Prenatal Diagnosis of Microduplication of Fetal Chromosome 17 Following Noninvasive Prenatal Testing

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Case Report

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Abstract

Background

Chromosome 17q12 duplication syndrome is a disease caused by the complete or partial duplication of q12 in the long arm of chromosome 17, there were no cases reported about the prenatal diagnosis of the syndrome. Most of the fetal phenotype of the syndrome may not be evident during the pregnancy, which means the syndrome was only be discovered accidentally or missed during the prenatal examination.

Objective

Noninvasive prenatal testing (NIPT) is widely used in the screening of common fetal chromosome aneuploidy. However, reports on chromosomal microduplication and microdeletion are rare. The aim of the study was to investigate the application value of NIPT for the detection of chromosomal microduplication.

Case presentations:

We found two cases of microduplication in the long arm of chromosome 17(17q12), they were first detected by NIPT and then were further diagnosed by copy number variation (CNV) analysis based on chromosome microarray analysis (CMA). The CMA results of prenatal diagnosis showed that the microduplications in 17q12 (one was 1.5Mb, the other was 1.9Mb) were consistent with the NIPT results. The amniotic fluid karyotype analysis showed no abnormalities. Finally, because it was pathogenic copy number variant, both of the parents chose to terminate the pregnancy.

Conclusion

In the study, two cases of microduplication fragment in the long arm of chromosome 17 were detected by NIPT and were confirmed by CMA. To our knowledge, this is the first report of prenatal diagnosis of chromosome 17q12 duplication syndrome following NIPT. This suggests that NIPT is an effective method to screen chromosome microduplications in prenatal diagnosis, especially for the chromosome 17q12 duplication syndrome.

1. Background

Fetal chromosomal abnormality is one of the most important causes of neonatal birth defects. Due to its high sensitivity and specificity, noninvasive prenatal testing (NIPT) is widely used in the prenatal screening of common fetal chromosome aneuploidy, including trisomy 21, trisomy 18 and trisomy 13[1, 2]. However, according to the reports, there are more than 1600 species syndromes which are caused by chromosomal microduplication or microdeletion, and more than 1% are pathogenicity or suspected

pathogenicity. Actually, NIPT can detect all chromosomes due to the low-coverage whole genome sequencing of maternal plasma cell-free DNA. Recently, chromosomal microduplication or microdeletion were also be reported could be detected by NIPT[3].

Chromosome 17q12 duplication syndrome is a disease caused by the complete or partial duplication of q12 in the long arm of chromosome 17. There is no specific treatment for the syndrome, so the prenatal diagnosis is significant for early management and prevention. As the clinical phenotypes of the fetus during the pregnancy were not evident, majority cases were missed or maybe discovered by accident. The prenatal diagnosis of the syndrome still presents as a challenge because of its untypical clinical phenotypes.

In our prenatal diagnosis center, we found two cases of mid-pregnancy patients with abnormal chromosome 17 duplication. The NIPT results suggested that 2.0Mb microduplication was in chromosome 17. Karyoutype analysis and CMA were used to confirm the clinical value of NIPT in chromosome microduplication.

2. Case Presentations

One patient was 32-year-old with a single fetus (pregnancy 1, parturition 0) at gestational age of 18 weeks 6 days. The other one was in the same situation as the first patient, except that she was 33-year-old and gestational age was 21 weeks 6 days. The fetal developmental mileages were normal and the ultrasound findings were normal during the whole pregnancy.

After genetic counseling and informed consent, two patients received NIPT in the prenatal diagnostic center of Changzhou Maternity and Child Health Care Hospital Affiliated to Nanjing Medical University. The results showed that 21-trisomy, 18-trisomy, 13-trisomy were negative, but a microduplication of about 2.0Mb was found in the long arm of chromosome 17 at q12. After the recalling and genetic counseling again, both of them accepted the prenatal diagnosis. Therefore, prenatal diagnosis were carried out after amniocentesis with karyotype and chromosomal microarray analysis (CMA). The karyotype analysis showed no abnormalities. This duplication fragment, confirmed by CMA, was pathogenic. The incomplete penetrance rate was 21%. Finally, both of the two patients chose induced labor.

3. Materials And Methods

3.1 Noninvasive prenatal testing

A sample of whole blood (8 mL) was collected from all study participants and placed in an EDTA anticoagulant tube. These samples were centrifuged within 8 hours to extract the plasma. Low-pass (×0.1 genome coverage) massively parallel sequencing on the NextSeqCN500 platform (Illumina, USA) was performed in all cases. The detailed technical procedure was reported previously [4] .

3.2 Chromosome karyotype analysis

Following the principle of informed and voluntary, karyotype analysis were performed as described previously[5]. The amniocentesis was performed under the guidance of ultrasound in pregnant women. Then, two technicians dependently performed karyotyping using the GSL-120 instrument (Leica Biosystems Richmond, Inc.) and CytoVision Automated Cytogenetics Platform software. At least five cell karyotypes were analysed, and 20 karyotypes were counted.

3.3 Chromosomal microarray analysis (CMA)

Amniotic fluid (10 mL) was collected, and genomic DNA was extracted using a QIAamp DNA Blood Mini Kit (Qiagen Inc., Valencia, CA), amplified (250 ng), labelled, and hybridised to a CytoScan HD array platform (Affymetrix) according to the manufacturer's protocol. A single nucleotide polymorphism (SNP) array test was performed using a CytoScan 750K microarray chip (Affymetrix). After hybridisation, the chip was washed with buffer and scanned using a laser scanner. The data were analysed using Chromosome Analysis Suite ver. 3.0 (ChAs) software[6].

4. Results

4.1 Noninvasive prenatal testing

NIPT results suggested the Z-score of chromosome 17 was 8.97 and showed that there was a duplication of 2 Mb (34,500,000–36,499,999), indicating that chromosome 17 had a duplication of fetal DNA fragments in patient one. There was a same duplication of 2 Mb in chromosome 17 at the same region as the first patient except for a Z-score of 7.49 in patient two (Fig. 1).

4.2 Chromosome karyotype analysis

Both of them had no obvious abnormalities in fetal chromosome structure after amniotic fluid karyotype analysis (Fig. 2).

4.3 Chromosomal microarray analysis (CMA)

The CMA analysis results were a little different in the size of duplication fragments. One showed arr[hg19] 17q12(34,440,088 – 36,311,009)x3, indicating a duplication of about 1.9Mb on chromosome 17q12, containing 23 OMIM genes. The other was arr[hg19] 17q12(34,822,465 – 36,351,919)x3, which means a duplication of about 1.5Mb on chromosome 17q12, including 17 OMIM genes(Fig. 3). Features associated with this duplication encompass some combination of cognitive impairment, speech and motor developmental delay, brain anomalies, dysmorphic facial features, behavioral abnormalities (such as aggression or selfinjury), esophageal atresia, renal anomalies, epilepsy, and others[12]. The pre-diagnosis CMA was consistent with the NIPT results.

5. Discussion

Copy number variants at chromosome 17q12 including deletions and duplications have been associated with a spectrum of phenotypes. They are two distinct chromosomal aberrations. Deletions are well described and duplication is emerging as a new genetic syndrome. It has been reported that the estimated prevalence of patients with 17q12 deletion was 1.6 per 1,000,000 citizens, and the 17q12 duplication was 4.6 per 1,000,000 citizens in Denmark at the end of 2014. There was no other national prevalence data been reported. Recurrent genomic rearrangements of chromosome region 17q12, ranging from ~ 300 to ~ 2.1 Mb, have been described to be associated with a variable clinical phenotypes, including autism, behavioral abnormalities, facial dysmorphism, renal disease, joint laxity, esophageal atresia, anal atresia and endocrine abnormalitiesa. Neurological symptoms were the most common features associated with 17q12 duplications, including learning disability, seizures, and structural brain anomalies[7–15]. The incomplete penetrance rate was 21%.

Currently, all studies about 17q12 duplications are limited to phenotyped patients with 17q12 duplication or the family who was recruited through the identification of a duplication of 17q12 in the proband. There were no reports about prenatal screenings and diagnoses of 17q12 duplications. We analyzed the reason was that it was hard to find the fetal cases. At present, the detection techniques for fetal chromosome microdeletions and microduplications mainly include FISH and CMA. Because of the invasiveness and a 1%-3% risk of abortion, these techniques only be used as clinical diagnostic tools[16], not as clinical screening tools, and there are lots of strict restrictions before the amniocentesis, not just anyone who wants to do it.

As described above, different patients of the 17q12 duplication syndrome may have different phenotypes. Neurological symptoms (including learning disabilities, delayed language development and so on) were the most common features associated with 17q12 duplications, which means the ultrasound results usually would be normal during all the whole pregnancy period, and because of no obvious ultrasound indication, the patients are not allowed to perform the amniocentesis. So more effective methods of screening are needed for detecting the 17q12 duplication syndrome.

NIPT, as a new prenatal screening method, has many advantages, concluding a simple and noninvasive operation and a relatively easy quality control[17].NIPT is becoming more and more accepted by clinicians and patients. We have known that it is very efficient and accurate for the detection of common fetal chromosome aneuploidy, especially for chromosome 13, 18 and 21. Recently, some studies have found that NIPT through deeper sequencing can screen some microdeletions and microduplications, which are greater than 300 Kb in fetal genomes[18–22]. However, there are no reports of 17q12 duplication syndrome screened by NIPT previously.

In our study, we have successfully used NIPT to detect two patients with microduplications of about 2 Mb in fetal chromosome 17, then CMA was used to further pinpoint the specific duplication regions, confirming the results of NIPT. This chromosome 17q12 duplication syndrome would be missed if the two patients did not choose NIPT as their prenatal testing, which means NIPT maybe gave a clue for the possibility of chromosome abnormity.

Our cases indicated that NIPT was also useful as a clue to the chromosome microdeletions and microduplications.

6. Conclution

We reported the first cases of prenatal diagnosis of 17q12 duplication syndrome following the NIPT, which indicates that NIPT can detect fetal chromosome 17 abnormalities, including microduplications. The clinical application of NIPT screening can give a clue for the possibility of chromosome abnormity, reduce the number of invasive prenatal diagnoses, reduce the incidence of related abortion, and significantly improve the detection rate of fetal chromosomal abnormalities, including microduplications.

Declarations

Ethics Approval and Consent to Participate

The study design and protocol were reviewed and approved by the ethics committee of Changzhou Maternity and Child Health Care Hospital affiliated to Nanjing Medical University (No. 2017003). All pregnant women received genetic counseling and signed a written consent before the test.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

All data generated or analyzed during this study are included in the published article.

Competing Interest

The authors declare that they have no competing interests.

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Authors' contributions

Bin Zhang conceived and designed the experiments. Ye Shi and Fang-xiu Zheng, Jing Wang and Bin Zhang performed the experimental work. Qin Zhou and Ying-ping Chen performed the amniocentesis and were responsible for clinical consultation. Fang-xiu Zheng and Jing Wang analysed the data. Ye Shi contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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References

1. Allyse MA, Wick MJ. Noninvasive prenatal genetic screening using cell-free DNA. JAMA.2018;320(6):591-2.
2. Nshimyumukiza L, Menon S, Hina H, et al. Cell-free DNA noninvasive prenatal screening for aneuploidy versus conventional screening: a systematic review of economic evaluations. Clin Genet. 2018;94(1):3-21.
3. Hu H, Wang L, Wu J, et al. Noninvasive prenatal testing for chromosome aneuploidies and subchromosomal microdeletions/microduplications in a cohort of 8141 single pregnancies. Hum Genomics.2019;13(1):14.
4. Gregg AR, Skotko BG, Benkendorf JL, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet Med. 2016;18(10):1056-1065.
5. Yu B, Lu BY, Zhang B, et al. Overall evaluation of the clinical value of prenatal screening for fetal-free DNA in maternal blood. Medicine (Baltimore) 2017;96:e7114.
6. Jing Wang, Zhi-Wei Wang, Qin Zhou,et al. Lower detectability of non-invasive prenatal testing compared to prenatal diagnosis in high-risk pregnant women. Ann Transl Med 2019;7(14):319.
7. Bierhals T, Maddukuri SB, Kutsche K, et al. Expanding thephenotype associated with 17q12 duplication: Case report and review of the literature. Am J Med Genet Part A. 2013;161A:352-359.
8. Brandt T, Desai K, Grodberg D, et al. Complex autism spectrumdisorder in a patient with a 17q12 microduplication. Am J Med Genet Part A. 2012; 158A:1170-1177.
9. Faguer S, Decramer S, Chassaing N, et al. Diagnosis, management, and prognosis of HNF1B nephropathy in adulthood. Kidney Int. 2011;80:768-776.
10. Hardies K, Weckhuysen S, Peeters E, et al. Duplications of 17q12 can cause familial fever-related epilepsy syndromes. Neurology. 2013;81:1434-1440.
11. Mefford HC, Clauin S, Sharp AJ, et al. Recurrent reciprocal genomic rearrangements of 17q12 are associated with renal disease, diabetes, and epilepsy. Am J Hum Genet 2007;81:1057-1069.
12. Mitchell E, Douglas A, Kjaegaard S, et al. Mefford HC. Recurrent duplications of 17q12 associated with variable phenotypes. Am J Med Genet A. 2015; 167A:3038-3045.

13. Nagamani SC, Erez A, Shen J, et al.2010. Clinical spectrum associated with recurrent genomic rearrangements in chromosome 17q12. Eur J Hum Genet. 2010;18:278-284.
14. Smigiel R, Marcelis C, Patkowski D, et al. Oesophageal atresia with tracheoesophageal fistula and anal atresia in a patient with a de novo microduplication in 17q12. Eur J Med Genet. 2014; 57:40-43.
15. Szatkiewicz JP, O'Dushlaine C, Chen G, et al. 2014. Copy number variation in schizophrenia in sweden. Mol Psychiatry. 2014;19:762-773.
16. Valayatham V, Subramaniam R, Juan YM, et al. Indications for invasive prenatal diagnostic procedures at a dedicated fetal medicine centre: an 8 year audit 2003–2010. Med J Malaysia.2013;68(4):297-300.
17. Gil MM, Quezada MS, Revello R, et al. Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol.2015;45(3):249-266.
18. Srinivasan A, Bianchi D, Huang H,et al. Noninvasive detection of fetal subchromosome abnormalities via deep sequencing of maternal plasma. Am J Hum Genet. 2013;92(2):167-176.
19. Lo YM, Chan KC, Chiu RW. Noninvasive fetal trisomy 21 detection using chromosome-selective sequencing: a variation of the molecular counting theme. Expert Rev Mol Diagn. 2012;12(4):329-331.
20. Yao H, Zhang L, Zhang H, et al. Noninvasive prenatal genetic testing for fetal aneuploidy detects maternal trisomy X. Prenat Diagn.2012;32(11):1114-1116.
21. Bianchi DW, Parsa S, Bhatt S, et al. Fetal sex chromosome testing by maternal plasma DNA sequencing: clinical laboratory experience and biology. Obstet Gynecol. 2015;125(2):375-382.
22. Phan MD, Vo BT, Nguyen TV, et al. Reducing false positive rate of fetal monosomy X in non-invasive prenatal testing using a combined algorithm to detect maternal mosaic monosomy X. Prenat Diagn. 2019, Epub;39(4):324-327.

Figures

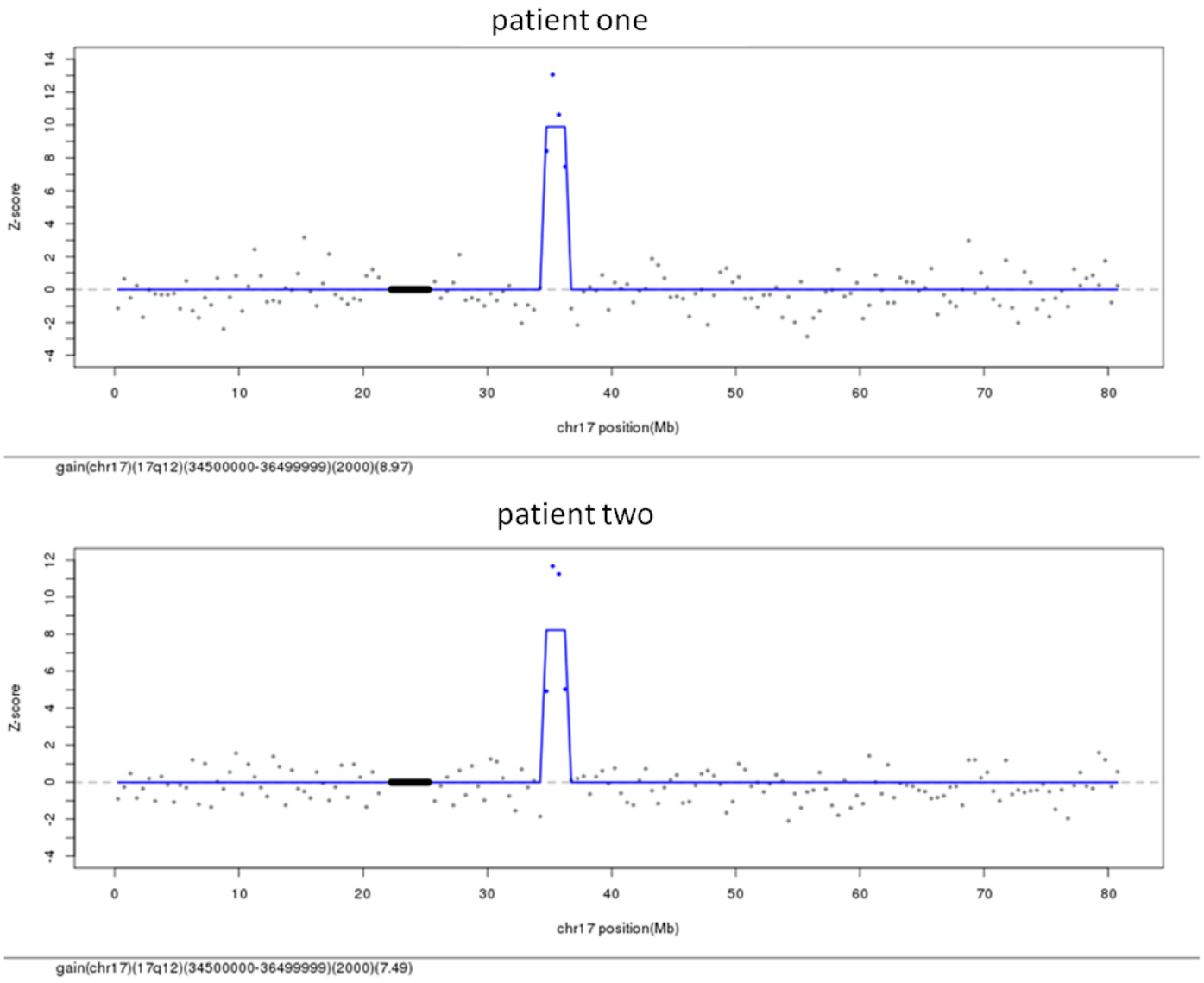

Figure 1

NIPT studys of maternal plasma showing a Z-score of 8.97/7.49 for fetal chromosome 17 and a duplication of 2 Mb from 34.5Mb-36.5Mb region.

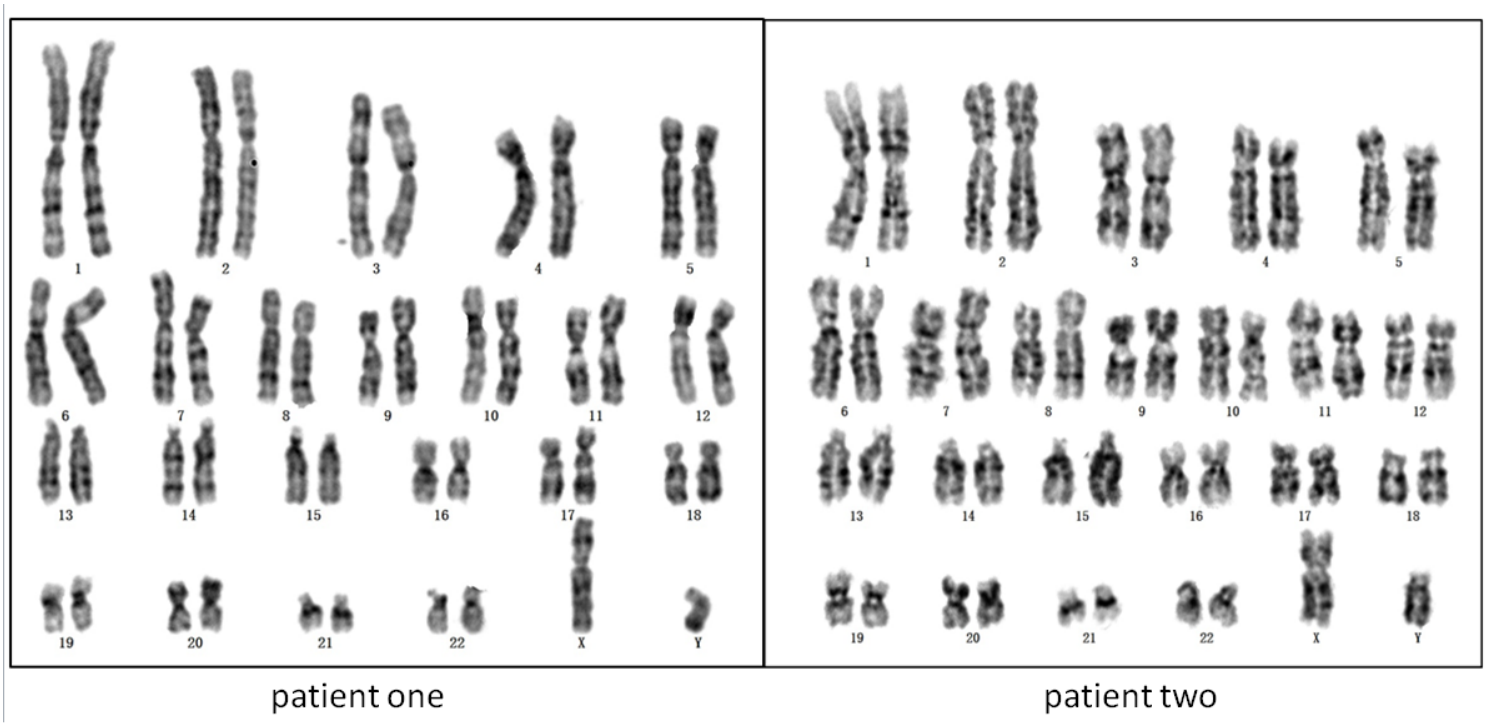

Figure 2

Karyotype analysis of maternal amniotic fluid showing no significant fetal chromosomal abnormalities.

patient one

patient two

Figure 3

CMA analysis of maternal amniotic fluid showing that a duplication of 1.9 Mb on chromosome 17q12 (arr[hg19] 17q12(34,440,088-36,311,009)x3) in patient 1, but 1.5 Mb (arr[hg19] 17q12 (34,822,465-36,351,919)x3) in patient 2.