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# Prenatal identification of carrier status for autosomal recessive disorders on chromosomal microarray

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## Abstract

**Objective:** Chromosomal microarray (CMA) is primarily used for the diagnosis of chromosomal deletions and duplications that have a direct phenotype based solely on that copy number variation (CNV) without other genetic changes. However, CNVs that contain a gene associated with a recessive disorder confer risk for that disorder should a second pathogenic variant be present in the other copy of the gene. The study aimed to propose a protocol to be considered for follow up testing after the detection of CNV containing an autosomal recessive gene on prenatal sample via chromosomal microarray.

**Methods:** We present 5 cases involving prenatal diagnosis where CMA identified changes in an autosomal recessive gene conferring carrier status and discuss management of this finding.

**Results:** Algorithm of selecting different diagnostic genetic testing after the detection of CNV containing an autosomal recessive gene on prenatal sample via chromosomal microarray has been created to help practitioners involved in this process.

**Conclusion:** We recommend that CNV's involving autosomal recessive genes identified by CMA be treated as any other carrier status. The parents should be encouraged to pursue genetic testing to determine their carrier status of the autosomal recessive conditions and/or additional prenatal diagnostic test on the fetus.

**Keywords:** Prenatal genetic test, autosomal recessive, chromosomal microarray, copy number variation, microdeletion/duplication

## Introduction

Chromosomal microarray is an accepted tool for diagnosis of chromosomal microdeletions and microduplications in both prenatal and post-natal patients.[1, 2] Many of these deletions and duplications present with a known phenotype as a dominant disorder (for example: 7q11.23 deletion for Williams syndrome and 22q11.2 deletion for Velo-Cardio-Facial syndrome).

CMA can also identify areas of homozygosity conferring risk for autosomal recessive disorders, which is usually non-specific to a particular disorder.[3] However, in some cases the microdeletions or microduplications involve recessive disorders and establish carrier status, which is not an unexpected outcome of the chromosomal microarray, but typically not the reason that such testing is elected OMIM (Online Mendelian Inheritance in Man) lists 7889 recessive genes out of approximately 20,000 to 25,000 human genes, therefore is should not be surprising that copy number variations encompass recessive genes. Alabdullatif et al. in 2017 identified 11% of individuals with recessive disorders caused by mutations in regions of homozygosity (ROH) candidate genes in a consanguineous population and increased the overall diagnostic yield of CMA related disorders to 26% from 15% with only pathogenic CNVs and ROHs suggesting uniparental disomy (UPD) in this population. Single nucleotide polymorphism (SNP) microarray detects regions of homozygosity allowing for identification of recessive disorders.[3,4] In one study of 14,574 consecutive microarrays in pediatric patients,[5] 6% of cases were found to harbor one or more ROHs over 10 Mb in

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805 families. Autosomal recessive disorders were confirmed in seven of nine cases from eight families because of the finding of suspected gene within a ROH. This study demonstrates that ROHs are much more frequent than previously recognized (2% in a clinical report of ~3000 cases studied by SNP microarray) and could be attributed to consanguinity, UPD, or simply uncovering previously undetected pregnancies at risk for autosomal recessive disorders. Protocols have yet to be formalized for managing patients who have been unexpectedly identified as a carrier of an autosomal recessive disorder via prenatal CMA.

When a copy number variation is found via prenatal CMA in a recessive gene, genetic counselors and patients face decisions about additional testing, which can be complicated, costly, and time consuming. There is little guidance related to these cases in the medical literature leading to an absence of specific management guidelines. We present 5 cases wherein autosomal recessive carrier status was identified by chromosomal microarray in prenatal specimens and propose a protocol to be considered for follow up testing.

## Methods

Cases were ascertained through routine chart review of patients seen for prenatal genetic counseling. All 5 couples elected invasive prenatal testing (amniocentesis) with SNP chromosome microarray with a copy number variation (CNV) that included a gene associated with a clinically recognized recessive disorder. Follow up information about post-prenatal diagnosis test decisions was known.

SNP microarray analysis was performed using the Affymetrix® Cytoscan® HD array [Affymetrix® and CytoScan® are Registered Trademarks of Affymetrix, Inc.]. which uses over 743,000 SNP probes and 1,953,000 NPCN probes with a median spacing of 0.88 kilobases. Total genomic DNA was extracted from sample type provided and digested with NspI and then ligated to NspI adaptors. PCR products were purified and quantified. Purified DNA was fragmented and biotin labeled and hybridized to the Cytoscan (registered trademark) HD Gene Chip. Data was analyzed using Chromosome Analysis Suite. The analysis was based on the GRCh37/hg19 assembly. The test was developed and its performance characteristics determined by Laboratory Corporation of America. Positive evaluation criteria includes:

1. DNA copy number loss of greater than 1 megabase (Mb) or gain of greater than 2 Mb outside known clinically significant regions with at least one OMIM (Online Mendelian Inheritance in Man) gene.
2. DNA copy gain/loss within or including a known clinically significant gene of 25 kilobases (kb) or greater.

## Results

### Cases

#### Case 1

Patient was referred for prenatal genetic counseling at 13 weeks of gestation due to positive multiple marker biochemical screening indicating increased risk for Down syndrome (1/25) and Trisomy 18 (1/89). Patient elected non-invasive prenatal testing (NIPT), which failed due to low fetal fraction. Patient then elected amniocentesis with karyotype and microarray. Result showed a normal female karyotype of 46,XX and microarray identified a 362 kb deletion of 2p21 that included three OMIM genes: SLC3A1, PREPL, and CAMKMT,. SLC3A1, PREPL, and CAMKMT are associated with hypotonia-cystinuria syndrome and congenital Myasthenic syndrome 22. SLC3A1 is associated with hypotonia-cystinuria, an autosomal recessive disorder that is characterized by neonatal hypotonia, growth retardation, and cystinuria. PREPL is associated with Congenital Myasthenic syndrome 22, an autosomal recessive disorder that is characterized by muscle weakness and developmental delay.

The couple had no remarkable family history, notably no history of muscular or biochemical issues, and no known consanguinity. They reported no history of miscarriage and have two healthy children together.

The couple were offered parental testing for the CNV, and parental and fetal full gene sequencing for the 3 genes in the CNV: SLC3A1, PREPL, and CAMKMT. Couple elected follow up parental CNV testing and fetal full gene sequencing for the 3 genes in the CNV. The deletion was determined identified to be maternal in origin (familial deletion). The patient carries the same 362 kb deletion of 2p21 as the fetus and thus carries the autosomal recessive SLC3A1, PREPL, and CAMKMT gene deletion. Given the remaining possibility of a mutation on the other allele, follow up fetal testing to include full sequencing and deletion/duplication studies of the SLC3A1, PREPL, and CAMKMT genes was requested which required a repeat amniocentesis as sufficient cells for testing were not available from the original amniocentesis specimen. During the ultrasound for the second amniocentesis procedure at 20 weeks gestation, echogenic dilated bowel was visualized. Patient previously had genetic screening for cystic fibrosis for 97 common mutations that was negative. Therefore, in addition to previously planned follow-up testing, fetal infection studies (cytomegalovirus, toxoplasmosis, and parvovirus), a fetal MRI, and CFTR sequencing and deletion/duplication studies were elected by the

patient. Gene sequencing and deletion/duplication via CNV counter with the NGS assay on the fetal sample for CFTR, SLC3A1, PREP1, and CAMKMT revealed the same heterozygous deletion as was previously identified, but no additional pathogenic or likely pathogenic variants or copy number variant was found, predicting that the fetus is a heterozygous carrier for SLC3A1, PREPL, and CAMKMT. Risk was assessed as low risk for these4 recessive disorders. Additionally, while fetal infection studies were negative, fetal MRI showed increasingly dilated bowel loops. The pregnancy proceeded with continuing follow-up ultrasounds and postnatal planning related to the echogenic dilated bowel. The patient was advised to inform family members of their carrier risk and recommendation for genetic counseling and testing prior to reproduction. Pregnancy proceeded uneventfully and was delivered at term. Newborn had mildly dilated loops of bowel but was clinically well.

### Case 2

Patient was referred for follow up genetic counseling at 19 weeks of gestation due to a positive second trimester biochemical screening indicating an increased risk for Down syndrome (1/110). She subsequently elected to have amniocentesis with karyotype and chromosomal microarray for diagnostic results. Results showed a normal male karyotype of 46, XY and microarray identified a 798 kb interstitial deletion of 21q22.3q22.3 that included 11 OMIM genes and was classified as a variant of uncertain significance. Three of the genes deleted: TMPRSS3, RSPH1 and WDR4 are associated with autosomal recessive disorders. TMPRSS3 is associated with autosomal recessive non-syndromic sensorineural hearing loss. RSPH1 is associated with an autosomal recessive form of primary ciliary dyskinesia: A disorder characterized by abnormalities of motile cilia leading to respiratory infections, chronic inflammation and bronchiectasis. WDR4 is associated with recessive conditions including microcephaly, growth deficiency, seizures and brain malformations as well as Galloway-Mowat syndrome type 6.

The couple had a history of 2 pregnancy losses of unknown etiology and a previous pregnancy with trisomy 18 (unknown karyotype). Previously, the couple had normal blood karyotype analysis and reported no known consanguinity. Family history was otherwise unremarkable.

The couple were offered parental testing for the CNV via qPCR, and parental and fetal full gene sequencing and deletion/duplication studies for the genes associated with clinical syndromes: TMPRSS3, RSPH1 and WDR4. Couple elected follow-up parental CNV analysis and fetal full gene sequencing and deletion/ duplication studies for the three known genes of interest listed above. The deletion was identified to be maternal in origin (familial deletion). The patient carries the same 798 kb interstitial deletion of 21q22.3q22.3 as the fetus. Fetal full gene sequencing for the three genes of interest was performed concurrently for parents and fetus and was negative for any additional copy number variants besides the previously known full gene deletions at 21q22.3. The fetus was predicted to be an unaffected carrier for the disorders tested with low risk for the recessive disorder. The couple elected to continue with their pregnancy. The patient was advised to inform family members of their carrier risk and recommendations for genetic counseling and testing prior to reproduction. The pregnancy proceeded uneventfully and a normal newborn at term was delivered.

### Case 3

Patient was referred for genetic counseling at 11 weeks of gestation due to a prior pregnancy with multiple anomalies that was found to have an unbalanced karyotype with der(4)t(4;11)(q32.2;q24.3). She was a 36-year-old G2P0 woman with no other family history. Parental karyotypes were normal and there was no other remarkable family history, suggesting the abnormality found in the previous pregnancy was de novo. Patient elected prenatal diagnosis by chorionic villus sampling with karyotype and chromosomal microarray. Results showed a normal female karyotype of 46,XX, and microarray identified a 265 kb interstitial deletion of 16p12.2 that included 3 OMIM genes: METTL9, IGSF6, and OTOA, which was classified as a female with autosomal recessive gene deletion. The first 2 genes are not associated with a known clinical phenotype. OTOA is associated with autosomal recessive non-syndromic sensorineural hearing loss (Deafness, autosomal recessive 22); both deletions and point mutations within this gene have been found in affected individuals.

The couple had no other remarkable family history, specifically there was no history of hearing loss and no known consanguinity.

The couple were offered parental testing for the CNV via qPCR, and parental and fetal full gene sequencing and deletion/duplication studies for the OTOA gene. Couple elected follow up parental CNV analysis and declined further parental and fetal OTOA testing. The deletion was identified to be maternal in origin (familial deletion). The patient carries the same 265 kb deletion at 16p12.2 as the fetus and thus carries the autosomal recessive OTOA gene deletion. The risk for OTOA-related hearing loss was assessed as an approximate 1% for carrier risk for the partner without the CNV and overall, 2% chance for the fetus to be affected.[6] This risk was acceptable to them,

and they indicated that hearing loss was not an indication for which they would consider termination of pregnancy. The couple elected to continue with their pregnancy. The patient was advised to inform family members of their carrier risk and recommendation for genetic counseling and testing prior to reproduction. The pregnancy continued uneventfully, and a healthy infant was delivered at term. Newborn hearing screening was normal.

### Case 4

The patient was referred for genetic counseling at 12 weeks 6 days of gestation due to advanced maternal age and positive multiple marker biochemical screening indicating increased risk for Down syndrome (1/96). Patient elected amniocentesis with karyotype and chromosomal microarray. Result showed a normal female karyotype of 46,XX and microarray identified a 105 kb interstitial deletion of 4q22.2 that included one OMIM gene: GRID2. The GRID2 gene is associated with spinocerebellar ataxia type 18 (SCAR18). SCAR18 is an autosomal recessive neurologic disorder that is characterized by delayed psychomotor development, severely impaired gait, ocular movement abnormalities, and intellectual disabilities. Rare cases of autosomal dominant inheritance were reported by Coutelier et al. in 2015.[7]

The couple had no remarkable family history, notably no history of neurologic issues and no known consanguinity.

GRID2-related ataxia is a rare condition with an incidence of less than 1 in 1,000,000 (Orphanet: Autosomal recessive congenital cerebellar ataxia due to GRID2 deficiency). The couple was counseled about the low incidence for this disorder.[8] The couple were offered parental testing for the CNV, and parental and fetal GRID2 full gene sequencing and deletion/duplication analysis. The patient elected follow up testing for the CNV for herself and GRID2 analysis for the fetus. Her partner declined all testing. The CNV was identified to be maternal in origin (familial deletion). The patient carries the same 105 kb interstitial deletion of 4q22.2 as the fetus and thus carries the autosomal recessive GRID2 gene deletion. No additional variants were identified in the fetal GRID2 genes. Both the patient and the fetus are predicted to be carriers for SCAR18 with low risk of being affected. The patient was advised to inform family members, including two previous children of their carrier risk and recommendation for genetic counseling and testing prior to reproduction. The pregnancy continued to term uneventfully, and the infant was normal on the newborn period. No postnatal testing was elected.

### Case 5

Patient was referred for genetic counseling at 14 weeks of gestation due to an increased nuchal translucency measurement of 3.8mm. Patient elected amniocentesis with karyotype, chromosomal microarray, and fetal Noonan syndrome testing. Fetal Noonan syndrome testing was normal. Karyotype result showed a normal female karyotype of 46,XX. Microarray identified a 30 kb interstitial deletion of 5q13.2q13.2 that included one OMIM gene: MCCC2. This gene is associated with autosomal recessive 3-Methycrotonyl-CoA carboxylase 2 (3MCC) deficiency, an organic acid disorder where individuals are unable to correctly process the amino acid leucine. This condition has a variable presentation with most individuals being asymptomatic, but it has been described as including infant or childhood-onset episodes of feeding difficulties, hypotonia, lethargy and, if left untreated, can progress to developmental delay and seizures. Of note, this condition is present on the Newborn Screen in California, where the patient planned delivery.

This pregnancy was achieved through in vitro fertilization using a sperm donor due to a history of male factor infertility. Preimplantation genetic testing for common trisomies was performed on the embryo. There was no known consanguinity and no reported biochemical disorders in the patient's family history. Family history information on the donor was not available. Expanded carrier screening was performed on the donor and patient, with no carrier matches identified (the patient was found to be a carrier of phenylalanine hydroxylase deficiency, however the donor was negative). 3MCC deficiency was on the carrier panel performed and both donor and patient screened negative. The residual carrier risk following a negative result in the Caucasian population is 1 in 1,200 based on the residual risk statistics by the genetic test laboratory.

Parental testing for the CNV and fetal testing for 3MCC deficiency with full gene sequencing and deletion/duplication analysis was discussed. After reviewing the natural history of 3MCC deficiency, the residual risks of both genetic parents being carriers in the context of negative expanded carrier screening, and the subsequent risk to the fetus, the couple elected to decline all further parental and fetal testing and continue the pregnancy. The pregnancy continued to term uneventfully. Newborn screening for biochemical disorders was reported as normal and no additional testing was performed.

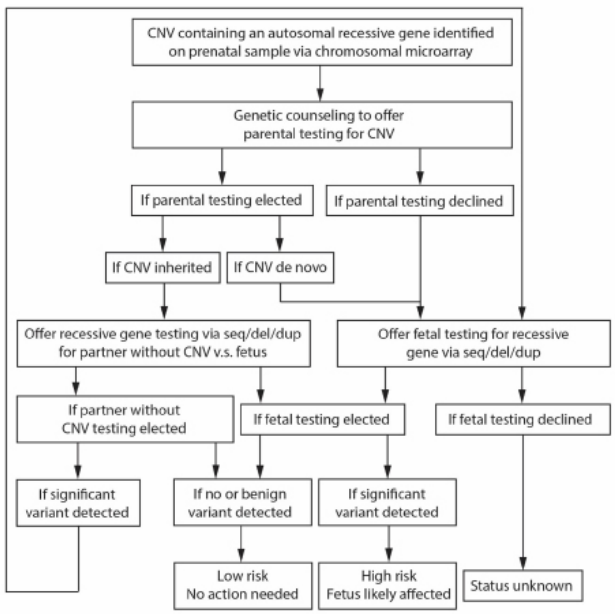


**Fig 1.** Algorithm of selecting different diagnostic genetic testing after the detection of CNV containing an autosomal recessive gene on prenatal sample via chromosomal microarray

## Discussion

Rare autosomal recessive single gene disorders are an important source of morbidity and premature mortality for affected families. When considered collectively, they account for an important public health burden, which is frequently under-recognized.[9] For this reason, it is important to appropriately evaluate pregnant patients when there is increased risk for a recessive disorder. CMA results with copy number variations involving recessive disorders confer such risk.

The issue is that when a CNV containing such a gene is identified, it confers increased risk for such a disorder and a strategy to evaluate this risk should be standard. There have long been recommendations for populations carrier screening for testing of both genetic parents of a pregnancy to assess risk.[10,11] However, this situation is distinct as prenatal diagnosis has already been performed with a fetal sample obtained. We would surmise that couples who elect prenatal diagnosis with chromosome microarray are information seeking and therefore wish to resolve this risk with as much information as possible. We do recognize that the recommendations for additional testing confer increased psychological burden. Review of studies addressing the burden of genetic testing suggest that people tend to consider genetic tests as valid information to take important preventive decisions and that reviewed studies, people experience no significant long-term increase in distress and anxiety, or adverse impacts on quality of life.[12] One issue that we noted is that providing information about the numeric risk is helpful as for couples as most of the disorders are low incidence with low carrier frequency. There are also difficulties with logistics in this testing as there may be limitations on the amount of fetal specimen available for testing (i.e. quantity of DNA) and cost. Additional testing requires additional funding usually requested from insurers or if not authorized, a financial burden may fall on the family. It is also important to acknowledge that all tests have limitations, and that full gene sequencing and duplication/deletion analysis detects most but not all significant gene variants. Depending on the laboratory protocol, there may be a chance that a variant of uncertain significance will be reported causing more concern and less certainty as a false positive without true clinical significance.

As per prior reviews: Genetic tests should be proposed along with proper psychological support and counseling focused on users' genetic health literacy; perception of risk, beliefs about disease controllability, in order to foster fruitful medical decisions.[12]

Based on our experience, we would make the following recommendations, when detecting a CNV that contains a recessive gene:

1. When identified in a prenatal sample, follow up deletion/duplication studies for both genetic parents to determine if the CNV was familial or de novo would be recommended.
2. If the CNV is familial, testing for the gene(s) included in the CNV should be offered for both the other biological parent and fetus, to include full sequencing and deletion/duplication testing. This testing can be done either sequentially, testing the other biological parent first, if time permits, or concurrently if the gestational age of the pregnancy is advanced. Full gene study with sequencing and deletion/duplication studies for the fetus is also a testing option to resolve the CNV.
3. If the CNV is de novo, single gene testing of both genetic parents and/or fetus is appropriate to assess risk.
4. Comprehensive genetic counseling is needed for these families including parents and other family members so that they can fully understand their carrier status and risk for specific autosomal recessive genetic conditions and make informed reproductive decisions for their current situation and future pregnancies.
5. Pre-test counseling prior to diagnostic procedures utilizing CMA should include discussion of the possibility that additional testing may be needed to clarify

the clinical significance when a CNV is identified. This counseling should also include discussion of the natural history and incidence of the disorder in question.

It is our goal that establishing guidelines for the identification of such variants will lead to improved genetic counseling and management for these situations in future.

## Conclusion

Chromosomal microarray is becoming a widely available prenatal diagnostic tool for the diagnosis of genetic disease, and it is being used increasingly in prenatal diagnosis. When a CNV identified by chromosomal microarray includes an autosomal recessive gene, it poses unique challenges for the interpretation of risk to the fetus. Additional genetic testing of the biological parents or the fetus or both is needed to clarify the fetal status.

We have set out a scheme for management of such a result to outline testing that should be recommended to evaluate the situation if additional information is desired by the parents and providers. Genetic testing for such genes in this setting should include full gene sequencing and deletion/duplication analysis to identify if there is a variant within the gene that may confer risk for the related autosomal recessive disorder.

Our supposition is that as chromosomal microarray gets more commonly used so this situation will be more frequent, these recommendations will help practitioners to resolve such a situation.

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