PRE390

Identification of a duplication on chromosome 21 in a pregnant patient through prenatal cell-free DNA screening over multiple pregnancies

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1. Introduction

Prenatal cell free DNA (cfDNA) screening is a widely used method to screen for fetal aneuploidies in pregnancy. While designed to identify fetal aneuploidies, deletions and duplications present in the pregnant patient have also been identified through cfDNA. To provide reliable results and limit false positives and false negatives, a cfDNA screen should be able to differentiate between findings of patient origin and fetal origin in order to correctly interpret fetal status. Here we present a case of chromosome 21 (chr21) duplications found in the same pregnant individual across three separate pregnancies, one singleton, one affected singleton with trisomy 21, and a twin pregnancy, without precluding the interpretation of fetal aneuploidy.

2. Methods

Patient blood samples submitted for cfDNA screening were subjected to DNA extraction, library preparation, and whole genome massively parallel sequencing (MPS) as described by Jensen et al.[1] Samples were retrospectively reviewed for the presence of a chr21 duplication suspected to originate in the patient, then compared to diagnostic results obtained from the clinical provider or via diagnostic samples submitted to Labcorp for confirmation.

3. Case Report

Following retrospective review of patients identified as having a chr21 duplication on cfDNA screening, we identified one patient in which two chr21 duplications were identified in three separate pregnancies. These duplications were outside the scope of testing and were of limited clinical utility, therefore they were not included on the report or communicated to the provider. The patient initially presented at age 35 and underwent cfDNA screening at 13 weeks gestation. CfDNA screening using MPS for trisomies 21, 18, and 13 (T21, T18, T13) was negative. Review of cfDNA trace data (**Figure 1**) identified two duplications on chr21 of ~0.8 Mb and ~0.35 Mb in size suspected to be of patient origin. Results were confirmed as a euploid pregnancy through birth outcome. Less than two years later, the same patient was referred for cfDNA screening at 9 weeks gestation. CfDNA screening using MPS for T21, T18, T13, and sex chromosome aneuploidies was positive for T21. The cfDNA trace data (**Figure 2**) identified the same two chr21 duplications of ~0.8Mb and ~0.35Mb suspected to be of patient origin. A true positive for T21 was confirmed in the fetus through karyotype on amniocentesis. Following these pregnancies, the patient was again referred for cfDNA screening in a twin pregnancy at 9 weeks gestation. CfDNA screening using MPS for T21, T18, and T13 was negative. The cfDNA trace data (**Figure 3**) again identified the same two chr21 duplications of ~0.8 Mb and ~0.35 Mb suspected to be of patient origin. Results were confirmed as a euploid twin pregnancy through birth outcome.

4. Conclusions

While intended to identify fetal aneuploidies, it is possible for cfDNA to also identify findings, such as a deletion or duplication, which are suspected to originate in the pregnant patient. These findings could impact the interpretation for fetal aneuploidy. In these cases, the cfDNA screen should be able to differentiate between these findings of patient versus fetal origin to enable appropriate interpretation of the fetal status. The patient presented in this case report was found to have the same two duplications on chr21 in each of three separate pregnancies. These duplications were outside the scope of testing and were of limited clinical utility, therefore they were not included on the report or communicated to the provider. The patient's three separate analyses illustrate the ability of cfDNA screening at one lab to reliably predict both an affected pregnancy and unaffected pregnancy despite a finding on the same chromosome derived from the pregnant patient. This demonstrates that with proper laboratory algorithms and experienced laboratory personnel, small copy number variants in the pregnant patient may not always preclude interpretation for fetal status for the whole chromosome or result in false positive or false negative results.

Figures

Figure 1. Trace data for the patient's first pregnancy illustrating two duplications of chr21 suspected to be of patient origin, shown in mauve.

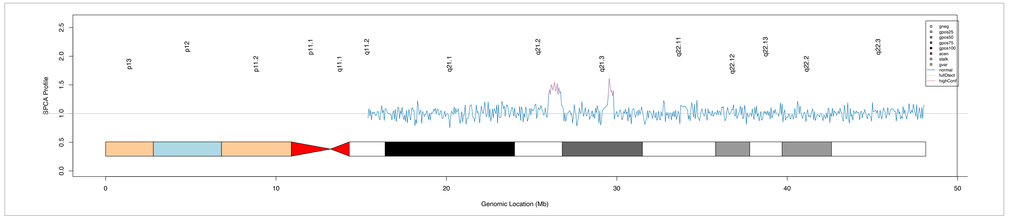


Figure 2. Trace data for the patient's second pregnancy illustrating trisomy 21 in the fetus, shown in mauve, and two duplications of chr21 suspected to be of patient origin, shown in blue.

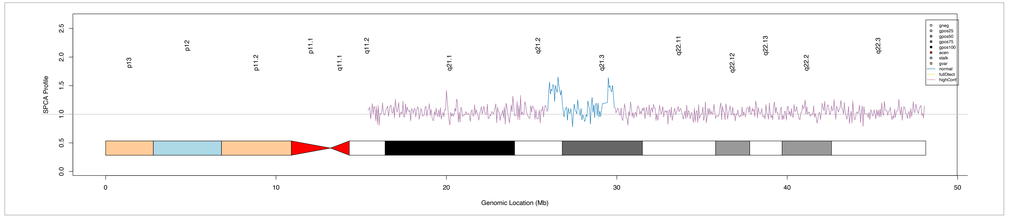
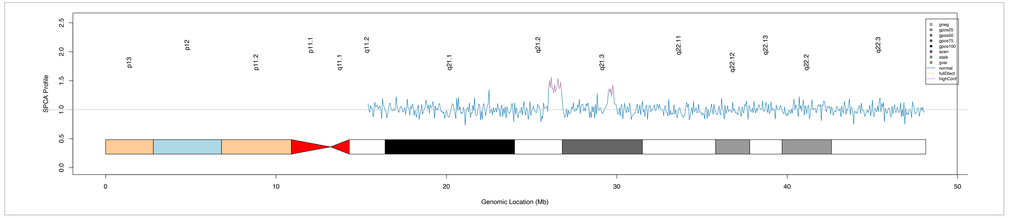


Figure 3. Trace data for the patient's third pregnancy, a twin pregnancy, illustrating two duplications of chr21 suspected to be of patient origin, shown in mauve.



References

1. Jensen TJ, Zwiefelhofer T, Tim RC, et al. High-throughput massively parallel sequencing for fetal aneuploidy detection from maternal plasma. *PLoS One*. 2013; 8(3):e57381. doi:10.1371/journal.pone.0057381. Epub 2013 Mar 6.

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