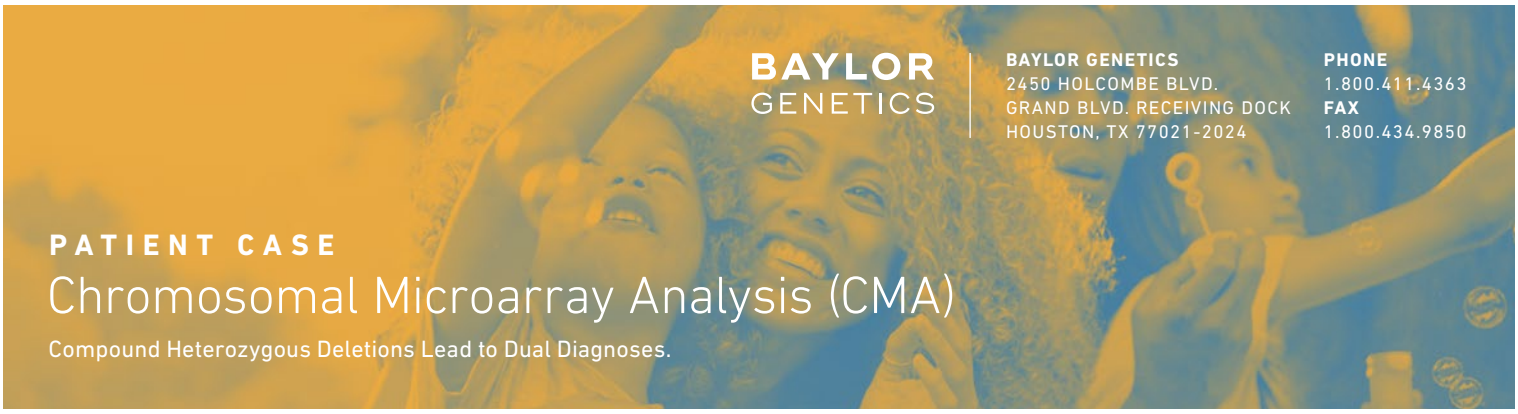

BAYLOR GENETICS

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PATIENT CASE

Chromosomal Microarray Analysis (CMA)

Compound Heterozygous Deletions Lead to Dual Diagnoses.

Initial Presentation:

- Newborn baby boy with tetralogy of fallot

Genetic Tests Performed/differential diagnosis:

- Prenatal cell free DNA-screening was high risk for 22q11.2 deletion syndrome
- Initial differential diagnosis included 22q11.2 deletion syndrome and other chromosomal abnormalities such as Down syndrome associated with congenital heart disease

Findings from CMA:

- CMA using Baylor Genetics' comprehensive array detected compound heterozygous deletions in the long arm of chromosome 22, indicating dual diagnoses
  - The 1st deletion was a 2.5 Mb common deletion at band 22q11.21. Deletions of this region are the cause of 22q11.21 deletion syndrome (also known as DiGeorge Syndrome)
  - The 2nd deletion on the opposite chromosome was a pathogenic .023 Mb deletion encompassing exons 3-9 of the *C22orf25 gene* (also known as *TANGO2*)
    - Of note, the *TANGO2 gene is included in this patient's 2.5Mb deletion causing DiGeorge syndrome*. Thus, CMA showed a homozygous deletion for exons 3-9 of *TANGO2*, which is consistent with a diagnosis of MECRCN
    - Homozygous variants in *TANGO2* cause metabolic encephalomyopathic crises associated with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration (MECRCN) (OMIM # 616878). This homozygous deletion in *TANGO2* has been previously reported in patients with MECRCN (PMID: 26805781)

Impact on Medical Management:

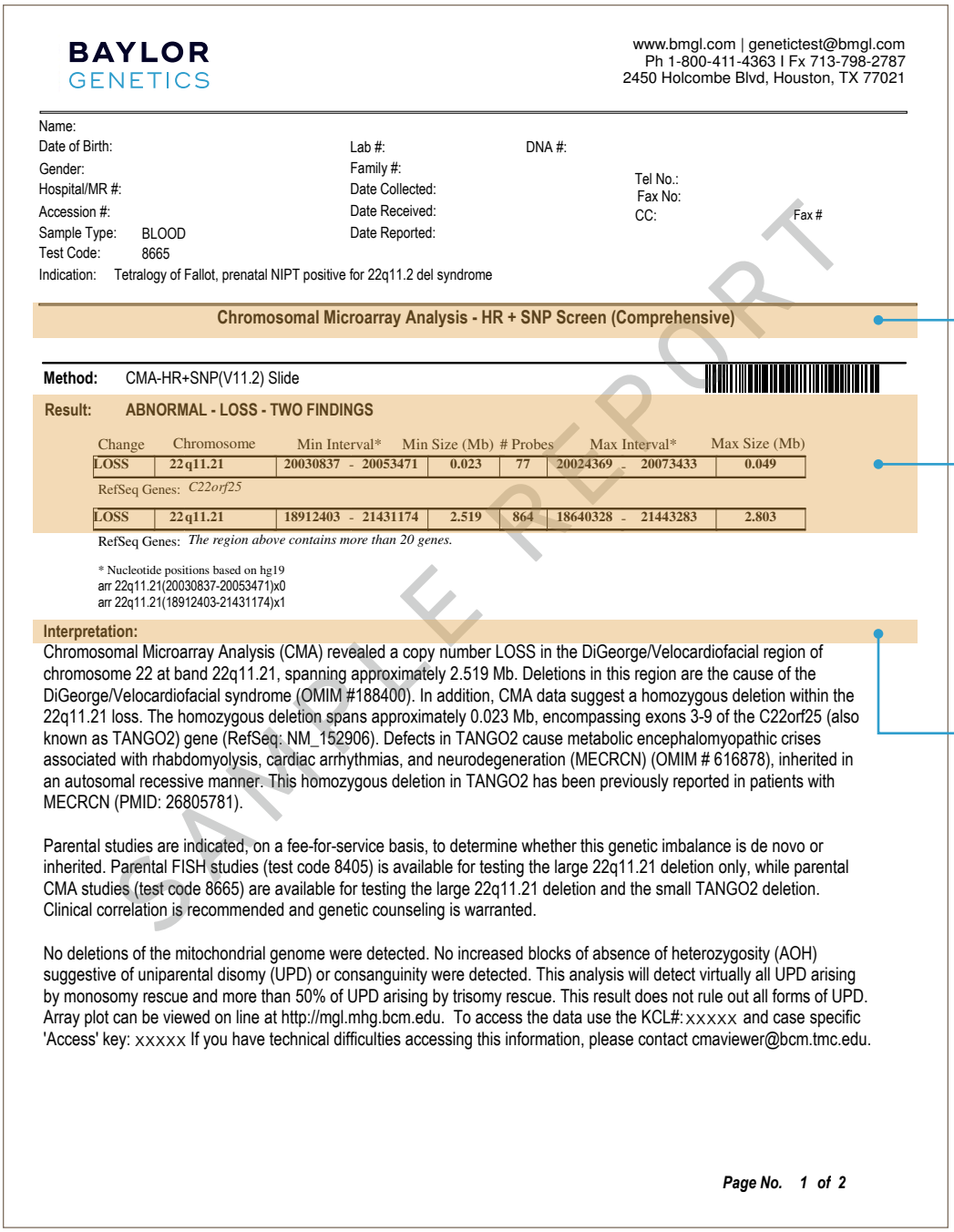
- Patients with MECRCN may benefit from daily supplementation with a multivitamin including all eight B vitamins or a B-complex vitamin
- Additionally, there are clinical practice recommendations for management of children with 22q11.2 deletion syndrome[1]

This patient presented with a narrow phenotype, however actually has complex dual diagnoses. This case demonstrates the ability of CMA to detect multiple CNVs in a single patient, and in this case elucidated an early diagnosis for a disorder where treatment exists.

References:

1. Óskarsdóttir, S., Boot, E., Crowley, T. B., Loo, J. C. Y., Arganbright, J. M., Armando, M., Baylis, A. L., Breetvelt, E. J., Castelein, R. M., Chadehumbe, M., Cielo, C. M., de Reuver, S., Eliez, S., Fiksinski, A. M., Forbes, B. J., Gallagher, E., Hopkins, S. E., Jackson, O. A., Levitz-Katz, L., Klingberg, G., McDonald-McGinn, D. M. (2023). Updated clinical practice recommendations for managing children with 22q11.2 deletion syndrome. Genetics in Medicine: official journal of the American College of Medical Genetics, 25(3), 100338. https://doi.org/10.1016/j.gim.2022.11.006

CMA allowed for the identification of a dual diagnosis in a patient with a narrow phenotype. Parental studies are recommended to determine if either copy number variant was inherited or *de novo*.



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Name:
Date of Birth:
Gender:
Hospital/MR #:
Accession #:
Sample Type: BLOOD
Test Code: 8665
Indication: Tetralogy of Fallot, prenatal NIPT positive for 22q11.2 del syndrome

Lab #:
Family #:
Date Collected:
Date Received:
Date Reported:

DNA #:

Tel No.:
Fax No:
CC: Fax #

Chromosomal Microarray Analysis - HR + SNP Screen (Comprehensive)

Method: CMA-HR+SNP(V11.2) Slide

Result: **ABNORMAL - LOSS - TWO FINDINGS**

Change	Chromosome	Min Interval*	Min Size (Mb)	# Probes	Max Interval*	Max Size (Mb)
LOSS	22q11.21	20030837 - 20053471	0.023	77	20024369 - 20073433	0.049

RefSeq Genes: *C22orf25*

LOSS	22q11.21	18912403 - 21431174	2.519	864	18640328 - 21443283	2.803

RefSeq Genes: *The region above contains more than 20 genes.*

* Nucleotide positions based on hg19
arr 22q11.21(20030837-20053471)x0
arr 22q11.21(18912403-21431174)x1

Interpretation:

Chromosomal Microarray Analysis (CMA) revealed a copy number LOSS in the DiGeorge/Velocardiofacial region of chromosome 22 at band 22q11.21, spanning approximately 2.519 Mb. Deletions in this region are the cause of the DiGeorge/Velocardiofacial syndrome (OMIM #188400). In addition, CMA data suggest a homozygous deletion within the 22q11.21 loss. The homozygous deletion spans approximately 0.023 Mb, encompassing exons 3-9 of the C22orf25 (also known as TANGO2) gene (RefSeq: NM_152906). Defects in TANGO2 cause metabolic encephalomyopathic crises associated with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration (MECRCN) (OMIM # 616878), inherited in an autosomal recessive manner. This homozygous deletion in TANGO2 has been previously reported in patients with MECRCN (PMID: 26805781).

Parental studies are indicated, on a fee-for-service basis, to determine whether this genetic imbalance is de novo or inherited. Parental FISH studies (test code 8405) is available for testing the large 22q11.21 deletion only, while parental CMA studies (test code 8665) are available for testing the large 22q11.21 deletion and the small TANGO2 deletion. Clinical correlation is recommended and genetic counseling is warranted.

No deletions of the mitochondrial genome were detected. No increased blocks of absence of heterozygosity (AOH) suggestive of uniparental disomy (UPD) or consanguinity were detected. This analysis will detect virtually all UPD arising by monosomy rescue and more than 50% of UPD arising by trisomy rescue. This result does not rule out all forms of UPD. Array plot can be viewed on line at http://mgl.mhg.bcm.edu. To access the data use the KCL#: xxxxx and case specific 'Access' key: xxxxx If you have technical difficulties accessing this information, please contact cmaviewer@bcm.tmc.edu.

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Test Name

Key findings summary with copy number variant information. One heterozygous and one homozygous deletion encompassing portions of chromosome 22 were identified.

The findings listed above are further explained including the copy number variants sizes and symptom/ disorder associations.