P-811

Examination of prenatal cases referred for uniparental disomy 16: Referral patterns, positive associations and key findings

Andrea Penton, PhD, FACMG; Alexandra Arreola, PhD, FACMG; Inder Gadi, PhD, FACMG; Gloria Haskell, PhD, FACMG; Karen Phillips, PhD, FACMG; Amanda Sussman, PhD, FACMG; Jim Tepperberg, PhD, FACMG; Stuart Schwartz, PhD, FACMG; Labcorp, Research Triangle Park, NC

Introduction

Chromosome microarray analysis is routinely used prenatally to detect chromosome gains or losses. The presence of single-nucleotide polymorphisms (SNPs) in the analysis will not only help elucidate and confirm gains and losses, but also reveal runs of homozygosity in the probands. This homozygosity is suggestive of the possibility of uniparental disomy (UPD) and further testing for UPD may be attempted because of the homozygosity, presentation of ultrasound (US) findings, or because of the reason for referral.

Trisomy 16 is a common aneuploidy in which most fetuses are spontaneously lost by the 12th week of gestation. One line of thought is that fetuses with trisomy 16 that survive longer have some level of correction to disomy. Previous investigations suggest that some of these fetuses may be lost later in gestation due to intrauterine growth retardation (IUGR) resulting from uniparental disomy 16 (UPD 16). However, opposing lines of thought refute this proposal and suggest that UPD 16 fetuses are phenotypically normal.

In this study, 26 fetuses have been examined for UPD 16. This study shows the determination of UPD 16 is straightforward and that there does not appear to be a correlation with recognizable phenotypic abnormalities at birth.

Methods

In this study, we report on 26 prenatal patients ascertained over the past six years that were studied to determine if they had uniparental disomy for chromosome 16 (Tables 1 and 2). All of the samples were obtained as amniotic fluid samples (except for case 25). Initial SNP microarray studies were done utilizing the CytoScan™ HD and CytoScan™ HD Accel arrays (ThermoFisher Scientific).

After the initial studies, SNP-UPD analyses were performed. For fetuses with both parental samples, the Mendelian Inherited Error (MIE) was studied. In cases of biparental inheritance, the MIE for the chromosome of interest will be less than 0.20. In cases of UPD, the MIE for the chromosome of interest will be greater than 5.00. When only one parent was available, the percent of parental and fetal AB genotypes were examined to determine UPD for the chromosome of interest if the MIE in the parent submitted was consistent with relatedness. When the %AB was >95%, this was consistent with UPD in the parent available for study.

Patients were ascertained because of a variety of indications including: ten with an increased risk of trisomy 16 detected by cfDNA analysis, three of the ten also having a terminal ROH region; one with a prior chorionic villus sampling (CVS) showing trisomy 16; three with prior preimplantation genetic testing for aneuploidy (PGT-A) studies indicating trisomy or monosomy 16; two with parental translocations of 16; and ten referred in for reasons unrelated to chromosome 16 abnormalities, but because initial SNP analysis revealed a region of homozygosity on chromosome 16 seen in the initial analysis (Tables 1 and 2).

CASE NO.	FETAL SEX	MATERNAL AGE	GESTATION AGE	MIE (MAT)	MIE (PAT)	%AB (MAT)	%AB (PAT)	UPD ORIGIN	INITIAL REFERRAL	UPD REFERRAL
1	FEMALE	34.1	22.9 WKS	0.01	7.83	99.4%	36.9%	MATERNAL	SKELETAL DYSPLASIA	16 ROH - TERMINAL (12.8 MB)
2	FEMALE	37.3	16.5 WKS	0.01	10.13	99.2%	36.2%	MATERNAL	NIPT - TRISOMY 16	16 ROH - TERMINAL (17.5 MB)
3	FEMALE	38.6	16.0 WKS	0.04	12.82	97.8%	36.5%	MATERNAL	NIPT - TRISOMY 16	16 ROH - TERMINAL (44.9 MB)
4	MALE	33.6	16.3 WKS	0.01	7.5	99.7%	41.8%	MATERNAL	MSS - LOW PAPP-A	16 ROH - TERMINAL (21.7 MB)
5	FEMALE	39.7	28.1 WKS	0.01	11.14	99.5%	34.5%	MATERNAL	ABN US (NOS)	16 ROH - TERMINAL (15.8 MB)
6	FEMALE	27.6	18.3 WKS	0.03	10.13	97.9%	39.4%	MATERNAL	ABN US - CHD	16 ROH - TERMINAL (40.1 MB)
7	MALE	34.5	20.4 WKS	0.01	6.58	99.4%	42.9%	MATERNAL	ABN US - NT	16 ROH - TERMINAL (13.9 MB)
8	FEMALE	23.9	22.0 WKS	0	N/A	99.9%	N/A	MATERNAL	NIPT - TRISOMY 16	NIPT - TRISOMY 16; ROH - TERMINAL (5.87 MB)
9	FEMALE	33	17.3 MB	0	N/A	99.6%	N/A	MATERNAL	IUGR/ABNORMAL PLACENTA	16 ROH - TERMINAL (24.0 MB)
10	FEMALE	38.5	16.5 WKS	6.14	0.07	48.9%	49.7%	PATERNAL SEGMENTAL	AMA	16 ROH - TERMINAL (30.4 MB)

Table 1. Characteristics of cases referred confirmed to be UPD 16. This table shows the reason for referral and determination to confirm UPD 16 in ten cases. All cases were obtained as amniotic fluid.

CASE NO.	FETAL SEX	MATERNAL AGE	GESTATION AGE	MIE (MAT)	MIE (PAT)	%AB (MAT)	%AB (PAT)	UPD ORIGIN	INITIAL REFERRAL	UPD REFERRAL
11	FEMALE	32.8	21.4 WKS	0.07	0.09	52.4%	51.7%	BIPARENTAL	CVS - MOSAIC TRISOMY 16	CVS - MOSAIC TRISOMY 16
12	FEMALE	40.6	NG	0.07	N/A	49.0%	N/A	BIPARENTAL	NIPT - TRISOMY 16	NIPT - TRISOMY 16
13	MALE	25.8	21,1 WKS	0.07	0.11	48.2%	52.4%	BIPARENTAL	NIPT - TRISOMY 16; IUGR, THICK PLACENTA, ABNORMAL GENITALIA	NIPT - TRISOMY 16
14	MALE	32.1	17.6 WKS	0.14	0.13	47.6%	48.4%	BIPARENTAL	NIPT - TRISOMY 16	NIPT - TRISOMY 16
15	MALE	30.5	16.2 WKS	0.08	0.11	45.7%	54.2%	BIPARENTAL	NIPT - TRISOMY 16	NIPT - TRISOMY 16
16	FEMALE	30.7	26.2 WKS	0.17	0.09	47.7%	56.0%	BIPARENTAL	NIPT - TRISOMY 16; IUGR	NIPT - TRISOMY 16
17	MALE	44.2	16.1 WKS	0.04	N/A	54.0%	N/A	BIPARENTAL	PGT-A - TRISOMY 16	PGT-A - TRISOMY 16
18	FEMALE	28.4	22.0 WKS	0.06	0.06	49.8%	51.1%	BIPARENTAL	ABN US - NOS	ROH - INTERSTITIAL (18.0 MB)
19	FEMALE	27.7	21.3 WKS	0.09	0.11	47.3%	49.0%	BIPARENTAL	AMA	ROH - TERMINAL (15.8 MB)
20	FEMALE	37.2	24.3 WKS	0.1	0.09	59.0%	49.0%	BIPARENTAL	NIPT - TRISOMY 16, IUGR	NIPT - TRISOMY 16
21	FEMALE	39	17.2 WKS	0.09	0.1	47.8%	48.6%	BIPARENTAL	PGT-A - TRISOMY 16,20	PGT-A - TRISOMY 16, 20
22	FEMALE	28.8	18.1 WKS	0.14	0.06	64.9%	47.3%	BIPARENTAL	CARRIER SMN1	ROH - INTERSTITIAL (15.1 MB; 28.5 MB)
23	MALE	36.3	NG	0.05	0.08	50.3%	49.7%	BIPARENTAL	PARENTAL TRANSLOCATION (10;16)	PARENTAL TRANSLOCATION (10;16)
24	MALE	43.3	15.4 WKS	0.07	0.07	48.3%	58.3%	BIPARENTAL	PGT-A - MONOSOMY 16	PGT-A - MOSOSOMY 16
25	MALE	31.8	13.5 WKS	0.05	0.08	46.30%	50.30%	BIPARENTAL	MATERNAL TRANSLOCATION (9;16)	MATERNAL TRANSLOCATION (9;16)
26	FEMALE	35.3	17.0 WKS	0.08	0.14	50.70%	49.40%	BIPARENTAL	NIPT - TRISOMY 16, IUGR	NIPT - TRISOMY 16

Table 2. Characteristics of cases referred for UPD but shown to be biparental. This table shows the reason for referral and determination to rule out UPD in 16 referred cases. All cases were obtained as amniotic fluid, except case 25, which was obtained as a chorionic villus sample.

Results

In this study, 26 prenatal patients were referred to determine if they had UPD for chromosome 16 (Tables 1 and 2).

- Nine of the 26 prenatal samples analyzed were confirmed to have complete UPD 16. The average MIE in these cases was 9.45 with a range of 6.58 - 12.82. In the biparental cases, the average MIE was 0.09 with a range of 0.04 - 0.17.
- Two UPD cases did not have paternal samples; in those cases, the %AB averaged 99.7% (all of the UPD cases %AB averaged 99.2% with a range of 97.9 - 99.9%). The biparental %AB averaged 51.1% with a range of 45.7 - 64.9%.
- All of the UPD 16 cases were maternal in origin.
- All patients with confirmed UPD had a terminal region of homozygosity (ROH) on chromosome 16 (ranging from 5.87 - 44.88 Mb), compared with only one of 16 patients that demonstrated biparental inheritance.
- Overall, the most common reason for the initial microarray analysis referral was because of a cfDNA finding of trisomy 16. Three of these cases had confirmed UPD 16 and all demonstrated a terminal UPD; whereas the remaining seven with this same referral showed biparental inheritance (and had no terminal UPD).
- While five patients with US abnormalities had confirmed UPD, the abnormalities detected were not consistent among the group and were not associated with a particular pattern. However, one patient in this group was reported to have IUGR, a finding previously suggested to be associated with UPD 16. Four patients in the biparental group also had IUGR.
- None of the PGT-A, CVS trisomy 16 or prenatal translocation 16 referrals demonstrated UPD 16, and none had a terminal ROH.
- In addition, one patient (not included in the discussion above) was referred because of advanced maternal age (AMA). Initial SNP microarray analysis of the fetus revealed a terminal ROH, prompting an SNP-UPD analysis revealing segmental UPD, not involving the entire chromosome that was paternal in origin.

Discussion

UPD 16 has long been of interest because of the suggestion that chromosome 16 may contain imprinted genes and UPD 16 may be associated with phenotypic findings. In this study, we have examined 26 prenatal patients that were referred to the laboratory to determine if a fetus had UPD 16. We determined which of these fetuses had UPD 16, possible ascertainment differences between the groups with and without UPD 16, mechanisms resulting in trisomy 16 and UPD 16, and possible phenotypic consequences of UPD 16.

Ascertainment of patients

Although there are various reasons for initiating UPD studies, the most important indication for UPD testing in this study was the presence of a terminal ROH, as 91% of the patients with a terminal ROH had UPD. Those patients with a terminal ROH and UPD included three of ten patients with an abnormal cfDNA finding and five of ten patients that underwent CMA analysis primarily for ultrasound findings.

Trisomy 16 and UPD mechanism

Trisomy 16 is the most common trisomy identified in humans, occurring in at least 1% of detectable pregnancies and in 7-8% of all spontaneous abortions. Virtually all cases of trisomy 16 are caused by maternal non-disjunction errors in meiosis I, and no other trisomy has as high a proportion of maternal errors. Additionally, trisomy 16 does not appear to be associated with a maternal age effect.

This study is consistent with prior studies in that all cases of UPD 16 were maternal in origin. Additionally, all had a terminal region of homozygosity (either p or q arm), which would be suggestive of crossing-over and an initial meiosis I error. In contrast, only one of 17 biparental cases demonstrated a terminal region of homozygosity, indicating that a terminal ROH is highly correlated with UPD 16 but not indicative of UPD 16.

Phenotype – mosaic trisomy 16 and UPD 16

While non-mosaic trisomy 16 is rarely seen after the first trimester, mosaic trisomy 16 and UPD 16 are detected prenatally and postnatally. It has been suggested that IUGR is specifically associated with UPD 16, but most of the data is inconsistent. In this study, of the nine fetuses determined to have UPD 16, only one showed IUGR, five were ascertained due to abnormal prenatal screening, and there were no consistent phenotypic abnormalities in the four remaining cases with US findings. Indeed, in this study IUGR was detected at a higher frequency in the biparental cases, four of which showed IUGR and were also referred because of abnormal cfDNA testing. Therefore, based on this work and previous studies, it is likely that UPD 16 is not associated with any phenotypic abnormalities and that fetuses with IUGR and prior evidence of trisomy 16 (cfDNA trisomy 16) may have a mosaic trisomy 16 placenta.

Conclusions

This is the largest known study to date of a cohort of patients with UPD 16. The results show that:

- All whole chromosome UPD 16 cases are of maternal origin and display a terminal ROH. This is consistent with maternal meiosis I non-disjunction and crossing-over, followed by trisomy rescue and prior studies of the origin of trisomy 16.
- While the referral indication is important for understanding UPD 16, the occurrence of a terminal ROH appears to be integral.
- We found no evidence of a consistent phenotypic finding with UPD 16. However, five patients (one with UPD, four biparental) had IUGR. This phenotype is more likely to be associated with residual placental trisomy 16 rather than with UPD. This study continues to build on our understanding of UPD 16, its origin and lack of consistent phenotype.

ACMG Annual Clinical Genetics Meeting; March 18-22, 2025; Los Angeles, CA