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POLISH GYNECOLOGY
GINEKOLOGIA POLSKA
ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGICZNEGO
THE OFFICIAL JOURNAL OF THE POLISH GYNECOLOGICAL SOCIETY

ISSN: 0017-0011

e-ISSN: 2543-6767

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DOI: 10.5603/GP.a2022.0121

Article type: Research paper

Submitted: 2021-08-25

Accepted: 2021-11-29

Published online: 2023-04-26

ORIGINAL PAPER / OBSTETRICS

Prenatal detection of chromosomal abnormalities and copy number variants in fetuses with corpus callosum agenesis

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ABSTRACT

Objectives: The corpus callosum is the main pathway that connects interhemispheric communication. Agenesis of corpus callosum (ACC) have not consistently detected replicate genetic risk factors, potentially due to Etiological heterogeneity of this trait. This study aimed to retrospectively analyze the molecular basis for the ACC and the potential genotyping-phenotyping association and provide the basis for genetic

counselling.

Material and methods: Karyotyping and chromosomal microarray analysis were performed for copy number variants.

Results: Three cases had 1p36 deletions, two cases had 2q31.2 and 2p16.3 microdeletions, one case had microdeletion of Xq26.3q27.1, five cases involved derived chromosomes due to unbalanced translocations. These cases had variable deletions and duplications with partial overlapping. Phenotypically, besides agenesis of corpus callosum and other brain morphological abnormalities as well as heart abnormalities.

Conclusions: ACC may occur alone or be related to other abnormal clinical phenotypes, and its genetic mechanism is very complicated. These results revealed ACC is associated with a variety of chromosomal abnormalities. The findings of the present study expand the genotypes associated with ACC, and further delineation of the genotype–phenotype correlations for ACC. With current applications of chromosome microarray analysis, congenital submicroscopic copy-number variations in fetuses can be detected more effectively.

Key words: agenesis of corpus callosum; chromosomal abnormalities; amniocentesis; chromosomal microarray analysis; karyotype

INTRODUCTION

The pathogenesis of ACC involves complex interactions of many factors, which are related to heredity, infection, poisoning, environment and immunity. Certain neurological impairments and disabilities have been associated with ACC in children [1]. One or more genes are mutated, or chromosomal aberrations result in approximately 20% of ACC [2–4]. The majority of cases are apparently sporadic, although monogenic, X-linked, autosomal dominant and recessive causes of ACC have been identified [5, 6]. Chromosome microarray analysis (CMA) has been used to uncover genetic variations associated with ACC in recent years.

ACC occurs as an isolated defect or associated with other anatomical malformations [7]. For instance, the haploinsufficiency of zinc finger protein ZNF462, is related to corpus callosum dysgenesis, ACC is characterized by many congenital anomalies that include craniosynostosis, metopic ridging, ptosis, and developmental delay [8]. An abnormal homozygous CDK10 mutation also causes agenesis of the corpus callosum, global developmental delay, growth retardation, sensorineural deafness, and vertebral anoma [9]. De novo mutations in MAST1 reported to cause MCC-CH-CM, a disease characterized by corpus callosum enlargement, cerebellar hypoplasia, and cortical dysplasia [10]. To date over 200 distinct chromosome rearrangements have been reported in the agenesis of corpus callosum genetic etiology [11–13].

The aims of this study were to provide a better understanding of the chromosomal abnormalities and the corpus callosum agenesis in prenatal diagnosis, we performed an analysis on prenatal diagnosis of 10 corpus callosum structural abnormal fetuses using the CMA.

MATERIAL AND METHODS

We performed chromosomal analysis on cultured amniotic fluid cells samples after informed consent, using GTG-banding according to standard procedures and according to the nomenclature of the International System for Human Cytogenetic Nomenclature (ISCN) 2016 [14].

QIAamp DNA Blood Mini Kit (Qiagen, Venlo, The Netherlands) was used to isolate genomic DNA from amniotic fluid (10 mL), and the concentration and quality of genomic DNA were assessed using a Nanodrop 2000 (Thermo Fisher Scientific, Waltham, MA, USA). In this study, CMA data were processed with the Affymetrix Cytoscan 750k array kit from Affymetrix (Santa Clara, CA, USA), and then analyzed with Chromosome Analysis Suite (ChAS) software (v3.1, r8004) [15, 16].

Clinical features

Fetal ultrasound revealed that three cases (case 2, 3, 5, and 10) showed agenesis of corpus callosum and fetal cerebral ventriculomegaly, two cases (9, 10) not only had the above ultrasound abnormalities, but also accompanied by pericardial effusion and narrowed cavum septi pellucidi, respectively. Three cases (6, 7, and 8) displayed absence of corpus callosum and cavum septi pellucidi, and two cases (4 and 9) exhibited cardiac abnormalities. Case 4 showed the absence of corpus callosum, polyhydramnios and a complex cardiac defect－severe tricuspid regurgitation with mild stenosis. Fetus 1 had aberrant corpus callosum and ependymal cyst. Detailed information about the clinical findings is listed in Tables 1 and 2.

Furthermore, according to family history of pregnancy and childbirth, the first pregnancy of the same parents of fetus 2 was induced because of the absence of corpus callosum at 6-months gestation. The pregnant woman of case 3 had also given birth to a boy showed ACC, who had a microdeletion at chromosome 1q43q44 and microduplication at chromosome 7q3.

Results of karyotyping and CMA

Karyotype analysis was performed for 10 fetuses, and enunciated that case (3, 4, 8) inherited the chromosome 1 deletion from the unaffected parent who underwent a balanced chromosome translocation between chromosome 1 and other chromosome. Case 9 has inherited the derived chromosome 20. Case (1, 4) involving the loss of the telomeric portion of the short arm of chromosome 1. Among the remaining five cases had normal karyotype. The karyotyping results are listed in Table 2.

Chromosomal microarray analysis detected pathogenic CNVs in eight fetuses, one case with likely pathogenic CNV, and the other was considered with VOUS. The CMA results have demonstrated that the losses include deletions of 1p, Xq, 1q, 2p, 2q, and 17p, whereas the gains are of 7q, 6q, 5p and 8p. The size of the deletion or duplication segment was between 0.1 and 35.2 Mb. Among fetuses two yielded a live birth, with the remaining eight being terminated. Premature death was observed for two born-alive fetuses (Tab. 2).

DISCUSSION AND CONCLUSIONS

Through karyotyping and CMA, we systematically investigated the distribution and further evaluated the detection rates of chromosomal abnormalities in fetuses with different types of ACC, a retrospective study of 10 ACC-affected fetuses was conducted. It was found that CMA significantly increased the detection rates with ACC over karyotyping, improving by 50% the detection rate in fetuses with normal karyotypes. There have been several reports of neurodevelopmental disorders associated with deletions or duplications found in fetal ACC.

The corpus callosum is a major white matter structure mediating inter-hemispheric information transfer, A key role is played by it in preserving hemispheric specialization [17, 18]. ACC is a common congenital brain malformation that can occur in isolation or as a component of a congenital syndrome, it is associated not only with less interhemispheric, but also with less right interhemispheric language network connectivity in line with reduced verbal abilities [19, 20]. Furthermore, neuromotor impairment, cognitive, and epilepsy was frequently present, regardless of ACC subtype [13, 21]. The complex causes of fetal ACC make comprehensive evaluation and prenatal diagnosis by karyotyping and CMA highly recommended.

CMA has a significantly higher detection rate for chromosomal abnormalities than routine karyotyping because of its high resolution for detecting CNVs [22, 23]. In the present study, there were in all 10 cases with chromosomal abnormalities detected by CMA, the number was higher than what was found by karyotyping (50%, 5/10). A number of pathogenic CNVs are present, such as deletions of 1p36.33p36.31, Xq26.3q27.1, 2p16.3, and 2q31.2, duplications of 8p23.3p11.1, four cases contained complex and multiple rearrangements, (Tab. 2), were identified, as reported in cases of developmental delays and/or learning difficulties, congenital heart disease, macrocephaly, attention deficit hyperactivity disorder and seizures [24], speech and language delay, autism spectrum disorder, intellectual disability [25], corpus callosum abnormalities [26], malformations of the brain, spinal cord, and vertebrae [27], and so on. As of now, AKT3 within 1q43-q44 in case 3 and 8 is the only ACC candidate gene

identified from one of these regions [28, 29]. In general, CMA is superior to karyotyping in detecting variant genomic anomalies in fetal ACC.

There may be variation in exome depth and expression of causal genes in patients with similar CNVs. The penetrance of the ACC was very high, although non-attainment full penetrance (100%), especially for deletions of certain loci, such as 1q42-q44 and 6q25-q27 and inversion duplication deletions of 8p [11, 30, 28, 31–34]. It is also possible that location effects of CNVs on nearby genes may be a contributing factor in a small number of patients. In particular, ventriculomegaly also occurs in patients who have deletions of chromosome 1p36.32p35.1. Despite this, there is evidence of ACC loci on distal 1p36 with variable penetrance of the ACC in combination with other structural brain abnormalities [11].

In this research, termination of pregnancy (n = 6) or premature death (n = 2) in all cases of pathogenic CNV. Pregnancy terminations were also performed in cases of possible pathogenic CNV. Only one of VOUS cases also underwent termination of pregnancy because of the severe brain structure abnormality of the fetus. This study did not consider benign and potentially benign CNVs. Unfortunately, Case 1 developed developmental delay, epilepsy, hypotonia, hearing loss, susceptibility to colds and fever after birth, and died after being hospitalized several times. Case 6 was a premature low birth weight infant who died after only two hours of survival.

By using CMA during pregnancy, we identified pCNVs and likely pCNVs in 4 cases (40%) that were not detectable by karyotype analysis. A VOUS case was not detectable by karyotype analysis, too. CMA was more sensitive than karyotype analysis in detecting chromosome duplication and deletion and may reveal more genes and genomic loci involved in callosal development [17]. It is widely known that CMA could easily be included in prenatal diagnostic panels after fetal ultrasound abnormality positive findings, and the identification of the underlying etiology by CMA would give couples the option of continuing with pregnancy or terminating it in an informed manner [16].

The symptoms of agenesis of the corpus callosum range from none to severe neurodevelopmental disorders, including mental retardation, epilepsy, learning disabilities, depression, schizophrenia, delusional disorder, conduct disorder, and conversion symptoms, and patients with syndromic agenesis of corpus callosum have more severe clinical symptoms than isolated [13, 35]. Although corpus callosum dysplasia is a highly non-specific feature caused by the interaction of multiple factors and genes, and the diversity of its clinical phenotypes makes it more challenging in genetic counseling. Therefore, during prenatal genetic counselling, pregnant women should be informed in detail about a spectrum of phenotypic outcomes may be observed in this syndrome.

As a conclusion, we reported the prenatal diagnosis of chromosomal microdeletion and microduplication syndrome in ten ACC fetuses using CMA testing. CMA should be actively applied to prenatal diagnosis of fetal ultrasound abnormalities. A clinical basis may be provided for prenatal diagnosis and genetic counseling for ACC based on the findings of the present study.

Ethics approval and consent to participate

The Ethics Committee of the Fourth Military Medical University has approved this study and informed parental consent has been obtained for the invasive prenatal diagnosis.

Consent for publication

Images and other clinical information relating to the case have been published for academic purposes with the informed written consent of the parents.

Availability of data and materials

Data sets used and/or analyzed in this study can be obtained from correspondents according to reasonable requirements.

Funding

This work was supported by Key Research and Development Program of Shaanxi (2019ZDLSF01-06), University Joint Project-General Project of Shaanxi Province

(2020GXLH-Y-009) and scientific and technological projects for social development of Shaanxi Province (2016SF-254).

Acknowledgements

We would like to thank all of those who contributed to this study.

Conflict of interest

All authors declare no conflict of interest.

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Table 1. Information about the 10 fetuses with ACC

Case	1	2	3	4	5	6	7	8	9	10
Mother age	33 years	31 years	30 years	40 years	29 years	27 years	36 years	29 years	29 years	29 years
Gestation history	G2P1A0	G2P0A1	G2P1A0	G6P1A4	G1P0A0	G1P0A0	G3P0A2	G1P0A0	G3P0A2	G2P1A0
Fetus age	23 weeks	26+5 weeks	31 weeks	30 weeks	27 + 3 weeks	27 + 6 weeks	23 + 4 weeks	30 weeks	23 + 6 weeks	28 + 4 weeks
Fetus sex	F	F	F	M	M	M	M	F	M	M
Fetus sample	AF	AF	AF	AF	UC	AF	AF	AF	AF	AF
Reason for ascertainment	UT(+)	UT(+); miscarriage histor years	UT(+); miscarriage histor years	UT(+)	UT(+)	UT(+)	UT(+)	UT(+)	UT(+)	UT(+)

A — abortion; AF — amniotic fluid; F — female; G — gestation; M — male; P — parturition; UC — umbilical cord; UT(+) — abnormalities on ultrasound testing

Table 2. Ultrasound findings, and the results of karyotyping and CMA analysis

Case	Ultrasound findings	Karyotype	CMA results			Pregnancy outcome
			Genomic coordinates（hg19）start-end	Size (Mb)	Results	
1	Widened *cavum septi pellucidi*; slender *corpus callosum*; ependymal cyst	46,XX,del(1)(p36)	1p36.33p36.31(1,028,553-5,851,366)x1	4.8 Mb	pCNVs	PD
2	Agenesis of corpus callosum; fetal cerebral ventriculomegaly	46,XX	Xq26.3q27.1(136,388,326-139,518,268)x1	3.1 Mb	pCNVs	TOP
3	Agenesis of corpus callosum; fetal cerebral ventriculomegaly	46,XX,der(1)t(1;7)(q43;q36.1)	7q36.1q36.3(150,301,319-159,119,707)x3; 1q43q44(242,702,622-249,224,684)x1	6.5 Mb; 8.8 Mb	pCNVs	TOP
4	Congenital heart disease; Polyhydramnios; agenesis of *corpus callosum*	46,XY,der(1)t(1;6)(p36.2;q25.3)	1p36.33p36.22(849,466-10,365,183)x1; 6q25.3q27(156,607,002-170,914,297)x3	14.3 Mb; 9.51 Mb	pCNVs	TOP
5	Absent of corpus callosum; fetal cerebral ventriculomegaly	46, XY	1p36.32p35.1(4829059-33858873)×1–2 hmz	28 Mb	likely pCNVs	TOP
6	Absent of corpus callosum and *cavum septi pellucidi*	46, XY	2p16.3(5073053-50943528)x1	213 kb	pCNVs	PD
7	Absent of corpus callosum and *cavum septi pellucidi*	46, XY	17p13.3(1477255-3063414)x1; 2q12.2q12.3(106856366-108527327)x1	1.59Mb; 1.67 Mb	pCNVs	MFPR
8	Absent of corpus callosum and *cavum septi pellucidi*	46,XX,der(1)t(1;5)(q43;p13.3)	5p15.33p13.3(113,576-33,241,655)x3; 1q43q44(236,958,159-249,224,684)x1	33.1 Mb; 12.3 Mb	pCNVs	TOP
9	Agenesis of corpus callosum; fetal cerebral ventriculomegaly; pericardial effusion	Mos 46,XY,der(20)t(8;20)(p11;p13) / 46,XY	8p23.3p23.1(158,048-8,648,314)x3; 8p23.1p11.1(8,672,304-43,824,035)x3	8.49 Mb; 35.2 Mb	pCNVs	TOP
10	Agenesis of corpus callosum; fetal cerebral Ventriculomegaly; Narrowed *cavum septi*	46, XY	2q31.2(178,772,408-178,901,916)x1	129 kb	VOUS	TOP

Mb —

megabase pair; MFPR — multifetal pregnancy reduction; pCNVs — pathogenic copy number variants; PD — Premature death; TOP — ternimation of pregnamcy; VOUS — variants of unknown significance