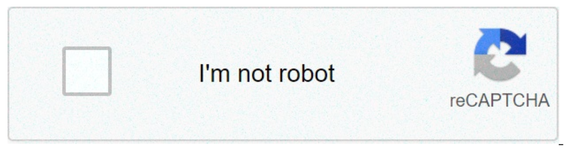

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Karyotype 46 xy means

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The pre-publication history for this paper can be accessed here: Page 2 Case Sex assignment Current age (years) Age at first visit(months) Urethral meatus Vaginal introitus Right gonad (site,type) Left gonad (site, type) 1 M 14 0.5 PS - LS, DT LS, S 2 M 20 8 SCR - LS, DT LS, DT 3 F 4 2.5 Normal male - AB, DT I, DT 4 F 16 0.2 SCR - AB, DT AB, S 5 M 9 0.7 Normal male - I,NB1 I, NB1 6 M 25 4 SCR - LS, DT LS, DT 7 F 19 204 SCR - AB, DT AB, DT 8 M 15 8 Normal male - AB, S AB, DT 9 M 23 1.7 PS - LS, NB I, DT 10 M 2.5 25 PS - LS, T AB, S 11 M 17 6 PS - I, S I, DT 12 M 4 6 SCR - LS, T AB, DT 13 M 12 144 PS - LS, DT LS, DT - absent, + present, AB abdominal, DT dysgenetic testis, F female, I inguinal, LS labioscrotal, M male, NB not biopsied, PER perineal, PS penoscrotal, S streak, SCR scrotal, T testis. 1High FSH levels in the first months of life and infancy. Simply put, chromosomes are the structures that hold our genes. Genes are the individual instructions that tell our bodies how to develop and keep our bodies running healthy. In every cell of our body there are 20,000 to 25,000* genes that are located on 46 chromosomes. These 46 chromosomes occur as 23 pairs. We get one of each pair from our mother in the egg, and one of each pair from our father in the sperm. The first 22 pairs are labeled longest to shortest. The last pair are called the sex chromosomes labeled X or Y. Females have two X chromosomes (XX), and males have an X and a Y chromosome (XY). Therefore everyone should have 46 chromosomes in every cell of their body. If a chromosome or piece of a chromosome is missing or duplicated, there are missing or extra genes respectively. When a person has missing or extra information (genes) problems can develop for that individuals health and development. Each chromosomes has a p and q arm; p (petit) is the short arm and q (next letter in the alphabet) is the long arm. Some of the chromosomes like 13, 14, and 15 have very small p arms. When a karyotype is made (see below) the q arm is always put on the bottom and the p on the top. The arms are separated by a region known as the centromere (red in picture), which is a pinched area of the chromosome. The chromosomes need to be stained in order to see them with a microscope. When stained the chromosomes look like strings with light and dark bands. Each chromosome arm is defined further by numbering the bands, the higher the number, the further that area is from the centromere. How are Chromosome Disorders Diagnosed — Methods of Cytogenetic Investigation Chromosome disorders are of conditions, caused by constitutional numerical or structural abnormalities of chromosomes. Normally every cell of the human body has 46 chromosomes, organized in 23 pairs (22 pairs of autosomes, identical in males and females) and one pair of sex chromosomes – XX in females and XY in males. The only exceptions are egg–cells and sperm–cells, which have only haploid set of chromosomes. All normal egg–cells have karyotype 23,X; the sperm–cells may be 23,X and 23,Y. Fertilization of the egg–cell by 23,X–sperm will lead to development of female, fertilization by 23, Y–sperm will produce male organism 46,XY. Diagnosis of chromosomal disorders requires analysis of chromosomes. Experienced clinicians (geneticists, dysmorphologists) may diagnose many chromosomal disorders by clinical examination. But even if clinical diagnosis is obvious, it has to be confirmed by cytogenetic examination, because almost all chromosomal disorders may exist in different cytogenetic variants with very different prognosis for the family. Therefore, cytogenetic testing is necessary even in patients with a clear clinical diagnosis. Standard cytogenetic examination requires analysis of chromosomes on the stage of metaphase (metaphase analysis). At this stage of cell division all chromosomes became clearly visible structures. All chromosomes may be recognized by their size, position of a centromere and characteristic pattern of dark and light bands, which can be seen after special staining. A cytogeneticist counts number of chromosomes in each of studied cells and compares its size and banding pattern with a standard. If the studied cells have 46 chromosomes with normal structure karyotype of the person considered as normal. If there are some abnormalities it may be evidence of a chromosomal disorder. Basically (in normal conditions) all cells of the organism have the same karyotype. Therefore, theoretically all cells may be used for cytogenetic examination. However, the preferential types of cells for chromosomal examination are cells of chorionic villi or amniocytes (in prenatal diagnosis of karyotype) and lymphocytes (for postnatal examination). Prenatal examination of karyotype is usually performed for several groups of pregnant women. It was shown that pregnancy by a fetus with some chromosomal syndromes (trisomy 21 and trisomy 18) is frequently accompanied by an increase or decrease of several biochemical components of serum. Almost all trisomies (trisomies 13, 18 and 21) occur more often in fetuses of "older" woman (especially after 35 years of age). Age and biochemical parameters (taken together) allow calculation of the risk for Down's syndrome. If this risk is higher that arbitrarily chosen level (for example, higher than 1%) prenatal examination of karyotype is recommended. Some abnormalities of the fetus, which are noted upon ultrasound examination may be another indication for prenatal cytogenetic diagnosis. The examination may be necessary also for the families where one of the parents is a carrier of a balanced structural chromosomal rearrangement – translocation, inversion, insertion or any complex rearrangement. There are several ways to obtain cells, identical to fetal cells. The most known test to obtain cells at early stage (~10–11 weeks) is chorionic villus sampling. Under the control of ultrasound the special instrument is inserted via uterine cervix or thorough the abdominal wall. A small piece of placenta with growing chorionic villi is taken for analysis. Short term cultivation is usually needed. Amniocentesis is a predominant way to obtain cells for prenatal diagnosis. Small amount (5–10 ml) of amniotic fluid is taken from the amniotic cavity via transabdominal amniocentesis. This procedure is usually performed at 14–17 weeks of pregnancy. Amniotic fluid has plenty of amniotic cells. After centrifugation almost all amniotic cells are concentrated at the bottom of the tube. ~1 ml of suspension from the bottom of the tube is placed on the cover slides in the small Petri dishes. A special medium is added to facilitate growth of amniotic cells. After a short-term cultivation (usually 6–7 days) the cells are ready for analysis. A cytogeneticist counts ~20 cells at least from 2 flasks and karyotypes several cells. In some centers the cytogeneticist looks on the cells through the microscope, other centers prefer automatic analysis, when the cytogeneticist looks on the screen of the special computer designed for the selection and analysis of metaphases. There is photographic documentation for every studied person. The results are provided to the patient and (if the results show a chromosomal disorder) the family may decide to continue pregnancy or to terminate it. Technically amniocentesis may be performed also in a more advanced pregnancy. However amniotic cells obtained after 22 weeks had worse growth potentials (than amniotic cells at 14–17 weeks). If karyotype at late pregnancy became really necessary samples of fetal blood may be obtained by puncture of fetal umbilical cord (under guidance of ultrasound). Practically, prenatal cytogenetic diagnosis is a very good method to reduce numerical abnormalities, mostly trisomies. Its role in detection of chromosomal disorders, caused by structural abnormalities is far less, because most women pregnant with fetuses having structural chromosomal defects are young and do not have biochemical indications for amniocentesis. The only (but very important) exceptions are families with structural chromosomal abnormalities in one of the parents. In these families prenatal diagnosis of the karyotype may be crucial for decision about fate of the pregnancy. Actually, the last group of families may benefit from preconceptional diagnosis. This method (or better these methods) may allow selection of normal egg–cells for further fertilization in vitro and implantation of the embryo with already known karyotype. If a balanced rearrangement (usually translocation) is found in a father, his sperm cells are used for simultaneous fertilization of several egg–cells with karyotyping of the very early pre–implantational embryo and implantation of the embryo having normal karyotype. In that case the family does not have to decide fate of unborn fetus. However, there are many technical limitations regarding usage of these methods. Post–natal cytogenetic diagnosis is based in vast majority of situations on examination of the lymphocytes of the peripheral blood. Cells of the peripheral blood are mature cells, they grow and divide in the bone marrow, spleen and lymphatic nodes. Adding of specific stimulator phytohemagglutinin (PHA) is necessary to obtain division of lymphocytes, obtained from peripheral blood. Small amount of blood (less than 1 ml) mixed with PHA and special medium is cultivated in thermostat at 37°C during 72 hours. After it the obtained suspension of dividing cells is treated by Colchicine, which blocks cellular division. Hypotonic solution is added to provide better spreading of chromosomes on the slides. Special staining allows visualization of the chromosomes as structures having an individual pattern of distribution of dark and light bands. Further steps (analysis itself) are basically the same as in analysis of amniotic cells for prenatal diagnosis. However, the standard (visual) cytogenetic analysis does not allow recognition of small deletions or duplications. Even in ideal technical conditions level of recognition is about 5-6 millions of base pairs (Mb). Practically, however, deletions or duplications less than 10 Mb hardly may be recognizable. Fluorescence in situ hybridization (FISH) is a method, which may improve quality of cytogenetic diagnosis in patients, where some structural abnormalities may be suspected. There are probes to some specific segments of DNA. These probes are tagged by fluorescent stains. In normal condition the person will have two areas of hybridization (2 hybridization spots) on the homologous chromosomes. When the patient has a hybridization spot only on one of the homologous chromosomes it means that this segment of DNA on the other homologous chromosome is lost. Vice versa, three spots of hybridization may indicate evidence of a duplication of this segment of DNA. This method may be used also for the study of undivided (interphase) cells, obtained, for example, from a buccal smear (or uncultivated amniotic fluid). Practically, FISH may be used for exclusion (or confirmation) of trisomies or relatively frequent deletions, for example del 22q11.2, which causes diGeorge syndrome or del 7q11.23, which causes Williams syndrome. Limitations of FISH examination are obvious: a) if you have normal results with probes "a", "b" and "c" it means that a patient does not have deletions or duplications for these regions, but does not exclude abnormalities for regions "d" and "e", which have not been tested; b) FISH does not give precise coordinates of the deleted segment. Sometimes, the patient may have mosaicism: the condition, when he/she has several clones of cells with different chromosomal complement. Mosaicism is very common for numerical anomalies of sex chromosomes, but not so common for autosomal trisomies and for structural chromosomal abnormalities. The methods of cytogenetic examination for diagnosis of mosaicism are the same but number of studied cells should be increased. Usually the number of cells with different karyotypes is shown in brackets after the standard formula. For example, the formula 47,XX,+21 [80]/46,XX [20] means that the patient have mosaic trisomy 21 with trisomy in 80% of cells. There are some rare conditions, where an abnormal karyotype may be found predominantly (or even exclusively) in fibroblasts, whereas the lymphocytes show a normal karyotype. This situation is typical for mosaic tetrasomy 12p (Pallister–Killian syndrome) and frequent in some "rare" trisomies. Skin biopsy and cultivation of skin fibroblasts may be necessary for cytogenetic examinations to confirm (or exclude) these syndromes. FISH examination of interphase cells using probes for 12p may facilitate diagnosis of Pallister–Killian syndrome. The ultimate goal of all these methods is diagnosis of constitutional (inherited) chromosomal abnormalities. Structure of chromosomes may be changed in various tumors. The methods for examination of these acquired chromosome abnormalities are out of our scope. Non-invasive prenatal diagnosis (NIPD) of chromosomal disorders is a new method introduced in recent years. Almost all human DNA is organized into chromosomes and located in cells. However, a small part of DNA exists outside the cells. It is a so-called cell-free DNA (cfDNA). When a woman is pregnant a small part of the fetal cfDNA enters the maternal blood through the placenta. Analysis of the maternal blood allows 1) to distinguish maternal and fetal cfDNA, and 2) to analyze presence of some specific components in fetal cfDNA. If a fetus has additional chromosomes 13, 18, 21 or X as well as monosomy X these abnormalities may be discovered analyzing fetal DNA obtained from a maternal blood. It has been shown that NIPD detects virtually all cases of trisomy 18 or trisomy 21 as well as the vast majority of other trisomies or monosomy X. Normal NIPD test results also offer the opportunity to avoid CVS or amniocentesis, which are more traumatic and (in rare cases) may lead to a miscarriage. NIPD may be performed after 10 weeks of pregnancy. Although there are some reports of discovery of structural abnormalities (deletions or partial trisomies) via NIPD it is too early to say for certain that this method is reliable for diagnosis of such conditions. Currently medical insurances cover the cost of NIPD for pregnant women over 35 years old and for the families with chromosomal abnormalities in a previous child or fetus. What is a Karyotype? A karyotype is an actual photograph of the chromosomes from one cell. The cells analyzed are usually white blood cells from a regular blood draw or from a prenatal specimen. After staining the chromosomes can be seen as banded strings under 1,000 x magnification. They are analyzed by specially trained cytogenetic technologists, Ph.D cytogeneticists, or medical geneticists. Cytogenetics is a word for the study of chromosomes. After analysis under the microscope a picture (karyotype) is printed. karyotype Normal Male Karyotype – a female would have two Xs instead of an X and Y. In a karyotype the chromosomes can appear bent or twisted. This is normal and is simply reflecting how they are sitting on the slide. Chromosomes are flexible structures made up of DNA. The coding order of that DNA makes up the genes. Chromosomes are analyzed during a time in the cell cycle when they are compact. During other times in the cell cycle the chromosomes unwind into long strands of DNA. At that time we would not be able to see them under the microscope. If you were to pull out all the chromosomes into long strands of DNA there would be over 7 feet of DNA in each cell! Thats about 80 billion miles of DNA in the average human adult! Sometimes when chromosomes are analyzed a High Resolution Analysis is performed. This means the chromosomes are examined when they are a little longer than a standard analysis. Since they are longer more bands can be seen. This is usually done when a small deletion or duplication is thought to be present. There are different types of staining that make the chromosomes look differently. The stain which is used depends on what type of abnormality cytogeneticists think they might be seeing. This helps to help clarify the results. How are Chromosomes and Chromosome Abnormalities Labeled? In 1960 the first meeting to propose a standard system of naming the chromosomes took place. Since that time this method of describing chromosomes and chromosome abnormalities has been revised and added to several times. It has produced an International Standard of Cytogenetic Nomenclature. This allows one lab to write out the chromosome findings. Any other lab will know what they have found without looking at the karyotype. Here are some examples: 46,XX – Normal Female Karyotype 46,XY – Normal Male Karyotype These descriptions say there are 46 chromosomes and that it is a male or female. 46,XX,del(14)(q23) Female with 46 chromosomes with a deletion of chromosome 14 on the long arm (q) at band 23. 46,XY,dup(14)(q22q25) Male with 46 chromosomes with a duplication of chromosome 14 on the long arm (q) involving bands 22 to 25. 46,XX,r(7)(p22q36) Female with 46 chromosomes with a 7 chromosome ring. The end of the short arm (p22) has fused to the end of the long arm (q36) forming a circle or ring 47,XY,+21 Male with 47 instead of 46 chromosomes and the extra chromosome is a 21. (Down Syndrome) There are literally millions of types of abnormalities. If your child has a chromosome abnormality the above nomenclature describes exactly what it is. Ask your genetic counselor, physician, or health care professional to describe the chromosome abnormality found. Below are a few of the codes used in the standard nomenclature. add = Addition material of unknown origin del = Deletion de novo = A chromosome abnormality which has not been inherited der = Derivative Chromosome dic = Dicentric dup = Duplication fra = Fragile Site idic = Isodicentric chromosome ins = Insertion inv = Inversion i or iso = Isochromosome mar = Marker chromosome mat = Maternal origin Minus sign (-) = Loss mos = Mosaic p = Short arm of chromosome pat = Paternal origin Plus sign(+) = Gain q = Long arm of chromosome r = Ring chromosome rcp = Reciprocal rea = Rearrangement rec = Recombinant chromosome rob = Robertsonian translocation t = translocation tel = Telomere (end of chromosome arm) ter = Terminal end of chromosome upd = Uniparental disomy ? = Uncertain It is important to note that most chromosome abnormalities occur as a accident in the egg or sperm. Therefore every cell in the body would have the abnormality. Some abnormalities can happen after conception and individuals can have a mosaicism (some cells with the abnormality and some without). Chromosome abnormalities can be inherited from a parent, like a translocation, or be de novo (new in that individual). If an examination was performed using array-CGH technology the formula will show not only the deleted or duplicated areas, but also the breakpoints, indicating the start and end of the deleted or duplicated segment. For example, if the standard cytogenetic formula looks like del(8)(q13.2q13.3), the same person's formula re-examined by array technique will look like: arr[hg19] 8q13.2q13.3 (69,902,365-72,554,018)x1. This shows that the deleted segment is from position 69,902,365 till position 72,554,018. Usually a conclusion includes a list of genes lost upon such deletion. The same is true for duplication. The standard formula may look like dup(18)(q22.1q22.3). The same person examined by array techniques may have the formula: arr [hg19] 18q22.1q22.3 (63,719,224-69,023,919)x3. [hg19] indicates which version of human genome system was used to determine the position of the breakpoints. Hg 19 is the newest version. What is a Chromosome Deletion? A chromosomes deletion is when a part of a chromosome(s) has been deleted. A deletion can occur on any chromosome, at any band, and can be any size (large or small). What a deletion causes depends on how big a piece is missing and what genes are missing in the section (i.e. where the deletion is). Under chromosome analysis the section that is missing can usually be determined. However it is difficult to compare one child with a particular deletion to another with the same deletion. Remember that looking at the chromosomes is the big picture, like looking at an encyclopedia set from about 10 feet away. We are usually able to detect the deletion. Some are too small to see and other technologies can be used, but it is impossible to say at exactly what spot the deletion started and ended. So one individual might have a few more genes deleted than another individual with the same deletion. In the above example the area in the blue brackets is not present (deleted) in its pair designated by the red arrow. The other 22 pairs of chromosomes were normal (not shown). The nomenclature for this deletion would be: 46,XX,del(1)(q24q31) Female with a deletion of chromosome 1 on the long arm (q) between bands q24 to q31. Some deletions occur more frequently and are associated with a particular syndrome such as 46,XX,5p-, also called cri-du-chat syndrome. Gene Mutation versus Chromosome Deletion Contemporary methods of molecular genetics can reveal numerous changes within a gene. Some of these changes technically may be deletions, when there is a loss of several nucleotides or even several exons within one gene. [Almost every gene consists of several exons (parts that participate in coding the proteins) and introns (basically non-coding areas necessary for the structural integrity of a gene). Exons may be compared with the bricks in a wall, whereas introns are like the cement areas]. The changes limited to one gene should be considered mutations. Chromosomal disorders by definition are conditions when there is loss or excess of a significant segment of the chromosome involving at least several consecutive genes. It does not exclude the possibility that only one of several lost genes may be the main player responsible for all (or almost all) of the clinical manifestations in the patient. What is a Chromosome Duplication? A duplication is just that, a duplication of a section of a chromosome. A duplication is sometimes referred to as a partial trisomy. Trisomy refers to three. Therefore if a duplication exists, that individual has three copies of that area instead of two. This means there are extra instructions (genes) present that can cause an increased risk for birth defects or developmental problems. In the picture, red arrows point to identical bands on each chromosome. The blue arrow points to a duplication of the band at the red arrow. You can see that the chromosome on the right is longer. The nomenclature for this abnormality would be: 46,XY,dup(7)(q11.2q22) Male with a duplication of chromosome 7 on the long arm (q) between bands 11.2 to 22. What is a Chromosome Ring? A ring chromosome can happen in two ways. One is demonstrated in the picture; the end of the p and q arm breaks off and then stick to each other. The blue parts of each are lost thus resulting in loss of information. Second, the ends of the p and q arm stick together (fusion), usually without loss of material. However the ring can cause problems when the cell divides and can cause problems for the individual. It is also possible to have a ring and be apparently healthy with no delays in development. As with all chromosome abnormalities it depends on what is actually found, the size of the ring, how much material was lost, which chromosomes are involved etc. What is a Chromosome Translocation? Translocations can be a little tricky. Above is an example of a balanced translocation. The long arms of chromosome 7 and 21 have broken off and switched places. So you can see a normal 7 and 21, and a translocated 7 and 21. This individual has all the material needed, just switched around (translocated), so they should have no health problems, because it is balanced. However there can be a problem when this person has children. Remember that when the egg or sperm is made, each parent gives one of each chromosome pair. What would happen if this person gave the normal seven and the 21p with 7q attached? Look below: unbalanced translocation There is an extra copy of 7q. If you count them you will find three copies of 7q instead of two. And there is only one copy of 21q. Therefore this is unbalanced, there is extra and missing information that can lead to birth defects, cognitive abnormalities, and an increased risk for miscarriage. For many unbalanced rearrangements it is not possible to predict what abnormalities to expect. What is a Chromosome Inversion? An inversion consists of two breaks in one chromosome. The area between the breaks is inverted (turned around), and then reinserted and the breaks then unite to the rest of the chromosome. If the inverted area includes the centromere it is called a pericentric inversion. If it does not, it is called a paracentric inversion. Notice that in a pericentric inversion one break is in the short arm and one in the long arm. Therefore an example of a cytogenetic nomenclature might read 46,XY,inv(3)(p23q27). A paracenteric inversion does not include the centromere and an example might be 46,XY,inv(1)(p12p31). When a parent has an inversion there is an increased risk for offspring with an incorrect amount of genetic material. This can lead to babies with birth defects and/or abnormal development or an increased risk for miscarriage. The possible pregnancy outcomes for an individual with an inversion is rather complicated and depends on how big the inversion is, where it is, and what type of inversion is present, paracentric or pericentric. There are many inversions that occur in the general population that are called normal variants. Including Inv(9) and Inv(2). These inversions are not related to an increased risk of birth defects and/or developmental difficulties. This has been a simplified description of chromosomes and their abnormalities. Chromosome analysis is full of exceptions and results that can be difficult to interpret. The information above is for educational purposes only. If you have a question about a specific chromosome abnormality please contact your physician or a genetic professional. You can find a genetic counselor through the National Society of Genetic Counselors Homepage at: www.nsgc.org Jeff Shaw M.S. Genetic Counselor Dr. Iosif Lurie Medical Geneticist CDO would like to thank the following labs for contributing example karyotypes for this article: Centura Health Penrose-St. Francis Health Services Cytogenetics Lab Colorado Springs, CO