REVIEW

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

Silvia Kalantari ![ORCID],[1] Isabel Filges ![ORCID] [1,2]

[1]Medical Genetics, Institute of Medical Genetics and Pathology, University Hospital Basel and University of Basel, Basel, Switzerland
[2]Department of Clinical Research, University Hospital Basel and University of Basel, Basel, Switzerland

Correspondence to
Dr Isabel Filges, Medical Genetics, University Hospital Basel, Basel 4031, Switzerland; isabel.filges@unibas.ch

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.[1] 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).[2] The first kinesins discovered belong to the kinesin-1 family (*KIF5A*, *KIF5B* and *KIF5C*), and they form a hetero-tetramer of two heavy chains and two light chains (*KLC1-4*).[2] *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.[2] 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.[3]

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.[4] 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.[5] 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.[6] 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.[7]

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.[8] 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
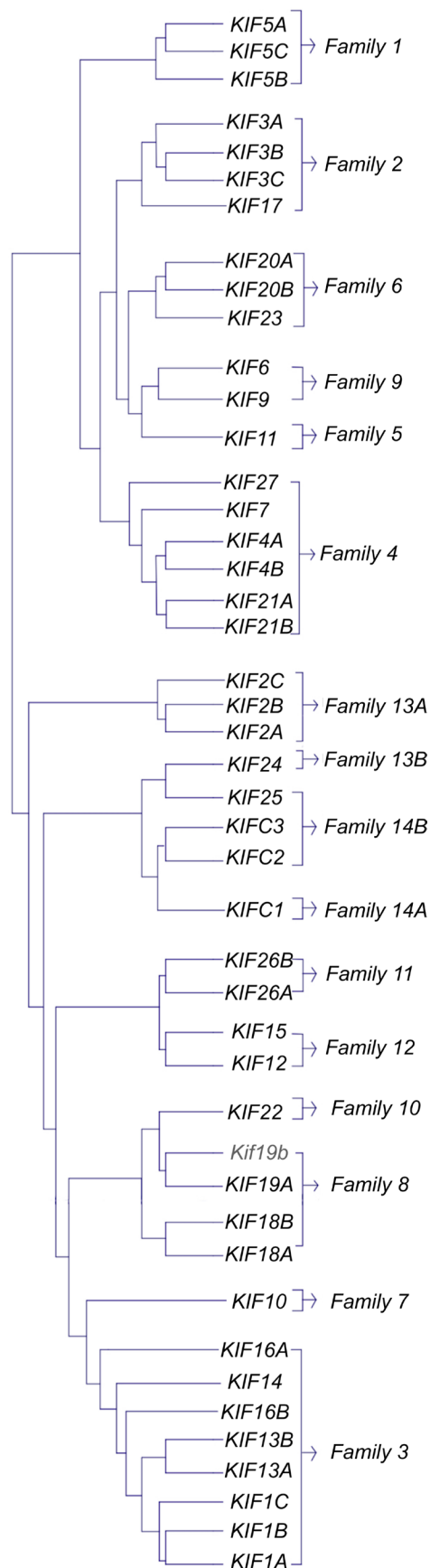
Figure 1 Phylogenetic tree of mammalian kinesin superfamily genes identified in the human (and mouse) genome and classified in 16 subfamilies (from kinesin 1 to 14B) (adapted from Hirokawa *et al*[3]).

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 'kinesin-opathies' 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).[2] 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.[3] 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.[9] 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.[3]

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.[10]

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	*KIF5A*	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
	KIF5C	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
	KLC2	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	*KIF3C*	Sporadic infantile spasm syndrome[58]	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	*KIF1A*	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
	KIF1B	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
	KIF1BP / KIAA1279	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
	KIF1C	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
	KIF14	Meckel syndrome 12, #616 258	IUGR, corpus callosum agenesis, cerebral and cerebellar hypoplasia, flexion arthrogryposis, renal agenesis and microcephaly	1q32.1	AR	Truncating variants
		Primary microcephaly type 20, #617 914	Microcephaly, ID, autistic features; highly variable severity	1q32.1	AR	See table 2 for details.
	KIF16B	Novel autosomal recessive ID syndrome[49]	Facial dysmorphism, microcephaly, hypospadias and chordae, intellectual disability, seizures, brain atrophy and thinning of the corpus callosum	20p12.1	AR	Missense variants PX domain
Kinesin 4	*KIF7*	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
	KIF4A	Mental retardation, X-linked 100, #300 922	Intellectual disability, seizures and mild facial dysmorphisms	Xq13.1	XLR	In-frame deletion, splicing affected
		Isolated hydrocephalus[11]	Hydrocehalus internus at 22 weeks of gestation	Xq13.1	Candidate gene/XLR	Missense variant Coiled-coil domain
	KIF21A	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	*KIF11*	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	*KIF10/ CENPE*	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

Table 1 Continued

Kinesin family	KIF gene	Associated phenotypes, OMIM	Clinical description	Cytogenetic location	Inheritance	Variant type
Kinesin 10	KIF22	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	KIF26B	Autosomal dominant spinocerebellar ataxia[59]	Spasticity and gait/limb ataxia and very slow progression.	1q44	AD	Missense variants Tail region
		Pontocerebellar hypoplasia with arthrogryposis[50]	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	KIF12	Renal hypodysplasia[52]	Congenital megabladder, renal hypodysplasia and congenital vesicoureteral reflux	9q32	Candidate gene/AD	CNV (duplication)
		High gamma-glutamyltransferase choleastasis[60]	Neonatal choleastasis, paucity of bile ducts, mild renal pelvic abnormalities with unremarkable kidney function	9q32	AR	Truncating/missense variants Kinesin motor domain
	KIF15	Braddock-Carey-like syndrome[54]	Microcephaly, congenital thrombocytopenia, Pierre-Robin sequence and agenesis of the corpus callosum	3p21.31	AR	Nonsense variants Coiled-coil domain
Kinesin 13	KIF2A	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.[11]

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.[12]

Functional disruption of *KIF* genes in knockout mice often results in embryonic lethality, for example, for *Kif18A*, *Kif10*, *Kif3A*, *Kif3B* and *Kif5B*,[13–17] 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.[18] KIF26B is

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

A significant number of KIFs play a prominent role in ciliogenesis and cilia function. They regulate cilia length, ciliary assembly/disassembly and can have motile cilia-specific functions.[21] 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.[7] *KIF7* variants
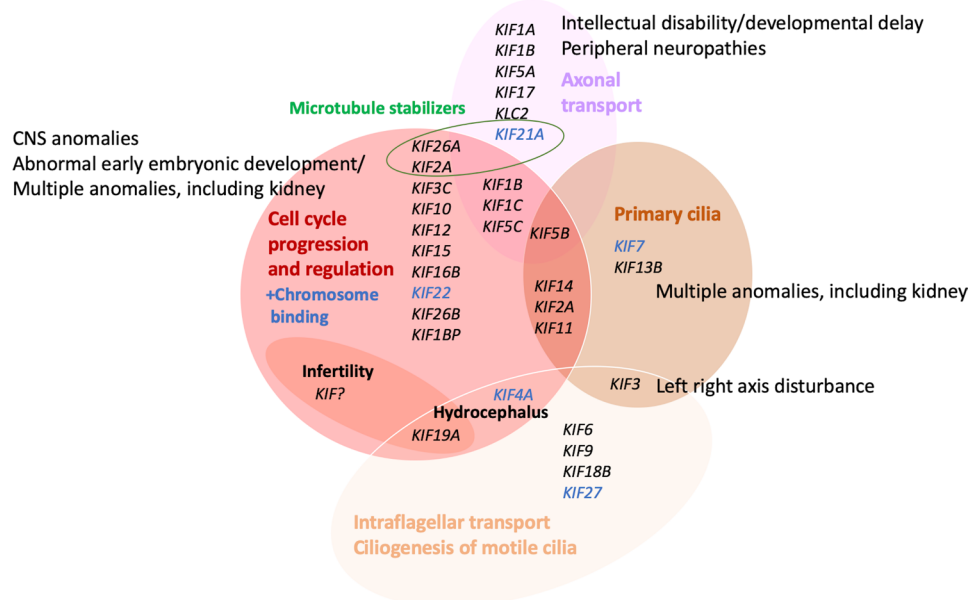

Figure 2 Assignment and clustering of *KIF* genes to various functions and relation to birth defect or monogenic phenotype groups. Detailed phenotypes are shown in tables 1 and 3. Cancer and multifactorial conditions are not included. CNS, central nervous system.

cause hydrolethalus, acrocallosal, and Joubert and Al-Gazali-Bakalinova syndromes.[22] *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.[3]

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.[9]

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.[3] 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.[5] 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*)[23 24] 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[25] 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 [26] 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.[27]

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.[28] The cell-permeable small-molecule mitotic inhibitor monastrol was discovered in 1999[29] 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 *monoastral* 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.[28 30] 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.[28]

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.[5] KIF12 is implicated in the pathogenesis of type 2 diabetes, protecting pancreatic β cells from the oxidative stress caused by nutritional excess.[5] Variants in *KIF1B* or *KIF21B* confer susceptibility to multiple sclerosis (OMIM %612596, #126200).[31 32] *KIF5A* was associated with Amyotrophic lateral sclerosis (OMIM #617921).[33] KIF3 complex and KIF17 were recently uncovered to be involved in schizophrenia.[34 35] 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[36] 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 and 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).[37] 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,[38] confirmed a phenotypical overlap. An increased
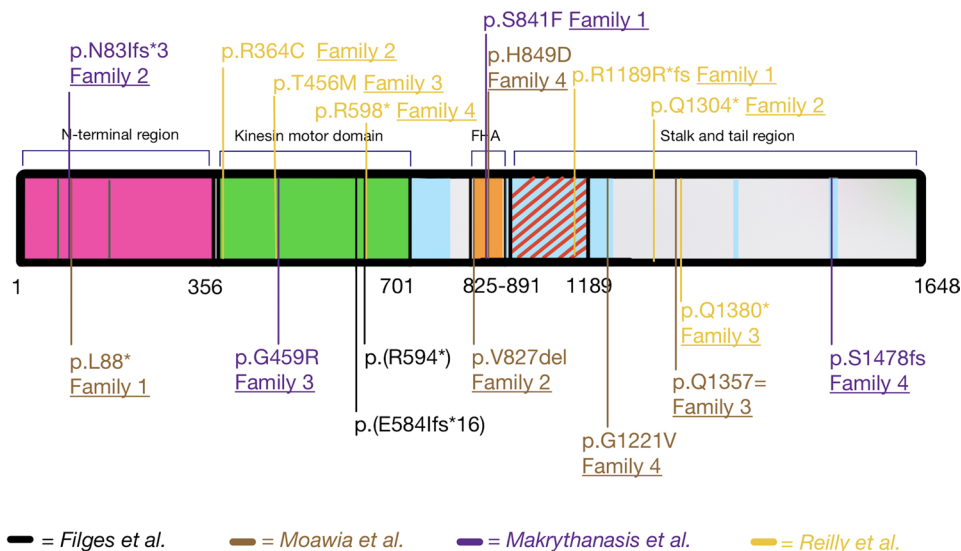
Figure 3 Structure of KIF14 and summary of all published *KIF14* variants affecting function.[10 37 41 42] The N-terminal region (aa 1–356) is important for its interactions with PRC1 and the protein's localisation at the central spindle and midbody; the kinesin motor domain (aa 358–701) is responsible 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).[61] 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[39] 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.[40]

Filges *et al* pointed out that *KIF14* should be considered a candidate gene for viable postnatal phenotypes, including isolated microcephaly.[34] Additional individuals with autosomal recessive variants in *KIF14* and isolated primary microcephaly were then described[9 41 42] (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.[43] 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.[44] Further nine cases had an associated renal phenotype, which ranged from bilateral renal agenesis to cystic or non-cystic renal hypodysplasia.[42] 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.[42] 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.[45] *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.[21 42] 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.[46]

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*[9 26 30 31]

Family	Individuals affected (n)	Consanguinity	CNS phenotype	Kidney phenotype	Prenatal lethal wGA	*KIF14* sequence variant	Functional domain
Filges *et al*[37]	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 *et al*[10] Family 1	3	+	Microcephaly with simplified gyral pattern	–	–	c.263A>T p.Leu88*/ p.Gly58 Leu181del	PRC1 binding
Moawia *et al*[10] Family 2	2	+	Microcephaly with simplified gyral pattern	–	–	c.2480_2482delTTG p.Val827del	FHA domain
Moawia *et al* Family 3	3	+	Microcephaly	–	–	c.4071G>A p.Gln1357=/ p.Leu1296Trpfs*46	C-terminal tail
Moawia *et al*[10] 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 *et al*[41] Family 1	2	+	Intellectual disability	–	–	c.2522C>T p.Ser841Phe	FHA domain
Makrythanasis *et al*[41] Family 2	2	+	Microcephaly, optic atrophy, ASD	–	–	c.246delT p.Asn83Ilefs*3	PRC1 binding
Makrythanasis *et al*[41] Family 3	2	+	Microlissen-cephaly frontal cerebral atrophy, partial agenesis of CC	–	–	c.1375G>A p.Gly459Arg	Motor domain
Makrythanasis *et al*[41] Family 4	2	+	Microcephaly	–	15; 17	c.4432delA p.Ser1478fs	C-terminal tail
Reilly *et al*[42] Family 1	1	–	Microcephaly, CC agenesis, brainstem hypoplasia	Cystic RHD	18	c.35672?_4072+?del p.Arg1189Argfs*9	C-terminal tail
Reilly *et al*[42] Family 2	3	–	Microcephaly, holoprosencephaly	BRA[2], RHD[1]	33; 37+1; 18+3	c.3910C>T, c.1090C>T p.Gln1304*, p.Arg364Cys	C-terminal tail Motor domain
Reilly *et al*[42] 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 *et al*[42] Family 4	4	–	Microlissencephaly	Cystic RHD[2], RHD[1], BRA[1]	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.[12 22 37 44 47–51]

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

KIF7 variants were related to macrocephaly in the presence of congenital hydrocephalus (hydrolethalus syndrome LS2, OMIM # 614120). Isolated hydrocephalus was reported for *KIF4A* in a single case.[11]

Foetal akinesia and arthrogryposis (*KIF5C*[12], *KIF14*[34] and *KIF26B*[50]) 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*[50]), clubfoot (*KIF1A*[51]), rocker-bottom feet (*KIF26B*[50]) and congenital lymphoedema of the limbs (dorsa of feet, lower extremities and, rarely, hands) in cases with *KIF11* gene mutations.[48] 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).[22]

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

IUGR is recurrently detected (*KIF5C*[12], *KIF14*[37], *KIF10*[53], *KIF15*[54] and *KIF2A*[12]) 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

Structural congenital anomaly		Kinesin 1 KIF5C	Kinesin 3 KIF1A	KIF14	KIF16B	Kinesin 4 KIF7	KIF4A	Kinesin 5 KIF11	Kinesin 7 KIF10	Kinesin 11 KIF26B	Kinesin 12 KIF12	KIF15	Kinesin 13 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*[34], and hydrolethalus syndrome (OMIM #614120), caused by variants in *KIF7*.[22] 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 microphthalmy, 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[55] 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[56] and rasopathies,[57] 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.[56]

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.[5] Kinesin motors are most important for the
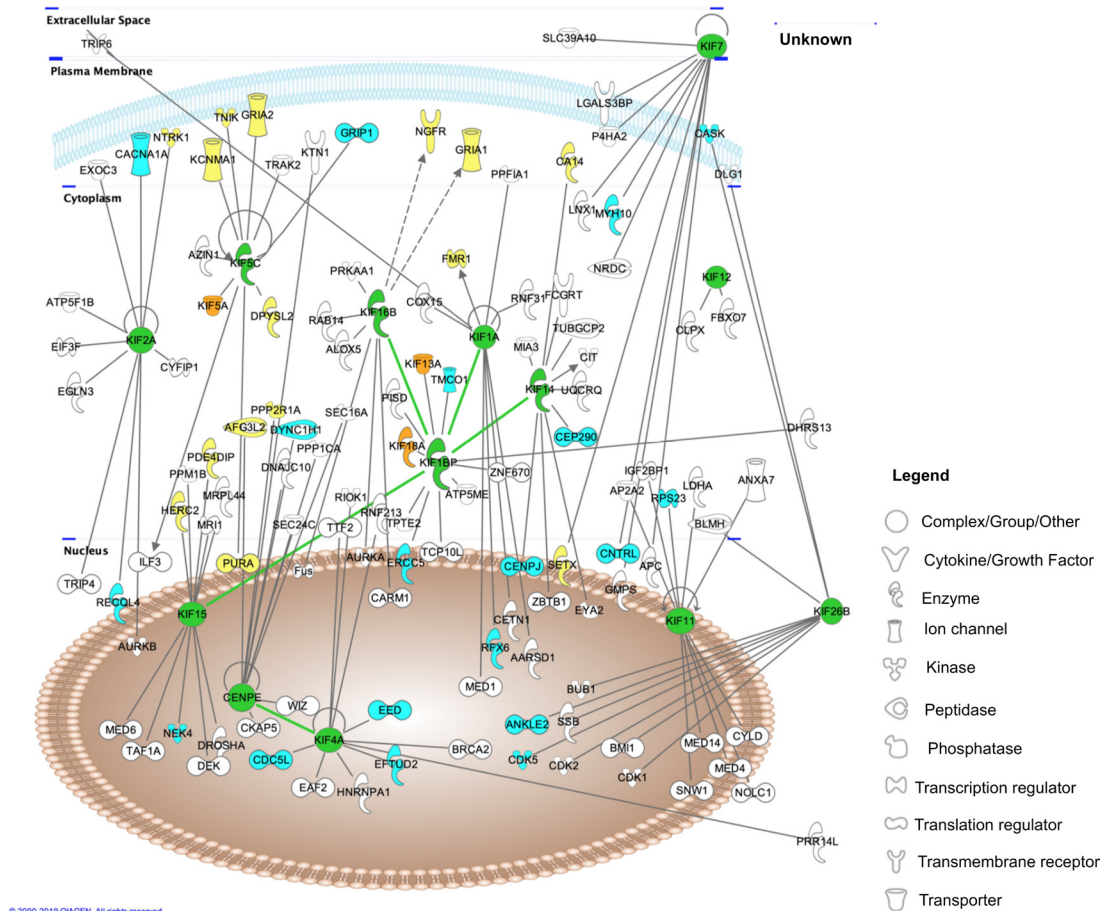
Figure 4 IPA of the 13 kinesins known to be involved in birth defects with respect to their position in the cell. Proteins displayed on the right side of the figure, below the tag 'other', are those for which no subcellular location is known. Birth defect-related kinesins and their connection with each 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.

ORCID iDs
Silvia Kalantari http://orcid.org/0000-0002-9459-9741
Isabel Filges http://orcid.org/0000-0002-2149-6354

REFERENCES

1 Vale RD, Reese TS, Sheetz MP. Identification of a novel force-generating protein, kinesin, involved in microtubule-based motility. *Cell* 1985;42:39–50.
2 Miki H, Setou M, Kaneshiro K, Hirokawa N. All kinesin superfamily protein, KIF, genes in mouse and human. *Proc Natl Acad Sci U S A* 2001;98:7004–11.
3 Hirokawa N, Noda Y, Tanaka Y, Niwa S. Kinesin superfamily motor proteins and intracellular transport. *Nat Rev Mol Cell Biol* 2009;10:682–96.
4 Zhao C, Takita J, Tanaka Y, Setou M, Nakagawa T, Takeda S, Yang HW, Terada S, Nakata T, Takei Y, Saito M, Tsuji S, Hayashi Y, Hirokawa N. Charcot-Marie-Tooth disease type 2A caused by mutation in a microtubule motor KIF1Bbeta. *Cell* 2001;105:587–97.
5 Hirokawa N, Tanaka Y. Kinesin superfamily proteins (KIFs): various functions and their relevance for important phenomena in life and diseases. *Exp Cell Res* 2015;334:16–25.
6 Zhong A, Tan F-Q, Yang W-X. Chromokinesin: kinesin superfamily regulating cell division through chromosome and spindle. *Gene* 2016;589:43–8.
7 Niwa S. Kinesin superfamily proteins and the regulation of microtubule dynamics in morphogenesis. *Anat Sci Int* 2015;90:1–6.
8 Osterman MJK, Kochanek KD, MacDorman MF, Strobino DM, Guyer B. Annual summary of vital statistics: 2012-2013. *Pediatrics* 2015;135:1115–25.
9 Wang D, Nitta R, Morikawa M, Yajima H, Inoue S, Shigematsu H, Kikkawa M, Hirokawa N. Motility and microtubule depolymerization mechanisms of the Kinesin-8 motor, KIF19A. *Elife* 2016;5:1–24.
10 Moawia A, Shaheen R, Rasool S, Waseem SS, Ewida N, Budde B, Kawalia A, Motamemy S, Khan K, Fatima A, Jameel M, Ullah F, Akram T, Ali Z, Abdullah U, Irshad S, Höhne W, Noegel AA, Al-Owain M, Hörtnagel K, Stöbe P, Baig SM, Nürnberg P, Alkuraya FS, Hahn A, Hussain MS. Mutations of KIF14 cause primary microcephaly by impairing cytokinesis. *Ann Neurol* 2017;82:562–77.
11 Meier N, Bruder E, Lapaire O, Hoesli I, Kang A, Hench J, Hoeller S, De Geyter J, Miny P, Heinimann K, Chaoui R, Tercanli S, Filges I. Exome sequencing of fetal anomaly syndromes: novel phenotype-genotype discoveries. *Eur J Hum Genet* 2019;27:730–7.
12 Poirier K, Lebrun N, Broix L, Tian G, Saillour Y, Boscheron C, Parrini E, Valence S, Pierre BS, Oger M, Lacombe D, Geneviève D, Fontana E, Darra F, Cances C, Barth M, Bonneau D, Bernadina BD, N'guyen S, Gitiaux C, Parent P, des Portes V, Pedespan JM, Legrez V, Castelnau-Ptakine L, Nitschke P, Hieu T, Masson C, Zelenika D, Andrieux A, Francis F, Guerrini R, Cowan NJ, Bahi-Buisson N, Chelly J. Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly. *Nat Genet* 2013;45:639–47.
13 Mohun T, Adams DJ, Baldock R, Bhattacharya S, Copp AJ, Hemberger M, Houart C, Hurles ME, Robertson E, Smith JC, Weaver T, Weninger W. Deciphering the mechanisms of developmental disorders (DMDD): a new programme for phenotyping embryonic lethal mice. *Dis Model Mech* 2013;6:562–6.
14 Chauvière M, Kress C, Kress M. Disruption of the mitotic kinesin Eg5 gene (Knsl1) results in early embryonic lethality. *Biochem Biophys Res Commun* 2008;372:513–9.
15 Lin F, Hiesberger T, Cordes K, Sinclair AM, Goldstein LSB, Somlo S, Igarashi P. Kidney-specific inactivation of the KIF3A subunit of kinesin-II inhibits renal ciliogenesis and produces polycystic kidney disease. *Proc Natl Acad Sci U S A* 2003;100:5286–91.
16 Nonaka S, Tanaka Y, Okada Y, Takeda S, Harada A, Kanai Y, Kido M, Hirokawa N. Randomization of left-right asymmetry due to loss of nodal cilia generating leftward flow of extraembryonic fluid in mice lacking KIF3B motor protein. *Cell* 1998;95:829–37.
17 Tanaka Y, Kanai Y, Okada Y, Nonaka S, Takeda S, Harada A, Hirokawa N. Targeted disruption of mouse conventional kinesin heavy chain, kif5B, results in abnormal perinuclear clustering of mitochondria. *Cell* 1998;93:1147–58.
18 Ueno H, Huang X, Tanaka Y, Hirokawa N. KIF16B/Rab14 molecular motor complex is critical for early embryonic development by transporting FGF receptor. *Dev Cell* 2011;20:60–71.
19 Zhou R, Niwa S, Homma N, Takei Y, Hirokawa N. KIF26A is an unconventional kinesin and regulates GDNF-Ret signaling in enteric neuronal development. *Cell* 2009;139:802–13.
20 Wang L, Tanaka Y, Wang D, Morikawa M, Zhou R, Homma N, Miyamoto Y, Hirokawa N. The Atypical Kinesin KIF26A Facilitates Termination of Nociceptive Responses by Sequestering Focal Adhesion Kinase. *Cell Rep* 2018;24:2894–907.
21 Reilly ML, Benmerah A. Ciliary kinesins beyond IFT: cilium length, disassembly, cargo transport and signalling. *Biol Cell* 2019;111:79–94.
22 Putoux A, Thomas S, Coene KLM, Davis EE, Alanay Y, Ogur G, Uz E, Buzas D, Gomes C, Patrier S, Bennett CL, Elkhartoufi N, Frison M-HS, Rigonnot L, Joyé N, Pruvost S, Utine GE, Boduroglu K, Nitschke P, Fertitta L, Thauvin-Robinet C, Munnich A, Cormier-Daire V, Hennekam R, Colin E, Akarsu NA, Bole-Feysot C, Cagnard N, Schmitt A, Goudin N, Lyonnet S, Encha-Razavi F, Siffroi J-P, Winey M, Katsanis N, Gonzales M, Vekemans M, Beales PL, Attié-Bitach T. KIF7 mutations cause fetal hydrolethalus and acrocallosal syndromes. *Nat Genet* 2011;43:601–6.
23 Melo US, Macedo-Souza LI, Figueiredo T, Muotri AR, Gleeson JG, Coux G, Armas P, Calcaterra NB, Kitajima JP, Amorim S, Olávio TR, Griesi-Oliveira K, Coatti GC, Rocha CRR, Martins-Pinheiro M, Menck CFM, Zaki MS, Kok F, Zatz M, Santos S. Overexpression of KLC2 due to a homozygous deletion in the non-coding region causes SPOAN syndrome. *Hum Mol Genet* 2015;24:6877–85.
24 Yamada K, Andrews C, Chan W-M, McKeown CA, Magli A, de Berardinis T, Loewenstein A, Lazar M, O'Keefe M, Letson R, London A, Ruttum M, Matsumoto N, Saito N, Morris L, Del Monte M, Johnson RH, Uyama E, Houtman WA, de Vries B, Carlow TJ, Hart BL, Krawiecki N, Shoffner J, Vogel MC, Katowitz J, Goldstein SM, Levin AV, Sener EC, Ozturk BT, Akarsu AN, Brodsky MC, Hanisch F, Cruse RP, Zubcov AA, Robb RM, Roggenkäemper P, Gottlob I, Kowal L, Battu R, Traboulsi EI, Franceschini P, Newlin A, Demer JL, Engle EC. Heterozygous mutations of the kinesin KIF21A in congenital fibrosis of the extraocular muscles type 1 (CFEOM1). *Nat Genet* 2003;35:318–21.
25 Duis J, Dean S, Applegate C, Harper A, Xiao R, He W, Dollar JD, Sun LR, Waberski MB, Crawford TO, Hamosh A, Stafstrom CE. KIF5A mutations cause an infantile onset phenotype including severe myoclonus with evidence of mitochondrial dysfunction. *Ann Neurol* 2016;80:633–7.
26 Ma D-D, Wang D-H, Yang W-X. Kinesins in spermatogenesis. *Biol Reprod* 2017;96:267–76.
27 Camlin NJ, McLaughlin EA, Holt JE. Motoring through: the role of kinesin superfamily proteins in female meiosis. *Hum Reprod Update* 2017;23:409–20.
28 Rath O, Kozielski F. Kinesins and cancer. *Nat Rev Cancer* 2012;12:527–39.
29 Mayer TU, Kapoor TM, Haggarty SJ, King RW, Schreiber SL, Mitchison TJ. Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. *Science* 1999;286:971–4.
30 Myers SM, Collins I. Recent findings and future directions for interpolar mitotic kinesin inhibitors in cancer therapy. *Future Med Chem* 2016;8:463–89.
31 Aulchenko YS, Hoppenbrouwers IA, Ramagopalan SV, Broer L, Jafari N, Hillert J, Link J, Lundström W, Greiner E, Dessa Sadovnick A, Goossens D, Van Broeckhoven C, Del-Favero J, Ebers GC, Oostra BA, van Duijn CM, Hintzen RQ. Genetic variation in the KIF1B locus influences susceptibility to multiple sclerosis. *Nat Genet* 2008;40:1402–3.
32 Goris A, Boonen S, D'hooghe M-B, Dubois B. Replication of KIF21B as a susceptibility locus for multiple sclerosis. *J Med Genet* 2010;47:775–6.
33 Brenner D, Yilmaz R, Müller K, Grehl T, Petri S, Meyer T, Grosskreutz J, Weydt P, Ruf W, Neuwirth C, Weber M, Pinto S, Claeys KG, Schrank B, Jordan B, Knehr A, Günther K, Hübers A, Zeller D, Kubisch C, Jablonka S, Sendtner M, Klopstock T, de Carvalho M, Sperfeld A, Borck G, Volk AE, Dorst J, Weis J, Otto M, Schuster J, Del Tredici K, Braak H, Danzer KM, Freischmidt A, Meitinger T, Strom TM, Ludolph AC, Andersen PM, Weishaupt JH, Weyen U, Hermann A, Hagenacker T, Koch JC, Lingor P, Göricke B, Zierz S, Baum P, Wolf J, Winkler A, Young P, Bogdahn U, Prudlo J, Kassubek J, German ALS network MND-NET. Hot-Spot KIF5A mutations cause familial ALS. *Brain* 2018;141:688–97.
34 Alsabban AH, Morikawa M, Tanaka Y, Takei Y, Hirokawa N. Kinesin *Kif3b* mutation reduces NMDAR subunit NR 2A trafficking and causes schizophrenia-like phenotypes in mice. *Embo J* 2020;39:1–19.
35 Tarabeux J, Champagne N, Brustein E, Hamdan FF, Gauthier J, Lapointe M, Maios C, Piton A, Spiegelman D, Henrion E, Millet B, Rapoport JL, Delisi LE, Joober R,

Fathalli F, Fombonne E, Mottron L, Forget-Dubois N, Boivin M, Michaud JL, Lafrenière RG, Drapeau P, Krebs M-O, Rouleau GA, Synapse to Disease Team. De novo truncating mutation in kinesin 17 associated with schizophrenia. *Biol Psychiatry* 2010;68:649–56.

36 Filges I, Friedman JM. Exome sequencing for gene discovery in lethal fetal disorders--harnessing the value of extreme phenotypes. *Prenat Diagn* 2015;35:1005–9.

37 Filges I, Nosova E, Bruder E, Tercanli S, Townsend K, Gibson WT, Röthlisberger B, Heinimann K, Hall JG, Gregory-Evans CY, Wasserman WW, Miny P, Friedman JM. Exome sequencing identifies mutations in KIF14 as a novel cause of an autosomal recessive lethal fetal ciliopathy phenotype. *Clin Genet* 2014;86:220–8.

38 Fujikura K, Setsu T, Tanigaki K, Abe T, Kiyonari H, Terashima T, Sakisaka T. Kif14 mutation causes severe brain malformation and hypomyelination. *PLoS One* 2013;8:e53490.

39 Carleton M, Mao M, Biery M, Warrener P, Kim S, Buser C, Marshall CG, Fernandes C, Annis J, Linsley PS. RNA interference-mediated silencing of mitotic kinesin KIF14 disrupts cell cycle progression and induces cytokinesis failure. *Mol Cell Biol* 2006;26:3853–63.

40 Gruneberg U, Neef R, Li X, Chan EHY, Chalamalasetty RB, Nigg EA, Barr FA. KIF14 and citron kinase act together to promote efficient cytokinesis. *J Cell Biol* 2006;172:363–72.

41 Makrythanasis P, Maroofian R, Stray-Pedersen A, Musaev D, Zaki MS, Mahmoud IG, Selim L, Elbadawy A, Jhangiani SN, Coban Akdemir ZH, Gambin T, Sorte HS, Heiberg A, McEvoy-Venneri J, James KN, Stanley V, Belandres D, Guipponi M, Santoni FA, Ahangari N, Tara F, Doosti M, Iwaszkiewicz J, Zoete V, Backe PH, Hamamy H, Gleeson JG, Lupski JR, Karimiani EG, Antonarakis SE. Biallelic variants in KIF14 cause intellectual disability with microcephaly. *Eur J Hum Genet* 2018;26:330–9.

42 Reilly ML, Stokman MF, Magry V, Jeanpierre C, Alves M, Paydar M, Hellinga J, Delous M, Pouly D, Failler M, Martinovic J, Loeuillet L, Leroy B, Tantau J, Roume J, Gregory-Evans CY, Shan X, Filges I, Allingham JS, Kwok BH, Saunier S, Giles RH, Benmerah A. Loss-Of-Function mutations in KIF14 cause severe microcephaly and kidney development defects in humans and zebrafish. *Hum Mol Genet* 2019;28:778–95.

43 Jayaraman D, Bae B-I, Walsh CA. The genetics of primary microcephaly. *Annu Rev Genomics Hum Genet* 2018;19:177–200.

44 Heidet L, Morinière V, Henry C, De Tomasi L, Reilly ML, Humbert C, Alibeu O, Fourrage C, Bole-Feysot C, Nitschké P, Tores F, Bras M, Jeanpierre M, Pietrement C, Gaillard D, Gonzales M, Novo R, Schaefer E, Roume J, Martinovic J, Malan V, Salomon R, Saunier S, Antignac C, Jeanpierre C. Targeted Exome Sequencing Identifies PBX1 as Involved in Monogenic Congenital Anomalies of the Kidney and Urinary Tract. *J Am Soc Nephrol* 2017;28:2901–14.

45 Dubreuil V, Marzesco A-M, Corbeil D, Huttner WB, Wilsch-Bräuninger M. Midbody and primary cilium of neural progenitors release extracellular membrane particles enriched in the stem cell marker prominin-1. *J Cell Biol* 2007;176:483–95.

46 Lang PY, Gershon TR. A new way to treat brain tumors: targeting proteins coded by microcephaly genes? *Bioessays* 2018;40.

47 Valence S, Poirier K, Lebrun N, Saillour Y, Sonigo P, Bessières B, Attié-Bitach T, Benachi A, Masson C, Encha-Razavi F, Chelly J, Bahi-Buisson N. Homozygous truncating mutation of the KBP gene, encoding a KIF1B-binding protein, in a familial case of fetal polymicrogyria. *Neurogenetics* 2013;14:215–24.

48 Ostergaard P, Simpson MA, Mendola A, Vasudevan P, Connell FC, van Impel A, Moore AT, Loeys BL, Ghalamkarpour A, Onoufriadis A, Martinez-Corral I, Devery S, Leroy JG, van Laer L, Singer A, Bialer MG, McEntagart M, Quarrell O, Brice G, Trembath RC, Schulte-Merker S, Makinen T, Vikkula M, Mortimer PS, Mansour S, Jeffery S. Mutations in KIF11 cause autosomal-dominant microcephaly variably associated with congenital lymphedema and chorioretinopathy. *Am J Hum Genet* 2012;90:356–62.

49 Alsahli S, Arold ST, Alfares A, Alhaddad B, Al Balwi M, Kamsteeg E-J, Al-Twaijri W, Alfadhel M. KIF16B is a candidate gene for a novel autosomal-recessive intellectual disability syndrome. *Am J Med Genet A* 2018;176:1602–9.

50 Wojcik MH, Okada K, Prabhu SP, Nowakowski DW, Ramsey K, Balak C, Rangasamy S, Brownstein CA, Schmitz-Abe K, Cohen JS, Fatemi A, Shi J, Grant EP, Narayanan V, Ho H-YH, Agrawal PB. De novo variant in KIF26B is associated with pontocerebellar hypoplasia with infantile spinal muscular atrophy. *Am J Med Genet A* 2018;176:2623–9.

51 Lee J-R, Srour M, Kim D, Hamdan FF, Lim S-H, Brunel-Guitton C, Décarie J-C, Rossignol E, Mitchell GA, Schreiber A, Moran R, Van Haren K, Richardson R, Nicolai J, Oberndorff KMEJ, Wagner JD, Boycott KM, Rahikkala E, Junna N, Tyynismaa H, Cuppen I, Verbeek NE, Stumpel CTRM, Willemsen MA, de Munnik SA, Rouleau GA, Kim E, Kamsteeg E-J, Kleefstra T, Michaud JL. De novo mutations in the motor domain of KIF1A cause cognitive impairment, spastic paraparesis, axonal neuropathy, and cerebellar atrophy. *Hum Mutat* 2015;36:69–78.

52 Westland R, Verbitsky M, Vukojevic K, Perry BJ, Fasel DA, Zwijnenburg PJG, Bökenkamp A, Gille JJP, Saraga-Babic M, Ghiggeri GM, D'Agati VD, Schreuder MF, Gharavi AG, van Wijk JAE, Sanna-Cherchi S. Copy number variation analysis identifies novel CAKUT candidate genes in children with a solitary functioning kidney. *Kidney Int* 2015;88:1402–10.

53 Mirzaa GM, Vitre B, Carpenter G, Abramowicz I, Gleeson JG, Paciorkowski AR, Cleveland DW, Dobyns WB, O'Driscoll M. Mutations in CENPE define a novel kinetochore-centromeric mechanism for microcephalic primordial dwarfism. *Hum Genet* 2014;133:1023–39.

54 Sleiman PMA, March M, Nguyen K, Tian L, Pellegrino R, Hou C, Dridi W, Sager M, Housawi YH, Hakonarson H. Loss-Of-Function mutations in KIF15 underlying a Braddock-Carey Genocopy. *Hum Mutat* 2017;38:507–10.

55 Bastian M, Heymann S, Jacomy M. Gephi: an open source software for exploring and manipulating networks 2009. Proceedings of the Third International Conference on Weblogs and Social Media, ICWSM; May 17-20, San Jose, California, USA, 2009:1–2.

56 Badano JL, Mitsuma N, Beales PL, Katsanis N. The ciliopathies: an emerging class of human genetic disorders. *Annu Rev Genomics Hum Genet* 2006;7:125–48.

57 Rauen KA. The RASopathies. *Annu Rev Genomics Hum Genet* 2013;14:355–69.

58 Dimassi S, Labalme A, Ville D, Calender A, Mignot C, Boutry-Kryza N, de Bellescize J, Rivier-Ringenbach C, Bourel-Ponchel E, Cheillan D, Simonet T, Maincent K, Rossi M, Till M, Mougou-Zerelli S, Edery P, Saad A, Heron D, des Portes V, Sanlaville D, Lesca G. Whole-exome sequencing improves the diagnosis yield in sporadic infantile spasm syndrome. *Clin Genet* 2016;89:198–204.

59 Nibbeling EAR, Duarri A, Verschuuren-Bemelmans CC, Fokkens MR, Karjalainen JM, Smeets CJLM, de Boer-Bergsma JJ, van der Vries G, Dooijes D, Bampi GB, van Diemen C, Brunt E, Ippel E, Kremer B, Vlak M, Adir N, Wijmenga C, van de Warrenburg BPC, Franke L, Sinke RJ, Verbeek DS. Exome sequencing and network analysis identifies shared mechanisms underlying spinocerebellar ataxia. *Brain* 2017;140:2860–78.

60 Ünlüsoy Aksu A, Das SK, Nelson-Williams C, Jain D, Özbay Hoşnut F, Evirgen Şahin G, Lifton RP, Vilarinho S. Recessive Mutations in *KIF12* Cause High Gamma-Glutamyltransferase Cholestasis. *Hepatol Commun* 2019;3:471–7.

61 UniProt Consortium. UniProt: a worldwide hub of protein knowledge. *Nucleic Acids Res* 2019;47:D506–15.