SUPPLEMENTAL MATERIALS

Table 3 Appendix:
Case descriptions and references for *KIF* genes which were associated with congenital anomalies detectable prenatally.

KIF5C

(1) Poirier K, Lebrun N, Broix L, Tian G, Saillour Y, Boscheron C, et al. Mutations in *TUBG1*, *DYNC1H1*, *KIF5C* and *KIF2A* cause malformations of cortical development and microcephaly. Nat Genet. 2013;45(6):639–47.

Four brothers with severe malformations of cortical development. The proband had intrauterine growth retardation, severe arthrogryposis, and microcephaly (-4 SD at birth). Brain MRI showed frontal and perisylvian polymicrogyria and a thin corpus callosum with a normal brainstem and cerebellar vermis. The unaffected mother subsequently had 3 medical abortions of similarly affected male fetuses who showed fetal akinesia associated with polymicrogyria, gyral simplification, delayed development of the cerebellum and brainstem, and abnormal positioning of the corticospinal tracts.

KIF1A

(2) Lee JR, Srour M, Kim D, Hamdan FF, Lim SH, Brunel-Guitton C, et al. De novo mutations in the motor domain of *KIF1A* cause cognitive impairment, spastic paraparesis, axonal neuropathy, and cerebellar atrophy. Hum Mutat. 2015;36(1):69–78.

Fourteen individuals, including two monozygotic twins. The recurring clinical signs in these patients are microcephaly, cerebral and cerebellar atrophy. Clubfoot was described in one of the 14 patients. IUGR and decreased fetal movements were noticed in one.

KIF1BP

(3) Valence S, Poirier K, Lebrun N, Saillour Y, Sonigo P, Bessières B, et al. Homozygous truncating mutation of the *KBP* gene, encoding a KIF1B-binding protein, in a familial case of fetal polymicrogyria. Neurogenetics. 2013;14(3–4):215–24.

Two fetuses from the same consanguineous couple. They were both affected by severe polymicrogyria. The first female fetus had ventriculomegaly and microcephaly at 32 gestational weeks (GW) at ultrasound (US). Ultrafast fetal MRI scans at 34 + 1 GW showed bilateral multiple infolding of the cortex in the frontal lobes and the Sylvian fissure, hypoplastic brainstem and hypoplastic corpus callosum. The fetus was confirmed microcephalic (3rd percentile), and dysmorphic features (receding forehead and hypertelorism) and bilateral clubfeet were noticed.
In the second fetus ventricular dilatation and deceleration of head growth were noted at 30 GW US. Fetal MRI at 34 GW showed microcephaly, asymmetric ventriculomegaly, polymicrogyria and hypoplastic corpus callosum. The cerebellum was normal, but the brainstem appeared hypoplastic. No facial dysmorphisms were apparent.

KIF14

(4) Filges I, Nosova E, Bruder E, Tercanli S, Townsend K, Gibson WT, et al. Exome sequencing identifies mutations in KIF14 as a novel cause of an autosomal recessive lethal fetal ciliopathy phenotype. Clin Genet. 2013;86(3):220–8.

Two female fetuses from the same non-consanguineous family. The first pregnancy was interrupted at 21+4/7 GW because of the predicted lethal outcome. The fetus had indeed already been found to have intrauterine growth restriction (IUGR), complex brain malformations (microcephaly, agenesis of occipital lobes and cerebellar hypoplasia with agenesis of the vermis), renal agenesis and oligohydramnios. All the US findings were confirmed at autopsy, together with the findings of uterine hypoplasia, severe flexion arthrogryposis of all joints, minor skeletal anomalies, bifid uvula and secondary facial features resulting from oligohydramnios. The second pregnancy was terminated at 18+5/7 GW because of recurrence of oligohydramnios and fetal multiple congenital anomalies. At autopsy microcephaly, arhinencephaly, agenesis of corpus callosum, cerebellar hypoplasia with partial agenesis of the vermis, bilateral cystic dysplasia and hypoplasia, ureteral hypoplasia, uterine hypoplasia, vaginal hypoplasia, flexion arthrogryposis and minor skeletal anomalies were described.

(5) Moawia A, Shaheen R, Rasool S, Waseem SS, Ewida N, Budde B, et al. Mutations of KIF14 cause primary microcephaly by impairing cytokinesis. Ann Neurol. 2017;82(4):562–77.

Ten cases from four consanguineous families. All cases except one were detected postnatally, despite the fact that microcephaly and reduced cerebral cortex with simplified gyral pattern might have been already identified at prenatal US and MRI. One case from family 4 was a fetus, whose pregnancy was interrupted at 24GW because of lissencephaly, ventriculomegaly, cerebellar hypoplasia and agenesis of the corpus callosum. The clinical presentation was overall less severe compared to the two cases described by *Filges et al*.

(6) Makrythanasis P, Maroofian R, Stray-Pedersen A, et al. Biallelic variants in KIF14 cause intellectual disability with microcephaly. *Eur J Hum Genet*. 2018;26(3):330-339.

Eight cases from four consanguineous families. The two cases coming from family 4 had severe microcephaly identified at prenatal US and pregnancy interruption at 15 and 17 WG was carried out. The two fetuses had had normal intrauterine growth and did not show any other significant malformative phenotype. The clinical picture of the other six postnatal cases described in this paper was mainly characterized by intellectual disability and some cerebral anomalies described at brain CT (e.g. simplified gyral pattern, cerebellar hypoplasia, partial agenesis of the corpus callosum).

(7) Reilly ML, Stokman MF, Magry V, et al. Loss-of-function mutations in KIF14 cause severe microcephaly and kidney development defects in humans and zebrafish. *Hum Mol Genet*. 2019;28(5):778-795.
Eleven cases from four non-consanguineous families. All of them were detected at prenatal US and lead to pregnancy interruption between 18 and 37+1 GW. Microcephaly and lissencephaly were described for all the cases, together with anomalies of the kidneys, which ranged from bilateral renal agenesis to renal cystic dysplasia.

KIF16B
(8) Alsahli S, Arold ST, Alfares A, Alhaddad B, Al Balwi M, Kamsteeg EJ, et al. KIF16B is a candidate gene for a novel autosomal-recessive intellectual disability syndrome. Am J Med Genet. 2018;176(7):1602–9.
Two cases are described in this paper. Microcephaly was detected at birth. Diffused thinning of corpus callosum was seen for this patient at 6 years of age, when brain magnetic performance imaging was carried out for the first time. This might have been already apparent at prenatal MRI.

KIF7
(9) Putoux A, Thomas S, Coene KLM, Davis EE, Alanay Y, Ogur G, et al. KIF7 mutations cause fetal hydrolethalus and acrocallosal syndromes. Nat Genet. 2011;43(6):601–6.
Twelve cases belonging to nine consanguineous and non-consanguineous families with a focus in decscription on the first family with four affected fetuses with hydrocephaly (two out of four fetuses), exencephaly (two out of four fetuses), postaxial polydactyly of the hands, hallux duplication and cleft palate (two out of four fetuses). Hydrolethalus (OMIM #614120) and Acrocallosal syndromes (OMIM #200990) are described as being two phenotypes at different ends of the phenotypic spectrum of *KIF7*-associated disease.

(10) Dafinger C, Liebau MC, Elsayed SM, et al. Mutations in KIF7 link Joubert syndrome with Sonic Hedgehog signaling and microtubule dynamics. *J Clin Invest*. 2011;121(7):2662-2667.
Four cases from three consanguineous and non-consanguineous families. All of them presented with the molar tooth sign at cerebral MRI. Case 1 also had agenesis of the corpus callosum and hands and feet polydactyly (not specified whether preaxial or postaxial).

(11) Bayoumi R, Saar K, Lee Y-A, Nürnberg G, Reis A, Nur-E-Kamal M, et al. Localisation of a gene for an autosomal recessive syndrome of macrocephaly, multiple epiphyseal dysplasia, and distinctive facies to chromosome 15q26. J Med Genet. 2001;38(6):369–73.
Four cases belonging to the same large family with multiple consanguinity. CT scan of the brain on two out of four cases showed agenesis of the corpus callosum and frontotemporal brain atrophy.

KIF4A
(12) Meier N, Bruder E, Lapaire O, Hoesli I, Kang A, Hench J, et al. Exome sequencing of fetal anomaly syndromes: novel phenotype–genotype discoveries. Eur J Hum Genet. 2019; (5):730-737
A single case of prenatally detected isolated hydrocephalus at 22+3 GW is described in this paper.

KIF11
(13) Ostergaard P, Simpson MA, Mendola A, Vasudevan P, Connell FC, Van Impel A, et al. Mutations in KIF11 cause autosomal-dominant microcephaly variably associated with congenital lymphedema and chorioretinopathy. Am J Hum Genet.2012;90(2):356–62.
Twenty-seven cases from fifteen families. The patients presented with microcephaly, ranging from mild to severe, eye abnormalities, chorioretinopathy being the most commonly found, but including microphtalmia. Congenital lymphedema was present in fourteen cases and was typically confined to the dorsa of feet.

KIF10
(14) Mirzaa GM, Vitre B, Carpenter G, Abramowicz I, Gleeson JG, Paciorkowski AR, et al. Mutations in CENPE define a novel kinetochore-centromeric mechanism for microcephalic primordial dwarfism. Hum Genet. 2014;133(8):1023–39.
Two siblings from a non-consanguineous family. The first affected boy had a history of IUGR during pregnancy and decreased fetal activity. Primary microcephaly was noticed at birth, including a sloping forehead. At brain MRI there was a simplified gyral pattern, thin cortex and a mildly disproportionate cerebellar hypoplasia. The second sibling was a girl, who also had a history of prenatal IUGR and primary microcephaly.

KIF26B

(15) Wojcik MH, Okada K, Prabhu SP, Nowakowski DW, Ramsey K, Balak C, et al. De novo variant in KIF26B is associated with pontocerebellar hypoplasia with infantile spinal muscular atrophy. Am J Med Genet. 2018;176(12):2623–9.

One case. The pregnancy was complicated by polyhydramnios and reduced fetal movements. Primary microcephaly. The girl had camptodactyly, congenital dislocation of both hips, bilateral rocker-bottom feet and arthrogryposis of both upper extremities. The brain MRI performed at 3 days of age showed microcephaly, a thinned corpus callosum, delayed myelination with abnormal increased T2 signal and pontocerebral hypoplasia.

KIF12

(16) Westland R, Verbitsky M, Vukojevic K, Perry BJ, Fasel DA, Zwijnenburg PJG, et al. Copy number variation analysis identifies novel CAKUT candidate genes in children with a solitary functioning kidney. Kidney Int. 2015;88(6):1402–10.

A single case is described. The patient had congenital megabladder, renal hypodysplasia and congenital vesicoureteral reflux. Clinical features are not otherwise specified.

KIF15

(17) Sleiman PMA, March M, Nguyen K, Tian L, Pellegrino R, Hou C, et al. Loss-of-Function Mutations in KIF15 Underlying a Braddock-Carey Genocopy. Hum Mutat. 2017;38(5):507–10.

A single case from a consanguineous family. The child had IUGR, microcephaly, microphthalmia and congenital thrombocytopenia, microretrognathia and cleft palate.

KIF2A

(1) Poirier K, Lebrun N, Broix L, Tian G, Saillour Y, Boscheron C, et al. Mutations in *TUBG1*, *DYNC1H1*, *KIF5C* and *KIF2A* cause malformations of cortical development and microcephaly. Nat Genet. 2013;45(6):639–47.

Two cases are described. The clinical features of patient 1 are primary microcephaly, frontal band heterotopia, posterior predominant pachygyria and thin corpus callosum at brain MRI. The second patient had congenital microcephaly and posterior predominant pachygyria, a thick cortex and a thin corpus callosum at brain MRI. The MRI scans were performed in the two patients at 3 weeks and 5 weeks of age, respectively.

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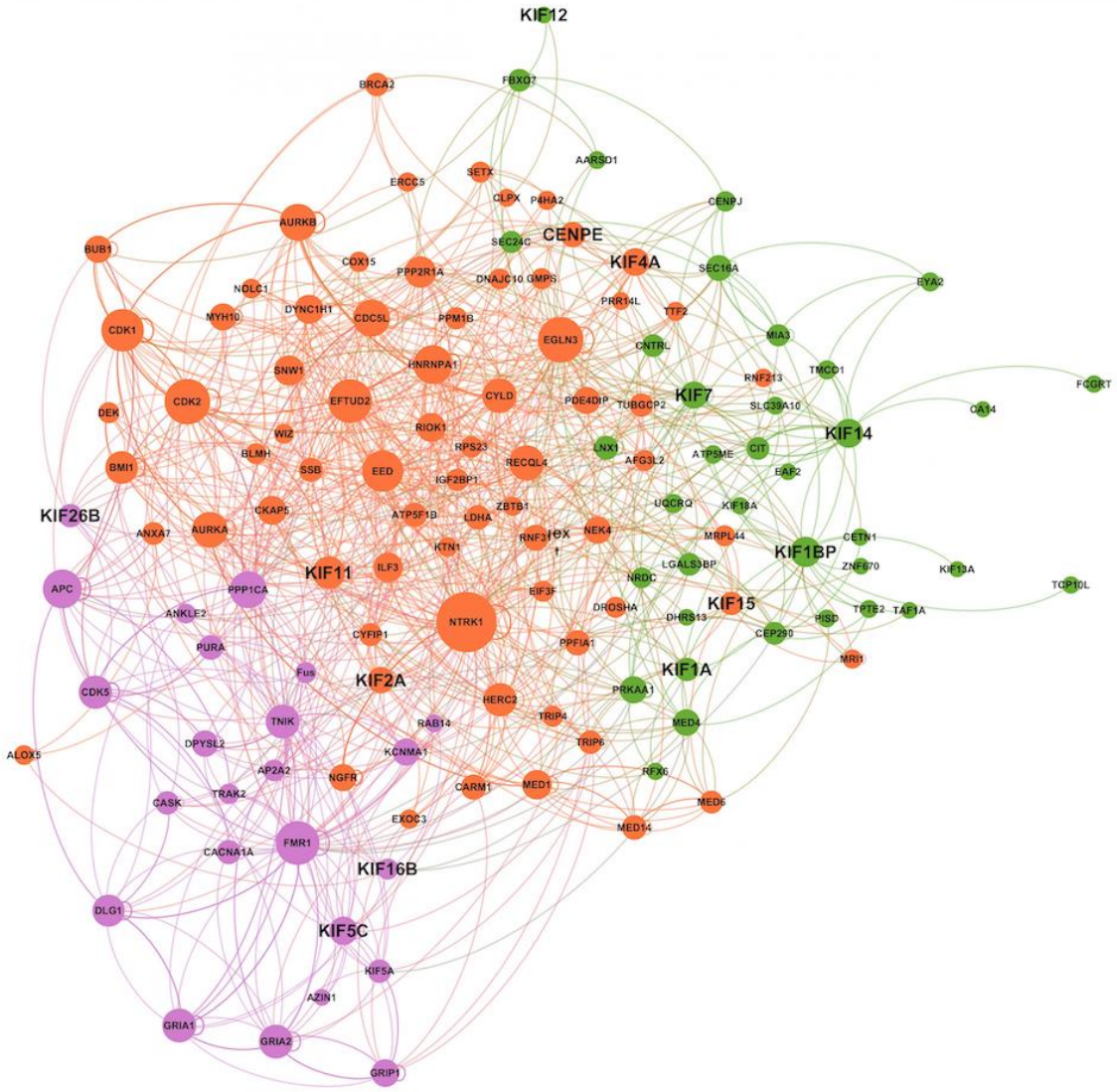
Table 4: Canonical Pathways related to the kinesins' protein network for birth defects. The first row of the second column for each entry lists the related downstream proteins, the second row shows the kinesins involved.

Canonical pathway	**Downstream proteins**
	Kinesins
Axonal Guidance Signaling	AFG3L2, CDK5, DPYSL2, HERC2, KIF7, NGFR, NTRK1
	KIF5C, KIF7, KIF15
CDK5 Signaling	CACNA1A, CDK5, NGFR, PPP1CA, PPP2R1A
	KIF2A
Synaptogenesis signaling pathway	AP2A2, CDK5, GRIA1, GRIA2
	KIF1A, KIF5C, KIF14, KIF16B
Synaptic long term depression	CACNA1A, GRIA1, GRIA2, PPP2R1A
	KIF2A, KIF5C, KIF16B
Dopamine DARPP32 feedback in cAMP signaling	CACNA1A, CDK5, PPP1CA, PPP2R1A,
	KIF2A
mTOR signaling	EIF3F, PPP2R1A, PRKAA1, RPS23
	KIF5C
Superpathway of Inositol phosphate compounds	PPFIA1, PPP1CA, SEC16A, TPTE2
	KIF5C, KIF7, KIF10
HIPPO signaling	DLG1, PPP1CA, PPP2R1A
	KIF26B
Glutamate receptor signaling	GRIA1, GRIA2, GRIP1
	KIF5C, KIF16B
Synaptic long-term potentiation	GRIA1, GRIA2, PPP1CA
	KIF5C, KIF16B
Mitotic roles of polo-like kinase	CDK1, KIF11, PPP2R1A
	KIF5C, KIF11
Endocannabinoid neuronal synapse pathway	CACNA1A, GRIA1, GRIA2
	KIF2A, KIF5C, KIF10, KIF16B
CREB signaling in neurons	CACNA1A, GRIA1, GRIA2
	KIF2A, KIF5C, KIF16B
PPAR signaling	MED1, NGFR, SNW1
	KIF5C
Cell cycle control of chromosomal replication	CDK1, CDK2, CDK5
	KIF5C
Opioid signaling pathway	AP2A2, CACNA1A
	KIF2A
GABA receptor signaling	AP2A2, CACNA1A
	KIF2A, KIF5C, KIF14
Signaling by Rho-family GTPases	CIT, CYFIP1
	KIF5C
Factors promoting cardiogenesis in vertebrates	APC, CDK2
	KIF5C
RhoA signaling	CIT, KTN1
	KIF5C
NER pathway	KIF5C, KIF11

Figure 4 (supplemental): Protein network representation created using Gephy, based on the IPA data. Each node represents a protein of the dataset and the lines (edges) represent the connections between the nodes. The size of each node represents the number of edges connected to other nodes (degree). The color of the nodes denotes the division into three modularity classes, clusters of nodes highly interconnected with other nodes of the same class and loosely connected with nodes belonging to other classes.


KIF12
BRCA2
FBXO7
AARSD1
ERCC5
SETX
CLPX
P4HA2
CENPJ
AURKB
CENPE
BUB1
SEC24C
KIF4A
COX15
PPP2R1A
DNAJC10
GMPS
SEC16A
RYA2
NDLC1
PRR14L
TTF2
MYH10
DYNC1H1
CDC5L
PPM1B
CDK1
EGLN3
CNTRL
MIA3
SNW1
HNRNPA1
RNF213
TMCC1
FCGRT
CDK2
EFTUD2
CYLD
PDE4DIP
TUBGCP2
KIF7
SLC30A10
CA14
DEK
WIZ
RIOK1
KIF14
BLMH
RPS23
LNX1
ATP5ME
CIT
BMI1
SSB
EED
RECQL4
AFG3L2
EAF2
IGF2BP1
KIF26B
CKAP5
ATP5F1B
LDHA
ZBTB1
UQCRQ
KIF18A
ANXA7
AURKA
RNF31
HOX
NEK4
MRPL44
CETN1
KTN1
KIF1BP
KIF11
ILF3
LGALS3BP
ZNF670
KIF13A
APC
PPP1CA
NRDC
TCP10L
EIF3F
KIF15
ANKLE2
DROSHA
DHRS13
HSD
TPTE2
TAF1A
NTRK1
CEP290
CYFIP1
PURA
PPFIA1
MRI1
Fus
KIF2A
KIF1A
CDK5
HERC2
PRKAA1
TNIK
TRIP4
MED4
RAB14
DPYSL2
TRIP6
ALOX5
KCNMA1
AP2A2
NGFR
RFX6
CARM1
MED1
TRAK2
CASK
MED6
EXOC3
MED14
FMR1
CACNA1A
KIF16B
DLG1
KIF5C
KIF5A
AZIN1
GRIA1
GRIA2
GRIP1