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Prenatal phenotyping of fetal tubulinopathies: A multicenter retrospective case series

Bobby K. Brar, MD[1], **Marisa Gilstrop Thompson, MD**[2], **Neeta L. Vora, MD**[3], **Kelly Gilmore, MD**[3], **Karin Blakemore, MD**[1], **Kristen A. Miller, MGC**[1], **Jessica Giordano, MS**[4], **Andreas Dufke, MD**[5], **Beatrix Wong, MS**[6], **Samantha Stover, MS**[7], **Billie Lianoglou, MS**[8], **Ignatia Van den Veyver, MD**[9], **Esther Dempsey, MBBS**[10], **Mara Rosner, MD**[1], **Karen Chong, MD, Ph.D.**[11], **David Chitayat, MD**[11], **Teresa N. Sparks, MD**[12], **Mary E Norton, MD**[12], **Ronald Wapner, MD**[4], **Kristin Baranano, MD, Ph.D.**[13], **Angie C. Jelin, MD**[1] **the Fetal Sequencing Consortium**

[1.]Department of Gynecology and Obstetrics, Division of Maternal-Fetal Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA

[2.]Department of Obstetrics and Gynecology, Christiana Care Medical Center, Newark, DE, USA

[3.]Department of Obstetrics and Gynecology, Division of Maternal – Fetal Medicine, The University of North Carolina School of Medicine, Chapel Hill, NC, USA

[4.]Department of Obstetrics and Gynecology, Columbia University Irving Medical Center, New York, NY, USA

[5.]Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany

[6.]Division of Human Genetics, Cincinnati Children's Hospital Center, Cincinnati, OH, USA

[7.]Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, TN, USA

[8.]Department of Surgery, University of California, San Francisco, San Francisco, CA, USA

[9.]Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX, USA

[10.]St George's University of London, Molecular and Clinical Sciences Research Institute, London, UK

[11.]The Prenatal Diagnosis and Medical Genetics Program, Department of Obstetrics and Gynecology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

[12.]Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, San Francisco, CA, USA

[13.]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Correspondence: Bobby Brar, MD, Johns Hopkins Hospital, 600 N. Wolfe Street, Phipps 228, bbrar1@jhu.edu, Cell: 951-288-5851.

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The authors report no conflicts of interest. Our data is original and is not being considered for publication in any other journal.

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Abstract

Objective: Tubulinopathies refer to conditions caused by genetic variants in isotypes of tubulin resulting in defective neuronal migration. Historically, diagnosis was primarily via postnatal imaging. Our objective was to establish the prenatal phenotype/genotype correlations of tubulinopathies identified by fetal imaging.

Methods: A large, multicenter retrospective case series was performed across nine institutions in the Fetal Sequencing Consortium. Demographics, fetal imaging reports, genetic screening and diagnostic testing results, delivery reports, and neonatal imaging reports were extracted for pregnancies with a confirmed molecular diagnosis of a tubulinopathy.

Results: Nineteen pregnancies with a fetal tubulinopathy were identified. The most common prenatal imaging findings were cerebral ventriculomegaly (15/19), cerebellar hypoplasia (13/19), absence of the cavum septum pellucidum (6/19), abnormalities of the corpus callosum (6/19), and microcephaly (3/19). Fetal MRI identified additional central nervous system features that were not appreciated on neurosonogram in 8 cases. Single gene variants were reported in *TUBA1A* (13), *TUBB* (1), *TUBB2A* (1), *TUBB2B* (2), and *TUBB3* (2).

Conclusion: The presence of ventriculomegaly with cerebellar abnormalities in conjunction with additional prenatal neurosonographic findings warrants additional evaluation for a tubulinopathy. Conclusive diagnosis can be achieved by molecular sequencing, which may assist in coordination, prognostication, and reproductive planning.

Introduction:

Tubulinopathies, also known as tubulin-related cortical dysgenesis, are a heterogeneous group of autosomal dominant disorders which consist of brain malformations caused by pathogenic variants in the genes that encode tubulin.[1] Microtubules consist of multiple alpha and beta tubulin heterodimers, which are encoded by separate genes and have distinct cellular properties. Consequentially, a disruption in tubulin impairs microtubule stability, which leads to abnormal neuronal cell proliferation, migration, and differentiation, and halts axon growth and guidance.[2] Clinically, the tubulinopathies have historically been diagnosed radiographically with brain malformations including, but not limited to, lissencephaly, microlissencephaly, dysgyria, a dysmorphic basal ganglia, and dysplasia of the cerebellum. Patients with tubulinopathies additionally almost all have motor and cognitive impairments, and can be affected with epilepsy, facial diplegia, and strabismus.

With improvements in fetal imaging and the rapid evolution of molecular sequencing, prenatal diagnosis of a tubulinopathy is now possible via fetal ultrasound and magnetic resonance imaging (MRI) followed by molecular confirmation with the identification of a pathogenic variant in *TUBA1A*, *TUBB*, *TUBB2A*, *TUBB2B*, *TUBB3*, or *TUBG1*.[3] While the literature on the prenatal phenotype of the tubulinopathihes is scarce, two characteristic prenatal imaging patterns have previously been described. The first pattern consists of a severe form with enlarged germinal matrices, microlissencephaly, and a kinked brainstem. A second more mild form has also been described, which presents with an asymmetric brainstem, dysgenesis of the corpus callosum, lack of Sylvian fissure operculization, and distortion of the anterior part of the interhemispheric fissure.[4] Given the limited published

information on in utero manifestations of tubulinopathies, our objective was to further elucidate their prenatal phenotypic features by leveraging a larger number of cases through the Fetal Sequencing Consortium and performing a detailed review of fetal imaging and molecular findings. We hypothesized that fetal imaging can serve as a useful tool in the workup of prenatal tubulinopathies and that additional sonographic and MRI screening markers exist beyond those already described.

Methods:

We performed a retrospective case series of pregnancies with a confirmed molecular diagnosis of a fetal tubulinopathy over a two-year period and across nine tertiary care referral centers (Johns Hopkins, Columbia, University of California San Francisco (UCSF), University of Tuebingen, Cincinnati Childrens Hospital, Baylor, St George's University Hospital, University of North Carolina, and Mount Sinai Hospital) in the Fetal Sequencing Consortium. The inclusion criteria consisted of all pregnancies with a molecularly diagnosed fetal tubulinopathy. The institutional review board at Johns Hopkins Hospital approved this study along with approval at each institution. All ultrasounds were interpreted by a board certified maternal – fetal medicine (MFM) subspecialist or radiologist, and all pregnant individuals received pretest and posttest genetic counseling by certified genetic counselors.

Targeted multi - gene panels with a multitude of genes known to be associated with central nervous system (CNS) malformations and disorders, exome sequencing (ES), or genome sequencing (GS) identified the diagnosis of a tubulinopathy in all included cases. Both ES and GS were performed with broad panel analysis, rather than with a gene agnostic approach. Variants were classified according to the American College of Medical Genetics (ACMG) criteria as pathogenic, likely pathogenic, or variant of uncertain significance (VUS). Only cases with variants meeting likely pathogenic or pathogenic criteria were included for analysis. Proband samples included amniocytes, chorionic villi, neonatal cord blood, or neonatal peripheral blood. Parental DNA was extracted from peripheral blood or saliva kits. All gene panels were performed through GeneDx, and ES and GS were performed and interpreted at a number of laboratories including Johns Hopkins DNA Diagnostic Laboratory, Baylor Genetics Laboratories, Columbia University Precision Genomics Laboratory, UCSF Genomic Medicine Laboratory, University of North Carolina Molecular Genetics Laboratory, Medical Genetics Tuebingen, Prevention Genetics, and Congenica. For each case, we extracted maternal demographics, maternal comorbidities, fetal ultrasound reports, fetal brain MRI reports, family history findings, genetic screening results, diagnostic genetic testing results, delivery variables, and neonatal imaging reports.

Results:

A total of 19 pregnancies had a confirmed molecular diagnosis of a fetal tubulinopathy. There were no cases of a fetal tubulinopathy in which sonographic abnormalities were not apparent prenatally. Mean maternal age at the time of delivery or pregnancy termination was 32.2 (range 25 – 41), mean gravidity was 2.6 (range 1 – 7), and mean parity was 1.2 (range 0 – 5). Nine out of 19 pregnant patients self identified as European, 3 as Hispanic or Latina, 3 as Asian, 2 as Black or African American, and in two pregnancies the maternal

race/ethnicity was unknown. Two pregnancies were exposed to maternal tobacco use, and no pregnancies were exposed to alcohol or illicit drugs. All pregnancies were spontaneously conceived. The most common maternal comorbidities identified were hypertensive disorders of pregnancy and major depressive disorder (two cases each), followed by hypothyroidism, anemia, and migraines (all with one pregnancy affected each).

All were singleton pregnancies. Six pregnancies underwent first trimester aneuploidy screening with nuchal translucency assessment, PAPP-A, and beta hCG; 5 had normal results, while one (case 14) demonstrated an elevated risk for Trisomy 18. Eight pregnancies had cell free DNA screening and in 7 the results were low risk while one (case 4) had no results due to insufficient fetal fraction. All pregnancies had diagnostic testing with chromosomal microarray analysis (CMA), and two pregnancies had a copy number variant identified. The proband in case 19 was diagnosed with a maternally inherited likely benign 293 kilobase deletion at 6q22.3 and the proband in case 14 had multiple regions of homozygosity in the setting of known parental consanguinity (Table 1). In addition to CMA, four pregnancies had additional genetic testing via general CNS multi-gene panels, fourteen probands underwent ES, and one pregnancy underwent GS (Table 1). Single gene variants were reported in *TUBA1A* (13 cases), *TUBB2B* (2 cases), *TUBB3* (2 cases), *TUBB2A* (1 case), and *TUBB* (1 case). All single gene variants were classified as likely pathogenic or pathogenic by the ACMG classification system and all variants were heterozygous, with an inheritance pattern that was either unknown or *de novo* (Table 1).

The mean gestational age at which a CNS abnormality was first detected on ultrasound exam was 21.3 weeks (range 12 – 32 weeks 3 days). Cerebral ventriculomegaly was present on fetal neurosonogram in 11 out of 19 (58%) pregnancies. Additional sonographic abnormalities included cerebellar hypoplasia in 8 cases, absence of the cavum septum pellucidum (CSP) in 6 cases, and agenesis of the corpus callosum (ACC) in 3 cases. Microcephaly was seen by ultrasound in two cases and mega cisterna magna, cystic hygroma, Dandy Walker malformation, bilateral choroid plexus cysts, and severe hydranencephaly were each seen by ultrasound in one case (Table 1).

Fetal MRI was performed in 15 out of 19 pregnancies, and the mean gestational age at MRI was 26.4 weeks (range: 19 weeks 5 days – 37 weeks). Prenatal MRI findings included ventriculomegaly in 13/15 (86.7%) cases, cerebellar hypoplasia in 10/15 (66.7%) cases, abnormalities of the corpus callosum in 6/15 (40%) cases, and microcephaly in 3/15 (20%) cases. The proband in case 18 had discordant ultrasound and MRI findings. Prenatal ultrasound noted possible ACC; however, the corpus callosum was subsequently confirmed to be present by fetal MRI and neonatal MRI after delivery. Fetal MRI identified a number of CNS features that were not identified by ultrasound, including abnormalities of sulcation and cortical folding, lissencephaly, hypoplasia of the pons, prominence of the medulla, global cerebral loss, and kinking of the brainstem. Prenatal ultrasonographic findings, MRI findings, and diagnostic genetic testing results are listed in greater detail in Table 1.

Thirteen out of 19 pregnancies in our case series underwent pregnancy termination, three pregnancies were delivered via a normal spontaneous vaginal delivery, two pregnancies underwent caesarean delivery, and one pregnancy had an unknown route of delivery (Table

1). Of the six continuing pregnancies, one neonate (case 4) demised one day after delivery and two neonates (case 1 and case 7) diagnosed with epilepsy necessitated treatment with anticonvulsant therapy. One neonate (case 5) underwent a prolonged neonatal intensive care unit admission of 197 days due to complications of short gut syndrome secondary to necrotizing enterocolitis. In five cases, prenatally suspected CNS findings were confirmed postnatally and postnatal imaging additionally noted pachygyria in 2 cases, polymicrogyria in 1 case, and dysgyria in 1 case. Confirmatory neonatal imaging was not performed on case 4 due to short interval of demise after delivery.

Discussion:

This study provides further phenotypic information on the prenatal imaging findings identified by screening ultrasound in cases with fetal tubulinopathy; specifically, cases predominantly presented with non-isolated ventriculomegaly. Prenatal imaging findings in our case series were otherwise concordant with those that have been reported previously in association with tubulinopathies. Cabet et. al reported on two distinct cerebral imaging patterns seen prenatally in five fetuses affected by a tubulinopathy. The two distinct patterns described by the authors were a severe form with enlarged germinal matrices, microlissencephaly, and a kinked brainstem and a mild form characterized by an asymmetric brainstem, dysgenesis of the corpus callosum, lack of Sylvian fissure operculization, and distortion of the anterior part of the interhemispheric fissure.[4] The findings from our case series reaffirm the association of these prenatal imaging findings with tubulinopathies; three cases in our series demonstrated a kinked brainstem, six cases demonstrated abnormalities of the corpus callosum, one case demonstrated a flat appearing Sylvian fissure, and one case demonstrated microlissencephaly.

Our series expands upon the previously reported prenatal tubulinopathy phenotype. Ventriculomegaly was the most common feature appreciated on fetal imaging in our cohort, being seen in 15 out of 19 tubulinopathy cases. Prenatal ventriculomegaly was noted to be present in two prior cases of tubulinopathies in the literature. In one case, MRI at 21 weeks 5 days was notable for lateral ventriculomegaly and a dysplastic z-shaped brainstem, and in the other case ventriculomegaly was present in association with asymmetry of the brainstem and cerebellum.[5,6] Interestingly, in case 6 in our series, a z shaped configuration of the brainstem was also present, suggesting that this may be an ancillary prenatal finding of the tubulinopathies. Additionally, although prenatal ventriculomegaly was seen in the vast majority of cases in our series, it is notable that the ventriculomegaly was not isolated in any case, underlying the importance of evaluating for additional CNS malformations when fetal ventriculomegaly is identified.

Absence of the CSP was present on fetal imaging in six cases in our series of prenatally diagnosed tubulinopathies. When the CSP is not seen prenatally, there is an increased risk of additional CNS anomalies including, but not limited to, ACC (due to shared embryology between the corpus callosum and the CSP) and ventriculomegaly (due to pressure created fenestrations in the septum pellucidi).[7] Previous cases in the literature have not reported an association between an absent CSP and the tubulinopathies. Given that both ventriculomegaly and callosal abnormalities were seen at an increased frequency in

our series, it appears that the absence of the CSP in addition to other prenatal sonographic features is associated with the prenatal diagnosis of a tubulinopathy.

Cerebellar dysplasia in the absence of cysts is a well described finding in patients with tubulinopathies. In one large postnatal study examining the neuroimaging patterns found in individuals with variants in the tubulin genes, Romaniello et. al noted the presence of cerebellar anomalies in 86% (24/28) of patients. Patterns of cerebellar anomalies included cortical cerebellar dysplasia, vermian dysplasia, vermian hypoplasia, and rotation of the vermis with or without dysplastic features.[8] Our case series is consistent with the prior literature, although all cases with cerebellar abnormalities in our series described cerebellar hypoplasia rather than dysplasia. It is possible that postnatal MRI of cases with prenatally detected cerebellar hypoplasia would better delineate the exact pattern of cerebellar anomalies as compared to fetal MRI given the improvement in spatial resolution in the postnatal setting.[9] While postnatal MRI might better detect cerebellar abnormalities, prior studies have demonstrated that antenatal MRI is more accurate than post – mortem MRI and autopsies in the confirmation of ventriculomegaly.[10] This is particularly relevant given the inconsistent utilization of postnatal imaging and the lack of performance of autopsies in our series.

Two cases in our series (case 11 and case 17) presented with extracerebral abnormalities, which is not consistent with the prior phenotype of tubulinopathies.[4] The fetus in case 11 was diagnosed with a cystic hygroma on a first trimester sonogram, and the patient proceeded with a termination of pregnancy prior to undergoing her anatomy sonogram. In case 17, the fetus was noted to have CNS abnormalities including ventriculomegaly and a hypoplastic cerebellar vermis, in addition to extra CNS anomalies which included arthrogryposis and fixed posturing of the upper and lower limbs. Phenotypically, the proband in case 17 resembles a *KIAA1109*–related disorder, which shares a similar prenatal cerebral pattern as the tubulinopathies and differs based on the presence of extra CNS anomalies, the most common of which is arthrogryposis[11]. Given the neurofunctional role of tubulin, it is plausible that this is a novel genotype – phenotype correlation with *TUBB2B* that has not been previously described. Another notable genotype – phenotype correlation is that most fetuses with variants in TUBA1A had some degree of cerebellar hypoplasia (11/13) as well as bilateral ventriculomegaly (10/13). Additional correlations in our study were limited to the small number of affected fetuses with mutations in the other tubulinopathy genes.

Our series consisted of cases that had heterozygous single gene mutations in five of the six known tubulinopathy genes (*TUBA1A*, *TUBB*, *TUBB2A*, *TUBB2B*, *TUBB3*). No cases of variants in *TUBG1* were present in out cohort. More than 95% of individuals with a tubulinopathy have a *de novo* pathogenic variant, perhaps owing to the reduced reproductive fitness in affected individuals and severe pathogenicity of these variants. The rare cases in the literature in which a tubulinopathy is inherited have included variants in *TUBB3* and *TUBB2B*.[3] All of the cases in our series in which the inheritance was determined had a *de novo* variant. Pregnancies with an apparent *de novo* variant in a tubulinopathy gene have an approximate 1% risk of recurrence due to the possibility of germline mosaicism, which has been reported to occur in at least two families[12]. As is the case in many genetic

disorders, obtaining a molecular diagnosis has important implications for management, prognostic counseling, and recurrence risk assessment. In rare instances, such as in case 11, next generation sequencing results may be available before neuroimaging abnormalities are apparent.

Our study has several strengths. For one, this is the largest series to date examining the prenatal phenotype of tubulinopathies. We additionally identified variants in five out of the six tubulinopathy genes. We were able to successfully add to the prenatal tubulinopathy spectrum phenotype by identifying novel fetal imaging findings. Furthermore, we had the benefit of collecting cases within the Fetal Sequencing Consortium, allowing for in – depth analysis by a large network of clinical genetics experts. Our study has several limitations. Inheritance was unknown in 8 cases, and two of those cases included variants in *TUBB3* and one a variant in *TUBB2B*, which are the two genes in which parental inheritance has been previously reported. Despite a lack of a relevant family history in these 3 cases, it is possible that one or more of the parents of these probands were affected with reduced penetrance. Another pertinent limitation to consider is that while short term neonatal outcome data was available, we did not have access to long term outcomes. Data from long term outcomes would further assist with prognostic counseling and allow for additional genotype phenotype correlations. Lastly, our study was limited in that prenatal and postnatal MRI were not performed in all cases.

Despite the above limitations, this study contributes to the literature a basis for the prenatal phenotype of tubulinopathies. Our case series demonstrates the increased frequency of previously reported prenatal imaging findings of brainstem kinking, corpus callosum abnormalities, flat appearing Sylvian fissure, and microlissencephaly. We propose that two additional markers, ventriculomegaly and absence of the CSP, should be added to the prenatal phenotype and that prenatal suspicion for a tubulinopathy should be increased when these findings are present in association with additional CNS anomalies. This series highlights the indispensability of fetal MRI in the setting of CNS malformations such as ventriculomegaly and absent CSP, which can be associated with highly variable neurological outcomes and exhibit extensive etiologic and genetic heterogeneity. Careful interpretation of prenatal imaging including neurosonogram and fetal MRI can allow for appropriate genetic test selection, personalized prognostic counseling, and in some cases may alter pregnancy management decisions. Given that many of the findings with tubulinopathies are not unique to this diagnosis and can be seen with other single gene disorders, consideration should be given to performing ES with broad panel analysis when suggestive prenatal imaging features are present. Our study also highlights the importance of continued collaboration through prenatal sequencing consortiums to further characterize the prenatal phenotypes of individually rare and complex disorders.

Conclusion:

Tubulinopathies, which are a heterogeneous group of rare disorders caused by variants in genes encoding tubulin, present postnatally with complex brain malformations, motor and cognitive impairments, and epilepsy. Given the rarity of this group of conditions with prior prenatal diagnosis literature limited to case reports and small case series, maternal–fetal

medicine specialists may not place this group of disorders on their differential diagnosis in the setting of complex CNS anomalies. According to our large case series, ventriculomegaly, absence of the CSP, corpus callosal abnormalities, brainstem kinking, a flat appearing Sylvian fissure, microlissencephaly, and cerebellar hypoplasia may suggest a diagnosis of a tubulinopathy and should prompt genetic counseling and diagnostic genetic testing with exome sequencing. Fetal MRI should also be considered in the workup of a tubulinopathy given its ability to elucidate abnormalities of sulcation and cortical folding. Molecular testing for tubulinopathies with the fetal features we describe is important for earlier diagnosis, multidisciplinary coordination, prognostication, and reproductive planning.

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What is already known about this topic?

- The tubulinopathies are a heterogenous group of disorders caused by pathogenic variants in the genes that encode tubulin
- Tubulinopathies are global disorders of neuronal migration characterized by severe cognitive and motor impairment
- Most tubulinopathies are diagnosed postnatally; data on the prenatal phenotyping of the tubulinopathies is scarce with only two distinct phenotypes previously described

What does this study add:

- Ventriculomegaly, absence of the cavum septum pellucidum, corpus callosal anomalies, and cerebellar hypoplasia are cardinal prenatal sonographic findings that should raise the clinical suspicion of a tubulinopathy
- Fetal MRI is complementary in the diagnostic workup of a tubulinopathy
- With increasing use of prenatal sequencing efforts, molecular prenatal diagnosis of a tubulinopathy can be achieved, which will inform pregnancy management by assisting with multidisciplinary coordination, prognostication, and/or reproductive planning

Table 1:

Prenatal Imaging Findings, Genetic Testing Results, and Outcomes in Cases of Prenatally Diagnosed Tubulinopathies

Case	Ultrasound Findings, Gestational Age	MRI Findings, Gestational Age	Test Type	Gene/Inheritance	ACMG Variant Classification	Outcome
1	Bilateral ventriculomegaly, absent CSP, dilation of third ventricle – 19 weeks	Absent CSP, cerebellar hypoplasia, supratentorial ventriculomegaly, germinal matrix hemorrhage – 37 weeks	ES	*TUBA1A*, c.217A>G, heterozygous, unknown inheritance	Likely pathogenic	NSVD at 39 weeks
2	Absent CSP, cerebellar vermian hypoplasia, prominent frontal horns, underdeveloped third ventricle – 22 weeks	Not performed	Gene panel	*TUBA1A*, c.190C>T, heterozygous, unknown inheritance	Pathogenic	Pregnancy termination
3	Bilateral ventriculomegaly, absent CSP, mild cerebellar hypoplasia, prominent third ventricle, microcephaly – 26 weeks	Bilateral ventriculomegaly, cerebellar vermian hypoplasia, microcephaly, thin corpus callosum – 26 weeks	Trio ES	*TUBA1A*, c.1118G>A, heterozygous, *de novo*	Likely pathogenic	Pregnancy termination
4	Bilateral ventriculomegaly, cerebellar vermian hypoplasia – 21 weeks 3 days	Bilateral ventriculomegaly, cerebellar hypoplasia with brainstem kinking, hypotelorism – 24 weeks 3 days	Gene panel	*TUBA1A*, c.167C>T, heterozygous, unknown inheritance	Pathogenic	CS at 37 weeks
5	Bilateral ventriculomegaly, wavering midline falx – 20 weeks 4 days	Bilateral ventriculomegaly, cerebellar hypoplasia with abnormal brainstem kinking – 28 weeks 2 days	Gene panel	*TUBA1A*, c.1216C>T, heterozygous, unknown inheritance	Pathogenic	NSVD at 35 weeks
6	Cerebellar hypoplasia, micrognathia – 18 weeks	Cerebellar vermian hypoplasia, abnormal appearing gyration, agenesis of the corpus callosum, z- shaped configuration of brainstem – 23 weeks	Trio ES	*TUBA1A*, c.791G>A, heterozygous, *de novo*	Likely pathogenic	Pregnancy termination
7	Flat appearing parieto – occipital and Sylvian fissures – 31 weeks	Cerebellar hypoplasia and bilateral ventriculomegaly – 32 weeks	Trio GS	*TUBA1A*, c.521C>T, heterozygous, *de novo*	Likely pathogenic	CS at 41 weeks
8	Bilateral ventriculomegaly, cerebellar hypoplasia, microcephaly – 20 weeks 5 days	Bilateral ventriculomegaly, cerebellar hypoplasia, microcephaly, interhemispheric cysts – 21 weeks 4 days	Trio ES	*TUBA1A*, c.47T>C, heterozygous, *de novo*	Pathogenic	Pregnancy termination
9	Bilateral ventriculomegaly, absent CSP, agenesis of the corpus callosum – 29 weeks	Cerebellar vermian hypoplasia, dysplasia of the corpus callosum, microcephaly – 30 weeks 3 days	ES	*TUBA1A*, c.703G>T, heterozygous, unknown inheritance	Likely pathogenic	Pregnancy termination
10	Bilateral ventriculomegaly, cerebellar hypoplasia – 15 weeks 1 day	Supratentorial ventriculomegaly, cerebellar vermian hypoplasia, hooked appearance of the frontal horns, lissencephaly, pons hypoplasia – 22 weeks	Trio ES	*TUBA1A*, c.539C>T, heterozygous, *de novo*	Likely pathogenic	Pregnancy termination
11	Cystic hygroma −12 weeks	Not performed	Trio ES	*TUBA1A*, c.687G>C, heterozygous, denovo	Likely pathogenic	Pregnancy termination

Case	Ultrasound Findings, Gestational Age	MRI Findings, Gestational Age	Test Type	Gene/Inheritance	ACMG Variant Classification	Outcome
12	Bilateral ventriculomegaly with prominent horns of lateral ventricle, absent CSP – 19 weeks 4 days	Bilateral ventriculomegaly, prominence of lateral ventricles – 19 weeks 5 days	Trio ES	*TUBA1A*, c.197T>C, heterozygous, *de novo*	Likely pathogenic	Pregnancy termination
13	Agenesis of the corpus callosum – 15 weeks 2 days	Agenesis of the corpus callosum, bilateral ventriculomegaly, abnormal frontal and parietal cortical folding, cerebellar vermian hypoplasia with incompletely rotated vermis – 27 weeks 5 days	Trio ES	*TUBA1A*, c.473C>T, heterozygous, *de novo*	Likely pathogenic	Pregnancy termination
14	Dandy walker malformation, enlarged 4th ventricle, bilateral choroid plexus cysts, hypoplastic nasal bone – 20 weeks	Not performed	Trio ES	*TUBB*, c.185G>A, heterozygous, *de novo* Multiple regions of homozygosity on array	Likely pathogenic	Pregnancy termination
15	Mega cisterna magna and cavum vergae – 32 weeks 3 days	Global cerebral loss, ventriculomegaly with markedly diminished white matter, hypoplastic corpus callosum – 32 weeks 4 days	Trio ES	*TUBB2A*, c.1072C>A, heterozygous, *de novo*	Likely pathogenic	Pregnancy termination
16	Bilateral ventriculomegaly, absent CSP, cerebellar hypoplasia – 20 weeks	Supratentorial ventriculomegaly, posterior segment of the corpus callosum not well visualized – 21 weeks	ES	*TUBB2B*, c.1228G>A, heterozygous, unknown inheritance	Pathogenic	Pregnancy termination
17	Bilateral ventriculomegaly, cerebellar vermian hypoplasia, arthrogryposis, fixed posturing of upper and lower limbs – 15 weeks	Not performed	Trio ES	*TUBB2B*, c.1172G>T, heterozygous, *de novo*	Likely pathogenic	Pregnancy termination
18	Possible agenesis of the corpus callosum – 29 weeks	Corpus callosum present, bilateral ventriculomegaly, unusually shaped left lateral sulcus – unknown gestational age	ES	*TUBB3*, c.586G>A, heterozygous, unknown inheritance	Likely pathogenic	Full term with unknown mode of delivery
19	Bilateral ventriculomegaly – 20 weeks	Bilateral ventriculomegaly, asymmetric sulcation delay, abnormal brainstem transition with a prominent medulla – 24 weeks	Gene panel	Deletion of 293 kb at 6q22.3, maternally inherited *TUBB3*, c.836A>G, heterozygous, unknown inheritance	Likely benign Likely pathogenic	NSVD at 38 weeks 5 days

All probands had a chromosomal microarray, and abnormal variants are detailed above

Abbreviations: ACMG, American College of Medical Genetics; CSP, Cavum septum pellucidum; NSVD, Normal spontaneous vaginal delivery; ES, Exome sequencing; GS, Genome sequencing; CS; Caesarean section