.	Microcephaly, developmental delay, characteristic facial phenotype, chorioretinopathy, retinal folds and congenital lymphoedema	10q23.33	AD	Truncating variants
Kinesin 7	<i>KIF10/ CENPE</i>	Microcephaly 13, primary autosomal recessive, #616 051	Microcephaly, poor overall growth, developmental delay, dysmorphic facial features, severely simplified gyral pattern with partial agenesis of the corpus callosum and cerebellar hypoplasia	4q24	AR	Missense variants Coiled-coil region

Continued

Table 1 Continued

Kinesin family	KIF gene	Associated phenotypes, OMIM	Clinical description	Cytogenetic location	Inheritance	Variant type
Kinesin 10	<i>KIF22</i>	Spondyloepimetaphyseal dysplasia with joint laxity, type 2, #603 546	Short stature, distinctive midface retrusion, progressive knee malalignment (genu valgum and/or varum), generalised ligamentous laxity and mild spinal deformity	16p11.2	AD	Missense variants Kinesin motor domain
Kinesin 11	<i>KIF26B</i>	Autosomal dominant spinocerebellar ataxia <sup>59</sup>	Spasticity and gait/limb ataxia and very slow progression.	1q44	AD	Missense variants Tail region
		Pontocerebellar hypoplasia with arthrogryposis <sup>60</sup>	Progressive microcephaly, right germinolytic cyst, thinned corpus callosum, dysmorphic facial features, camptodactyly, congenital dislocations of both hips, congenital vertical talus (rocker-bottom feet), arthrogryposis of upper extremities and myoclonic seizures	1q44	Candidate gene/AD	Missense variant Kinesin motor domain
Kinesin 12	<i>KIF12</i>	Renal hypodysplasia <sup>52</sup>	Congenital megabladder, renal hypodysplasia and congenital vesicoureteral reflux	9q32	Candidate gene/AD	CNV (duplication)
		High gamma-glutamyltransferase cholestasis <sup>60</sup>	Neonatal cholestasis, paucity of bile ducts, mild renal pelvic abnormalities with unremarkable kidney function	9q32	AR	Truncating/missense variants Kinesin motor domain
	<i>KIF15</i>	Braddock-Carey-like syndrome <sup>54</sup>	Microcephaly, congenital thrombocytopenia, Pierre-Robin sequence and agenesis of the corpus callosum	3p21.31	AR	Nonsense variants Coiled-coil domain
Kinesin 13	<i>KIF24</i>	Cortical dysplasia, complex, with other brain malformations 3 (CDCBM3), #615 411	Microcephaly, early-onset epilepsy and various malformations of cortical development, including agyria, posterior or frontal pachygyria, subcortical band heterotopia and thin corpus callosum; severe developmental delay, spastic paraplegia, persistent hyperplastic primary vitreous and microphthalmia	5q12.1	AD	Missense variants Kinesin motor domain

Susceptibility loci are not included.

OMIM online mendelian inheritance of man, www.omim.org

AD, autosomal dominant; AR, autosomal recessive; CNV, copy number variant; IUGR, intrauterine growth retardation; PX, phox homology; XLR, X-linked recessive.

syndromic hydrocephalus. *KIF4A* was recently proposed as a candidate gene for hydrocephalus.<sup>11</sup>

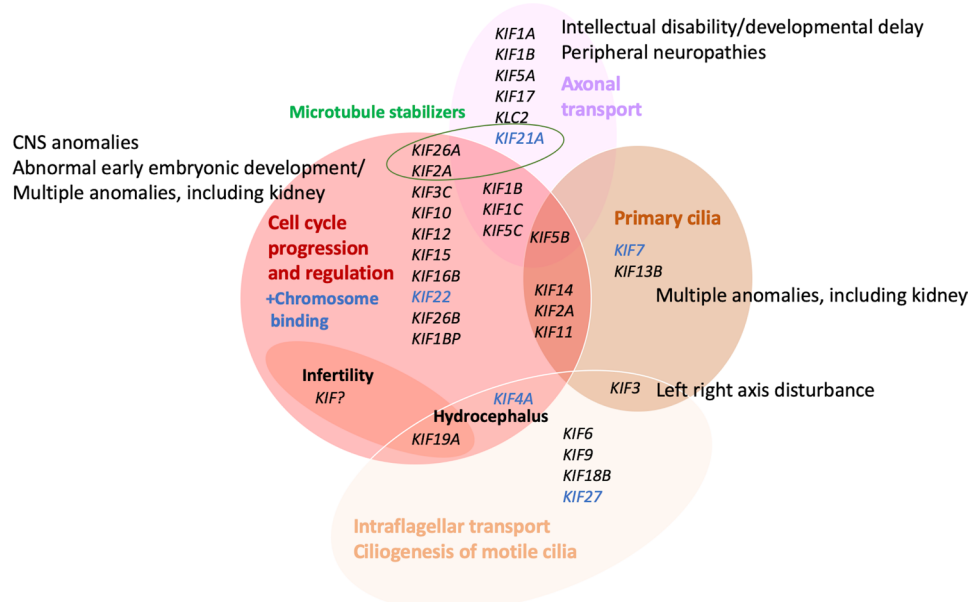
KIFs are involved in neuronal branching, and microtubule depolarisation, operated by *KIF2A* M-kinesin, was suggested to suppress collateral branch extension during brain development, leading to anomalies of cortical development, including agyria and pachygyria, subcortical band heterotopia and corpus callosum anomalies.<sup>12</sup>

Functional disruption of *KIF* genes in knockout mice often results in embryonic lethality, for example, for *Kif18A*, *Kif10*, *Kif3A*, *Kif3B* and *Kif5B*,<sup>13–17</sup> highlighting the importance of kinesins in embryonic and foetal development. A study on *KIF16B* demonstrated that microtubule-based trafficking is responsible for early development and stem cell survival.<sup>18</sup> *KIF26B* is

essential in kidney development, contributing to the adhesion of mesenchymal cells to the ureteric bud.<sup>3</sup> *KIF26A* was suggested to play a role in enteric nervous system development, because knockout mice develop a megacolon and enteric nerve hypoplasia,<sup>19</sup> and to negatively regulate nociceptive sensation.<sup>20</sup>

A significant number of KIFs play a prominent role in cilio-genesis and cilia function. They regulate cilia length, ciliary assembly/disassembly and can have motile cilia-specific functions.<sup>21</sup> Some KIFs, specifically found in primary cilia (PC), regulate the length of the axoneme and its disassembly when re-entering the cell cycle.

*KIF7*, also a key component of the Hedgehog signalling pathway, is responsible for cilia length regulation through suppression of microtubule polymerisation.<sup>7</sup> *KIF7* variants



**Figure 2** Assignment and clustering of *KIF* genes to various functions and relation to birth defect or monogenic phenotype groups. Detailed phenotypes are shown in tables 1 and 3. Cancer and multifactorial conditions are not included. CNS, central nervous system.



cause hydroletharus, acrocallosal, and Joubert and Al-Gazali-Bakalinova syndromes.<sup>22</sup> *Kif2A* knockout mice have severe brain defects, and *KIF2A* variants in humans lead to microcephaly because of cell-cycle delay in cellular progenitors resulting from cilia disassembly defects. *KIF24*, belonging to the same kinesin 13 family, plays a role in both microtubule depolymerising activity and regulation of the early steps of ciliogenesis. Other PC-related KIFs recently identified are *KIF5B*, *KIF1C* and *KIF13B*, and a potential role in cilia was hypothesised for *KIF11* and *KIF14*.

*KIF3* protein complex (*KIF3A*-*KIF3B*-*KAP3* heterotetramer) is a molecular motor necessary for intraflagellar transport (IFT) but is also involved in ciliogenesis of motile cilia. *Kif3a*-knockout or *Kif3b*-knockout mice are prenatally lethal, exhibiting anomalies similar to ciliopathy phenotypes, including the disturbance of left–right body determination.<sup>3</sup>

*KIF19A* is localised at the tip of motile cilia and performs motor and microtubule-depolymerising activities during IFT. *Kif19a*-knockout mice present with hydrocephalus and female infertility, common signs in ciliary defects, due to abnormally elongated cilia with altered motility, not able to generate proper fluid flow.<sup>9</sup>

Further KIFs, which may have specific roles in motile cilia, are *KIF27*, *KIF9*, *KIF6* and *KIF18B*. Regarding the involvement of numerous KIFs in cilia-related processes, it is not surprising that many disorders caused by variants affecting *KIF* gene function are presenting with anomalies reminiscent of ciliopathies.

Kinesin motors have a fundamental role in neuronal function, as they are responsible for the transport of synaptic vesicle precursors and transmitter receptors along axons and dendrites from the neuron body.<sup>3</sup> Molecular motor activity as for *KIF1A*, *KIF5* and *KIF17* is important for higher brain functions, such as learning and memory through regulation of synaptic transmission.<sup>5</sup> Dysfunction can be associated with intellectual disability and global developmental delay (table 1).

Impaired function can also result in peripheral neuropathies (*KIF5A*, *KLC2*, *KIF1A* and *KIF1B*) and ocular motility disorders (*KLC2* and *KIF21A*)<sup>23 24</sup> when axon elongation in the peripheral nervous system and optic nerve is affected. *KIF5A* variants are associated with epileptic phenotypes both in humans and mice<sup>25</sup> because the transport of neurotransmitter receptors is disturbed and inhibitory regulation is altered.

Due to their role in cell-cycle regulation, kinesins are important in male spermatogenesis and female oogenesis. They are involved in all steps of spermatogenesis<sup>26</sup> and, based on previous animal studies, they may represent a potential target to treat male infertility. In female meiosis, 13 *KIF* genes were studied in animal models. There is some evidence that kinesin expression is vulnerable to maternal ageing and environmental factors, such as oocyte cryopreservation and alcohol consumption. It may be promising to expand research in this field in order to clarify the mechanisms and factors contributing to oocyte quality decline.<sup>27</sup>

Many kinesins were extensively studied in the fields of cancer development, progression and therapy. Deregulation of the mitotic kinesins by both overexpression and decreased expression causes cancer progression or can be a prognostic marker in various tumours.<sup>28</sup> The cell-permeable small-molecule mitotic inhibitor monastrol was discovered in 1999<sup>29</sup> and was shown to arrest cells in mitosis by specifically inhibiting *KIF11*, a kinesin important for spindle bipolarity. The bipolar mitotic spindle is replaced by a *monastral* microtubule array surrounded by a ring of chromosomes, which gave the inhibitor its name. The mitotic spindle is now a well-known target of chemotherapy,

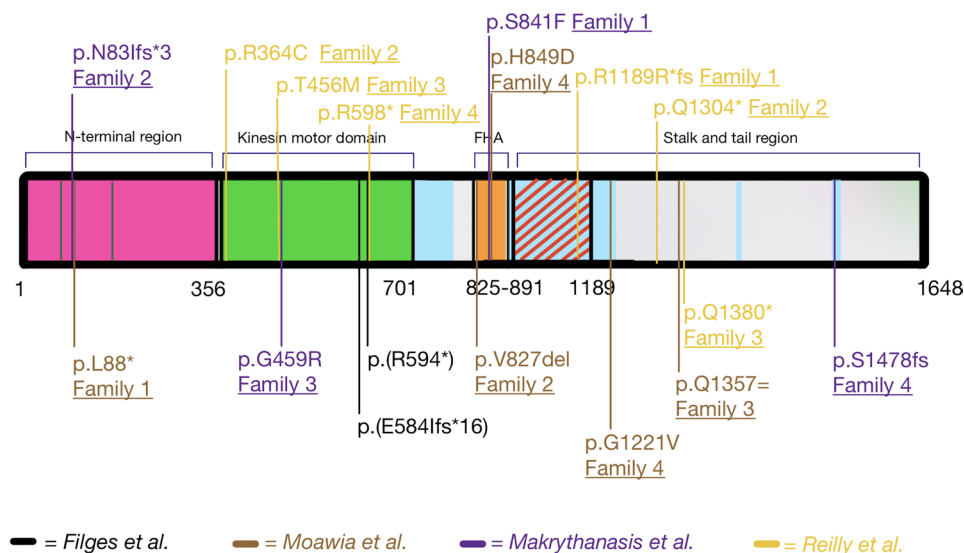
and inhibitors of the mitotic kinesins *KIF11*, *KIF10* and *KIF1C* are being studied for this purpose.<sup>28 30</sup> The redundancy of some kinesins allows them to escape pharmacological inhibition. For example, in the absence of *KIF10*, *KIF15* is able to replace all of its essential functions in spindle assembly. Cilia-related *KIF7*, *KIF13B* and *KIF27* are involved in SHh signalling and may be a future target in cancer research.<sup>28</sup>

Some kinesins confer susceptibility to a range of multifactorial, metabolic and neurodegenerative conditions. *KIF13B* contributes to the enhancement of endocytosis of low-density lipoprotein (LDL) receptor-related protein 1 that is involved in the recognition and internalisation of LDL and factor VIII. *Kif13b*-knockout mice have hypercholesterolaemia and higher factor VIII serum levels.<sup>5</sup> *KIF12* is implicated in the pathogenesis of type 2 diabetes, protecting pancreatic  $\beta$  cells from the oxidative stress caused by nutritional excess.<sup>5</sup> Variants in *KIF1B* or *KIF21B* confer susceptibility to multiple sclerosis (OMIM #612596, #126200).<sup>31 32</sup> *KIF5A* was associated with Amyotrophic lateral sclerosis (OMIM #617921).<sup>33</sup> *KIF3* complex and *KIF17* were recently uncovered to be involved in schizophrenia.<sup>34 35</sup> Further studies, however, are needed to clarify the precise role of KIFs in neurodegenerative processes and psychiatric conditions.

### **KIF14 -RELATED BIRTH DEFECTS: LESSONS LEARNT**

Advances in next-generation sequencing technologies have revolutionised our understanding of Mendelian disorders, including birth defect phenotypes, by sequencing the coding genome (exome) or entire genome at an unprecedented resolution in a comparably short time span. The technology has been extensively used for gene identification approaches in research for many years, enabling unparalleled genotype–phenotype correlations and the definition of novel pathways of related genes and disorders at an accelerated pace, traditionally focusing on postnatal disorders. Filges and Friedman<sup>36</sup> postulated that a number of novel disease genes causing birth defects could be identifiable through the investigation of lethal foetal phenotypes since they would represent the extreme end of allelic milder and viable postnatal phenotypes with less specific or recognisable anomaly patterns. Based on embryonically or perinatally lethal mouse models ([www.informatics.jax.org](http://www.informatics.jax.org) and [www.dmdd.org.uk](http://www.dmdd.org.uk)), it is estimated that knockout variants in about 30% of human protein coding genes may present with a phenotype of early lethality. The identification of *KIF14* loss of function variants in fetuses with a lethal multiple congenital anomaly syndrome and the subsequent description of the allelic postnatal viable phenotype and further functional characterisation of *KIF14* in developmental processes are recent examples of how to study those embryonic lethal phenotypes in order to understand the role of genes for which little to nothing is known.

Filges *et al* identified autosomal recessive compound heterozygous loss of function variants in *KIF14* using family-based exome sequencing in a recurrent severe lethal phenotype (OMIM #616258). It was the first human phenotype reported due to variants in the human *KIF14* gene (figure 3).<sup>37</sup> The two affected siblings presented with intrauterine growth retardation (IUGR), oligohydramnios, severe microcephaly, renal cystic dysplasia or agenesis, genital tract malformations (uterine hypoplasia and vaginal atresia), as well as cerebral and cerebellar hypoplasias with partial or total agenesis of the vermis, arhinencephaly, agenesis of occipital lobes/corpus callosum at second trimester ultrasound scan. Cross-species comparison to the *laggard* spontaneous mice mutant, characterised by homozygous variants of the *Kif14* gene,<sup>38</sup> confirmed a phenotypical overlap. An increased



**Figure 3** Structure of KIF14 and summary of all published *KIF14* variants affecting function.<sup>10 37 41 42</sup> The N-terminal region (aa 1–356) is important for its interactions with PRC1 and the protein's localisation at the central spindle and midbody; the kinesin motor domain (aa 358–701) is responsible for the microtubule-dependent ATPase activity; the FHA domain (aa 825–891); stalk and tail region (aa 891–1648) are necessary for the interaction with the protein CRIK (aa 901–1189, red diagonal lines). There are four additional coiled-coil domains (light blue-coloured areas).<sup>61</sup> FHA, forkhead associated. aa, amino acid.

number of binucleated cells in the tissue histology of the two fetuses were in concordance with the key role of KIF14 during mitosis participating in chromosomes' congression and alignment, as well as in cytokinesis<sup>39</sup> and the observation of binucleated cells as a consequence of failed cytokinesis in mammalian *KIF14* knockdown cells. During cytokinesis, PRC1 localises KIF14 at the central spindle and midbody, which in turn recruits citron rho-interacting kinase (CIT) to the midbody. CIT, in turn, acts as a negative regulator of KIF14 activity. Knockdown of *KIF14* in mammalian cells results in impaired localisation of CIT during mitosis.<sup>40</sup>

Filges *et al* pointed out that *KIF14* should be considered a candidate gene for viable postnatal phenotypes, including isolated microcephaly.<sup>34</sup> Additional individuals with autosomal recessive variants in *KIF14* and isolated primary microcephaly were then described<sup>9 41 42</sup> (table 2).

Impaired cytokinesis, increased apoptosis and reduced cell motility were confirmed in cells from the described patients, pointing to a new cellular pathway in the pathogenesis of microcephaly.<sup>43</sup> Apart from one case with small kidneys with increased echogenicity, none of these 18 patients had associated kidney anomalies. However, a targeted exome sequencing study in 204 unrelated patients with congenital anomalies of the kidney and urinary tract (CAKUT) reported two more cases of renal anomalies, bilateral hypoplasia or agenesis, caused by *KIF14* variants.<sup>44</sup> Further nine cases had an associated renal phenotype, which ranged from bilateral renal agenesis to cystic or non-cystic renal hypodysplasia.<sup>42</sup> Table 2 and figure 3 summarise *KIF14* variants and the associated phenotypes. Loss of function variants more likely lead to multiple congenital anomalies, while hypomorphic variants result in a milder phenotype without renal involvement, although phenotype–genotype correlations remain preliminary for the time being.

The phenotypical spectrum ranging from isolated primary microcephaly to congenital anomalies reminiscent of ciliopathy phenotypes suggested a complex role for KIF14 in developmental processes and raised a number of questions about the relationship between its established role in cell division and

its possible function in ciliary pathways. Functional studies of absent KIF14 protein in the development of human foetal tissues and mutant zebrafish provided evidence for similarities and differences between mitotic events occurring during proliferation in the development of both brain and kidney.<sup>42</sup> The observation that KIF14-stained midbodies accumulate within the lumen of the branch tips of ureteric buds in human foetal kidneys provided a key clue to better understand the mechanism through which the loss of KIF14 affects both brain and kidney development in humans. It was previously demonstrated that the secretion and accumulation of midbody remnants in the cerebrospinal fluid in mice during the early stages of brain development correspond to the amplification of neural progenitors.<sup>45</sup> *Kif14* mutant zebrafish phenotypes supported the hypothesis of a potential role for KIF14 in cilia. In vitro and in vivo analyses suggested that loss of *kif14* causes ciliary anomalies through an accumulation of mitotic cells in ciliated tissues but failed to establish a direct functional link.<sup>21 42</sup> Further mechanisms remain to be elucidated. Overexpression of KIF14 in various types of tumours was suggested to be a possible prognostic marker and a potential target for therapeutic purposes.<sup>46</sup>

### KINESINOPATHIES IN BIRTH DEFECT PHENOTYPES: RECURRENT THEMES

In the last few years, an increasing number of variants in *KIF* genes were described to cause isolated as well as multiple congenital anomalies. There is a huge variability of phenotypes caused by variants even within the same gene. However, we can identify recurrent clinical signs that should alert the clinician to suspect a *KIF* gene-related disorder and the molecular geneticist to include *KIF* genes in multigene-panel and genome-wide sequencing approaches. This will become particularly relevant in prenatal and perinatal medicine, which focuses on the detection of structural anomalies in the fetus and the newborn by using ultrasound and MRI or autopsy when the outcome is lethal. We have summarised the predominant and recurrent structural anomalies in kinesinopathies reported so far that would likely

**Table 2** Summary of phenotypes and genotypes of *KIF14*<sup>9 26 30 31</sup>

Family	Individuals affected (n)	Consanguinity	CNS phenotype	Kidney phenotype	Prenatal lethal wGA	<i>KIF14</i> sequence variant	Functional domain
Filges <i>et al</i> <sup>37</sup>	2	–	Microcephaly, agenesis of occipital lobes, CC and vermis	BRA, RHD	21+4; 18+5	c.1750_1751del, c.1780A>T p.Glu584Ilefs*16, p.Arg594*	Motor domain
Moawia <i>et al</i> <sup>10</sup> Family 1	3	+	Microcephaly with simplified gyral pattern	–	–	c.263A>T p.Leu88*/ p.Gly58 Leu181del	PRC1 binding
Moawia <i>et al</i> <sup>10</sup> Family 2	2	+	Microcephaly with simplified gyral pattern	–	–	c.2480_2482delTTG p.Val827del	FHA domain
Moawia <i>et al</i> Family 3	3	+	Microcephaly	–	–	c.4071G>A p.Gln1357=/ p.Leu1296Trpfs*46	C-terminal tail
Moawia <i>et al</i> <sup>10</sup> Family 4	2	–	Microcephaly, lissencephaly CC agenesis	Small kidneys, increased echogenicity	24	c.2545C>G, c.3662G>T p.His849Asp, p.Gly1221Val/ p.Gly1221 Lys1296delinsVal	FHA domain C-terminal tail
Makrythanasis <i>et al</i> <sup>41</sup> Family 1	2	+	Intellectual disability	–	–	c.2522C>T p.Ser841Phe	FHA domain
Makrythanasis <i>et al</i> <sup>41</sup> Family 2	2	+	Microcephaly, optic atrophy, ASD	–	–	c.246delT p.Asn83Ilefs*3	PRC1 binding
Makrythanasis <i>et al</i> <sup>41</sup> Family 3	2	+	Micro-lissencephaly frontal cerebral atrophy, partial agenesis of CC	–	–	c.1375G>A p.Gly459Arg	Motor domain
Makrythanasis <i>et al</i> <sup>41</sup> Family 4	2	+	Microcephaly	–	15; 17	c.4432delA p.Ser1478fs	C-terminal tail
Reilly <i>et al</i> <sup>42</sup> Family 1	1	–	Microcephaly, CC agenesis, brainstem hypoplasia	Cystic RHD	18	c.35672?_4072+?del p.Arg1189Argfs*9	C-terminal tail
Reilly <i>et al</i> <sup>42</sup> Family 2	3	–	Microcephaly, holoprosencephaly	BRA <sup>2</sup> , RHD <sup>1</sup>	33; 37+1; 18+3	c.3910C>T, c.1090C>T p.Gln1304*, p.Arg364Cys	C-terminal tail Motor domain
Reilly <i>et al</i> <sup>42</sup> Family 3	3	–	Microcephaly, CC agenesis, brainstem hypoplasia	Cystic RHD	24; 20+3; 18	c.1367C>T, c.4138C>T p.Thr456Met, p.Gln1380*	C-terminal tail Motor domain
Reilly <i>et al</i> <sup>42</sup> Family 4	4	–	Micro-lissencephaly	Cystic RHD <sup>2</sup> , RHD <sup>1</sup> , BRA <sup>1</sup>	27+4; 17+4; 21+2; 23	c.1792C>T p.Arg598*	Motor domain

ASD, autism spectrum disorder; BRA, bilateral renal agenesis; CC, corpus callosum; CNS, central nervous system; FHA, forkhead associated; PRC1, protein regulating cytokinesis 1; RHD, renal hypodysplasia; wGA, weeks gestational age

become apparent during the foetal period in table 3 and the syndromic disorders in table 1.

Consistent with the kinesins' role in the development of the central nervous system (CNS), brain anomalies of various degrees are a frequent clinical sign, particularly microcephaly, but include lissencephaly, polymicrogyria, thinned or agenesis of the corpus callosum, arhinencephaly, cerebral hypoplasia or atrophy, cerebellar hypoplasia or atrophy, brainstem hypoplasia and a molar tooth sign on brain imaging.<sup>12 22 37 44 47–51</sup>

Primary microcephaly can be detected prenatally or at birth<sup>12 22 47 48 50 51</sup> and can present as an isolated or syndromic condition as, for example, caused by variants in *KIF14*<sup>9</sup> or in *KIF11* (microcephaly with or without chorioretinopathy, lymphoedema or mental retardation; OMIM #152950).<sup>48</sup>

*KIF7* variants were related to macrocephaly in the presence of congenital hydrocephalus (hydrolethrus syndrome LS2, OMIM #614120). Isolated hydrocephalus was reported for *KIF4A* in a single case.<sup>11</sup>

Foetal akinesia and arthrogryposis (*KIF5C*<sup>12</sup>, *KIF14*<sup>34</sup> and *KIF26B*<sup>50</sup>) are likely secondary to the neurological compromise of the fetus but can also appear as an early sign of abnormal CNS

development, which should prompt specialist CNS sonographic and MRI evaluation of the fetus.

Further anomalies of the limbs include camptodactyly (*KIF26B*<sup>50</sup>), clubfoot (*KIF1A*<sup>51</sup>), rocker-bottom feet (*KIF26B*<sup>50</sup>) and congenital lymphoedema of the limbs (dorsa of feet, lower extremities and, rarely, hands) in cases with *KIF11* gene mutations.<sup>48</sup> In particular, *KIF7* gene variants have been related to various anomalies of the hands (tapered fingers, fifth finger clinodactyly, brachydactyly, preaxial or postaxial polydactyly, bifid terminal phalanges of the thumbs, spindle-shaped fingers, clinodactyly and soft tissue webbing) and feet (toe syndactyly, preaxial or postaxial polydactyly, and duplicated halluces).<sup>22</sup>

CAKUT and genital anomalies are reported in various kinesinopathies including renal agenesis or hypoplasia (*KIF14*<sup>37</sup> and *KIF12*<sup>52</sup>), ureteral hypoplasia (*KIF14*<sup>37</sup>), congenital megablastoid (*KIF12*<sup>52</sup>) and vesicoureteral reflux (*KIF12*<sup>52</sup>), uterine hypoplasia and vaginal atresia (*KIF14*<sup>37</sup>) and hypospadias and chordae (*KIF16B*<sup>49</sup>).

IUGR is recurrently detected (*KIF5C*<sup>12</sup>, *KIF14*<sup>37</sup>, *KIF10*<sup>53</sup>, *KIF15*<sup>54</sup> and *KIF2A*<sup>12</sup>) and is particularly relevant when occurring simultaneously with one of the other recurrent clinical

Table 3 KIF gene-related structural congenital anomalies recurrently described in prenatal phenotypes

		Kinesin 1		Kinesin 3		Kinesin 4		Kinesin 5	Kinesin 7	Kinesin 11	Kinesin 12		Kinesin 13
Structural congenital anomaly		KIF5C	KIF1A	KIF14	KIF16B	KIF7	KIF4A	KIF11	KIF10	KIF26B	KIF12	KIF15	KIF2A
CNS anomalies	Microcephaly	+	+	+	–	–	–	+	+	+	–	+	+
	Lissencephaly	+	–	+	–	–	–	+	+	–	–	–	+
	Thinned CC	+	–	–	+	–	–	–	–	+	–	–	–
	Agenesis of CC	–	–	+	–	+	–	–	+	–	–	–	–
	Arhinencephaly	–	–	+	–	+	–	–	–	–	–	–	–
	Cerebral hypoplasia	–	–	+	–	–	–	–	–	–	–	–	–
	Cerebral atrophy	–	+	–	–	+	–	–	–	–	–	–	–
	Cerebellar hypoplasia	–	–	+	–	–	–	–	+	+	–	–	–
	Cerebellar atrophy	–	+	–	–	–	–	–	–	–	–	–	–
	Brainstem hypoplasia	–	–	–	–	–	–	–	–	+	–	–	–
	Molar tooth sign	–	–	–	–	+	–	–	–	–	–	–	–
	Macrocephaly/hydrocephalus	–	–	–	–	+	+	–	–	–	–	–	–
Limbs	Hand anomalies	–	–	+	–	+	–	+	–	+	–	–	–
	Feet anomalies	–	+	–	–	+	–	+	–	+	–	–	–
CAKUT		–	–	+	–	–	–	–	–	–	+	–	–
Genital tract anomalies		–	–	+	+	–	–	–	–	–	–	–	–
IUGR		+	+	+	–	–	–	–	+	–	–	+	+

‘+’ indicates that the anomaly is described in the literature at least in one case, while ‘–’ indicates that an anomaly was never reported in association with a variant in the specific KIF gene to date. Clinical case descriptions and the respective references are appended in online supplementary material, table 3. CAKUT, congenital anomalies of the kidney and urinary tract; CC, Corpus callosum; CNS, central nervous system; IUGR, intrauterine growth restriction.

signs, indicating a potential syndromic KIF-related disorder. Oligohydramnios or polyhydramnios is most likely secondary to a primary organ anomaly.

There are a few kinesinopathy syndromes that have been specifically reported to be lethal, such as the ciliary phenotype (OMIM #616258), caused by variants in KIF14<sup>34</sup>, and hydro-lethalus syndrome (OMIM #614120), caused by variants in KIF7.<sup>22</sup> However, lethality is usually closely related to the specific major anomalies, and it can be hypothesised that such a lethal phenotype will exist for all KIF gene-related disorders.

Developmental delay, intellectual disability, seizures, and sensory and motor disturbances of the peripheral nervous system, as well as eye anomalies, such as microphthalmia, optic nerve pallor, fibrosis of extraocular muscles and chorioretinopathy, will escape detection in the foetal period but are reported in postnatal patients.

KINESIN PATHWAYS IN BIRTH DEFECTS

Functional studies of kinesins in birth defects are still sparse, and little is known about their networks and pathways. In order to improve our understanding, we used the Ingenuity Pathway Analysis (IPA Qiagen, Redwood City, California, USA) to visualise and analyse the connections between the 13 kinesin motor proteins associated with structural congenital anomalies (KIF5C, KIF1A, KIF1BP, KIF14, KIF16B, KIF7, KIF4A, KIF11, KIF10, KIF26B, KIF12, KIF15 and KIF2A) and in up to 10 of each of their most significant downstream proteins. The connections are defined as protein–protein interactions, activation, regulation of binding, expression, localisation, phosphorylation, protein–RNA interactions, molecular cleavage, ubiquitination, protein–DNA interactions, inhibition, translocation and transcription. Figure 3 displays the results. We used the software Gephy<sup>55</sup> to look for all possible interactions between all proteins of the network and also used the IPA data to retrieve the canonical pathways involved. Figure 4 and online supplementary material, table

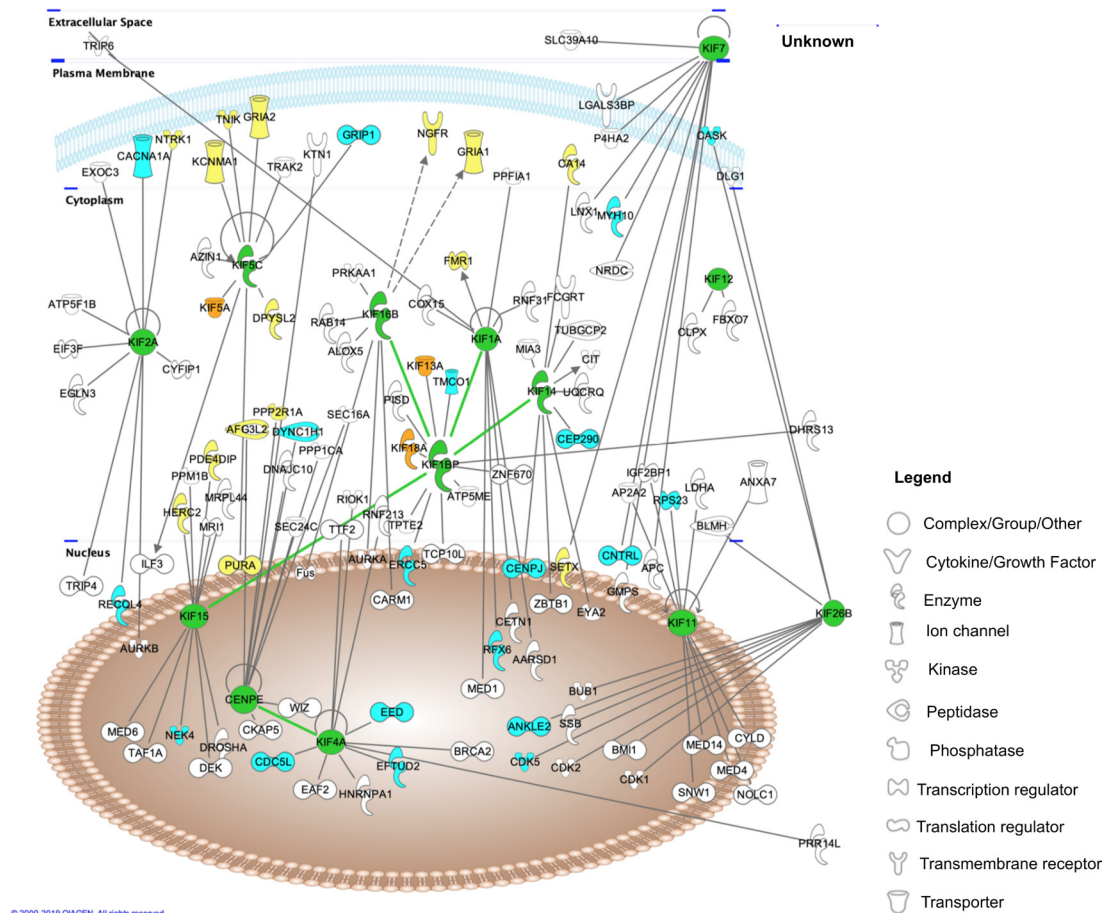
4, summarise the results. KIF7, KIF14 and KIF12 are located within the same network, and because of multiple connections between themselves and their downstream proteins, it is not surprising that they are all involved in kidney anomalies. IPA data are based on current publications and are therefore subject to bias because proteins that are most interconnected are also most probably those that have been more extensively studied. However, we consider the KIF genes coding for proteins seeming less important within the network to be strong candidates for future studies of human developmental disorders.

CLOSING REMARKS AND FUTURE PERSPECTIVES

Novel KIF genes are increasingly identified, and there is a growing body of literature demonstrating the impact of kinesin dysfunction in human disease. We propose to introduce the term kinesinopathies for conditions caused by variants in KIF genes, since recurrent and common functional and phenotypical themes can be observed. In analogy to ciliopathies<sup>56</sup> and rasopathies,<sup>57</sup> the delineation of the clinical, genetic and functional hallmarks of kinesinopathies will be important to better recognise these conditions, to understand the pathomechanisms and to ultimately improve the clinical management of the patients. Previously, the unified view of the phenotype characteristics of ciliary dysfunction allowed a tremendous increase in awareness, both in clinic and research, and the further identification of yet unrecognised ciliary disorders and the genes and proteins involved in their pathogenesis.<sup>56</sup>

Remarkable progress was achieved in assigning function to kinesins through their study in isolated and multiple congenital anomaly phenotypes. They are one large superfamily of molecular motors out of three (kinesins, dyneins and myosins), which is of key importance in several fundamental cellular processes using microtubules as rails for directional anterograde intracellular transport, including its regulation and modulating signal transduction.<sup>5</sup> Kinesin motors are most important for the





**Figure 4** IPA of the 13 kinesins known to be involved in birth defects with respect to their position in the cell. Proteins displayed on the right side of the figure, below the tag 'other', are those for which no subcellular location is known. Birth defect-related kinesins and their connection with each other are highlighted in green. Light blue-coloured downstream proteins are those which are known to cause birth defects when altered. Yellow-coloured proteins are those involved in neurological disorders overlapping with the clinical features of kinesinopathies. The legend of the biological function associated with every molecule is displayed on the right. Path Designer by IPA was used for the figure design. IPA, Ingenuity Pathway Analysis.

movement of chromosomes along the spindles during chromosome segregation, regulation of spindle formation, cell division and cytokinesis. These essential and broad cellular functions are critical for many physiological processes such as neuronal function and survival, some ciliary functions and ciliogenesis, determination of the left/right asymmetry of our body and regulation of organogenesis, thus explaining the impact and emerging recognition of kinesins in embryonic and foetal development. Defects can result in neuropathies, higher brain functions and structural brain anomalies. Multiple congenital anomalies, including the kidney and urinary tract and limb anomalies, are repeatedly reported. Microcephaly, which is usually not associated with genes implicated in specific ciliary mechanisms, and CNS anomalies are the most recurrent clinical signs in both the prenatal and postnatal phenotypes described so far. The discovery of the implication of *KIF14* in microcephaly further suggested a possible novel role of other microcephaly proteins in cytokinesis. A number of syndromic kinesinopathies present, however, with phenotype patterns reminiscent of ciliopathies. So far, however, a direct functional impact was confirmed in only a few and could not be demonstrated, for example, for *KIF14*, despite an overlapping clinical pattern. In turn, ciliopathies are a clinically and genetically heterogeneous group of conditions themselves. Studying tissue and cell type-specific function and

expression may help to further define the specific defects related to the individual aberrant kinesin.

The pleiotropic nature of human kinesinopathies, however, is just emerging, but their study promises to provide important insights into human developmental pathways. Seemingly unrelated clinical entities are highlighting a common theme. In a relatively short time span, monogenic *KIF*-related disorders were identified to present with often severe and lethal antenatal anomalies, with multiple or isolated congenital anomalies, neurodevelopmental and neurological disorders, or an increased susceptibility to multifactorial conditions. We focused on the emerging role of kinesins in structural congenital anomalies because, as illustrated for the *KIF14* gene, great potential to decipher allelic viable phenotypes and developmental pathways lies in the study of these human knockout phenotypes at the severe end of the phenotypical spectrum. Knockout variants in about 30% of human protein coding genes in our genome may present with a phenotype of early lethality, and *KIF* genes seem to play an important role in such fundamental processes of human development. Identifying and characterising the variants, genes and phenotypes will extend our knowledge on early human development and pathomechanisms, and will ultimately also improve the clinical utility of genome-wide sequencing approaches for prenatal and postnatal application by our

increased ability to interpret loss of function and hypomorphic variants alike. Furthermore, kinesins were extensively studied in cancer research and therapeutic strategies targeting their specific functions, such as the example of monastrol and other inhibitors of the mitotic kinesins may be adopted in the future. There are likely many more kinesinopathies to be unravelled in the field of birth defects because of their pivotal role in cellular logistics, but their recognition in clinics and research will depend on our ability to identify and characterise the common clinical, molecular and functional themes of these disorders and to use them to improve our understanding of their disease mechanisms.

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