Genetic testing in patients with possible foetal alcohol spectrum disorder

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ABSTRACT

Objective To assess the diagnostic yield of genetic conditions in patients referred to a regional genetics service to consider a diagnosis of foetal alcohol spectrum disorder.

Design Retrospective case series.

Setting A regional genetics centre in Yorkshire.

Patients All referrals to the Yorkshire Regional Genetics Service coded with mentions of maternal alcoholism or foetal alcohol were considered for inclusion. Exclusion criteria were follow-up patients, patients with missing case notes and patients failing to attend their appointment.

Methods Medical records were reviewed and the following information was extracted: referring specialty, reason for referral, gender, age at assessment by clinical genetics, accompanying individual, history of alcohol exposure in pregnancy, clinical examination details, neurodevelopmental deficits, genetic testing prior to referral, genetic testing organised by the genetics department and diagnosis made by clinical genetics.

Results and conclusion 110 patients were included. 130 tests were carried out, including 86 array comparative genomic hybridisation tests. The overall diagnostic rate for a contributing genetic disorder was 3.6%, all being chromosomal disorders and chromosome copy number variants.

What is already known on this topic?

- Genetic disorders can often have features similar to foetal alcohol spectrum disorder (FASD).
- Prior to the widespread use of array comparative genomic hybridisation (aCGH), previous cohorts reported genetic diagnostic rates of 7%–14%.

What this study adds?

- All children should have an aCGH test prior to genetics referral.
- The genetic diagnostic yield remains low despite widespread use of aCGH.
- There is benefit to further defining children with a higher probability of a genetic diagnosis who would benefit from a clinical genetics referral.

INTRODUCTION

Maternal consumption of alcohol during pregnancy is associated with the development of foetal alcohol spectrum disorder (FASD). Since first described in 1973,[1] the medical and behavioural problems associated with alcohol consumption in pregnancy have been well characterised.[2] Children with FASD can present with features similar to a number of genetic disorders, so these patients are often referred to clinical geneticists to exclude underlying genetic diagnoses and make a diagnosis of FASD. In previous studies, the genetic diagnostic rate in children referred to genetics teams ranges from 7.4% to 14.3%.[3–5]

This case series reports the genetic diagnoses made for patients referred for FASD assessment to a single genetics service over a 4-year period. During this study, the range and availability of genomic testing has changed rapidly, with paediatricians now requesting array comparative genomic hybridisation (aCGH) as a first-line test, and gene panels, exome and whole genome testing being more readily accessible.

METHODS

All referrals to the Yorkshire Regional Genetics Service (YRGS) between January 2013 and December 2017, that were coded with 'maternal alcoholism' or 'foetal alcohol' when the referral was received, were considered for inclusion. Only new referrals were analysed to allow an assessment of diagnostic yield following a new consultation with YRGS. Case notes were reviewed and the following information was recorded: referring specialty, reason for referral, gender, age at assessment by clinical genetics, accompanying individual, history of alcohol exposure in pregnancy (by the referrer and the genetics team), clinical examination details (by the referrer and the genetics team), neurodevelopmental deficits, genetic testing prior to referral, genetic testing organised by clinical genetics and diagnosis made by clinical genetics. Neurodevelopmental deficits were inferred from the patient's history and not from formal neurodevelopmental assessment results. Examination details recorded from the referral letter were occipitofrontal circumference (OFC), palpebral fissure length, and philtrum and lip assessment. The latter three features are the three sentinel facial features of FASD.[6] All patients were seen by a consultant clinical geneticist. Data were inputted into Microsoft Excel before statistical analysis, consisting of frequency and mean calculations.

RESULTS

One hundred and fifty-five referrals were made during the study period. Forty-five cases were excluded for reasons including unavailability of medical records, patients not attending the appointment, and referrals for patients previously seen and under follow-up with YRGS. One hundred and ten cases were included in the analysis (see online supplemental table 1).

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Table 1 Genetic investigations ordered in the 110 patients referred to YRGS

Investigation	Tests ordered before clinical genetics review (n)	Tests ordered by clinical genetics (n)	Result
Karyotype	12	4	XXX (confirmatory test following identification of XXX in aCGH). No other positive findings.
Fragile X	6	7	No positive findings.
aCGH	48	38	Four significant findings (see online supplemental table 2).
Clinical exome ► Overgrowth and intellectual disability 17-gene panel*. ► Syndromic intellectual disability 56-gene panel*. ► KBG syndrome 1-gene panel*. ► Cornelia de Lange 5-gene panel*. ► Perinatal skeletal dysplasia 64-gene panel*. ► Microcephaly 16-gene panel.	0	6	*HSPG2* VOUS (see online supplemental table 2). No other positive findings.
Gene panel ► *SBDS* and congenital neutropaenia panel (from cancer 155-gene panel)*. ► Rubinstein-Taybi 3-gene panel*. ► RASopathy 16-gene panel*.	0	3	No positive findings.
Single gene testing ► *FGFR3**. ► *PTEN**. ► *ESCO2*.	1†	3	No positive findings.
Other ► Fanconi anaemia stress test*. ► Myotonic dystrophy. ► 7-dehydrocholesterol level.	0	3	No positive findings.

*Patient who had the test had OFC ≤5th centile or ≥95th centile.
†Patient was seen by a previous clinical genetics centre that ordered the single gene test.
aCGH, array comparative genomic hybridisation; OFC, occipitofrontal circumference; VOUS, variant of uncertain significance; YRGS, Yorkshire Regional Genetics Service.

A mean of 22 patients were referred to YRGS annually (range 15–24). The majority of referrals (93%) came from paediatricians, with the main referral indication being to consider a diagnosis of FASD. Of the 110 patients, 58% were male, and the average age at the time of assessment was 7.6 years (range 6 months–26 years). Patients were usually accompanied to appointments by their parents (24%), foster carers (35%) or adoptive parents (20%). Other patients came with other family members and social workers.

The information provided on the referral letter was variable. Of the 110 referrals, 94% mentioned alcohol use in pregnancy, with 6% stating a possible diagnosis of FASD, but not explicitly mentioning maternal alcohol use in pregnancy. Looking at the three sentinel facial features, 12% of referrals commented on the patient's palpebral fissure length, 51% the philtrum, 45% the upper lip and 58% the OFC. Of the 110 children, 67% were normocephalic, 20% had OFC ≤5th centile and 13% had OFC ≥95th centile. Assessment of neurodevelopment was variable; 8% of referrals had some form of neurodevelopmental assessment (e.g. by Child and Adolescent Mental Health Services), 6% had an assessment pending, while the remaining 86% of referrals did not mention a neurodevelopmental assessment or had not had an assessment.

Table 1 summarises the genetic tests and results for patients in this study. The 110 cases included in this series had a total of 130 genetic investigations. Fifty-one patients had genetic tests organised following review by YRGS. Twenty patients (18%) had no genetic testing performed by either the referring clinician or the reviewing clinical geneticist. Fifty-nine patients had genetic testing prior to their clinical genetics review, which mainly consisted of aCGH tests (48 patients), karyotypes (12 patients) and testing for fragile X syndrome (6 patients). Paediatric teams requested the majority of these tests, apart from two aCGH arranged at a previous genetics review, a karyotype arranged by obstetrics and gynaecology, and a single gene test arranged by another genetics centre.

Of the 86 aCGH tests, 28 abnormalities were identified in 25 patients (29%). Following review by a clinical geneticist, five of these abnormalities were felt to be contributing to the patient's phenotype. A patient was found to be a carrier of a genetic disorder on aCGH testing. This finding was therefore not included as a significant result in our analysis and was also not thought to be contributing to the patient's phenotype. A table of variants identified can be found in online supplemental table 2.

There were no positive results from clinical exome, gene panels, single gene or other genetic investigations arranged. One patient was enrolled in 100,000 Genomes Project and the results are still pending. Two patients were enrolled in the Deciphering Developmental Disorders (DDD) research study, which performed exome sequencing, but no diagnoses have been made. One of the patients enrolled in the DDD study was found to have variants in two genes that were classified as likely benign and not contributing to the phenotype. Sixty per cent of the genetic tests beyond aCGH, fragile X syndrome testing and karyotype were performed in those with OFCs ≤5th centile and OFC ≥95th centile. These tests are highlighted in table 1. The microcephaly panel in a normocephalic child (20th centile) likely represents the different charts used to assess OFC in children over the age of 2 years. No diagnoses were made in the two children seen twice by the genetics services, although they had more extensive genetic investigation, suggesting that these children were re-referred as there was concern for another genetic diagnosis.

The overall genetic diagnostic rate was 3.6% (4 out of 110 cases) (online supplemental table 2).

Table 2 summarises the alcohol-related disorders diagnoses made by the genetics team in this cohort. Few diagnoses of foetal alcohol syndrome (FAS) or partial FAS were made (12%), with all but one of these diagnoses made in patients where alcohol exposure was confirmed, rather than suspected, in pregnancy. Just under half of the patients were deemed to have a phenotype not related to alcohol in pregnancy (47%).

Table 2 Diagnoses made by clinical geneticists in patients referred to YRGS

	Patients aged 6 and under (n=45), n (%)	Patients over 6 years of age (n=65), n (%)
FASD	4 (8.9)	4 (6.2)
Partial FASD	2 (4.4)	3 (4.6)
ARND	3 (6.7)	12 (18.5)
Alcohol contributed to phenotype	11 (24.4)	19 (29.2)
Alcohol did not contribute to phenotype	25 (55.6)	27 (41.5)

ARND, alcohol-related neurodevelopmental disorder; FASD, foetal alcohol spectrum disorder; YRGS, Yorkshire Regional Genetics Service.

DISCUSSION

We report the genetic test results of patients referred with possible FASD to YRGS. This is the largest series of patients described, including their aCGH results. The diagnostic yield for genetic abnormalities in this cohort is low (3.6%), with all diagnoses made being chromosomal abnormalities.

Previous studies have shown that chromosomal copy number variants (CNVs) are over-represented in cohorts of patients with FASD or suspected FASD,[5 7] and this study demonstrates the importance of aCGH being performed in all children with suspected FASD. Further analysis to assess diagnostic rates in those with proven or suspected alcohol exposure in pregnancy may have demonstrated differences in diagnostic yield between these groups. As this was a retrospective series, this analysis was limited as the quantity or duration of alcohol consumption in pregnancy was not well documented in the majority of cases. Often the term 'suspected' or 'confirmed' alcohol use was only available, with no indication as to how alcohol consumption was confirmed.

The patients assessed in this study were referred over a 4-year period. At the start of this study period, the genetics teams only requested aCGH and this is reflected by the 38 aCGH tests requested by the geneticists in this series. All children now referred to genetics for investigation of developmental delay or intellectual disability routinely have an aCGH performed prior to referrals arranged by the paediatric team. This study has shown that YRGS would not have made any additional diagnoses in these patients if all children had an aCGH prior to referral.

Although some of these patients had other features not in keeping with FASD, no other genetic diagnoses were made despite more extensive genetic testing. The use of intellectual disability gene panels is becoming more widespread, although no studies have yet investigated the diagnostic yield from panel testing, whole genome or exome sequencing in this cohort of patients. Potentially, further genetic diagnoses could be made with this testing in the future and this remains an area for further study. There may be other factors, such as children's often complex social backgrounds, which are influencing the neurodevelopmental progress of these children.

The diagnostic yield in this case series is lower than previously reported in the literature (7.4%–14.3%).[3–5] These studies included fewer patients and the proportion of patients who had aCGH was lower. Our lower diagnostic yield may represent a trend towards a lower threshold for patient referral for genetic assessment to consider a diagnosis of FASD or another genetic condition. In addition, as aCGH is now readily available to paediatricians, those with CNVs will be referred to genetics for discussion of these results, rather than a diagnosis of FASD.

If a paediatrician has a strong suspicion for FASD, various guidelines and diagnostic criteria are available. In the UK, the Scottish Intercollegiate Guidelines Network (SIGN) has recently published guidance titled 'Children and Young People Exposed Prenatally to Alcohol'.[6] When this guidance is rigorously applied, with an accurate and detailed history regarding alcohol consumption in pregnancy, a neurodevelopmental assessment and examination of the three sentinel facial features, the majority of FASD diagnoses can be made by the paediatric team. This study demonstrates that all children with suspected FASD should have an aCGH to exclude CNVs, which can be arranged by the paediatric team.

We agree with the SIGN guidance that not all children with possible FASD require review by clinical genetics, and routine referral may serve to delay their FASD diagnosis. There is, however, a need to further define those children who are more likely to have a genetic diagnosis and so would benefit from referral. From our experience, children with features that are not in keeping with FASD, including those with history of developmental regression, family history of intellectual disability, growth abnormalities, significant abnormalities on neuroimaging, and atypical facial features, are more likely to benefit from a clinical genetics review. The results of this study suggest children with an abnormal head circumference may particularly benefit. Further refinement of these recommendations will be achieved by further analyses of larger cohorts of children, particularly those seen more recently, where more extensive genetic testing has taken place. Given the increasing role of the clinical geneticist in multidisciplinary team meetings (MDTs), local discussion of children in an MDT setting between clinical genetics and paediatric teams may effectively identify those patients for clinical genetics referral.

Limitations of this case series include the low number for analysis and the retrospective collection of data. Information was often incomplete or not documented clearly, which limited the analyses possible, although these additional data would not change the diagnoses made in these children. The diagnostic terminology used by clinical geneticists was not uniform, with many diagnoses of 'alcohol contributed to phenotype', which is not a term used in guidelines. It is also not clear which diagnostic criteria were used by the clinical genetics team, limiting the ability to assess whether alcohol-related diagnoses were made correctly.

In summary, there is a low diagnostic yield from genetic investigations in patients with possible FASD referred to YRGS. This study supports the recommendation that all children should have an aCGH, with FASD diagnostic criteria being applied rigorously before a genetics referral is considered. Children with atypical features may benefit from a genetics review, although this requires confirmation in further studies.

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Data are available upon reasonable request. Please contact the corresponding author if required.

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