Molecular autopsy for fetal structural anomaly: the diagnostic and clinical utility of a multidisciplinary team approach

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Key words: perinatal post-mortem, molecular post-mortem, prenatal exome sequencing, whole genome sequencing, service evaluation
Contribution

What are the novel findings of this work?

We present a real-world analysis of the clinical utility of the perinatal MDT for the assessment of perinatal deaths with a suspected genetic cause. 123 cases were evaluated by the MDT in 2021. 30 genetic diagnoses were identified in 29 cases from 26 unrelated families. Post-mortem (PM) examination added clinically actionable phenotype data in 79% of cases.

What are the clinical implications of this work?

Genomic testing was a clinically useful addition to (but not a substitute for) PM examination in perinatal cases associated with structural anomalies. The MDT had clinical utility. Expedited broad genomic tests were appropriate for heterogeneous presentations. This approach can expand prenatal phenotypes and detect novel disease genes.
ABSTRACT

Objectives: In the West Midlands Regional Genetic Service, cases of perinatal death with a possible genetic diagnosis are evaluated by the Perinatal Pathology Genetic Multidisciplinary Team (MDT). The MDT assessed autopsy findings and considered genomic assessments. The objective of this retrospective service evaluation was to determine the clinical utility of the MDT. This is the first evaluation since the introduction of whole genome and whole exome sequencing in routine clinical care.

Method: The outcomes for all the perinatal MDT cases from January 2021 to December 2021 were examined. All cases received a full or partial post-mortem examination (PM) and a chromosomal microarray. Demographics, phenotype, MDT recommendations, genetic testing, diagnoses, outcomes, impact of PM and impact of genetic testing were collected from patient case notes.

Results: One hundred and twenty-three cases were discussed at the MDT meeting in 2021. Genetic evaluation was recommended in 84 cases and accepted in 64 cases. A range of genetic tests were requested according to indication and availability. Thirty diagnoses were identified in 29 cases from 26 unrelated families. The diagnostic yield was 24% (29/123) of all cases or 45% (29/64) of the cases with a suspected genetic diagnosis who underwent genetic testing. PM examination added clinically actionable phenotype data in 79% of cases. A genetic diagnosis enabled accurate counselling of recurrence risk and provision of appropriate follow-up, including prenatal testing and preimplantation diagnosis for patients with inherited conditions.
Conclusions: Genomic testing was a clinically useful addition to (but not a substitute for) PM examination in perinatal cases associated with structural anomalies. The MDT model helped assess cases and plan appropriate follow-up. Expedited whole genome sequencing or panel-agnostic analysis were most appropriate for heterogeneous presentations. This broad approach can also expand prenatal phenotypes and detect novel disease genes and should be a priority for future research.
Perinatal deaths affect approximately 0.5% of pregnancies in the UK (3,343 deaths in 2020) (1, 2). They are especially challenging for families when the cause of the death is unknown, which may have implications for planning future pregnancies (3, 4). An underlying genetic cause is common, especially in the presence of fetal structural anomalies (FSA), which affect up to 5% of pregnancies (5, 6). Thirty percent of fetuses with an FSA are associated with aneuploidy or copy number variants (CNV), detected with quantitative fluorescence polymerase chain reaction (QF-PCR) and chromosomal microarray (CMA), respectively. Prenatal exome sequencing (ES) detects a monogenic cause in an additional 30% of fetuses with FSA. This ranges from 6-80% depending on the phenotype, family history, and whether the case was screened by a clinical geneticist (7-15). Whole exome and genome sequencing technologies were commissioned by the NHS in England in October 2020.

Perinatal post-mortem (PM) is a valuable resource for investigating perinatal deaths, but the significant and sustained shortage of perinatal pathologists in the UK (16-19) has prompted the exploration of alternative ‘minimally invasive’ or ‘molecular’ protocols based on a combination of imaging, external examination and genetic testing (20-26). However, this approach may have limitations compared to a full post-mortem (22, 26, 27).

In the West Midlands regional genetic service, cases of perinatal death with a possible genetic diagnosis are evaluated by the Perinatal Pathology Genetic Multidisciplinary Team (MDT). The MDT incorporates an autopsy and genomics assessment. The objective of this service
The evaluation was to determine the clinical utility of the perinatal MDT to assess perinatal deaths associated with structural anomalies.

**METHODS**

The UK West Midlands Perinatal Pathology Service serves a population of 5.5 million people and fourteen obstetric centers. Prior to perinatal demise, most patients opted for NHS screening, which includes a 1st trimester dating scan and trisomy risk screen, 2nd trimester anomaly scan, and newborn screening (28). Additional investigations were offered if anomalies were detected. Perinatal cases therefore received a variable degree of work-up prior to the post-mortem. This ranged from no information (cases presenting with miscarriage at 14 weeks gestation after a normal 1st trimester scan) to cases with full fetal or neonatal work up, including MRI imaging and genetics evaluation. After parental consent, perinatal cases underwent a full or limited PM examination and a minimum of chromosomal microarray (CMA). Autopsies are performed by designated subspecialty perinatal pathologists following protocols and guidance of the Royal College of Pathologists (29, 30). This includes external examination, comprehensive internal examination, histology of relevant internal organs and X-rays in every case. Cases with unexplained abnormal findings with a likely underlying genetic cause are presented to the Perinatal Pathology Genetic MDT. Cases with isolated neural tube defects, or chromosomal abnormalities which explained the phenotype were not discussed. The monthly MDT is attended by perinatal pathologists, clinical geneticists, clinical scientists and fetal medicine specialists who consider potential diagnoses and recommend appropriate genomic investigations and follow-up.
This Service Evaluation was defined using the HRA decision tool (31), and prospectively approved and registered with the Birmingham Women’s and Children’s NHS Foundation Trust Clinical Audit Registration & Management System (reference CARMS-31104). Patients were consented prospectively for participation in service evaluation and audit. Cases were identified from MDT records (January 2021 – December 2021). A standardized proforma was used to retrospectively collect phenotype, genotype and outcome data from patient case notes.

Standard NHS diagnostic tests were performed in UKAS accredited medical laboratories as per the NHS test directory (32). NHS diagnostic tests included single gene tests, panel tests, exome and genome sequencing in prenatal, postnatal and post-mortem settings. Appropriate tests were selected with the guidance of the NHS test directory, clinical genetics and/or the Perinatal MDT. Specific tests (e.g. single gene test or panels) were usually used for specific phenotypes. Broad tests (e.g. whole genome sequencing with large panel analysis) were generally used for non-specific phenotypes. Rapid testing (turnaround time 7-14 days) was available when the outcome could affect the management of an ongoing pregnancy or the care of an acutely unwell child. All variants were classified as per the American College of Medical Genetics and Genomics (ACMG) and Association for Clinical Genomics Science (ACGS) consensus guidelines (33 - 35). The majority of exome and genome sequencing tests employed panel-based analysis methods, except for postnatal rapid whole exome sequencing. Specific methods are detailed in the Supplementary material.

RESULTS
Five hundred and eighty perinatal post-mortems were performed by the West Midlands pathology department in 2021. Of these, 123 (21%) had unexplained structural abnormalities with suspected genetic etiology. These were discussed at the MDT meeting. Eight cases (7%) received antenatal or postnatal exome sequencing prior to PM. Demographics are displayed in Table 1. The median gestation was 20 weeks. Sixty-four per cent of cases were male. The majority of referrals were European (71%), followed by South Asian (17%). Eleven per cent of couples were recorded as consanguineous.

The investigative course and outcomes are summarized in Figure 1. Genetic testing was not recommended by the MDT in 39/123 cases (32%) due to a likely polygenic, non-genetic or sporadic presentation. Of the 84/123 cases with a suspected genetic diagnosis, 64 accepted and received genetic testing.

**Diagnostic yield**

Thirty diagnoses were made in 29 cases from 26 unrelated families. One case was diagnosed with two autosomal recessive conditions. The diagnostic yield was 24% of all the cases discussed at MDT (n=29/123), or 34% (n=29/84) of cases thought by the MDT to be genetic. The yield increases to 45% (n=29/64) when examining cases who received appropriate genetic testing. There were three incidental findings and seven variants of uncertain significance, of which three were upgraded and two were downgraded following further discussion.
The diagnostic yield is depicted by phenotype in Figure 2. The diagnostic rate was highest in cases with multiple anomalies (43%, n=15/35) and when a specific genetic diagnosis was suspected (65%, n=11/17) (Supplementary Figure 1). The test modality and mean turnaround times (TATs) are shown in Table 2.

The most common diagnoses were Meckel syndrome and Fraser syndrome, which were each diagnosed in 3 cases (2 families) (Table 3, Table S1). Pathogenic copy number variants or unbalanced arrangements were seen in 3/30 cases (10%), while the rest were pathogenic or likely pathogenic single nucleotide variants. Sixty-nine percent of diagnosed fetuses were male (n=20/29), and 23% were born to consanguineous couples (n=6/26 families). The inheritance was autosomal recessive in 43% (n=13/30), autosomal dominant in 13% (n=4/30), X-linked in 7% (n=2/30) and de novo in 37% (n=11/30).

The diagnosis was made with rapid testing in 23% of cases (5 prenatal exome, 2 postnatal exome), and the remainder of tests were ‘routine priority’. The median TAT between perinatal death and diagnosis in ‘routine-priority’ cases was 232 days (single gene = 124 days, gene panel = 232 days, WGS = 440 days).

Clinical utility

The PM contributed clinically significant phenotype data in 79% of cases (n=97/123). This was defined as data which altered the differential diagnosis or decision to perform genetic testing. In 45% cases (n=55/123) the PM revealed significant additional features (e.g. an anomaly in a
different organ system). In 35% cases (n=42/123), the PM revealed an alternative non-genetic
cause, allowed confident diagnosis of a sporadic syndrome, or detected important normal
features (for example, the absence of renal cysts or ductal plate malformation in a fetus with
isolated encephalocele). In 18% cases (n=22/123) the PM added phenotype information
which did not alter the differential diagnosis or decision to test (e.g. dysmorphic features or
confirmation of previously detected anomalies). In 3% cases (n=4/123), no additional
information was obtained. All of these non-informative PM examinations were limited to
external examination or placenta only. PM was less likely to be significantly informative when
there was severe maceration or autolysis (e.g. intracranial examination where a feticide was
performed).

In addition, PM helped made a clinical syndrome diagnosis in 17% (17 genetic cases, 4
sporadic cases), reclassify uncertain variants in 10%, (n=12/123), interpret molecular findings
presenting with an unusual phenotype in 6% (n=7/123), and/or obtain good quality DNA
samples for genetic testing in 50%, (n=61/123). Stored DNA samples, collected for all cases
discussed at the MDT, will also enable genetic testing in the future if new methods or
information come to light.

Where genetic testing was complete, molecular diagnosis enabled accurate recurrence risk
counselling and provision of familial screening in 51% (n=29/64) and the availability of
prenatal testing and preimplantation genetic diagnosis in 32% (n=17/53).

Variants of uncertain significance and incidental findings
There were seven cases (6%) with class 3 variants of uncertain significance (VUS). Three were upgraded to likely pathogenic using protein modelling, detailed PM phenotype and/or segregation, and two were downgraded using the detailed PM phenotype and segregation analysis. Two incidental findings were detected with CMA (maternally inherited chromosomal microduplication syndrome and a carrier of \textit{ABCC6} deletion). In addition, one significant diagnostic finding (KBG syndrome due to a heterozygous de novo pathogenic \textit{ANKRD11} variant) was only a partial explanation for the phenotype. The diagnosis was not thought to be the cause of demise, which remained unexplained.

Genetic diagnosis confirmed by PM

In four cases, the detailed PM phenotype increased the certainty of the diagnosis with a severe or atypical prenatal presentation (Baraister-Winter syndrome, CHARGE syndrome, \textit{KAT6B}-related disorder, KBG syndrome). For example, a fetus with a pathogenic \textit{CHD7} variant presented prenatally with suspected craniosynostosis, which was not known to be a feature of CHARGE syndrome at the time. Post-mortem examination subsequently identified choanal atresia, arrhinencephaly and a small thymus, which is consistent with a prenatal diagnosis of CHARGE syndrome (36).

Subsequent pregnancy outcomes

Twenty-four couples were known to have at least one subsequent pregnancy between the 2021 MDT and Jan 2023. At the time of the pregnancy, 4/24 (17%) had a molecular diagnosis and 20/24 (83%) did not (no variant detected = 7/24, results pending = 13/24). Expedited
genetic testing during pregnancy was accepted in 7/13 pending cases, which detected a diagnosis in four cases (de novo=2, AR=1, XL=1).

In total, prenatal diagnosis or fetal sexing was available for 9/24 couples, which was accepted in five cases. 7/24 couples (30%) had a subsequent fetal loss (4 had miscarriages, 3 had TOP for confirmed recurrence), 2/24 were liveborn, 1/24 had a liveborn female affected with IP, and in 14/24 cases the final outcome was unknown or ongoing. One woman who had a recurrence had a normal prenatal exome (R412) in the first pregnancy, but WGS in the subsequent pregnancy detected a $CLCN4$ variant, consistent with a diagnosis of $CLCN4$-related neurodevelopmental disorder syndrome (37).

DISCUSSION

This service evaluation of an MDT-guided molecular autopsy for selected perinatal deaths demonstrated an overall diagnostic yield of 24%. Among tested, selected cases suspected by the MDT to have a genetic cause, the rate rose to 45% (n=29/64), comparable with reported rates of 37-52% in the literature (19, 31, 32). Molecular diagnosis enabled accurate counselling of recurrence risk and management options in future pregnancies, including prenatal diagnosis and PGD.

The service evaluation demonstrated the benefits of detailed PM phenotyping and the MDT approach. In the UK, sustained pressure on perinatal pathology services has led to the exploration of alternative examination protocols (24). In our series, PM examination was
clinically valuable and could not be substituted with genetic testing alone. In the majority of

cases, the detailed phenotype provided by PM allowed the MDT to make nuanced

recommendations on differential diagnoses, genetic testing, follow-up, and interpretation of

molecular findings. In four cases, the detailed PM phenotype increased the certainty of the
diagnosis when the prenatal presentation was severe or atypical (Baraister-Winter syndrome,
CHARGE syndrome, \textit{KAT6B}-related disorder, KBG syndrome). Detailed phenotyping, histology
and protein modelling studies also enabled a homozygous \textit{PIEZO1} variant of uncertain
significance to be upgraded to likely pathogenic, enabling PGD in a subsequent pregnancy.

PM tissue storage helped provide adequate quantity and quality of stored DNA for

subsequent testing. However, we did not have access to PM MRI scanning so were not able
to compare or evaluate this method.

We recommend that families who have experienced a perinatal death should be offered
expedited genomic tests, although this will present logistic challenges. Those who have
suffered a perinatal demise usually seek timely answers to guide reproductive decisions.

Urgent testing, with a TAT of 15 days, was available to families when testing could alter
management of an ongoing pregnancy or unwell neonate. However, WGS is the preferred
method for testing ‘non-urgent’ perinatal deaths in England. WGS was a high-yield method
but was associated with long TATs and a protracted consent process, which compounded
existing delays in processing PM reports due to a national shortage of perinatal pathologists
(16, 18, 19). The median time from death to diagnosis was 232 days with a gene panel, but
440 days with WGS. Unsurprisingly, in seven cases, testing was in progress or had not started
when the couple became pregnant and subsequently required expedited testing. Testing
during pregnancy adds additional stresses (38). In five cases, testing is still in progress over two years since the original MDT discussion. This service evaluation occurred shortly after the introduction of WGS testing. We expect the turnaround time to improve as services become more experienced, but this should be determined with ongoing service evaluation.

The MDT helped to guide the genetic test method. Targeted genomic tests were appropriate where a clinical diagnosis was suspected (e.g. FGFR2 mutation testing for bent bone dysplasia). This approach had a shorter TAT, simplified consenting, and reduced uncertain or incidental findings compared to whole genome or ES. However, in the UK, some of the panel and single gene tests used in this review have been replaced by WGS (e.g. the structural eye disorders panel used to detect Fraser syndrome).

Large panels or panel agnostic analysis of WGS or WES data is most appropriate for heterogeneous presentations and can expand prenatal phenotypes, especially when a detailed PM phenotype is available to interpret the molecular findings. The fetal anomalies gene panel, used in prenatal rapid ES, is limited to ~1200 genes known to present prenatally (39). Restricting analysis of genes during pregnancy can reduce challenging, uncertain or unexpected findings, interpretational burden and TAT (38). However, in two cases (CLCN4-related developmental disorder (37) and Mitochondrial DNA depletion syndrome), the causative genes were not known to be associated with a prenatal phenotype and were not included on the fetal anomalies panel. The diagnoses were later detected when the cases were reanalysed with larger panels or a panel-agnostic approach. The genes (TK2 and CLCN4) have since been added to the fetal anomalies panel. We also recently reported that biallelic
null *PKP2* variants cause a lethal perinatal onset cardiomyopathy; an important new gene-disease association (40). The diagnosis was possible due to the combination of panel-agnostic analysis and detailed PM phenotype.

Panel-agnostic analysis of perinatal cohorts has the potential to detect important novel disease genes and should be a future target of research. Only 4868 genes are linked with phenotypes in Online Mendelian Inheritance in Man (OMIM) (41). Our understanding of lethal or severe disease genes is usually limited to variants where some carriers survive to the postnatal period. Genes which may be associated with a prenatally lethal phenotype can be studied with animal models, cell viability studies and measures of constraint in the normal population. Indeed, over 7000 genes are linked with embryonic lethality in mice (42), and examination of constrained genes in normal populations detected eleven new candidate AR disease genes (43). These data should be combined with genetic analysis of perinatal pathology cohorts.

We present a real-world analysis of the clinical utility of the perinatal MDT (including PM and genomics investigations). This is the first evaluation since the introduction of routine WGS and WES for this group of patients. Our results may not be generalizable to populations with different demographics or healthcare systems (44). Data collection for follow-up of subsequent pregnancies was incomplete, so it was challenging to evaluate the clinical impact of recurrence.
Conclusions

Genomic testing was a clinically useful addition to (but not a substitute for) PM examination in perinatal cases associated with structural anomalies. The MDT model helped assess cases and plan follow-up. The TATs for ‘routine’ testing were suboptimal, and we argue that genomic testing for all perinatal deaths should be prioritized. In instances where a specific diagnosis was suspected, targeted testing was useful. Expedited whole genome sequencing or panel agnostic analysis were appropriate for heterogeneous presentations. This broad approach combined with PM examination can expand prenatal phenotypes and enable gene discovery, which should be a priority for future research.

Acknowledgements

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Table 1: Demographic details

<table>
<thead>
<tr>
<th>Demographic details</th>
<th>n=123 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>79 (64)</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>13 (11)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>87 (71)</td>
</tr>
<tr>
<td>Asian or Asian British</td>
<td>23 (19)</td>
</tr>
<tr>
<td>Black, Black British, Caribbean or African</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Mixed or multiple ethnic groups</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (3)</td>
</tr>
<tr>
<td><strong>Gestation</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;14 weeks</td>
<td>9 (7)</td>
</tr>
<tr>
<td>14-17</td>
<td>29 (24)</td>
</tr>
<tr>
<td>18-22</td>
<td>44 (36)</td>
</tr>
<tr>
<td>23-28</td>
<td>16 (13)</td>
</tr>
<tr>
<td>29-35</td>
<td>14 (11)</td>
</tr>
<tr>
<td>&gt;35</td>
<td>11 (9)</td>
</tr>
<tr>
<td><strong>Pregnancy outcome</strong></td>
<td></td>
</tr>
<tr>
<td>TOP</td>
<td>68 (55)</td>
</tr>
<tr>
<td>IUD</td>
<td>29 (24)</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>17 (14)</td>
</tr>
<tr>
<td><strong>PM type</strong></td>
<td></td>
</tr>
<tr>
<td>Full</td>
<td>109 (89)</td>
</tr>
<tr>
<td>Limited</td>
<td>14 (11)</td>
</tr>
</tbody>
</table>
Table 2: Test modality

<table>
<thead>
<tr>
<th>Test modality</th>
<th>Total diagnostic yield n (%)</th>
<th>Dx</th>
<th>VUS</th>
<th>IF</th>
<th>Failed or cancelled</th>
<th>Median [range] TAT days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Array (n=123)</td>
<td>3/123 (2)</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>9 [7 – 27] - rapid 62.5 [14 – 132] - routine</td>
</tr>
<tr>
<td>Panel (n=15)</td>
<td>5 (33)</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>82.5 [27 – 175]</td>
</tr>
<tr>
<td>Exome (n=25)</td>
<td>8 (32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Rapid prenatal (R21) (n=6)</td>
<td>5 (84)</td>
<td>3</td>
<td>2 ↑</td>
<td>0</td>
<td>0</td>
<td>15 [7 – 29]</td>
</tr>
<tr>
<td>- Rapid postnatal (R14) (n=9)</td>
<td>2 (22)</td>
<td>2</td>
<td>1 ↓</td>
<td>0</td>
<td>0</td>
<td>14 [7 – 32]</td>
</tr>
<tr>
<td>- Other (e.g. R412) (n=8)</td>
<td>1 (13)</td>
<td>1</td>
<td>1 ↓</td>
<td>0</td>
<td>0</td>
<td>83 [14 – 208]</td>
</tr>
<tr>
<td>Genome (n=26)</td>
<td>8 (31)</td>
<td>7</td>
<td>1 ↑</td>
<td>0</td>
<td>3</td>
<td>201 [84 – 624]</td>
</tr>
<tr>
<td>Single gene (n=11)</td>
<td>4 (36)</td>
<td>4</td>
<td>1 ↓</td>
<td>0</td>
<td>0</td>
<td>29(5 – 128)</td>
</tr>
</tbody>
</table>

Dx = diagnosis (likely pathogenic or pathogenic variant), IF = incidental finding, VUS = variant of uncertain significance. ↑upgraded VUS. ↓downgraded VUS. R21, R14, R412 are test codes for standard NHS diagnostic tests as per the NHS test directory (27) (also see supplementary methods). Two diagnoses were made with targeted testing of familial variant.
### Table 3: Molecular diagnosis

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Diagnosis</th>
<th>Gene / CNV</th>
<th>Diagnosis (n=30), [families (n=26)]</th>
</tr>
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<tbody>
<tr>
<td>de novo</td>
<td>CHARGE syndrome</td>
<td>CHD7</td>
<td>2 [2]</td>
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<tr>
<td></td>
<td>Baraitser-Winter syndrome</td>
<td>ACTB</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Bent bone dysplasia</td>
<td>FGFR2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Cornelia de Lange</td>
<td>NIPBL</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Di George syndrome*</td>
<td>22q11.23</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>KAT6B-related disorder</td>
<td>KAT6B</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>KBG syndrome</td>
<td>ANKRD11</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Noonan syndrome</td>
<td>PTPN11</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Osteogenesis imperfecta type 2</td>
<td>COL1A2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Confined placental mosaicism*</td>
<td>Partial aneuploidy of chromosome 2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Alveolar Capillary Dysplasia with Misalignment of the Pulmonary Veins</td>
<td>FOXF1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Branchiootorenal syndrome (BOR)</td>
<td>EYA1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Congenital heart defects, multiple types, 7</td>
<td>FLT4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Unbalanced chromosomal translocation*</td>
<td>Deletion of 10pter to p13 and Duplication of 20pter to p12.3</td>
<td>1</td>
</tr>
<tr>
<td>inherited</td>
<td>Fraser syndrome</td>
<td>FRAS1, FREM2</td>
<td>3 [2]</td>
</tr>
<tr>
<td>AR</td>
<td>Meckel syndrome</td>
<td>RPGRIP1L, TMEM138</td>
<td>3 [2]</td>
</tr>
<tr>
<td></td>
<td>PIEZO1-related generalised lymphatic dysplasia</td>
<td>PEIZO1</td>
<td>2 [1]</td>
</tr>
<tr>
<td></td>
<td>B thalassaemia major</td>
<td>HBB</td>
<td>1</td>
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<td></td>
<td>Nijmegen breakage disorder</td>
<td>NBM</td>
<td>1</td>
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<td></td>
<td>Congenital hydrocephalus 1</td>
<td>CCDC88C</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial DNA depletion syndrome</td>
<td>TK2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Multiple Pterygium Syndrome</td>
<td>CHRNA1</td>
<td>1</td>
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<tr>
<td></td>
<td>XL Incontinenta pigmentosa</td>
<td>IKBKG</td>
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<td>CLCN4-related neurodevelopmental disorder</td>
<td>CLCN4</td>
<td>1</td>
</tr>
</tbody>
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CNV = copy number variants. *CNVs or cytogenetic diagnosis.