CASE REPORT

Molecular Cytogenetic Characterization of a Patient Diagnosed with Dimorphic Anemia Carrying De Novo Rare Ring Chromosome 7 along with T(7;9)

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ABSTRACT

A case of a derivative chromosome 7 formed by a ring chromosome 7 and t(7;9) was found who presented with dimorphic anaemia with no other anomaly. Ring chromosome 7 was characterized by conventional and molecular cytogenetic techniques.

Keywords: Ring 7, Dimorphic anemia, Molecular cytogenetics, Whole chromosome paint

INTRODUCTION

Ring chromosome is formed when a break occurs in each arm of the chromosome, resulting two 'sticky' ends and subsequent end-to-end fusion. Ring chromosome 7 is a rare chromosome anomaly that leads to variable phenotypes. Zackai *et al* in 1973[1] has described two cases for the first time. Ring chromosomes are frequently unstable during mitosis. Other cells in an individual carrying ring chromosome are usually monosomic or exhibit partial trisomy with a small ring.[2] The frequency reported for the ring chromosomes is 1/25000 recognized conceptions; almost all the chromosomes are involved in the formation of ring chromosome and about 50% are supposed to derived from the group of acrocentric chromosomes.[3]

On the other hand, dimorphic refers to anemia that has two different causes acting together, iron and vitamin B12 deficiency.[4] This is the first case of ring chromosome 7 with t(7;9) in dimorphic anemic patient. The phenotypic expression of the patient with ring chromosome 7 is varying in different condition; most of the patient demonstrates mental retardation, developmental delay, microcephaly, few with dermatological problems including cafe-au-lait spots, nevus flammeus and dark nevi.[5] The variable phenotypes may be due to the deletion of different genes in the terminal region of chromosome 7, instable ring or due to level of mosaicism.

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CASE DETAILS

The patient presented here is 7 years old male with complaint of tiredness and nausea. No other dysmorphism noted at presentation. Hematological report reveals hypochromia and dimorphic red cells with microcytes and macrocytes. RBC distribution was reduced. WBCs were mature and show low normal count with 6.0 × 10^9/L and with normal distribution. Platelets are normal. No hemoparasite is seen. The patient is diagnosed with dimorphic anemia. He is a second child of non-consanguineous parents with no linked family history.

Cytogenetic evaluation was done by karyotyping using a standard protocol.[6] A minimum of fifty well spread metaphases were scored, photographed and analysed using (Cytovision software V7.2, Richmond USA). Parental karyotype was normal confirming de novo origin of ring chromosome 7 in the proband. The final karyotype of the proband reveals "46,XY,der(7) t(7;9)(p13;p24) r(7)(p13q36)" (Figure 1a and 1b), This ring chromosome was further characterized by FISH using LSI D7S486 for chromosome 7q31 and CEP7 (Vysis, Abbott molecular, USA) (Figure 2) and two metaphase slides were used for

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whole chromosome paint (WCP) 7 and 9 (Kreatech, USA). The probes were hybridized to metaphases using standard protocol as discussed earlier and viewed under fluorescence microscope (Olympus, BX 51, USA) (Figure 3).

DISCUSSION

As mentioned above, the ring chromosome is formed by end-to-end fusion with minimal or no loss of genomic material. Ring chromosomes are often unstable during mitosis; as a result, it is common to find a ring chromosome in very minimal portion of cells, resulting mosaicism. The remaining cells in the individual are usually monosomic or partial-trisomy. Some cells maintaining the ring chromosomes as a supernumerary ring chromosome whereas some may lose it.

The karyotype of the patient presented in this case was complicated and unique. All the metaphases analysed were found to have ring chromosome 7 along with t(7;9) involving same chromosome 7. Previous reported cases of supernumerary ring chromosome 7 showed a majority of cells with a normal karyotype, in addition to some cells with a partial trisomy containing small rings.[7-13] Here we present a 7 year old boy diagnosed as dimorphic anemia; karyotype result shows a ring chromosome 7 along with translocation of 7p with 9p. All the ring chromosomes has intact 7q D7S486 region along with one centromere (Figure 2), confirms involvement of chromosome 7 in ring formation. Although, FISH for WCP 7 and 9 revealed that there is unbalanced translocation occurred between chromosome 7 and 9 where deleted part of chromosome 7p was lost. According to the human chromosome 7 map (http://www.ncbi.nlm.nih.gov) of the National Centre for Biotechnology Information (NCBI), there are no functional genes located within the missing distal region of 7q. The 7p region which has been translocated to chromosome 9p carries six important genes (GLI3, GLI-Kruppel family member GLI3; PPIA, peptidylprolyl isomerase A (cyclophilin A); PSMA2, proteasome (prosome, macropain) subunit, alpha type, 2; CDC2L5, cell division cycle 2-like 5 (cholinesterase-related cell division controller); IKZF1, IKAROS family zinc finger 1 (Ikaros) and IGFBP3, insulin-like growth factor binding protein 3).

There are very few studies available on cytogenetic abnormalities in acquired anemia. Chromosomal abnormalities were found in 4% of total 183 cases in one case study with large series.[14] In the present case, a majority

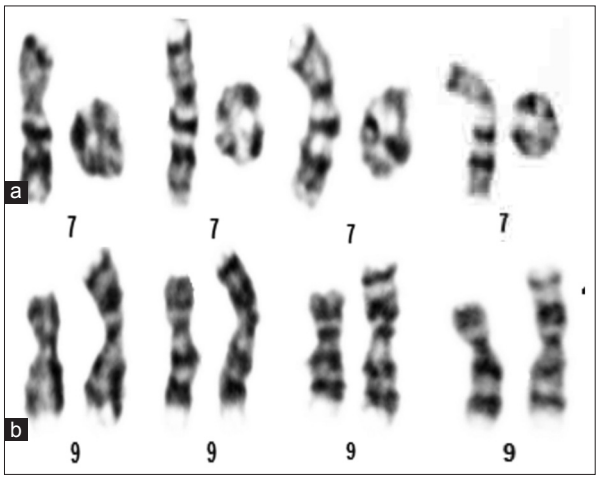

Figure 1: Partial G-banded karyotypes shows normal and abnormal ring chromosome 7 (a). Unbalance translocation involving chromosomes 7 and 9 at bands 9p24 (b)

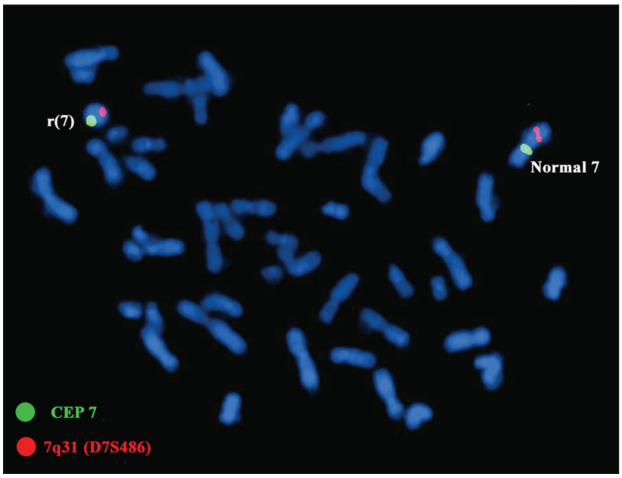

Figure 2: Metaphase FISH analysis using LSI D7S486 and CEP 7 probe confirms that the ring is monocentric and there will be possible terminal deletion happened at the terminal end

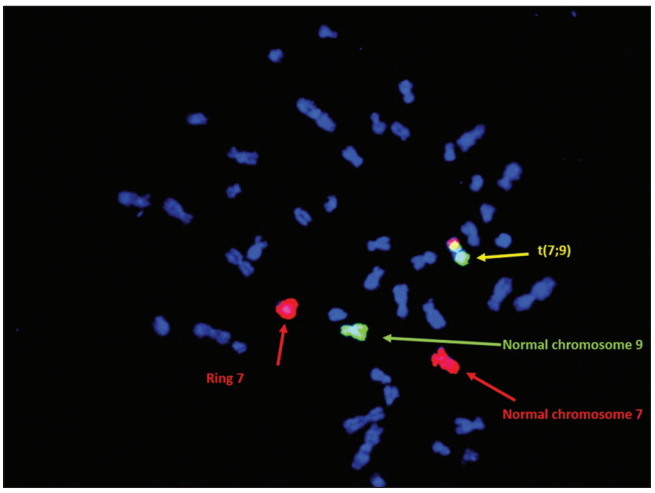

Figure 3: FISH analysis using WCP 7 (red) and 9 (green) confirmed one red signal for normal chromosome 7, one ring with red signal, one green signal for normal chromosome 9 and one derivative chromosome with fused red and green signal of unbalance t(7;9) shown by respective colour arrow

of the cells (90%) were composed of ring 7 with t(7;9), and all the large rings appeared to be stable; this is likely associated with survival of the patient. This abnormality is unique and novel and upto our knowledge, not reported so far. However, it is also possible that other tissues, beside the peripheral blood lymphocytes, had a normal karyotype; but no other tissues were available for analysis. The influence of gene dosage effects resulting from ring chromosome 7 were likely the cause of the abnormal clinical characteristics of the patient presented over here.

It is evident that the phenotype of r(7) patient does not correlate with either the breakpoints of the ring at current banding resolutions. More severe abnormalities are due to deletion of subtelomeric chromosome segments. Cote et al[15] suggested that a 'ring syndrome' exists with a peculiar phenotype, including extreme somatic retardation together with an otherwise almost normal appearance with or without minor abnormalities and mild or moderate mental retardation,independently of thechromosome involved, as long as the whole chromosomeis present in the original ring.

In summary, we describe a unique case of derivative chromosome 7 formed due to ring chromosome 7 and t(7;9) in dimorphic anemic patient for the first time. Molecular cytogenetic techniques represent the most convenient way to prove initial diagnosis.

To support our data, we have performed FISH analysis to rule out whether ring chromosome contains centromere or not by using LSI D7S486 probe. This test also helped us to rule out how much material on the *q* arm has been deleted. To prove the existence of t(7;9), we have used WCP 7 and 9. The breakpoint we have reported here is not present in the literature.

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