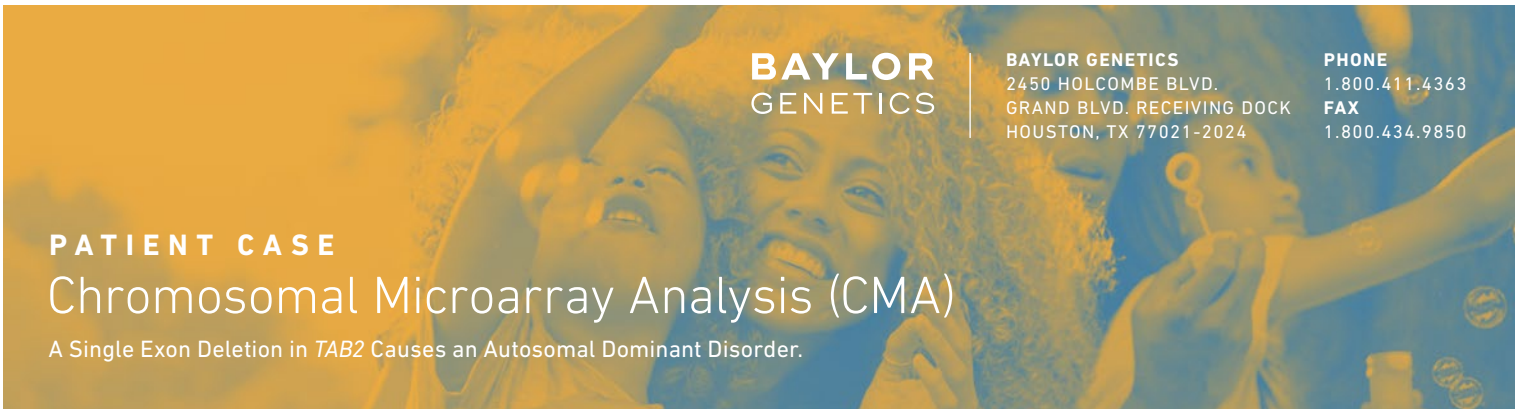

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PATIENT CASE

Chromosomal Microarray Analysis (CMA)

A Single Exon Deletion in *TAB2* Causes an Autosomal Dominant Disorder.

Initial Presentation:

- Newborn baby girl with patent ductus arteriosus and atrial septal defect

Genetic Tests Performed/differential diagnosis:

- The patient had no prior genetic testing
- Initial differential diagnosis included chromosome disorders associated with congenital heart defects

Findings from CMA:

- A comprehensive array with exon level detection of >5000 genes detected a 3 Kb pathogenic deletion encompassing exon 7 (last exon) of the *TAB2* gene within chromosome band 6q25.1
- This final exon deletion includes a portion of the *TAK1* binding domain and the entire highly conserved Np14 zinc finger (NZF) domain. The NZF domain is essential for *TAB2* to activate *TAK1*. Loss-of-function variants in *TAB2* are associated with congenital heart defects, multiple types, 2 (OMIM # 614980), which is an autosomal dominant disorder characterized by variable congenital heart defects, dysmorphic facial features, connective tissue disease, and short stature

Impact on Medical Management:

- The diagnosis can inform medical management and allow the patient to be monitored for potential comorbidities. Parental testing was recommended and would help inform recurrence risk for this family

This case demonstrates the ability of CMA in the detection of small single exon deletions associated with Mendelian disorders that may go undetected by a microarray with a lower resolution.

A high-resolution array with exon by exon coverage of >5000 genes detected a single exon deletion within the *TAB2* gene that explain the patient's current features. Parental studies are recommended to determine if the 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: patent ductus arteriosus, atrial septal defect

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

DNA #:

Tel No.:
Fax No:

Chromosomal Microarray Analysis - HR + SNP Screen (Comprehensive)

Method: CMA (Oligo V12.1) Slide

Result: **ABNORMAL - LOSS - PATHOGENIC**

Change	Chromosome	Min Interval*	Min Size (Mb)	# Probes	Max Interval*	Max Size (Mb)
LOSS	6q25.1	149730442 - 149732992	0.003	5	149724802 - 149751919	0.027

RefSeq Genes: *TAB2*

* Nucleotide positions based on hg19
arr[GRCh37] 6q25.1(149730442_149732992)x1

Interpretation:

Chromosomal Microarray Analysis (CMA) revealed a copy number LOSS within chromosome band 6q25.1 of approximately 3 Kb in size including exon 7 (of 7 total) of the TAB2 gene. This final exon deletion includes amino acids 647-693 (NM_001292034.3), which includes a portion of the TAK1 binding domain and the entire highly conserved Np14 zinc finger (NZF) domain. The NZF domain is essential for TAB2 to activate TAK1, and includes important sites of post-tranlational modifications. Loss of function variants in TAB2 are associated with Congenital heart defects, nonsyndromic, 2 (OMIM: 614980), which is characterized by variable congenital heart defects, facial dysmorphism, connective tissue disease, and short stature. Cardiac defects may present as valvular defects, cardiomyopathy, septal defects, arrhythmias, or complex cardiac defects such as tetralogy of Fallot. Connective tissue disease is variably penetrant and may include hernias, hypermobility, soft velvety skin, aortic or coronary artery dilation, or hearing loss. Parental CMA studies (test code 8665) are recommended, on a fee-for-service basis, to determine whether this genetic imbalance is de novo or inherited. Clinical correlation is recommended, and genetic counseling is warranted.

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.

Disclaimer:
Chromosomal Microarray Analysis (CMA) is a molecular test designed to detect losses or gains representing deletions or duplications for a wide array of clinically significant regions of the human genome. The test will detect virtually all of the cytogenetically defined microdeletion and microduplication syndromes as well as significant exonic changes of selected genes in the nuclear genome. However, CMA will not detect balanced translocations, inversions, point mutations, uniparental disomy, imprinting defects or genomic imbalances in regions not represented in this version of the microarray. The performance of this assay for detection of low-level mosaicism (<10%) has not been established. The failure to detect an alteration at any locus does not exclude the diagnosis of any of the disorders represented on the microarray. Based on the specific version of array used, the reported coordinates for duplications and deletions can differ slightly among family members due to variation in probe coverage between different arrays.

Methodology: DNA samples extracted from the patient's specimen and a genotyped normal control were differentially labeled and co-hybridized to a 400K BGL custom Agilent oligonucleotide array (CMA-HR+SNP) to assay copy number changes in the sample. The average resolution of the array is approximately 10 Kb per probe in the targeted region (with exonic coverage of >4,200 genes) and 30 Kb per probe in the backbone. In addition to exon level copy number, this array also includes 60,000 probes used for SNP analysis for the detection of uniparental disomy (UPD) and absence of heterozygosity (AOH). AOH less than 10 Mb in size will not be reported. Copy number variations (CNVs) <300 Kb with no known phenotypic consequences are relatively common, and may not be reported depending on the gene content of the CNVs and their frequency in our internal database and the publicly available database of genomic variants (DGV). Copy number variations are also cross-referenced in relevant databases including, but not limited to, the Human Gene Mutation Database (HGMD), the DGV, gnomAD and DECIPHER databases, and the scientific literature. Genomic linear positions are given relative to NCBI build 37 (hg19).

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Test Name

Key findings summary with copy number variant information. One heterozygous deletion encompassing a portion of chromosome 6 was identified.

The findings listed above are further explained including the size of the copy number variant and its symptom/disorder association.