Prenatal Exome Sequencing for apparently isolated agenesis of the corpus callosum

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Introduction

Differences involving the corpus callosum can include complete or partial agenesis, hypoplasia and dysgenesis. These differences can be isolated (approximately 50% of cases) or associated with other anomalies, either intracranial or extracranial. Outcome data for fetuses with agenesis of the corpus callosom (ACC) is limited and of poor quality making prognostication very difficult. Occasionally isolated ACC has been reported as an incidental finding in an apparently normal individual, but can also be associated with a wide range of severity for developmental delay, intellectual disability, motor and coordination difficulties in at least 30%. For some, there may be severe/profound developmental delay and/or a poor outcome. The presence of additional features seen on ultrasound scan or with fetal MRI and/or genetic test results may help to provide the couple with more specific advice.

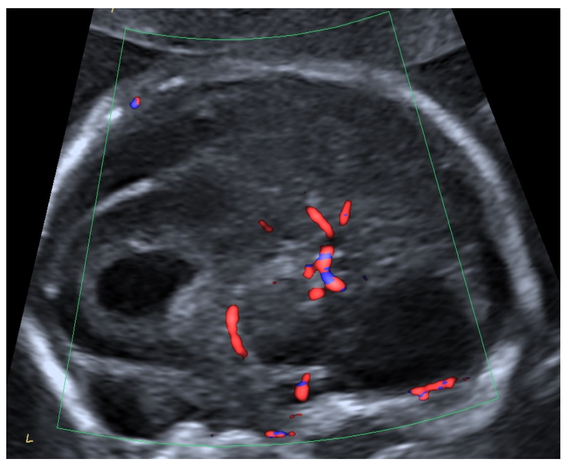
Rapid prenatal exome sequencing using a 'fetal anomalies' panel has been available in England since October 2020 which allows us to investigate fetuses with structural malformations due to a suspected monogenic disorder. Following a number of publications reporting a diagnostic rate from exome sequencing of 18-30% in cases of isolated ACC, the testing criteria were updated. These now include 'abnormality of the corpus callosum, either partial or compete agenesis – either in isolation or with other anomalies'. We reviewed our local experience of undertaking prenatal exome sequencing for this indication since it's inclusion.

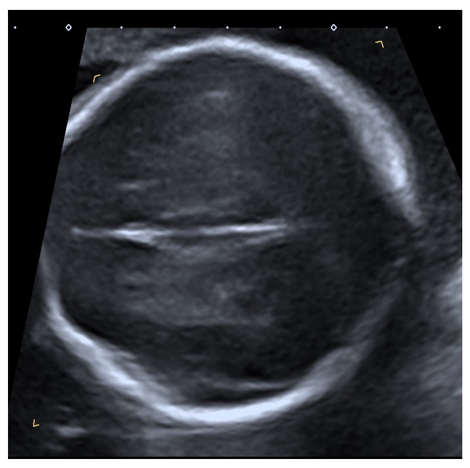
Results

The West Midlands Regional Genetics laboratory database was searched to identify cases and the clinical information, exome results and outcome for those with a diagnostic result were reviewed. Eleven cases of apparently isolated ACC (at the point of referral) were accepted by the West Midlands Regional Genetics Laboratory for rapid prenatal exome sequencing between May 2022 and April 2023. One case was not sequenced following the identification of a pathogenic CNV on SNP array. Of the remaining 10 cases; three likely pathogenic or pathogenic variants were identified.

Case 1

A routine anomaly scan identified ventriculomegaly and a referral was made to the Fetal Medicine Department. An ultrasound scan at 23+6 weeks gestation confirmed mild ventriculomegaly (posterior ventricles 10.5-11.5mm) and features suggestive of complete ACC. Amniocentesis was undertaken but the couple chose to terminate the pregnancy prior to the planned MRI and before genetic test results were reported. The post mortem examination confirmed complete ACC with no additional anomalies. Exome sequencing subsequently identified a de novo heterozygous pathogenic variant in *ARID1B* consistent with Coffin-Siris syndrome





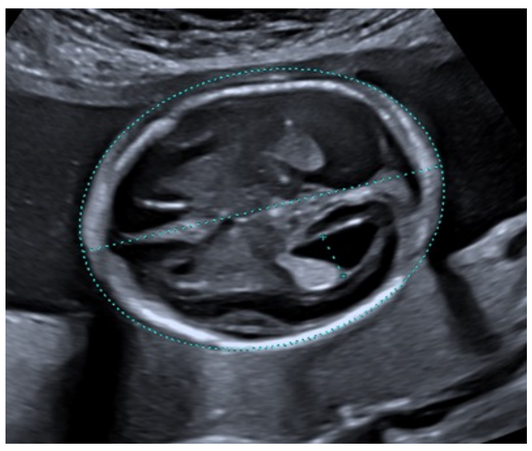
Variant Interpretation

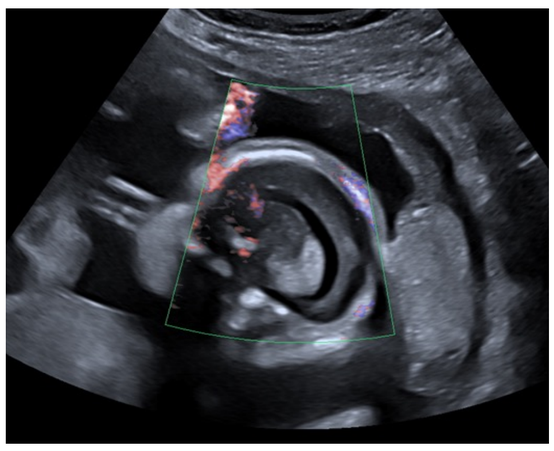
- ARID1B (NM_020732.3): c.5267_5270delAAAG p.(Glu1756Alafs*9)
- Variant reported multiple times in the literature and in patient databases in individuals with clinical features of Coffin Siris syndrome, and has been shown to have arisen de novo in a number of probands.
- De novo with biological relationships confirmed
- Variant predicted to result in the creation of a downstream stop codon leading to premature termination of translation.
- Variant has not been reported in population-based cohorts (gnomAD)

Conclusion: Pathogenic

Case 2

A routine anomaly scan raised concerns of a possible partial agenesis of the corpus callosum and a referral was made to the Fetal Medicine Department. An ultrasound scan at 20+4 weeks gestation confirmed isolated ACC with no additional intra- or extra-cranial anomalies. Amniocentesis was undertaken and this couple also chose to terminate the pregnancy prior to the MRI and before genetic test results were reported. Exome sequencing subsequently identified a heterozygous pathogenic variant in *ARID1B*, consistent with Coffin-Siris syndrome.





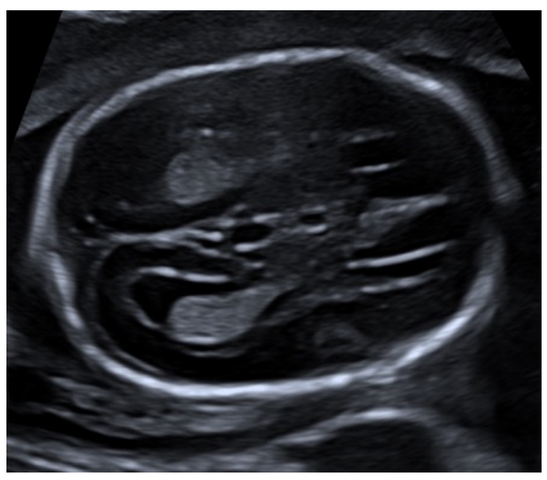
Variant Interpretation

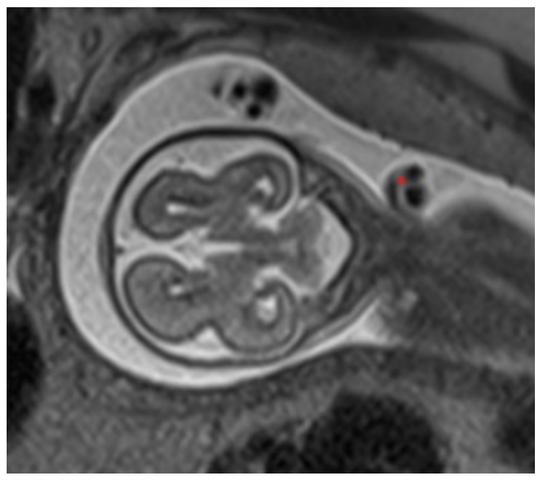
- ARID1B NM_020732.3: c.5715delT p.(Phe1905Leufs*69)
- This variant has not been reported in the literature
- De novo with biological relationships confirmed
- Variant is predicted to create a downstream stop codon leading to premature termination of translation.
- Variant has not been reported in population-based cohorts (gnomAD)

Conclusion: Likely Pathogenic

Case 3

The routine anomaly scan raised concerns about a possible brain anomaly and the couple were referred to the Fetal Medicine Department. An ultrasound scan at 20+2 weeks gestation was consistent with apparently isolated ACC and an amniocentesis was undertaken. A fetal MRI at 22+6 weeks gestation confirmed complete ACC and additional findings of small and abnormal development of the cerebral hemispheres. Exome sequencing identified a heterozygous pathogenic variant in *SON,* consistent with ZTTK syndrome. The couple chose to terminate the pregnancy following these results.





Variant Interpretation

- SON (NM_138927.2): c.2792delG p.(Gly931Alafs*7)
- This variant has not been reported in the literature
- De novo with biological relationships confirmed
- Variant is predicted to result in the creation of a downstream stop codon leading to premature termination of translation.
- There is an established association between SON variants of this type and ZTTK syndrome.
- Variant has not been reported in population-based cohorts (gnomAD)

Conclusion: Likely Pathogenic

Conclusions

Our clinical experience is in line with recent literature, which has suggested that isolated ACC is an appropriate indication for prenatal exome sequencing. The diagnostic rate of 27% in our cohort is similar to previously published literature in this area. Since ACC is associated with such a broad range of clinical outcomes, there is great benefit in additional investigations which can potentially provide more specific prognostic information. The use of MRI as an adjunct not only provides additional prognostic information but can also help to refine the phenotype and assist interpretation of exome results. Whilst the MRI is sometimes able to identify additional brain anomalies not seen by ultrasound, in our small cohort there was still a role for initiating the prenatal exome sequencing prior to the MRI being undertaken, especially if there is a delay in reaching an appropriate gestation for further imaging. In cases 1 and 2, the couples chose to terminate the pregnancy on the basis of the scan findings alone but for case 3, the prognostic information from the genetic diagnosis directly influenced pregnancy decisions.

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