Inheritance Ppattern of Fragile X-Syndrome in Iraqi Families.

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الخلاصة

تضمنت الدراسة خمس عوائل عراقية من أربع محافظات , و كان العديد من أفراد هذه العوائل يعانون من الكروموسوم الهش. وقد تم تحديد شجرة النسب للعوائل الخمس بوضوح و ذلك لتتتبع النمط الوراثي للكروموسوم الهش. تبين الدراسة إن هناك تناقضا واضحا في نسبة الجنس حيث يصاب الذكور فقط بالإناث يصبن فقط في حالة كونهن متماثلات الاقترانات (الحاملات للإصابة) المتغايرات فأنهن طبيعيات سريريا , ولكنهن ينقلن المرض إلى حوالي (35 %) من أولادهن , وهناك احتمالية (1 من 2) أن تكون بناتهن حاملات للمرض إن الكروموسوم الهش لا ينتقل أبدا بشكل مباشر من أب مصاب إلى أولاده ولكنه ينتقل من خلال بناته إلى الجيل الثاني مما يشير إلى طريقة الطفرة الجينية للوراثة.تؤكد هذه الدراسة على نمو جازم إن الكروموسوم الهش يورث على شكل مرض رابط للكروموسوم .

Abstract

This study included five Iraqi families from four provinces, many members who suffered from congenital fragile X chromosome. Five family pedigrees were drawn up very clearly to follow the pattern of fragile X chromosome. The study showed that there is marked discrepancy in the sex ratio, with only boys affected. Females are affected only if they were homozygous, Heter^{o}zygous (carrier) females were clinically normal but transmitted the disease to 35% of their sons, and there *is* one in two risks that their daughters too were carriers. The fragile X chromosome was never transmitted directly from affected father to his sons but through his daughters to next generation indicating the skip-generation of inheritance. This study suggeststhatfragile X chromosome is inherited as X chromosome linked disease.

Keywords

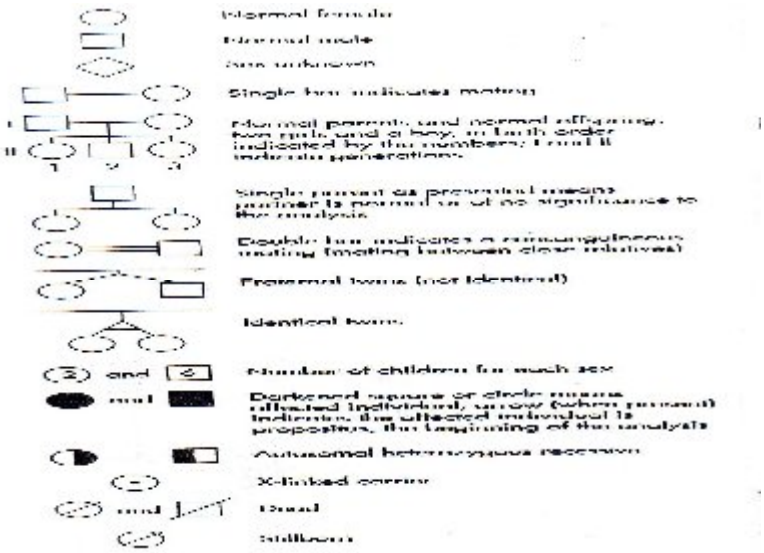
Fragile X chromosome, the syndrome is undoubtedly X- linked, it can not unequivocally be assigned to whether the dominant or the recessive category.

Introduction

The clinical features of the fragile X syndrome include large testes especially after puberty , large protuberant ears and a prominent chin . The average intelligence is in the moderately retarded range, but speech development is disproportionately delayed (1). Carrier females may be completely normal though one-third or more have learning difficulties and some are moderately retarded (2). It is well known that there is an excess of males in the mentally retarded population, but recognition that the maleexcess is chiefly the consequence of X-Linked genes is quite recent(3,4).A common form of X-linked mental retardation has now been defined in which there is a cytogenteic marker of the **X** chromosome and the marker or fragile site is a constriction near the distal end of Xq. (5) .The combination of a defect caused by a mutant gene but associated with a specific cryptogenic abnormality is unique in medical genetics (6). The fragile X is seen only in a proportion (35 percent) of cells of affected males and many carrier females do not show the fragile site at all (7). Genetic analysis of fragile X families has shown some unexpected findings (6, 8) .It appears that 20 percent of males who have the gene are not retarded and there are several large pedigrees in which unaffected males have transmitted the condition to all their daughters, who have had affected sons, thereby proving their carrier status(9) The mutation rate is estimated to 7.2* $l0^{-4}$, an extremely high figure for mutation rate in man(10). The mutation appears never to occur in eggs, but only in sperms; that are affected males themselves are never mutants. However, the mothers of affected males are always carriers and over hall of the mothers are themselves new mutant carriers (11). The hereditary pattern of the fragile X syndrome has not been documented in Iraq. The Iraqi family is firmly stable and family pedigree can be traced correctly and truly which offers a good chance to study the inherited disease.

Materials and methods

Five Iraqi families from four provinces (Qadisiah, Babelon , Mothana,and Najaf) were involved in this study . A kindred of each proband was obtained from him which led to the study of a large pedigree. An attempt was made to examine siblings , parents , material and paternal relatives in each kindred . A possibility was made to examine all alive members Psychological Medicine Clinic, however sometimes some family members were examined in their homes with aid of potable psychiatric Testing unit. All members were interviewed carefully to obtain and confirm the family history and to trace the generation and ancestors .The clinical condition of dead members was obtained from their relatives, and person said to be affected if more than members of his family confirmed that the international genetic symbols of family pedigrees were applied this work to draw up a family pedigree chart as following.



Symbols used in pedigree charts

Results

Family (1):

The mode of fragile X syndrome in this family is shown in figure (2).T his family is from Al-Qadisiah province distributed in rural and urban areas. The proband was employer who led to the study of a large pedigree comprising 98 members (28 members were dead at the time of the study) from six generations . The couple 11 and 12 had nine sib ships (4 and 5 daughters) one (118) was affected with fragile X. The sons 112 - 114 and 117 died before from marriage, but their daughter 113 had seven sibships (2 sons and 5 daughters) all of them were clinically normal. The daughters 119 married a man who had married before from another woman and had six children (5 sons and 1 daughter) iv (12-16). They produced six clinically normal children 1V (6-11). The other daughter 1118 was consanguineous married and had seven apparently normal sibships 1v (12-23) as well. Many consanguineous marriages were presenting the generation as seen in fig. (1).

These marriages resulted in 48 individuals in generation V. The situation in generation V revealed that fourteen cases (V2 , V6 , V7 , V8 , V 10 , V12 , V 14 , V22 , V24 , V28 . V29, V32, V33, V35) were all affected. Another finding in this generation that more than 35% of male were affected. Therefore mothers (1V1, IV3, 1V6, 1V14, 1V22, 1V23) of these males should be carriers to the disease and they passed it to the sons. In addition, these carrier mothers received the mutant X chromosome from their material ancestor (1117 and 111), these who in turn carrier to the disease as well, and they were the daughters of the effected father (118). Therefore the grand mother 12 should be a carrier for this disease. Another affected male V1 appeared in the generation V1 which may indicate that his mother should carry the mutant gene. On the other hand, the women 111 married affected man and produced the only effected boy111 who in turn married and brought five normal boys V (4-5) indicating that the father didn't transmit the disease to his sons .In these generation females who carry permutation are dotted. Affected individuals are presented by solid symbols. A normal transmitting male, who carries permutation of 70-90 repeat units, is designated normal transmitting male. The number of repetition increases each time

the mutation is passed through another female. Also only 5 % of the normal transmitting male's sister one affected and only 9% of his brothers are affected, while 40% of his grandsons and about 16 % of his grand daughters are affected. This family showed the skip-generation method of in heritance where the disease is passed to the next generation by carrier females.

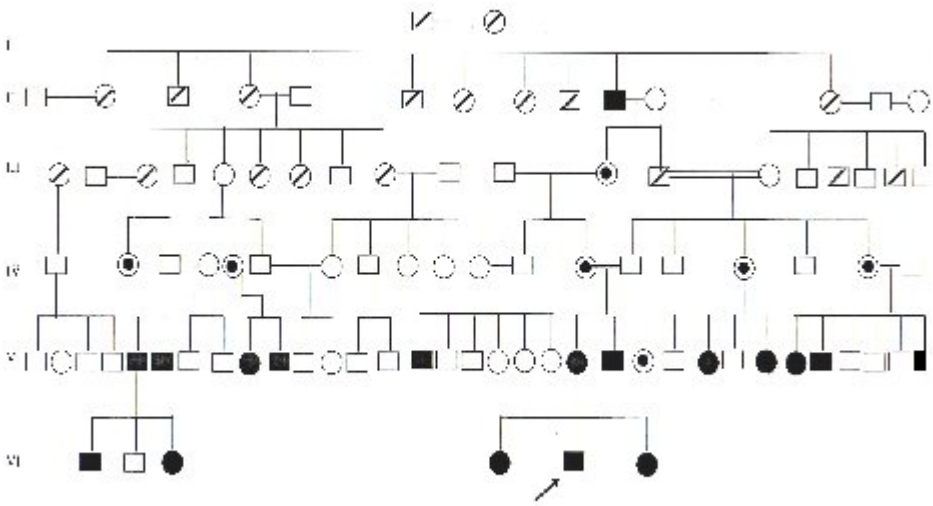


Fig. (1) pedigree of family (1) illustrating the transmission pattern of fragile x syndrome through six generations .

Family (2):

Pedigree illustrating the transmission of fragile **X** syndrome in family 2, The propand was farmer seen in the sycological in clinic of Qadisiah who led to the study of his family which comprised75members(15of them were deadat timeofstudy) from five generations .

The parents (generation) had six sibships their son 116 was affected with fragile X chromosome and their three alive daughters were phenotypically normal. In the generation 111 two male of springs were affected however their father were fragile X chromosome free. The situation was more severe in the generation many consanguineous marriages were presenting the generation 1V. As soon in fig. 2. And in this generation where four men were affected These affected men also had normal father. Therefore

mothers 1V6, 1V7, 1V8 and 1V9 and grandmothers 11 and 1V must carry the gene for fragile X chromosome. This pedigree reveals that all affected persons were males and no female were found suffering from this disease and illustrates the skin-generation method of inherence. The situation was more sever in the generation V where seven men were affected who represented about 35% of the total males is this generation.

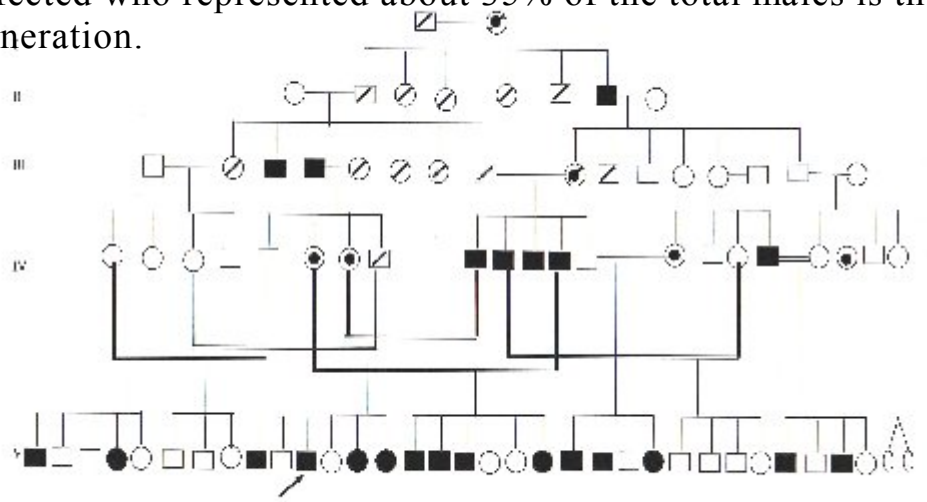


Fig. (2) pedigree of family (2) illustrating the transmission pattern of fragile x syndrome through five generations.

Family (3):

The proband of this family was a tailor in Al-Najaf. He kindly presented valuable efforts to study his family and draw up the pedigree (fig. 4. The number of members studied in family 3 was 44(ten of them were dead) distributed in five generation. The affected father in generation had four clinically normal sib ships. His both daughters 112, 113 had nine children each, three males 1113, 1115, 1116 were affected with fragile who constituted 40% of total males, it is interesting to see in this family that 1114 married twice, in first sibships. One of them was affected male .The second was consanguineous marriage from her affected cousin 1116 they produced five sib ships. Four males of them 1V7,1V8, 1V11 are found 1V10 was consanguineous marriage from her affected cousin 1V12 ,

they produced five sib ships (5 daughters) two was affected , here cousin female 1V 13 married from normal man and produced four sib ships (2 sons and 2 daughters) two males V11 , V13 was affected , Accordingly , the females 112 , 113 , and 1114 , 1117 should be carriers of fragile X syndrome . This pedigree also showed the skip-generation method of inheritance.

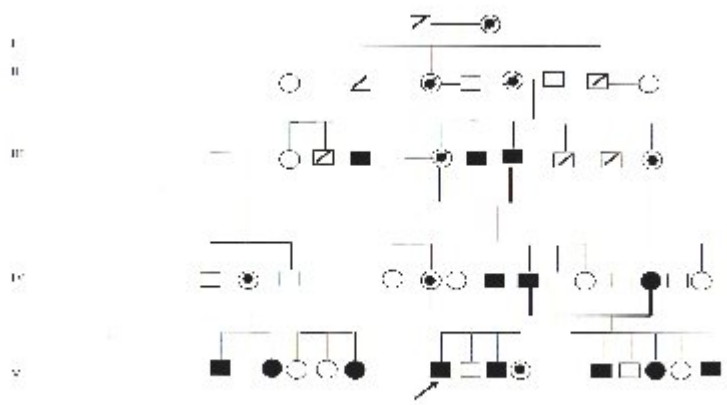


Fig. (5) pedigree of family (3) illustrating the transmission pattern of fragile x syndrome through five generations .

Family (4):

The pedigree of this family showing the pattern of the transmission of fragile syndrome through generation is given in fig. 4. This family is living in rural areas around AL Mothanan, comprising 58 individuals (ten of them are dead) in five generation. The daughter 116 had two fragile brothers and had been married twice from normal men. She produced one affected son from every marriage 1114 and 1116. Her daughter 1111 and 1112, and 1117 has affected sons as well: IV2, IV3, IV6, IV8 and IV10.Comprising about one half of the total males in this generation consanguineous marriage between the affected man IV6 and the apparently normal women IV4 resulted in three sib ships two female one of them was affected V5 and one affected boy V6 . All other females in the generation IV except the women IV12 produced affected sons. V11, V12, V20 and V22 clearly .The females IV9, IV10, IV12, IV13, IV14, IV15, IV16, and IV18

must carry. The fragile syndrome gene on the X chromosome. This disease was not transmitted from father to his sons as seen in this pedigree in which the affected father 1119 produced three normal daughter should be carriers for fragile , this pedigree also showed the skip-generation method of inheritance .

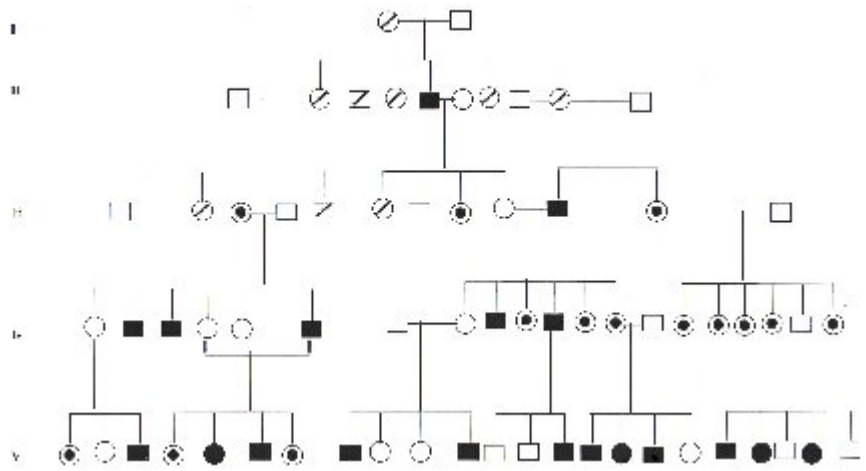


Fig. (4) pedigree of family (4) illustrating the transmission pattern of fragile x syndrome through five generations .

Family (5):

The proband of this family was working in a restaurant in Babylon who led to study of his family which comprised 34 members (10 of them were dead at the time of study) from four generation fig.5. The parents (generation 1) had seven sibships , their son 115 was affected with fragile syndrome and their four alive daughters were phenotypically normal**.** In the generation 111four male off springs were affected however their fathers were fragile free. It is interesting to see in this family the female 114 was married twice the first marriage was from normal men which resulted in sihships one of them was affected male 1v l. The second was consanguineous marriage from her affected cousin ii8 they produced six sib ships of them two males 1v6, 1v9 were affected and two females 1v7, 1v8 were carrier. Her cousin female 114 married from normal man and produced two boys one 1112 was affected. Accordingly the

females113, 1114 should be carriers for fragile, this pedigree also showed the skip-generation method of inheritance.

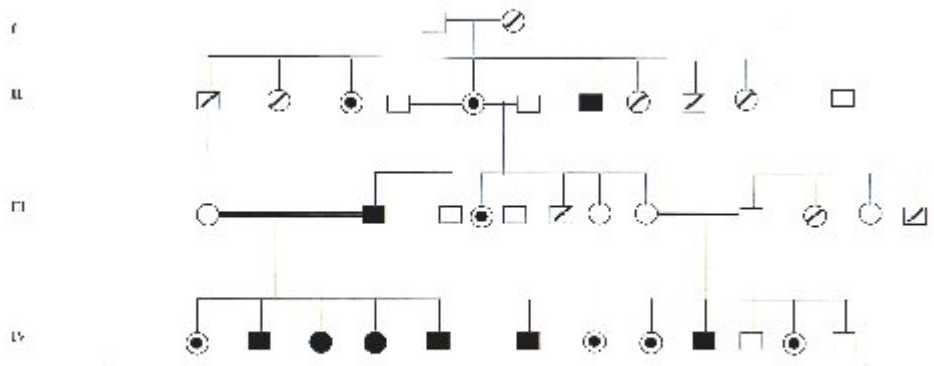


Fig. (5) pedigree of family (5) illustrating the transmission pattern of fragile x syndrome through four generations .

Discussion

Normal male has two chromosomes, (x,y) one of them chromosome X. The marker or fragile site is a constriction near the distal end of xq .Though the syndrome is undoubtedly X-linked; it can not unequivocally be assigned to either the dominant of the recessive category. carrier Females may be completely normal though one-third or more have learning difficulties and some are moderately retarded . The fragile X-Syndrome is seen in only a proportion (35 percent) of cells of affected males. Many carrier females do not show the fragile site at all, and in those who do show it the frequency was much lower than in affected males (12). Family I revealed that there was a marked discrepancy in the sex ratio , with only boys affected heterozygous female were clinically unaffected the parents 11 and 12 produced four sons one of them was affected.The offspring affected man either males or females

were fragile X free. Where as the next generation (Iv) showed that 35 percent of males were affected , This exhibited the skip-generation method of inheritance . In which males passed the trait through daughters about 35 percent of their sons, indicating that fragile X syndrome is inherited as an X chromosome (7, 13). Clearly, mothers of affected sons in this family must have carried the gene for fragile on their X chromosome: and it so happened that was this X chromosome when their sons received. The Female 117 was the second wife to the husband 1115 who had five sons normal from previous wife; she and her sister 1118 had phenotypically normal daughters and sons. The appearance of affected male have not occurred in this generation, however some of these daughters could be carriers of the disease. As expected that was true as the offsprings of these daughters showed several affected males but not females. Those males received the mutant X chromosome from their mothers and because they are homozygous, have any gene on X chromosome can express their effects even when they are recessive, they would be affected.On the other hand, the affected female who married the normal man 118 produced sons. These sons must be affected because he received X chromosome from their mothers, and because both chromosomes, of their mothers had mutant gene therefore any X chromosome received by him must be mutant. Therefore according to above findings clinically normal females produced affected males must be carriers gene of fragile syndrome. A female with affected child and affected brother or a female with more than one affected child is an obligate carrier as the alternative explanation of multiple new mutations is so unlikely (12-14).Similar findings were seen in family 2 in which all the affected members were male only.The pattern of transmission of X chromosome bearing the gene for fragile is perfectly plain , 114 and 118 received it as did two daughters of 114 : 118 , iiii3 and the only , one daughters of 118 : 11122 , some women didn't have fragile sons , They were 111 , 115 , 1112 , 1113 , 1114 and 1117, however one of them (1114) had no sons and the other might in fact prove heterozygous and fragile syndrome and might creep up

amongst their descendants . The skip-generation method of inheritance is obviously recognized in this family. The affected father 117 has no affected sib ships where as his daughter 11119 had affected son indicating that she was carrying the disease.The ship-generation method of inheritance also was noticed in family 3 through the offsprings of the affected male 11. The disease was passed through all his daughters in the average 35% of their sons as seen in generation 111(15). Family 4, 5 showed similar observation which revealed that fragile syndrome was restricted in males, and heterozygous females were apparently normal (16).The most striking thing in both families 3 , 4 , and 5 was the appearance of fragile syndrome affected females 1V5 (family3) , V6 (family4) and V6 family 5 . Both affected females were born due to consanguineous marriage between affected fathers and phenotypically normal mothers.

The mothers must be heterozygous (carriers) with one Mutant X chromosome that passed to their affected daughters who took the other mutant X chromosome form their affected father. Consequently, these affected female should be homozygous to the fragile gene. This is a strong confirmation to indicate that fragile syndrome is transmitted as X linked chromosome it can not unequivocally be assigned to either the dominant or the recessive category (15-16). The results expected from the meetings of heterozygous females had affected and normal sons in approximately equal proportion and this is in agreement with all X chromosome linked (17-18) .

In addition the results in this study have showed that:

1-Carrier females may be completely normal though one-third or more have learning difficulties and some moderately retarded.

2-The fragile X is seen in (35 percent) of cells of affected males. Many carrier females do not show the fragile site at all.

3-There are several large pedigrees in which unaffected males have transmitted the condition to all their daughters who have had affected sons, therefore proving their carrier status.

4-The mother of an affected male are always carriers, and over half of the mothers are themselves new mutant carriers.

5-For genetic counseling in fragile X families the mother of affected male can be assumed to be a carrier

6-The pedigrees showed the skip-generation method of inheritance in which the disease passed from affected father through all his daughters to on average 35% or so of their sons.

7-Carrier females were clinically normal. Accordingly these five pedigrees illustrate the typical features of X chromosome linked inheritance of fragile. Rustles obtained by other researchers have but few approaches for inheritance of fragile. A curious and unexplained preponderance of males has been noticed in fragile patients (19, 20, and 21). On the other hand, other investigators (22) suggested the autosamal dominant inheritance of fragile. Three fragile members belong to one family were noticed (20, 23). Although the hereditary pattern was not mentioned .In addition, ocular fragile showed an X chromosome linked mode of transmission (21, 24). Therefore fragile syndrome may behave as linked diseases.

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References

- Thompson , J.S. ; Thompson , N.W. Genetics in medicine 4th ed.Philadelphia : W.B. Suanders company ; 1986 ;64
- 2-de Vries BB., Hatley Dj,Oostra BA,Niermeijer MF,(1998) .The fragile X syndrome. *Jmed. Genet.* 35: 579-89.
- 3-Kaufinann WE, Reiss AI(1999). Molecular besis and cellular genetics of fragile syndrome . *Am .Jmed. Genet.* 88:11-24.

- 4-Carrel I cottle AA, Goglin KC, Willard HF (1999) .A first – generation X-inactivation profile of human X chromosome . *proc. Natl. Acad. se*; USA 96 : 14440-4
- 5.Hagerman , 2J. (1992).Annotation : Fragile X syndrome : Advances and controversy . *Journal of child psychology and psychiatric .33(7).1127-39*
- 6- Brockdroft no/(1998).The role of Xist in X Inactivations. *Curr.Opan.Genet.Der.* 8:328-333
- 7- Turk,J.Hagerman , R.J.,Barnicott,A.,and McEroy,J.(1994).The fragile X syndrome , in mental health retardation : recent advances and practices .*(ed. No Bouras)*, PP. 135-53.Cambridge University Press .
- 8-Thapar , A. Irving , L. Gotteman, I. etal (1994).The genetics of mental retardation . , *British Journal of Psychiatric* 134 ,747-58.
- 9- Plomin , R. (1995).Genetics and children's experiences in the family.Journal of child psychology and psychiatry 36(1),33-68.
- 10-Therman, E.(1993).Human chromosomes : structure , Behavior,effects . Springer Springer verlag , new York .
- 11.Gittendach M., Gngel W, Schmid M.A. (1997) .Analysis of structure and numerical chromosome abnormalities in sperm of normal men and carriers of constitutional chromosome aberrations ; *areviewHum. Genet.* 100 : 1-2, 1.
- **12- Dykens , E. M. Hodapp , R. and Leckman , J.F. (1994). Behavior and development in fragile X-Syndrome . Developmental clinical psychology and psychiatry 28.**
- **13- Holland, A. J. (1994). Downs syndrome and Alzheimer's disease. In mental health in mental retardation .recent advances and practices*(ed.N. Boures)*,PP.154-67.Cambridge University Press .**
- **Nahily.Yassen.(1995). Inheritance patron of Nystagmus in Iraqi families. *Dep. Of pathy. college of medicine , Uni of Tikret..***
- **15.Connox , .JM; Ferguson - Smith ,M.A. Essential medical genetics.2nd ed. Oxford : Blackwell scientific publications , 1987 :60.**

- **16-Wallace , CD.(1999) .Mitocondrial disease in man and mouse . *Science* 283:1482-8 .**
- **17- Carr, J.(1994). Annotation :long term outcome for people with Downs Syndrome. *Journal of child psychology and psychiatry* 35: 425-39.**
- **18- Cohn MM. (1982). The child with Multiple brith defects New York : *Raven press.***
- **19.Jorde . Garey . Bamshed , White Medical Genetics seconded Mosby :2000 : 99.**
- **Good man, RM, Gorlin R.J. (1983) . The malformed infant and child An illustrated guide . New York : *Oxford University press.***
- **21-Jin P, Warran st. (2000) . Understanding the molecular basis of fragile X Syndrome . *Hum. Molec. Genet*.9:901-908.**
- **22- Hagerman PJ, Creco cm, Hagerman RJ.(2003). A Cerebella ataxia syndrome among fragile X permutation carries cytogenet .Genome.*Res.* 100-206-12.**
- **23-Lachiewics Am , Dawson Dr, Spiridigliozzi , GA. (2000). Physical characteristics of young boys with fragile X-Syndrome reason for difficulties in making diagnosis in young males . *Am. J. Med. Genet.* 92:229-36.**
- **24-Nolin Sl, Brown WT. Glicksman A, Houck , GE, etal. (2003). Expansion of CGG repeats in female with permutation or intermediate alleles . *Am. J. Human . Genet.* 72; 454-464.**