

[05-041]

Next-Generation Sequencing of Congenital Pulmonary Airway Malformations

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Background

Congenital pulmonary airway malformations (CPAMs) are fetal lung tumors that can cause significant morbidity through mass effect and hydrops. Genetic mutations in *KRAS* have been implicated in type 1 and 3 CPAMs. We aimed to use next-generation sequencing (NGS) with a broad gene panel to identify genetic mutations in large CPAM tumors.

Methods

This retrospective, single-center, IRB-approved cohort study included infants with prenatally diagnosed large CPAMs who underwent surgical resection between 2020-2025. Formalin-fixed paraffin-embedded (FFPE) tumor samples underwent DNA extraction and sequencing using a 448-gene solid tumor NGS panel evaluating point mutations, small insertions/deletions, and copy number alterations.

Results

Five macrocystic CPAM samples from male infants were analyzed. Prenatal tumor volume ranged from 10.3 to 105.2 cm³ (CPAM volume ratio 1.21-3.48). Three patients (60%) required prenatal intervention. Of three successfully sequenced samples, all harbored oncogenic somatic *KRAS* mutations: G12V (VAF 30.95%) and G12D (VAF 19.97%, 9.62%). No other somatic pathogenic variants were identified.

Conclusions

This study demonstrates a high frequency of oncogenic *KRAS* mutations in macrocystic CPAMs with no other oncogenic variants identified, implicating *KRAS* as a potential primary driver. Given *KRAS* activates the mTOR pathway, this work provides a rationale for exploring mTOR pathway inhibition in high-risk fetal CPAM.

[05-042]

Pilot Study to Assess the Diagnostic Yield of Whole Genome Sequencing in Newborns with Neonatal Encephalopathy (The GENE Study)

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Background: Neonatal encephalopathy (NE) (~3/1000 births) is a major risk factor for neurodevelopmental impairment. Half of NE cases are associated with hypoxic ischemic etiologies (HIE) and the remainder with infections, fetal growth restriction or underlying genetic or metabolic disorders. No prospective studies have evaluated whole genome sequencing (WGS) diagnostic yield in NE.

Objective: Determine the diagnostic yield of WGS for genetic disorders in NE.

Methods: 48 NICU admitted NE newborns were prospectively screened with inclusion criteria: mild, moderate or severe NE; GA at birth ≥ 37 weeks; absence of cord prolapse or uterine rupture; negative blood culture; and fetal exposure to < 40 g of maternal magnesium. With IRB approved parental consent, NE related HPO term focused WGS was performed on newborn DNA. Positives were reflexed to parental sequencing for phasing and results reported to parents and clinicians.

Results: By Sarnat NE classification, most cases had mild or moderate severity (~equal numbers). On preliminary analysis, pathogenic, likely pathogenic or variants of unknown significance in relevant genes were identified in ~1/3 of subjects, several clearly causative.

Conclusions: WGS for NE has significant diagnostic yield. Variant detection, even in mild NE, may have important implications for immediate and long-term care and outcome.

[05-043]**Antenatal use of whole exome sequencing for work up of hydrops****Erin J Bailey, Michael J Beninati, Kathy Kenley, Janine Rhoades**

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Objective:

To describe the role of whole exome sequencing (WES) as a diagnostic tool for fetal hydrops.

Case Report:

A 31 year old G1P0 presented at 20 weeks' gestation with hydrops fetalis, including scalp edema and bilateral pleural effusions. Initial diagnostic work up was unremarkable, including FISH, microarray, infectious studies on amniotic fluid and fetal echo. Thoracentesis was performed with reaccumulation of pleural effusion within 48 hours. Patient underwent right thoracoamniotic shunt placement; however, follow up scan 4 days later demonstrated significant worsening of skin edema causing shunt displacement with recurrent pleural effusion. Ultimately, WES demonstrated compound heterozygosity for mutations in the TTN gene, consistent with congenital titinopathy. Such disorders are characterized by defective titin production, the largest protein in the human body. Prenatal disease is characterized by hydrops, growth restriction and cardiovascular dysfunction. Congenital recessive titinopathy is often lethal with severe hypotonia, muscle contractures, respiratory dysfunction, and dilated cardiomyopathy. After multidisciplinary counseling, patient elected for palliative care.

Conclusions:

WES is an important prenatal diagnostic tool that can guide management and counseling in pregnancies which an etiology for abnormalities was not able to be identified antenatally.

[05-044]

Genetic diagnoses and postnatal outcomes in a prenatal cohort of arthrogryposis multiplex congenita

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Introduction: Arthrogryposis multiplex congenita (AMC) is characterized by the presence of contractures in at least 2 body areas. Predicting prognosis in pregnancies complicated by AMC is challenging given clinical and genetic heterogeneity. Prenatal diagnosis can aid in understanding short and long-term outcomes.

Objective: We aim to describe the genetic diagnoses in pregnancies affected by AMC.

Methods: This was a retrospective cohort study of pregnancies and postnatal follow-up at our center (2014-2026) with prenatal ultrasound findings consistent with AMC.

Results: Ninety-three pregnancies were included, of which 44(47%) had an associated genetic diagnosis: 17(18%) aneuploidy (16 trisomy 18 and 1 trisomy 13), 3(3%) copy number variants (2 unbalanced translocations and 2 de novo deletions) and 24(26%) single gene disorders. Single gene disorders involved myopathic (GMPPB, ACTA1, MYH3), neurogenic (BICD2, ECEL1, ZC4H2 and L1CAM), neuromuscular junction (DOK7), connective tissue (TGFBRI) ion channel (SCN2A, SCN8A), skeletal (COL1A1, COL2A1, FGFR3, SOX9, SF3B4, LMBR1, FLNB), mitochondrial (VARS2), and multi-systemic (NIPBL, FANCB) genes. Among the 24 single gene disorders diagnosed, 14 had fetal or neonatal demise, 5 survived with severe neurologic disability, and 5 had normal neurological development.

Conclusion: Exome sequencing should be considered in the diagnostic workup of AMC given the high proportion of severe single gene disorders with this phenotype.

[05-045]

Maternal and neonatal outcomes in pregnancies complicated by Trisomy 18

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Introduction: Some parturients with Trisomy 18 (T18) fetuses decline palliative fetal care and accept maternal risks of obstetric procedures for potential neonatal survival benefit. We compared maternal and neonatal outcomes in T18 pregnancies managed by palliative vs. interventional obstetric pathways.

Objective: We compared parturients choosing fetal palliative care vs. those choosing fetal monitoring and cesarean for fetal indications among T18 pregnancies delivering at our center (2014-2026).

Results: Of 78 T18 pregnancies, 15 had fetal demise and 21 delivered elsewhere, leaving 42. Palliative care (N=12) and actively managed (N=30) groups were similar in median age (35[IQR 10] vs. 32 years[IQR 9]; $p = 0.16$), parity (1[IQR 3.2] vs. 1[IQR 2]; $p = 0.30$), BMI (29.5[IQR 7.5] vs. 31.0 kg/m²[IQR 7]; $p = 0.38$). The intervention group had higher cesarean rate [24/30(80%) vs. 0/12(0%), $p < 0.001$] and composite maternal morbidity (blood loss >500cc, postpartum stay > 3d, puerperal infection) (19/30[63%] vs 1/12[8%], $p = 0.0017$) compared with palliative care. Palliative care neonates had similar survival to discharge [3/12(25%) vs. 13/30(43%); $p = 0.32$] and surgeries [1/12(8%) vs. 10/30(33%); $p = 0.13$] compared to intervention neonates.

Conclusion: Maternal morbidity for patients undergoing obstetric intervention when delivering infants with T18 was higher than the palliative pathway. However, neonatal outcomes were similar.

[05-046]

Trisomy 18: An Analysis of Disease Burden and Survival After Surgical Intervention

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Background: Trisomy 18 (T18) is a rare chromosomal anomaly associated with poor survival. Given its high mortality, surgical decision-making and family counseling is complex.

Methods: The Epic Cosmos database was queried for patients born between 2016-2025 with T18 (ICD-10-CM Q91.0-Q91.3). Comorbidities, interventions, and survival were analyzed with descriptive and Kaplan-Meier survival analyses.

Results: 2,374 newborns with T18 were identified. Among 1,539 infants with survival data, 45% (n=685) survived to 7 days, 31% (n=484) to 30 days, and 4.7% (n=73) to 1 year. The most common surgical comorbidities were congenital heart disease (CHD) (n=1,603, 68%), urogenital anomalies (n=282, 12%), esophageal atresia/tracheoesophageal atresia (n=202, 8.5%), and omphalocele (n=174, 7.3%). 234 patients (9.9%) underwent any intervention; gastrostomy tube placement was most common (n=141, 5.9%) with median post-procedure survival of 756 days. Among those with CHD, 2.1% (n=34) underwent repair with post-procedure survival > 50% survival to date.

Conclusion: In T18, surgical comorbidities are common but survival to 30 days is low. Survival after surgery may be prolonged; further research is needed to define those who would most benefit from intervention.

[05-047]**Whole genome sequencing- first line test for prenatal investigation of congenital malformations?****Peter Conner**

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OBJECTIVES: Evaluating the performance of whole genome sequencing (WGS) in prenatally detected congenital malformations

METHODS: Prospective and retrospective study of 218 fetuses with different malformations. In 216/218 QF-PCR and/or chromosomal microarray were performed with normal results prior to WGS analysis.

RESULTS: A genetic variant was found in 49/218 (22.5%) of the clinical WGS analysis. 39% of the detected variants were not de novo and found to have an increased risk of recurrence in future pregnancies. The phenotypes of the cases were divided into six different groups with a diagnostic yield of 36% in multisystem malformations, 31% in skeletal, 25% in CNS, 16% in thoracic, and 12% in abdominal. The mean TAT for clinical WGS when ordered before 22 weeks of gestation was 12 days. Pregnancies with malformations displaying diagnostic results were more often terminated (73% vs 25%) compared to cases with fetal malformations displaying a normal WGS

CONCLUSIONS: The results from our study demonstrate that WGS including a CNV analysis is a potential first line test to apply when investigating prenatally detected fetal malformations. WGS may provide an explanation to the cause of the malformation in over half of the cases as chromosomal aberrations will be detected simultaneously.

[05-048]

When Monochorionic Is Not Identical: Heterokaryotypic Monochorionic Twins Following Risk-Reducing cfDNA

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Objective: Three monochorionic, diamniotic (MCDA) twin pregnancies with discordant anomalies had low-risk cell-free DNA (cfDNA) screening. Two cases were confirmed heterokaryotypic and monozygotic for 46,XY/47,XY,+18; third case confirmed heterokaryotypic and dizygotic 45X/46XY following prenatal diagnosis.

Case 1/2: Two sonographically-identified MCDA twin pregnancies with discordant anomalies both had low-risk cfDNA screening, one chromosome-counting, one PCR based. Amniocentesis prior to pregnancy termination confirmed each pregnancy with one euploid twin and one twin with Trisomy 18; selective reduction resulted in term birth of unaffected fetus in each pregnancy.

Case 3: A sonographically-identified MCDA pregnancy with low-risk cfDNA screening (Y-chromosome detected) was found with suspected disorder of sexual development and cystic hygroma in one twin. Amniocentesis and zygosity testing confirmed this monochorionic pair was heterokaryotypic and dizygotic, with karyotype 45X/46XY. Placental pathology revealed thin intraplacental membranes, with fetal vessels crossing under the chorionic plate.

Conclusions: In sonographically-defined MCDA pregnancies discordant for anomalies, low-risk cfDNA aneuploidy screening may be misleading. In monozygotic twins, post-zygotic errors may yield discordant karyotypes not discernable via cfDNA. Rarely, sonographic MC can arise in DZ twinning. Genetic diagnostic testing of both twins should be considered when discordant fetal anomalies are present, as anomalies may be a phenotypic expression of heterokaryotypy.

[05-049]

Prenatal detection of MN1-associated CEBALID syndrome presenting as isolated orofacial clefts

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Introduction

CEBALID syndrome (OMIM #618774), caused by pathogenic variants in MN1 (OMIM *156100), is a recently recognized neurodevelopmental disorder characterized by craniofacial anomalies, brain malformations, and developmental delay. To date, prenatal diagnosis has not been reported, likely due to the absence of distinctive fetal features. We present, to our knowledge, the first prenatal case of MN1-associated CEBALID syndrome manifesting as isolated orofacial clefts, highlighting important diagnostic pitfalls and the value of whole exome sequencing (WES) in such diagnostic settings.

Case

A 38-year-old Taiwanese woman (gravida 2, para 1) was referred for genetic counseling and prenatal evaluation. Cytogenetic analysis at 17 weeks identified a de novo balanced translocation, 46,XY,t(2;3)(q24;p25), with a normal chromosomal microarray, arr(X,Y)×1,(1-22)×2. At 22 weeks, ultrasound detected cleft lip and palate without additional structural abnormalities, particularly no detectable brain or craniofacial anomalies. Given the genetic heterogeneity of orofacial clefts, WES was performed. After filtering by a series of criteria, only one novel heterozygous MN1 frameshift variant, NM_002430.3:c.3001dup(p.His1001Profs*15), predicted to truncate MN1, was identified. The variant was a de novo event, and was classified as pathogenic according to ACMG-AMP criteria.

Conclusion

Here we report the first prenatal diagnosis of MN1-associated CEBALID syndrome presenting as isolated orofacial clefts.

[05-050]

Severe Fetal Anemia Secondary to ($\epsilon \gamma \delta \beta$)⁰ Thalassemia: A Case Series Demonstrating the Impact of Prenatal Surveillance and Intrauterine Transfusion

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Rare deletions involving the regulatory elements, including ($\epsilon \gamma \delta \beta$)⁰ thalassemia, impair both β and γ globin production and result in severe fetal anemia, hydrops fetalis, and intrauterine compromise. Experience with IUT in these conditions remains limited.

We present sequential pregnancies in a single family demonstrating the contrast between an unrecognized index pregnancy and a subsequently surveilled pregnancy managed with fetal therapy. In the index pregnancy, fetal hydrops was identified at 28 weeks of gestation, prompting delivery. The neonate required multiple transfusions and was later diagnosed with heterozygous ($\epsilon \gamma \delta \beta$)⁰ thalassemia. In a subsequent pregnancy, the patient declined invasive prenatal testing. Serial MCA peak systolic velocity surveillance beginning at 20 weeks demonstrated progressive fetal anemia with MCA PSV values up to 2.4 MoM, accompanied by evolving hydrops. One intraperitoneal and two intravascular transfusions were performed at approximately 20, 25, and 30 weeks of gestation, correcting fetal anemia and resolving hydrops. Delivery occurred by scheduled repeat cesarean at 35 weeks, with a favorable neonatal outcome.

This case highlights the importance of family history-driven surveillance, MCA Doppler monitoring, and timely IUT in optimizing outcomes in rare fetal hemoglobinopathies. Early recognition and multidisciplinary management are vital in optimizing outcomes in this rare but increasingly recognized condition.