Prenatal Diagnosis of the 22q11.2 Duplication Syndrome

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The 22q11.2 duplication syndrome is an extremely variable disorder with a phenotype ranging from normal to congenital defects and learning disabilities. Recently, the detection rate of 22q11.2 duplication has been increased by molecular techniques, such as array CGH. In this study, we report a familial case of 22q11.2 duplication detected prenatally. Her first pregnancy was terminated because of 22q11.2 duplication detected incidentally by BAC array CGH. The case was referred due to second pregnancy with same 22q11.2 duplication. We perfomed repeat amniocentesis for karyotype and FISH analysis. Karyotype analysis from amniocytes and parental lymphocytes were normal, while FISH analysis of interphase cells presented a duplication of 22q11.2 in the fetus and phenotypically normal mother. The fetal ultrasound showed grossly normal finding. After genetic counseling about variable phenotype with intrafamilial variability with 50% recurrence rate, the couple decided to continue the pregnancy. The newborn had no apparent congenital abnormalities until 2 weeks after birth.
We recommend that family members of patients with a 22q11.2 duplication be tested by the interphase FISH analysis. Also, we point out the importance of genetic counseling and an evaluation of the clinical relevance of diagnostic test results.

Key Words: 22q11.2 duplication, Prenatal diagnosis, FISH

Introduction

The chromosome 22q11.2 region is susceptible to rearrangements, and has long been implicated in genomic disease, such as DiGeorge/Velocardiofacial syndrome (DGS/VCFS), the most frequently identified genomic disorder of the region, der(22)t(11;22)syndrome and cat eye syndrome (CES), which are associated with either decreased or increased gene dosage[1, 2].

These deletions and duplications at 22q11.2 are the products of unequal crossover due to the misalignment of low copy repeats (LCRs)[3]. In theory both 22q11.2 deletion and duplication events are expected to occur with the same frequency[4]. However, until now, only about 63 cases of 22q11.2 duplications have been reported[5], which is a low number compared to the large number of 22q11.2 deletion cases reported. Furthermore, only one case of a 22q11.2 duplication has been

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described in prenatal diagnosis[6]. This difference may be explained by the technical difficulties in detecting duplications by fluorescent *in situ* hybridization (FISH) on metaphase spreads[7] and by the wide range and sometimes mild phenotypes of the patients.

Here, we report a familial case of the 22q11.2 duplication diagnosed prenatally.

Case report

The 29-year-old gravida 2, abortia 1 woman underwent amniocentesis at 20 weeks due to a history of recurrent 22q11.2 duplications. The first pregnancy was terminated at second trimester in other institute because the BAC array CGH of amniotic fluid performed due to increased risk for Down syndrome by maternal serum screening incidentally detected the 22q11.2 duplication. The second pregnancy showed the same result with 22q11.2 duplication by BAC array CGH of amniotic fluid. The apparently normal parents were referred to our hospital for further evaluation of the 22q11.2 duplication. The cytogenetic analysis of cultured amniocytes presented no abnormality. FISH analysis using the DiGeorge N25 chromosome region probe (Vysis, Downers Groove, IL, USA) showed three signals equal in size and intensity in 122 of 132 interphase cells (Fig. 1A). In 14 of 28 metaphase spreads, a double or more intense signal was detected on one chromosome 22.

In the parental karyotyping, the duplication could not be seen by GTL chromosome analysis at the 700 band-level (Fig. 1B). FISH analysis, performed on lymphocytes of the parents, revealed that the 22q11.2 duplication was inherited from the mother. Indeed, the majority of maternal interphase cells exhibited three equal signals (77%, 54 of 70). Only 30% (9 of 30) of the metaphase cells exhibited a double or more intense signal on one chromosome 22 (Fig. 1C). The mother showed an apparently normal phenotype. The fetal ultrasound showed grossly normal finding. After genetic counseling that the 22q11.2 duplication show variable phenotype with intrafamilial variability and the recurrent rate is about 50%, the couple decided to continue the pregnancy. The female baby was delivered at 41 weeks of gestation with an Apgar score of 9/10 and birth weight of 3,555g, length of 52.2 cm and head circumference of 36 cm. The baby showed good neonatal adaptation with no apparent congenital abnormalities until 2 weeks after birth with need for long term pediatric follow up.

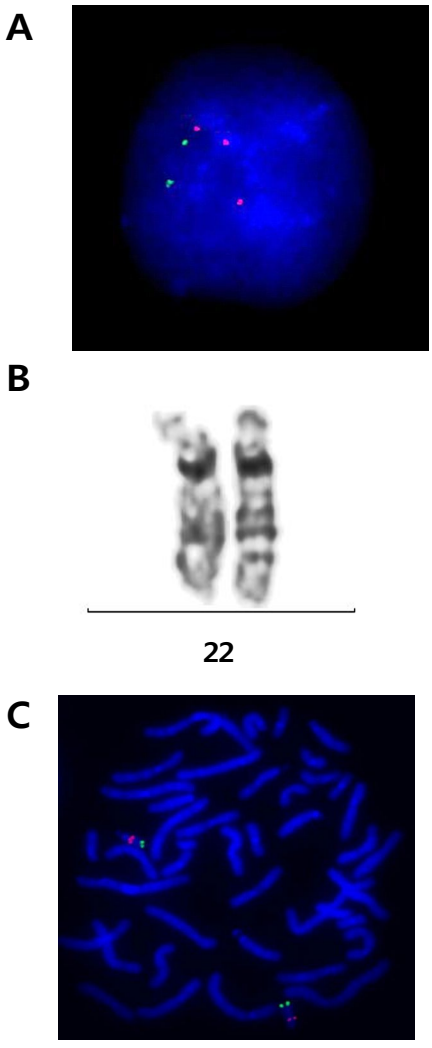

Fig. 1. Detection of the 22q11.2 duplication A: FISH analysis on fetal amniocytes using a DiGeorge syndrome critical region probe at 22q11.2 (N25: red signal; control probe at 22q13.3: green signal). Interphase cell show three signals. B: GTL-banded partial karyotype performed in the mother's lymphocytes. The 22q11.2 duplication is not visible. C: FISH analysis on mother's lymphocytes. The duplication is seen as a larger-sized signal compared with the normal chromosome 22.

Discussion

The 22q11.2 duplication phenotype ranges from normal to mental retardation, learning disabilities, delayed psychomotor development, growth retardation, and/or hypotonia[7].

Most individuals diagnosed with a 22q11.2 duplication have inherited the duplication from a parent. A parent who has the duplication 22q11.2 may have a normal or near-normal phenotype even if the genomic alteration appears to be identical in the child and the child has obvious clinical features[8].

In prenatal diagnosis, the phenotype resulting from a 22q11.2 duplication is difficult to predict. So far, only one prenatal diagnosis of 22q11.2 duplication has been described[6]. Here, the fetus with complex heart defects was incidentally diagnosed with 22q11.2 duplication using FISH by the DiGeorge critical region probe, which was inherited from a father with mild cognitive deficits. The second fetus with the same duplication showed a normal sonography finding and was normal at birth.

In our clinical study, the duplication in the fetus was inherited from the mother, who showed no obvious symptoms. The fetal ultrasound showed grossly normal finding. The newborn delivered at term and no apparent congenital abnormalities were noticed. However, in previous pregnancy, the fetus was terminated due to the 22q11.2 duplication detected by BAC array CGH without further evaluations such as family study using FISH in the other center. It is necessary to offer appropriate genetic counseling and to evaluate clinical relevance of test results before final decision. Although array CGH has a higher resolution than conventional karyotyping, making it possible to detect small deletions and duplications, it requires a careful clinical evaluation due to the complication in interpretation of copy number variation (CNV). We need to set up the concensus about indications of array CGH in prenatal field due to possibility of cases with incidentally prognostic dilemma.

The 22q11.2 duplication is not detectable by routine G-anded karyotyping. Most individuals with the 22q11.2 duplication are identified by molecular techniques, such as interphase FISH, array genomic hybridization (array CGH) and multiplex ligation-dependent probe amplification (MLPA)[9]. Interphase FISH is often used as a reflex test by the laboratory performing the array CGH testing to confirm the presence of a duplication[10]. In previous reports and in our case, the use of interphase FISH analysis was primarily responsible for the diagnosis. Interphase FISH is warranted in identifying this case, because the ability to see duplication on metaphase cells in 22q11.2, both by cytogenetic analysis and FISH, is limited. These finding illustrate the importance of scanning interphase nuclei when performing FISH analysis for any genomic disorder.

In conclusion, we recommend that family members of patients with a 22q11.2 duplication be tested for this genetic defect, and the interphase nuclei be scanned when performing FISH analysis. Additionally, we point out the importance of adequate genetic counseling and an evaluation of the clinical relevance of diagnostic test results before pregnancy termination.

국문초록

22q11.2 미세중복 증후군은 학습장애, 선천적 기형에서부터 정상에 이르기까지 다양한 표현형을 나타내는 증후군으로써, 22q11.2 미세결실 증후군인 DiGeorge 증후군과 동일한 위치에서 발생하는 질환이며, 이러한 원인은 유전적 불안정성이 높은 low-copy repeats (LCR) 부위에서 일어나는 유전체의 결손이나 중복에 의해 형성되는 것으로 보고되고 있다. 최근 array CGH가 임상분야에 적용됨에 따라 22q11.2 미세중복 증후군의 진단이 증가되고 있다.

이론적으로 22q11.2 부위의 미세중복이나 미세결실의 빈도는 동일하게 발생해야 하지만, 현재까지 미세결실에 비해 미세중복의 증례보고는 상대적으로 드물며 이는 증상이 없는 경우가 많기 때문인 것으로 알려져 있다. 특히 이전 보고에서 산전에 발견된 미세중복의 증례는 단 1례 만이 보고된 바 있다. 저자들은 산전에 진단된 22q11.2 미세중복 증후군 1례의 보고를 통해 유전상담의 중요성과 array CGH의 임상 적용에 관하여

논하고자 한다.

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