Diagnostic Utility of Chromosomal Microarray Analysis in Neonates:

A Comprehensive Multi-Year Study

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INTRODUCTION

Genomic imbalances are a frequent cause of congenital anomalies in neonates, and result in considerable morbidity and mortality. Although multiple, large studies have confirmed a major role for chromosomal microarray analysis (CMA) in pediatric evaluation, much less data exists specifically for the neonatal population. We undertook a comprehensive genotype-phenotype correlation analysis of all neonatal patients (≤29 days old) referred to our laboratory for CMA.

METHODS

This study included 1564 patients between the ages of 0-29 days over a 4 year period who were evaluated by chromosomal microarray analysis (CMA; 386 by oligonucleotide-aCGH and 1178 by single nucleotide polymorphism array). The reasons for referral and any additional clinical data were codified into phenotypic categories and enumerated.

RESULTS

Overall, clinically significant abnormalities were identified in 278 of 1564 patients (18%). Whole chromosome aneuploidy was identified in 95 cases (6.1%), segmental abnormalities in 178 cases (11.4%), and data suggestive of uniparental disomy (UPD) of an imprinted chromosome in 5 cases (0.32%). Variants of uncertain clinical significance (VOUS) were identified in 134 cases (8.6%), and multiple regions of homozygosity were reported in 60 cases (3.8%) (Table 1).

In terms of genotype-phenotype correlations, 47% of aneuploidy cases were referred for a suspected chromosome abnormality. Of the 178 cases with segmental abnormalities, the most frequent clinical indications included cardiac defects or suspected DiGeorge syndrome (N=58, 37%) and suspected chromosome abnormality in 43 (24%). Many patients had broader referral indications that overlapped two or more of the above categories (Table 2). There were 14 cases in which the abnormality was mosaic; mosaic aneuploidy in 6, mosaic segmental abnormalities in 6 and mosaic UPD in 2.

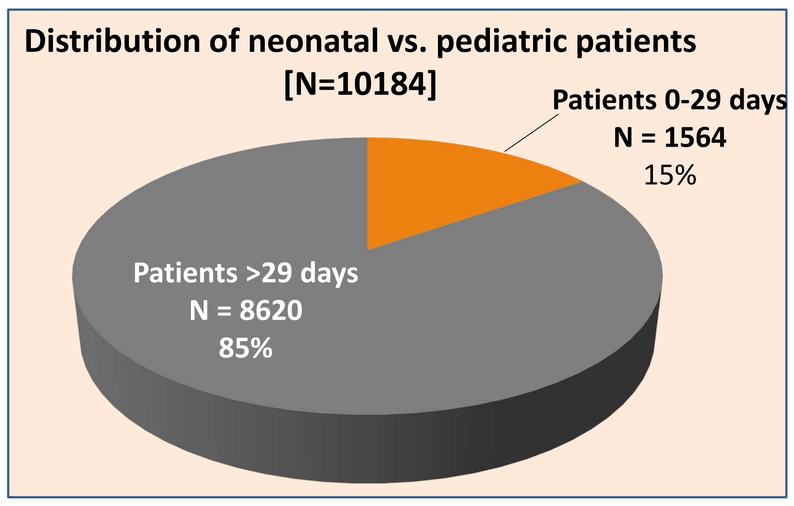


Table 1 *Overall CMA results in 1564 neonates*

CMA Results	N	Percentage
Normal genomic profile	1088	69.6%
Aneuploidy	95	6.1%
Segmental Loss/Gain	178	11.4%
VOUS	134	8.6%
Uniparental isodisomy	9*	0.6%
Multiple Regions of Homozygosity	60	3.8%

**5 cases involved imprinted chromosomes*

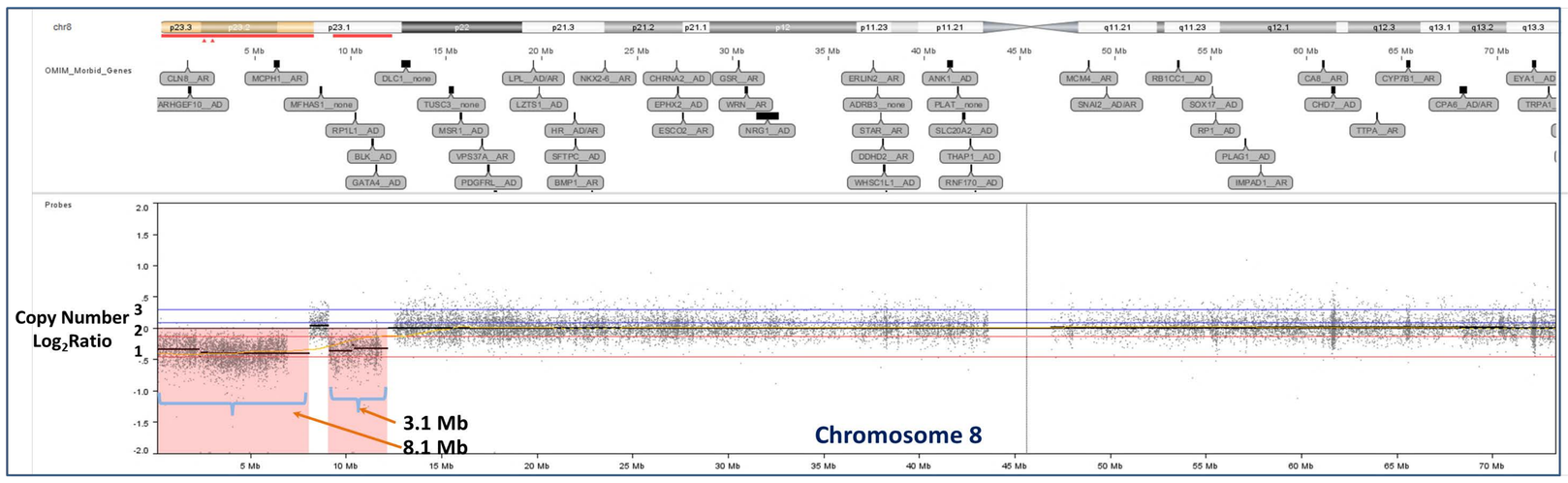
Table 2 *Genotype-Phenotype associations from CMA of neonates and their clinical indications*

GENOTYPE	PHENOTYPE GROUPS												
	EFCAs	MCAs	DFs	CNS	Cardiac	Resp.	GI	GU	Skeletal	Extr.	Head/Face	Growth	Other
Aneuploidy	45	13	6	4	19	3	8	6	1	6	6	2	29
Segmental Abnormalities	43	31	30	34	58	7	10	11	5	14	29	6	25
VOUS	38	21	14	22	35	7	17	6	3	9	13	8	25
UPD	4	0	1	2	1	1	0	1	0	0	1	0	3
≥2 ROHs	13	10	9	19	11	4	2	5	4	3	7	3	12
TOTAL	***143***	***75***	***60***	***81***	***124***	***22***	***37***	***29***	***13***	***32***	***56***	***19***	***94***

[*EFCA: Evaluate for chromosome abnormalities; MCAs: Multiple congenital anomalies; DFs: Dysmorphic features; CNS: Central nervous system; Resp.: Respiratory system; GI: Gastrointestinal system; GU: Genitourinary system; Extr.: Extremities]

Patient A: 1 day old female with diaphragmatic hernia

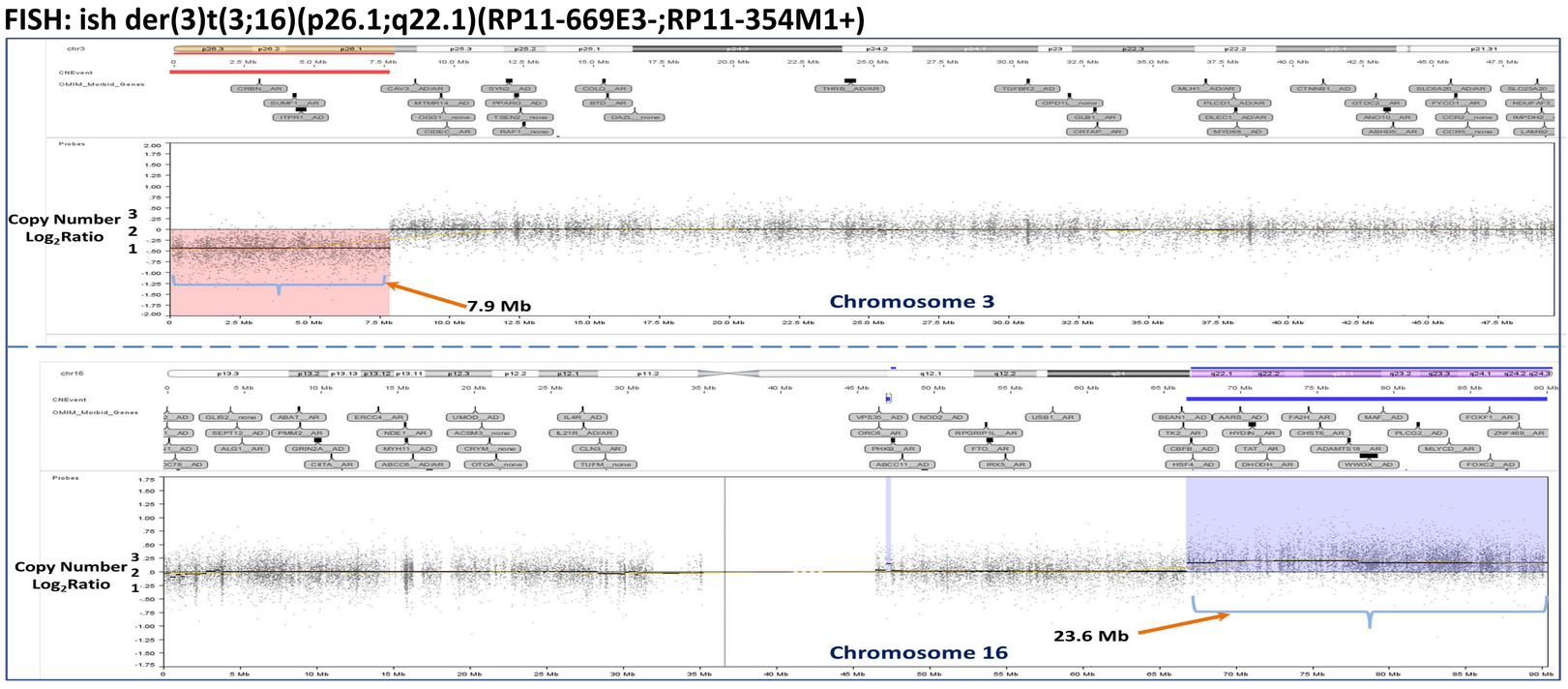
CMA: arr[GRCh37] 8p23.3p23.1(0-8,098,023)x1,8p23.1(9,102,421-12,190,651)x1 (8.1 Mb and 3.1 Mb, respectively)



Patient B: 15 day old female with cardiac anomalies

CMA: arr[GRCh37] 3p26.3p26.1(0-7,893,526)x1,16q22.1q24.3(66,779,149-90,354,753)x3 (7.9 Mb and 23.6 Mb, respectively)

FISH: ish der(3)t(3;16)(p26.1;q22.1)(RP11-669E3-;RP11-354M1+)



CONCLUSIONS

- ❖ SNP-based chromosomal microarray analysis has significant diagnostic value in identifying genomic imbalances in neonates
- ❖ A high detection rate (~18%) is achieved by high-resolution CMA analysis in neonates evaluated for a broad spectrum of syndromic and non-syndromic birth defects
- ❖ Precise and rapid molecular diagnosis by CMA enables appropriate management, making CMA an optimal diagnostic tool for evaluating newborns with abnormal phenotypes