The yield of fetal Chromosomal Microarray Analysis during pregnancies with an isolated renal malformation

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Background

Chromosomal microarray analysis (CMA) is part of the evaluation of congenital anomalies of the kidney and urinary tract (CAKUT). The prevalence of pathogenic CMA test results in cases of prenatal *isolated* renal malformation is unknown.

Study Objective

To determine the risk of pathogenic CMA results in fetuses with an isolated renal malformation compared to normal pregnancies and to fetuses with combined renal and extra-renal malformations.

Materials & Methods

A single center, retrospective observational study based on medical records of pregnant women who were referred for a prenatal nephro-genetic consultation at the Galilee Medical Center, Israel, between the years 1997-2018. Inclusion criteria were sonographic evidence of fetal CAKUT and performance of CMA during pregnancy. The rate of pathogenic CMA findings was compared between fetuses with isolated renal malformation and fetuses with combined renal and extra-renal malformation. Each group was then compared to the general population based on a national registry which includes 5541 CMA results of fetuses with a normal prenatal ultrasound (Sagi-Dain L et al. Chromosomal microarray vs. NIPS: analysis of 5541 low-risk pregnancies. Genet Med 2019;21(11):2462–7).

CMA results definition:

- Normal: no changes detected
- Pathogenic: detection of pathogenic copy number changes (pCNCs)
- Variants of unknown significance (VOUS) – unclear clinical significance.

Ethics: Approval for the study was obtained from the Galilee Medical Center IRB committee. All authors confirmed the accuracy of the reported data and analysis.

Statistical Analysis

Differences between groups for continuous variables were analyzed using student's two sample T-test or Mann Whitney U test according to the sample size and whether the normality assumption was violated. For ordinal data, Mann Whitney U test. Differences between groups for categorical variables were analyzed using the Chi-square test (with yates correction) or Fisher's exact test (if expectacy<5). The Relative risk measure for pathogenic CMA results was calculated with 95%CI. A two-sided p-value <0.05 was considered to be significant. Analysis was conducted in IBM SPSS version 25.

Results

A total of 70 fetuses were included in this study. Of those, 38 fetuses had an isolated renal malformation and 32 had renal and extra-renal malformations. Pathogenic CMA test results were found in 8 cases (11.4%) with no statistically significant difference between the subgroups within our cohort [5 cases (13.2%) in the isolated renal malformation and 3 cases (9.4%) in the renal and extra renal malformations].

The risk for pathogenic CMA test result in fetuses with isolated renal malformations was higher compared to the control group with normal prenatal sonography (13.2% vs 1.4%, P<0.001) with a relative risk of 10.15 (95% CI 1.63-63.13).

Figure 1 –Study Cohort

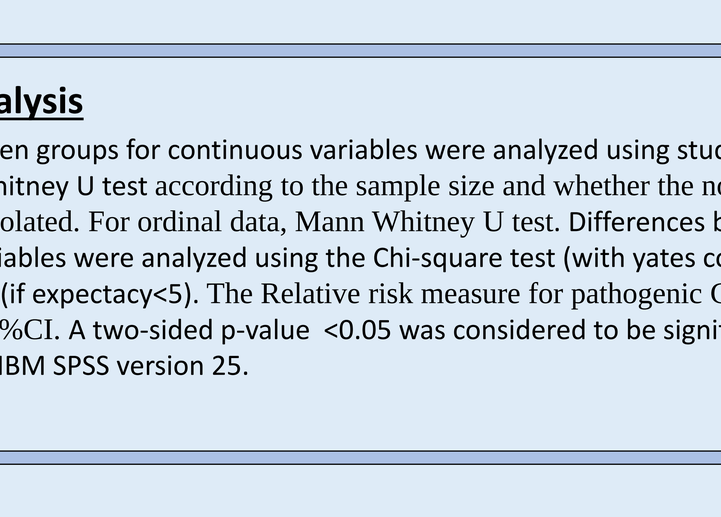

Table 1 – Maternal and clinical characteristics of study cohort

	Total (N=70)	Renal malformations (N=38)	Renal and extra renal malformations (N=32)	P value*
Maternal age, years, mean (SD)	31.5 (4.3)	32.2 (4.3)	30.6 (4.3)	0.144
Maternal Religion. N (%) Jewish Non-Jewish	53 (75.7) 17 (24.3)	33 (86.8) 5 (13.2)	20 (62.5) 12 (37.5)	0.025
Maternal renal disease N (%)	4 (5.7)	3 (7.9)	1 (3.1)	0.620
Maternal use of medication during pregnancy N (%)	12 (17.1)	9 (23.7)	3 (9.4)	0.202
Consanguinity N (%)	4 (5.7)	1 (2.6)	3 (9.4)	0.33
Sibling renal disease N (%)	2 (2.9)	1 (2.6)	1 (3.1)	1
Pregnancy type N (% from valid) Spontaneous IVF PGD Unknown N (% from total)	45 (90) 4 (8) 1 (2) 20 (28.6)	25 (96.1) 1 (3.8) 0 (0) 12 (31.6)	20 (83.3) 3 (12.5) 1 (4.2) 8 (25)	0.215
Number of fetuses N (%) Single Twin	69 (98.6) 1 (1.4)	38 (100) 0	31 (96.9) 1 (3.1)	0.457
Fetal female Gender N (%)	23 (32.9)	12 (31.6)	11 (34.4)	1
Gestational Age at Delivery, weeks, Median (range) Missing data N (%)	39 (29-41) 39 (55.7)	39 (33-40) 24 (63.2)	39 (29-41) 15 (46.9)	0.412
Birth weight (g) mean (SD) Missing data N (%)	3238.5 (552.3) 41 (58.6)	3295.7 (502.9) 23 (60.5)	3177.4 (536.1) 18 (56.2)	0.354

* Comparison between study groups

Table 2 – CMA test results in the study cohort and control group

Groups	Total (N=70)	Isolated renal malformations (N=38)	Renal and extra-renal malformations (N=32)	Normal prenatal US (N=5541)	P value
CMA results N (%)					
No changes detected	58 (82.9)	31 (81.6)	27 (84.4)	---	1*
VOUS	4 (5.7)	2 (5.3)	2 (6.3)	22 (0.4)	1*
pCNCs	8 (11.4)	5 (13.2)	3 (9.4)	78 (1.4)	0.719* <0.001#

CMA – chromosomal microarray analysis; VOUS - Variants of unknown significance; pCNCs - copy number changes;
*P value represents comparison between the 2 study groups: isolated renal malformations and renal and extra-renal malformations
P value represents comparison of pCNCs between the isolated renal malformations group and the control group with normal prenatal ultrasonography.

Conclusions

The risk for a pathogenic CMA test result among fetuses with an isolated renal malformation is higher compared to fetuses with normal prenatal ultrasound. CMA test should be considered in cases of prenatal CAKUT including *isolated* renal malformations.

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