

## Multi-autosomal chromosome aberrations role in primary amenorrhea

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### Abstract:

Primary amenorrhea which result commonly from sex chromosome aberration as genetic abnormalities, may result from one aberration in autosomal chromosomes or in association with sex chromosomal aberrations. Chromosomal analysis was performed for the 26 years old lady (married and infertile) with primary amenorrhea by using G-band technique. Four autosomal chromosomes are involved in producing primary amenorrhea with normal phenotype, secondary characteristics were associated with mosaic karyotypes the

1st: 46,XX,(3;5;10)(q13-23;q23-35;22-25),(5;19)(qter;p13.2),del(19p13.2).

2nd: 45,XX, ,(3;5;10)(q13-23;q23-35;22-25),del(12),del(12),del(19p13.2),(M).

The sex chromosomes look normal. The conclusion was that may be some autosomal chromosomes regulate reproductive development and may the alerted regions on chromosomes in recent study have effect somehow on regulation of reproductive development.

**keyword:** chromosomes, primary amenorrhea

### Introduction:

Primary amenorrhea is defined as the absence of menses by 16 years of age in the presence of normal secondary sexual characteristics or by 14 years of age when there is no visible secondary sexual characteristic development and the adolescent growth spurt. [1, 2]. It occurs 1-3% of the women of reproductive age [2]. Genetic factors in addition to endocrine disturbances and constitutional and environmental factors have an important role in causing primary amenorrhea, and about 15-63% of primary amenorrhea is caused by chromosomal abnormalities [3]. Amenorrhea accounts for 20% of patient with infertility [3]. The aim of the present study was to report a case of primary amenorrhea including balanced autosomal translocations and autosomal abnormalities with intact X chromosomes.

Case: The 26 years old young lady who is suffering primary amenorrhea with perfect normal phenotype. MRI report recorded rudimentary uterus (small size), anteverted,

homogenous texture, no ovaries could be visualized. While the secondary sexual characteristics were found normal development.

### Material and methods:

Chromosomes were prepared from 72-hour peripheral blood cells stimulated culture with phytohemagglutinine PHA (prepared in Iraqi Center for Cancer and Medical Genetics, Iraq). Standard procedures for cultures, harvests and slide preparation, were modified and performed in our laboratory according [4,5]. Briefly, 5 ml of heparinized peripheral blood were cultured in RPMI 1460 (Sigma-Aldrich, St. Louis, MO; Schnell drof, Germany) supplemented with 20% fetal bovine serum (Gibco, Grand Island, NY), and antibiotics (penicillin and streptomycin). Then, the culture exposed to 20 µg/ml Colcemid (Kreatech, Netherlands) for 30 minutes, followed by hypotonic treatment (KCL 0.075N) for 30 minutes. A fixation procedure with methanol: Glacial acetic acid (3:1) v: v was performed freshly. Chromosomes were analyzed with GTG-banding, and karyotyping was described according to ISCN, 2013 [5,6]. Re-culture for three times in order to note changing

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the conditions suffered by the patient such as the influence of drugs and resonance previously. Each time 20 metaphases were analyzed.

**Result:**

This case was revealed one of the rare statuses when primary amenorrhea is resulted by multi- autosomal aberrations, while the X-chromosomes were normal. The novel of this case that the three interstitial translocations were observed among chromosome 3, chromosome 5 ,chromosome 10 and deletion in the short arm of chromosome 19 in the same case. Sixty metaphases were analyzed,the case re-

vealed mosaic karyotype 98% of the cells show karyotype of 46,XX,der(3),-(5),-(5),t(5,19)(qter,p13.2),der(5),der(10),del(19p13.2) ;while 2% of the cell show 45,XX,der(3),der(5),der(10),del(12),del(12),del(19p13.2),(M).

The translocations were among three chromosomes: The region 3q13-23 may translocate to 5q23-35 while 5q23-35 may translocate to 10q23-25, while the 10q22-25 translocate to 3q13-23.while the deleted 19p may translocate to 5qter. Which result two complex translocations karyotype were:  
 1st: 46,XX,(3;5;10)(q13-23;q23-35;22-25),(5;19)(qter;p13.2),del(19p13.2).  
 2nd 45,XX,(3;5;10)(q13-23;q23-35;22-25-),del(12),del(12),del(19p13.2),(M).

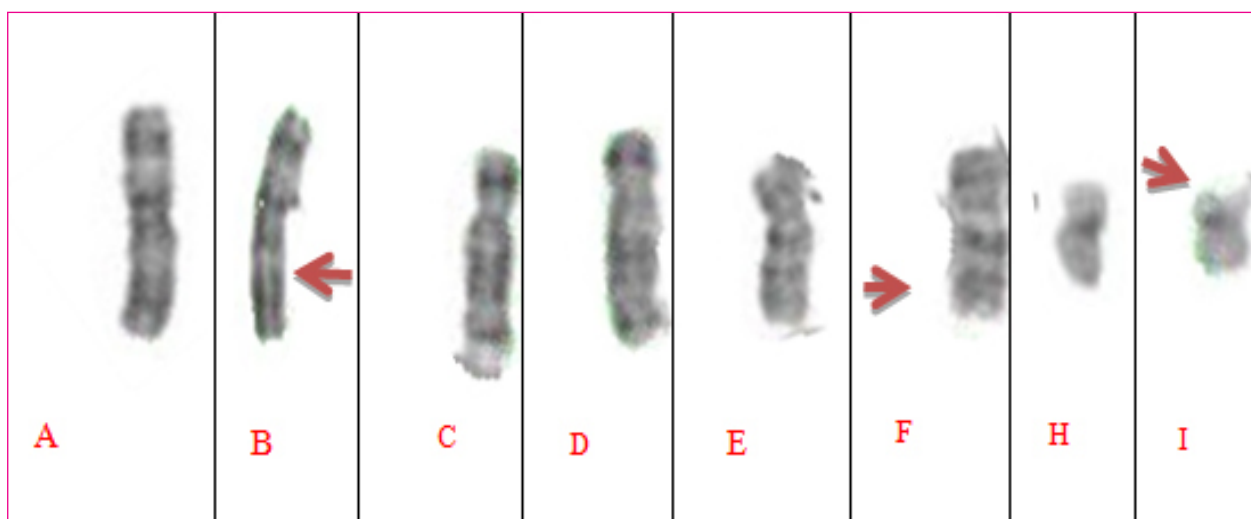


Figure 1: A: normal (3);B:der (3);C: )5q+);D: der(5);E: normal (10);F: der(10);H:normal (19);I:del(19p13.2).

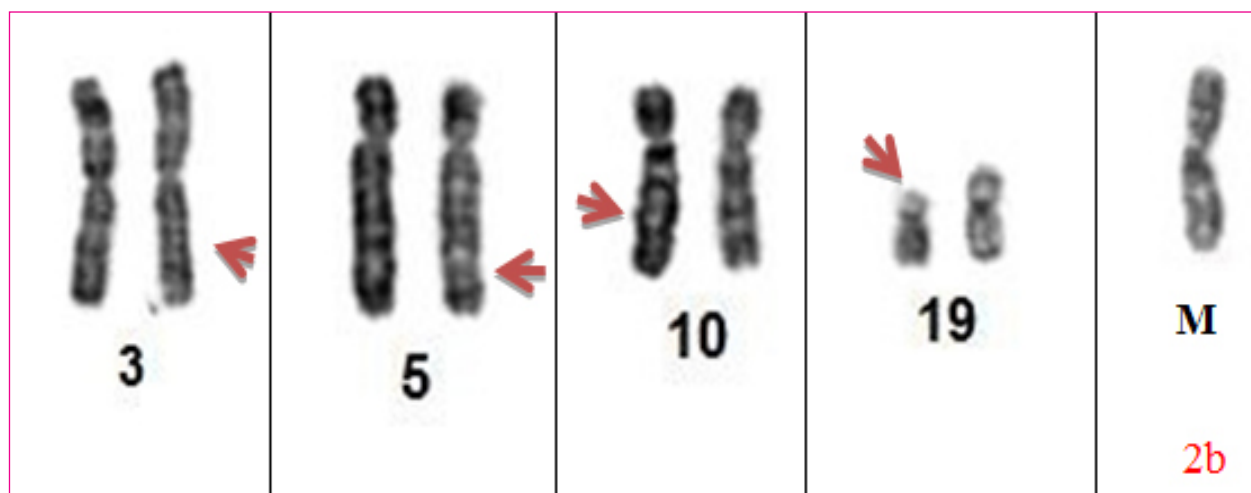
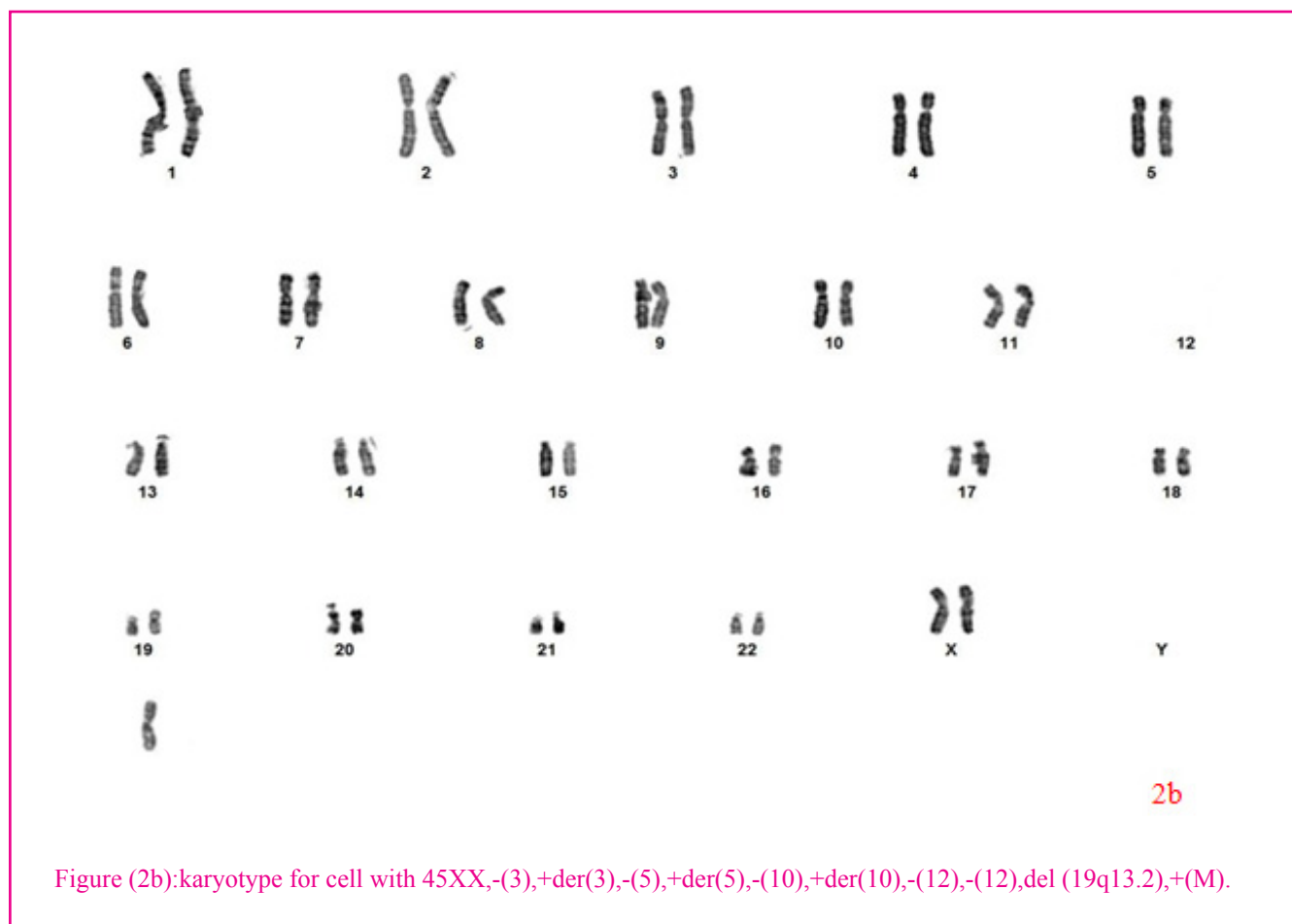


Figure2 :Partial karyotype for chromosomes( 3),(5),(10),(19) and marker (M).



## Discussion:

The presence of primary amenorrhea resulted of autosomal chromosome aberration in association with X-chromosome aberration or only one autosomal aberration was registered as one of a new case [7], but the novel of this report is the primary amenorrhea which result of multi-autosomal aberrations with normal X-chromosomes in the same case. There were complex rearrangements among four chromosomes three of them were interstitial translocations.

The region 3q13-23 translocate to 5q23-34 while 5q23-35 translocate to 10q22-25, while the 10q22-25 translocate to 3q13-23. while the deleted 19p may translocate to 5qter. The exchange of genetic material between sister chromatids and homologous chromosomes is a normal occurrence in somatic and germ cells. These types of exchange ensure mixing of the gene pool and appear to be obligatory for normal cell division. It is only when exchanges occur between non-allelic chromosomal regions that structural rearrangements result. Because chromosome breakage can theoretically occur anywhere within the human genome and the involved chromosome(s) can recombine in innumerable ways, the number of potential rearrangements that can result is immense, on the other hand, the rearrangements of

translocated segment may including a critical genes [8]. Genes are located along the chromosomes, and when there are structural abnormalities in these chromosomes, it is expected disruption of the genes and their functions. Some of the studies have recorded the role of the same chromosomal regions that showed the defect in our current study (3q13, 5q23-35, 10q22-25) which have recorded their roles in the occurrence of primary amenorrhea, but they were associated with the defect in the X-chromosome [7]. Other studies have shown the role of FOXL2 gene which is located in the region (3q23) in premature ovarian failure [9, 10]. FOXL2 (FOXL2 gene production) is a forkhead transcription factor essential for proper reproductive function in females and is central to ovarian development and maintenance [11, 12]. KA6B gene that located at 10q22.2 was recorded to have a role in genital development program [13]. Other study demonstrate that PTEN which located on 10q23.3 plays a fundamental role in the maintenance of chromosomal stability through the physical interaction with centromeres and control of DNA repair. It was proposed that PTEN acts as a guardian of genome integrity, and suggesting that PTEN is essential for embryonic development [14, 15]. This may explain the complex structural rearrangements that have been in our case and the present of second cell line without any copy of chromosome 12 and appearing of marker chromo-

some.

The other important chromosomal aberration is the deletion of chromosome 19p13.2 which is a location for AMH gene. The AMH gene responsible for producing a protein (Anti Mullerian Hormone) which is involved in male sex differen-

tiation. During development of male fetuses. If AMH protein distributed then the Müllerian duct cells never receive the signal for apoptosis. The Müllerian duct persists and becomes a uterus and fallopian tubes. The absence of AMH in female may result in premature ovary failure. [16].

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## عدد من التغيرات الكروموسومية الجسمية في انقطاع الطمث الابتدائي

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### الخلاصة:

انقطاع الطمث الابتدائي الذي يمثل احد التشوهات الجينية الناتجة بشكل شائع من تغيرات في الكروموسومات الجنسية او يمكن ان ينتج عن انحرافات في الكروموسومات الجسمية المرافقة لاحد الانحرافات في الكروموسومات الجنسية او ان تكون بشكل انتقال تبادلي واحد في الحالة المدروسة. الجديد في هذا التقرير انه تم تسجيل اربعة حالات من انحرافات الكروموسومات الجسمية فقط ولم تسجل حالة انحراف في الكروموسومات الجنسية في السيدة التي تبلغ 26 عاما (وهي متزوجة وتعاني العقم) ولها نمط مظهري طبيعي ولها خصائص جنسية ثانوية طبيعية. اعطت انحرافات الكروموسومات الجسمية هيئة كروموسومية مبرقشة وتحتوي انتقالات معقدة وحالات حذف كلي وجزئي وظهور كروموسوم موسوم جديد. حيث ان 98% من الخلايا تمثل الخط الاول و2% من الخلايا تمثل الخط الثاني:

.XX,(3;5;10)(q13-22;q23-34;23-25),(5;19)(qter;p13.2),del(19p13,46).

.XX,(3;5;10)(q13-22;q23-34;23-25),del(12),del(12),del(19p13.2),(M,45

ان المناطق الكروموسومات الجسمية التي تم تضررها تحوي جينات يمكن ان يكون له دور تنظيمي في تطور ونمو الاجهزة التناسلية بشكل سليم.