P810

Case report: Incidental diagnosis of Lynch syndrome by prenatal microarray

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Background

Chromosomal microarray is routinely offered to patients undergoing prenatal diagnosis. The increased diagnostic yield of microarray compared to karyotype is well-established in the prenatal setting. Chromosomal microarray may also identify incidental findings unrelated to the indication for testing. We present a case where chromosomal microarray performed due to positive serum screening identified a PMS2 deletion in the fetus, resulting in the incidental diagnosis of Lynch syndrome.

Case presentation

- A 30-year-old G1 patient was referred for genetic counseling to discuss abnormal microarray results from an amniocentesis. The patient pursued prenatal diagnosis due to a positive 1st trimester sequential integrated screen result for Down syndrome.
- Chromosome analysis showed a normal 46,XY karyotype. Chromosomal microarray revealed a pathogenic 136 kb interstitial deletion of chromosome 7p22.1. This region includes a partial deletion of the PMS2 gene, one of the genes associated with Lynch syndrome. The initial microarray result is shown in **Figure 1a.**
- Follow-up parental qPCR studies indicated that the deletion was maternally inherited, therefore diagnosing the fetus and patient with Lynch syndrome. The final microarray result is shown in **Figure 1b.**

Counseling for Lynch syndrome diagnosis:

- A three-generation pedigree was obtained. The patient reported a history of stomach or liver cancer in three grandparents, diagnosed in their 70s and 80s. No other family history of cancer was reported among the patient's parents, aunts and uncles (5 maternal and 7 paternal), and remaining grandparent. The relevant portion of the pedigree is shown in **Figure 2.**
- The patient was counseled that Lynch syndrome is an autosomal dominant hereditary cancer syndrome that increases lifetime cancer risks, primarily for colorectal and endometrial cancers. The recurrence risk for the 7p22.1 deletion and PMS2-associated Lynch syndrome in future pregnancies is 50%. Referral to a cancer genetics specialist was recommended, and the patient was directed to share this information with family members.

Counseling for CMMRD risk:

- Biallelic variants in the PMS2 gene are known to cause constitutional mismatch repair deficiency (CMMRD), an autosomal recessive childhood-onset cancer predisposition syndrome. Digenic inheritance of PMS2 variants with either a POLE or POLD1 variant has also been reported to cause a CMMRD-like phenotype.
- Although the fetal microarray did not identify a second deletion, sequence variants are below the resolution of this analysis. Therefore, full gene sequencing with deletion/duplication analysis of the PMS2, POLE, and POLD1 genes was offered on the fetal sample to rule out a second hit that could result in CMMRD. Testing was also offered to the father of the pregnancy to assess the risk for future pregnancies.
- Fetal testing of the PMS2, POLE, and POLD1 genes was performed and confirmed a heterozygous 68.4 kb pathogenic deletion within the PMS2 gene. No other variants were identified. Additional testing was declined for the father of the pregnancy.

Conclusions

This case highlights the complexities and ethical considerations surrounding pre-test and post-test genetic counseling for chromosomal microarrays in the prenatal setting. Patients should be informed of the potential for incidental findings, which may reveal unexpected genetic risks for both the fetus and parents. The risk for autosomal recessive conditions associated with hereditary cancer susceptibility genes also presents a unique post-test counseling challenge, requiring extensive counseling and additional testing for the couple and pregnancy. Finally, this case raises ethical considerations regarding the detection of adult-onset conditions on prenatal microarrays. Many professional societies have issued position statements recommending against prenatal genetic testing for known adult-onset conditions if pregnancy or childhood management will not be affected.

In this case, the incidental diagnosis of Lynch syndrome in a fetus raises concerns for the child's future autonomy. However, that must be weighed against the beneficence of diagnosing Lynch syndrome in a patient whose family history would not otherwise have prompted consideration of testing. The couple has been empowered in their reproductive decision-making, as they seek to pursue preimplantation genetic testing for future pregnancies. The patient's diagnosis may also benefit the extended family by prompting cascade testing in relatives.

Test: **Direct Prenatal SNP CMA**

Genotyping Targets: 2695000 Array Type: SNP

MICROARRAY RESULT: 136 KB INTERSTITIAL DELETION OF 7P22.1->7P22.1

INTERPRETATION: MALE WITH PATHOGENIC DELETION

arr[hg19] 7p22.1(5,986,514-6,122,672)x1

The whole genome SNP microarray (Reveal) analysis identified a **male** with an interstitial deletion of the chromosomal segment listed above.

This interval includes 3 OMIM genes (*PMS2, AIMP2, EIF2AK1*). Deletions and sequence variants in *PMS2* are associated with Lynch syndrome (OMIM: 600259), which is characterized by an increased risk for colorectal cancer and other tumors including the GI, urological, female reproductive tract, and skin (see references). Clinical management recommendations for *PMS2* may be found at NCCN.org.

Figure 1a. Prenatal microarray result showing the fetal 7p22.1 deletion, including a partial deletion of the PMS2 gene.

Test: **Reveal (SM) Adjunct Microarray**

Genotyping Targets: 2695000 Array Type: SNP

MICROARRAY RESULT: 136 KB INTERSTITIAL DELETION OF 7P22.1->7P22.1

INTERPRETATION: MALE WITH FAMILIAL INHERITANCE OF DELETION

PROBAND UPDATE

rsa[hg19] 7p22.1(6,068,289-6,068,422)x1 mat.
arr[hg19] 7p22.1(5,986,514-6,122,672)x1

Follow-up qPCR analysis targeting the **deleted** region on chromosome 7 found in the **prenatal** analysis revealed the same copy number change in the familial analysis.

Deletions and sequence variants in PMS2 are associated with Lynch syndrome (OMIM: 600259), which is characterized by an increased risk for colorectal cancer and other tumors including the GI, urological, female reproductive tract, and skin. Clinical management recommendations for PMS2 may be found at NCCN.org.

Figure 1b. Prenatal microarray result showing maternal inheritance of the 7p22.1 deletion.

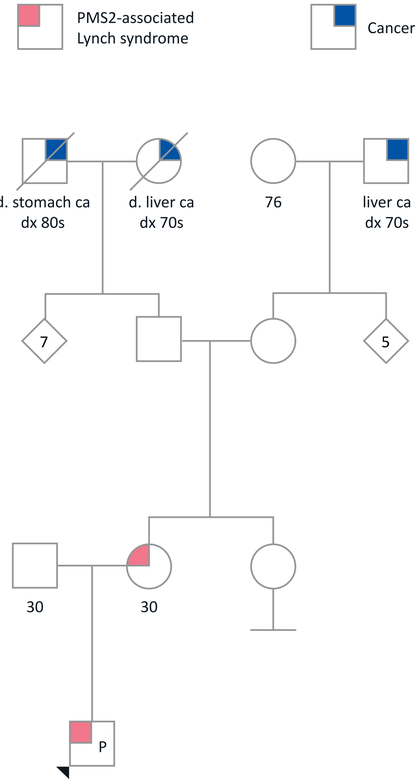

Figure 2. Relevant portion of the pedigree, showing the patient's cancer family history and the recent diagnosis of PMS2-associated Lynch syndrome for the fetus and patient.

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