

Ring Chromosome and Clinical Findings: Reports Cases of 4 Different Chromosomes in Beninese Population

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Abstract

Ring chromosome is a disorder in which one or both ends of chromosome are lost and joined, so they could show a ring-shaped structure. Patients with ring chromosome could therefore present with features of deletion of long or short arms of the chromosome syndromes or a combination of both. Phenotypic of these individuals depends on the size of the ring chromosome, amount of genetic material lost in breakage, the stability of the ring chromosome and the presence of secondary chromosomal aberrations including the varying degrees of mosaicism. Ring chromosomes accounts for a very low percentage of structural chromosomal abnormalities but could lead to a major clinical concern and complicated genetic counseling. Practitioner awareness must be permanently raised up to help in managing with efficacy patient with ring condition. We report here 4 cases of ring on chromosome 4, 9, 15 and X. We described their clinical finding and draw attention on common key signs that were present in the reported cases and also discussed recurrence risk.

Keywords: Ring chromosome; Intrauterine growth retardation; Developmental delay; Amenorrhea; Dysmorphism

Introduction

A ring chromosome is a chromosome whose arms have fused together to form a ring. Ring chromosomes were first discovered by Lilian Vaughan Morgan in 1926 [1]. Constitutional ring chromosomes have been identified for each of the human chromosomes and the overall frequency is estimated at 1 in 27:000 to 62:000 births [2]. Rings result from rare intrachromosomal fusions although mechanisms underlying chromosomal ring formation are not completely understood. These fusion events are hypothesized to arise from either unstable telomeres, which directly fuse, or from chromosomal breaks that resolve by fusion of the two chromosomal arms. Phenotype of these individuals depends on the size of the ring chromosome, amount of genetic material that is lost in breakage, the stability of the ring chromosome and the presence of other type of chromosomal abnormalities including mosaicism [3]. Ring chromosomes accounts for a very low percentage of structural chromosomal abnormalities and majority of the cases are sporadic arising *de novo* [4-6]. Most patients that carried a ring chromosome are phenotypically abnormal with dysmorphisms [2,6]. No case on ring chromosome has been reported from sub-Saharan African region. We report here four cases of ring including chromosomes 4; 9;15 and X with clinical findings and discuss phenotypic correlation with previously reported cases.

Cases Reports

The patients whom cases are analyzed beneath were received for genetic investigation at the Medical Genetic consultation in the pediatric ward in the Teaching Hospital of Cotonou, the main city in Republic of Benin, West Africa. This consultation started since year 2005 and patients are treated according the good practice in medicine and in genetic specially on genetic laboratory testing. Written and informed consent forms were signed for genetic material manipulation and picture diffusion for only scientific purposes.

Case 1

RH was received at the age of 18 months for malformation and developmental delay. His family history was unremarkable and the

pregnancy was normal. The physical examination at 18 months revealed growth retardation with the weight at 4 kg (<-3 SD), length at 61 cm (<-4 SD) and occipito-frontal-circumference at 36.5 cm (<-2 SD). Psychomotor delay was severe with absence of ability to sit. Facial dysmorphism included prominent forehead, broad and flattened nose, parallel noses edges, microcephaly, hypertelorism, short philtrum, prominent eyes with strabismus, opened mouth in permanence, micrognathia and hypoplastic ears (Figure 1a). Closure defects were present with cleft palate, preauricular and sacro-coccygial pits and hypospadias. Chromosomal analysis were performed for the patient and parents on peripheral blood using the G banding technique at 800 band resolution. The karyotype show a ring chromosome of the chromosome 4 (Figure 1b). Based on FISH's investigations, breakpoints were established approximatively at 4p16 and 4q34 bands. Therefore, patient's karyotype could be 46, XY, r(4) (p16q34). Parent's karyotype were normal.

Case 2

LH, a female, was received at the age of eight months for malformation. She was born to non-consanguineous parents. The pregnancy was unremarkable. She was delivered at 37 weeks of gestation by cesarean section due to vicious presentation. Neonatal adaptation was normal since she had cried immediately and Apgar score was 8-10-10 at the 1st, 5th and 10th minutes of life. Births' measurements were abnormal with weight at 1800 g (<-3DS); height at 44 cm (<-3DS) and head circumference at 29 cm (<-3DS). She suffered in her early life from

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pneumonia. Parents also complained from psychomotor delay with lack of sitting alone at eight months. Physical examination at eight months disclosed severe growth retardation with weight at 3,775 kg (-3DS), height at 54 cm (-3DS) and head circumference at 35 cm (-3DS); facial dysmorphism with microcephaly, wide and spaced eyes, upslanting palpebral fissures, inner epicanthic folds, strabismus, depressed nasal bridge, anteverted nares, long and poorly marked philtrum and macrostomia (Figure 2a). She also disclosed hypothyroidism. Ultrasound showed ductus arteriosus. Karyotyping from peripheral blood using high resolution GTG-banding techniques at 800 band revealed structural abnormality on chromosome 9 with a ring shape (Figure 2b). Chromosomal investigation result was then as followed: 46, XX, r (9). Parents' karyotypes were normal.

Case 3

MI was a boy of healthy and unrelated parents. He was seen at the age of 22 months for genetic consultation. Referral reasons were growth retardation and facial dysmorphism. The pregnancy was characterized by intra-uterine growth retardation. He was born at 39 weeks of gestation with 2.550 kg (<-2SD). Delivery was normal. Clinical examination revealed a failure to thrive (all growth parameters were under -3SD), psychomotor retardation (no speech at 22 months) and craniofacial dysmorphism. Dysmorphic features included microcephalia, hypertelorism, blepharophimosis, down slanting palpebral fissures, strabismus, fattened nose, hypoplasia alae, long philtrum, large ears and micrognathia (Figure 3a). Cytogenetic analysis from 72 hours lymphocyte culture showed pathological karyotype which resulted as follows: 46, XY, r(15) (Figure 3b). Parental karyotypes were normal.

Case 4

BS was received at the age of 22 years for secondary amenorrhea. She was born from non consanguineous parents and the pregnancy was unremarkable. She declared to have experienced once menstruation bleeding at the age of 18. After two episodes, no more menses came appeared. Clinical examination revealed height growth delay, hypogonadism with poor development of sexual features, low posterior airline and cubitus valgus deformation. The patient refused all usage of pictures regarding her medical record.

Discussion

The frequency of chromosomal abnormalities varies from country to country, one region to another with almost the same phenotype. In African countries, chromosomal pathologies were hidden by the huge prevalence and incidence of infectious diseases. Except sickle

cell anemia, which is a well known monogenic disease, chromosomal diseases are poorly described and rarely reported. In these sub-Sahara Africa countries, no accurate registry for chromosomal abnormalities exists. For this reason, no one could give the prevalence of these diseases in general population. In our knowledge, this is the first report on several cases of ring chromosome from a sub-Saharan country. But one must recognize the lack of genetic laboratory for routine screening of chromosomal abnormalities in Africa, especially in sub Saharan parts of the continent.

Ring chromosomes have been found with all human chromosomes. It's a rare form of structural chromosomal abnormality which commonly results from the breakage of the extremity of both short and long arms of the chromosome and subsequent ends joining. The site of breakage and the amount of chromosomal material lost varies from case to case. The cytogenetic variation in case of ring chromosome depends on the deleted material size, rate of sister chromatid exchange events and the viability of altered cell lines [2,3,7]. Therefore, phenotypic abnormalities associated with partial deletions can be found among patients with ring chromosomes [7]. Subtelomeric or telomere-to-telomere fusion of the chromosomes resulting in formation of complete rings was also reported, usually with a milder phenotypic changes due to the minimal loss of genetic material [8]. Advanced cytogenetic techniques, such as FISH and CGH array has allowed the detection of novel mechanisms of ring formation. Guilherme et al. by using the CGH array and FISH techniques has described the mechanism of formation of the ring

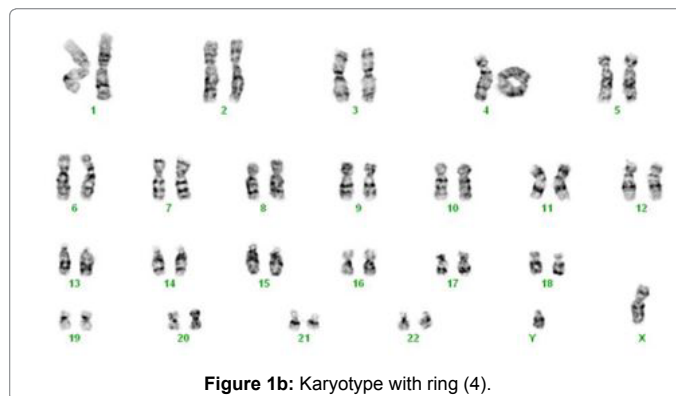


Figure 1b: Karyotype with ring (4).



Figure 1a: Phenotype of patient with r (4).



Figure 2a: Phenotype of patient with r (9).

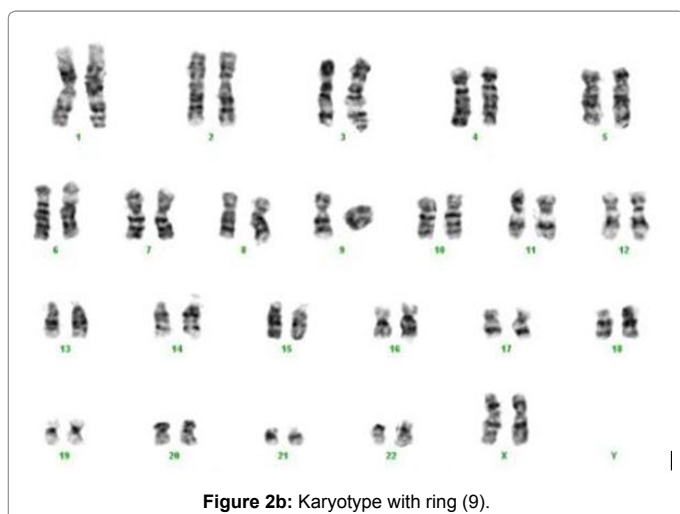


Figure 2b: Karyotype with ring (9).



Figure 3a: Phenotype of patient with r(15).

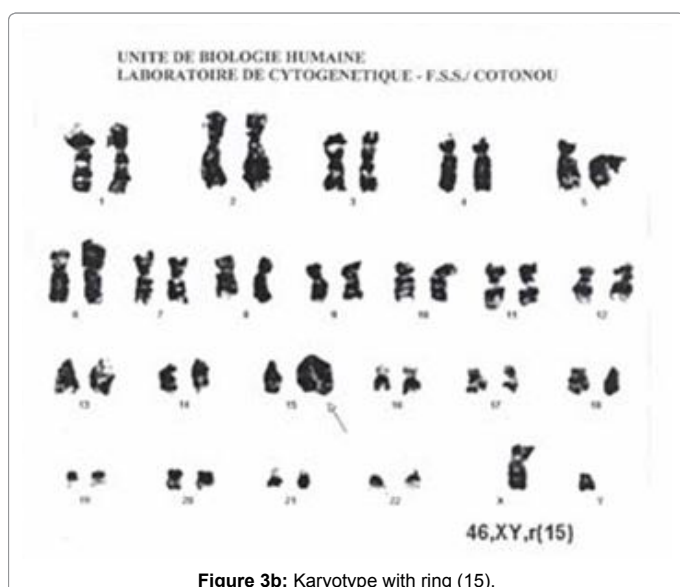


Figure 3b: Karyotype with ring (15).

chromosomes, including rings with deletion in one or both arms, complete rings, and rings formed by a complex mechanism, due to inversion-duplication-deletion [9].

Terminal deletion of the chromosome 4 is a well-known phenomena described as Wolf-Hirschhorn syndrome (WHS). The phenotype shown by the patients with ring chromosome 4 are partly due to the terminal deletion of the two arms of the chromosome. Terminal 4p16.3 deletion is known to be sufficient to produce the classical phenotype of WHS [10]. By using the FISH techniques, our patient had a deletion of 4p16 and 4q34 bands. His phenotype was characterized by severe psychomotor retardation with the absence of ability to sit up, speech delay, microcephaly, and hypertelorism and open mouth. These findings were previously reported [11]. The genes that are deleted in this critical region of chromosome 4 in those patients included *HAND2* gene which is expressed in the ventricular chambers of the developing heart and *SORBS2* gene which is expressed in epithelial tissue and cardiac muscle. These genes may potentially contribute to the cardiac defects that are described in some cases of WHS [10,11].

Ring 9 chromosome is a very rare disorder in which there is a loss of chromosomal material from both ends of the 9th chromosome and joining of the ends to form a ring. Some affected individuals may have variable malformations of the skull and facial region. Patients with identical r(9) breakpoints showed variable phenotypes. This could come from the submicroscopic variation in breakpoints, the ring instability, the modification of the expression due to genetic background or the fetal environment. The haplo-insufficiency of genes located in the deleted regions played critical roles in the patient phenotype as well [12,13].

The ring chromosome 15 is also a rare and it could be present in “pure” or in mosaic forms [14]. It results in a varied and unspecific phenotype depending on the size of the deletion. However, the recurrent form has been characterized by growth deficiency, mental retardation, and characteristic dysmorphic features that may include included microcephalia, hypertelorism, blepharophimosis, down slanting palpebral fissures, strabismus, fattened nose, hypoplasia alae, long philtrum, large ears and micrognathia. Sometimes, diagnosis of r(15) syndrome could mimic some other syndromes [15]. Some patient with r(15) could have a phenotype that is similar to one of Silver Russell syndrome [16]. This tendency is probably due to the loss of one copy of the *IGFR-1* gene (Insuline-Like Growth Factor Receptor 1). *IGF*-like receptor mutations are recognized to play a major role in pathogenesis of Silver Russell syndrome (SRS). The most important sign in this syndrome is severe postnatal growth retardation [17]. More signs such as ophtamological anomalies (amblyopic, divergent strabismus, hypertelorism, divergent strabismus, hypermetropia) could be found in some cases of r(15) syndrome [18].

Turner syndrome (TS) is a genetic disorders that affects about 1 in every 2500 female babies [19]. The genetic abnormality is localized on X chromosome. Approximately 50% of affected women missed an entire X chromosome and have a karyotype of 45, X. About 25% have a partial deletion of one of X chromosomes, whereas about 20% have varying degrees of mosaicism. The most common shape is a 45, X/46, XX karyotype. A small affected group carries an XY cell line [20]. Our case of ring chromosome is due to the loss of genetic material in one chromosome X. The most common feature of Turner syndrome is the short stature and sexual infantilism, which becomes obvious during the teenage. Our patient had secondary amenorrhea, short stature, sexual infantilism, cubitus valgus and posterior low airline. Turner syndrome is generally characterized by a primary amenorrhoea. But as reported here, some cases could express secondary amenorrhoea even if this pattern is very rare [21]. Turner syndrome shows important phenotypic variability, ranging from the classical form (girls with pubertal development and

stature growth delay) to those with few dysmorphic signs, which are almost indistinguishable from the general population presentation [22]. This could explain the delay in diagnosing the patient reported here. Turner syndrome is thought to be associated with the loss of the function in *SHOX* gene. This gene is important for bone development then for growth. The loss of one copy of this gene may cause short stature and skeletal abnormalities in women with Turner syndrome. The *SHOX* gene is part of a large family of homeobox gene which act during early embryonic period to control the formation of many body structures. It plays a particular role in growth and maturation of arm and legs's bones [23].

In our series, there are three common key-signs which were found in almost all of reported ring chromosome cases. These are intrauterine growth retardation, postnatal growth delay and psychomotor impairment. Growth restriction was found in all of the reported case while psychomotor delay was present in cases one, two and three. These key signs could help health workers in thinking about chromosomal diseases, especially ring chromosomes or deletion syndromes.

For all of reported patients, there is a risk of recurrence and it could be very high in cases. This forced author to investigate parents. Parental karyotype was normal. This condition directed towards *de novo* abnormalities. Genetic counseling could be done with assurance of poor risk recurrence in future but fetal karyotyping and well organized ultrasound monitoring could be of a great help in reducing recurrence. Prenatal diagnosis is possible and feasible for all cases of ring chromosome [24]. The diagnosis could be then done by obstetrical ultrasound based on signs such as IUGR, bones defaults and dysmorphic features. In case an abnormality was found, antenatal karyotype on the amniocytic fluid or on the foetal blood could help in the diagnosis.

Conclusion

Conventional karyotyping was used for cytogenetic diagnosis of the present cases, however the exact chromosomal breakpoints can only be confirmed by molecular cytogenetic methods such as FISH or and CGH. Unfortunately, these techniques are not available in sub Sahara Africa. Breaking points denitrification will help in improving understanding of phenotype-genotype correlation of this rings conditions. The phenotype of the ring chromosome in our study had some common key signs such as IUGR, psychomotor delay and facial dismorphism. These signs are sufficient to search for genetic consultation or ask for karyotyping.

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