

# Use of karyotype analysis in genetic counseling biology essay



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Complete set of metaphase chromosome is called karyotype. It is widely used to detect the chromosomal abnormalities that are related to the genetic diseases and various type of cancer. As the biomedical science advances, various kinds of techniques are used to analyze the human karyotype. These karyotype analysis are widely used in genetic counseling to minimize the risk of having unfortunate. By doing so, individual and families are realized to implement the genetic testing.

In genetic counseling, knowledge of karyotype analysis is greatly determined the inheritable diseases including cancer. Moreover, Pedigree construction based on Mendelian principles is used in old days to know the pattern of inheritance. In recent year, FISH (fluorescence in situ hybridization), PCR (polymerase chain reaction), CGH (comparative genomic hybridization) and SNP (single nucleotide polymorphism) arrays are developed for the promising future of human genetics. Among them FISH is the most currently diagnostic tool for the various chromosomal aberrations that can be visible in karyotype analysis. The most tested chromosomes are 13, 18, 21, 22, X and Y that account for 85% of chromosomal abnormalities (Rodrigo et al., 2010). But now, genetic scientists have been carried out the approaches towards all chromosome analysis. On the other hand, the high risk society is greatly interested to do pre pregnancy counseling to reduce the inheriting defective gene for the next generation. Therefore, use of karyotype analysis is more and more improved in genetic counseling for the screening and diagnosis as well as the treatment and prevention.

### Karyotyping

Karyotype construction and analysis is the powerful diagnostic method to identify the chromosomal studies in human genetic. Karyotyping is usually done at the metaphase of cell cycle in which the chromosome structure is the most condensed. Therefore, it is also known as complete set of metaphase chromosome (Nie et al., 1998).

There are 46 chromosomes in human (22 autosomes and sex chromosomes). Karyotype show the number of chromosomes, the sex chromosome content, the presence or absence of individual chromosomes and the nature and extent of any structural abnormalities. Karyotyping can be accessed under a microscope to examine the number and structural variants which must be size of 3 Mb or more. Only DNA sequencing can be observed smaller alterations (Klein and Tibboel, 2010).

Chromosomes in human karyotype are categorized into seven depend on their bands after staining procedure. Each group is arranged into A to G defined by size and centromere position. These banding patterns help to identify specific defect regions on the chromosome. Thus, the any defect in chromosome region can be described as an accurate address. For example; 1q2. 4 defines as chromosome number 1, q arm, region 2 and the banding 4 (Trask, 2002).

## Method

For karyotype construction, the specimen can be taken from the white blood cell, skin cells, amniotic fluid cells and the chorionic villus cells. Then the cells are prepared to enter the mitosis and arrested in the stage of

metaphase. Moreover, these preparations are treated with trypsin and <https://assignbuster.com/use-of-karyotype-analysis-in-genetic-counseling-biology-essay/>

staining to get the banding pattern. After that, video camera attached microscope directly send the images to the computer to generate the karyotypes (Yang et al., 2000).

Generally, it could be used to determine if chromosome of an adult have abnormality or defect that can be passed on to a child. The origin of complex chromosomal defect is identified by using standard G-band procedures, fluorescent staining and fluorescent in situ hybridization (FISH) and comparative genomic hybridization (CGH). FISH is a recent technology to detect the specific chromosome structure by using particular DNA probes. This method is more accurate and enables to see the micro-deletion and exact break point involved in each chromosome (Ligon et al., 2997).

Doing the karyotype analysis is benefit in pregnant women at the age of 35 and having the history of previous child with defect. Because of the risk of chromosome abnormalities dramatically increased in advanced maternal age and if the mother is an X-linked carrier, the recurrent risk is 1 to 2%.

Therefore, antenatal screening tests including karyotyping are carried out to a defined population who are at risk of having a specific condition. Different tests are done in different stages of pregnancy. Chorionic villus sampling is offered at 11-12 weeks of pregnancy, Amniocentesis is done at 16 weeks and fetal blood sampling is carried out at 18-22 weeks of pregnancy. Although these all procedures are having risk of miscarriage, they are suitable for the chromosomal and DNA analysis (Callen et al., 1988). Especially, for the detecting of trisomies in chromosome 13, 18, 21, X and Y which account for more than 85% of all fetal aneuploidies.

As a benefit, if a couple with a known risk to offspring, they can choose options to avoid or plan further pregnancy. If the male partner is affected, the couple has option for artificial insemination of sperm from a donor. If the female is affected with a dominant condition or X-linked carrier, the couple has option for egg donation from another female. Moreover, the relatively new procedure is pre-implantation genetic diagnosis. Initially, this process requires in vitro fertilization. If the fertilization occurred, one cell is removed from the stage of blastocyst and then investigated for the chromosomal disorder. If there is no defect, it will be returned to the uterus (Fukuda et al., 2007).

In the molecular genetics, DNA testing is divided into four main categories which are diagnostic testing, carrier detection, pre symptomatic testing for adult onset diseases and prenatal diagnosis. In the genetic counseling, karyotype analysis is widely used in carrier detection incase of balanced translocation carrier, autosomal dominant recessive, X-linked female carrier disorder in order to evaluate the risk of having an affected child.

Furthermore, karyotyping can be used as a pre symptomatic or predictive test in some individual who are at risk of an adult onset disorder to determine whether or not they carry the mutated gene for these disorders. This test is value for autosomal dominant condition because of having a chance is 50% if one parent is affected. For example, familial adenomatous polyposis, colon cancer, Huntington disease (Bodmer et al., 1991).

Chromosomal aberrations

Abnormalities of the chromosomes, these are large enough to be visible under the light microscope are termed chromosomal aberrations. They are usually classified into numerical abnormalities and structural abnormalities. Numerical aberration is the disordered of chromosome due to error in separation of chromosome in cell division. Aneuploidy represents gain or loss of a specific whole chromosome due to failure of paired chromosome in meiosis. The one with extra copy of chromosome is called trisomy and the one with missing copy of that chromosome is called monosomy. These can be seen either autosome or sex chromosome. Autosomal trisomy will result in early miscarriage and monosomy of an autosomal chromosome is not compactable with life. Autosomal trisomy is associated with increased maternal age (Harper et al., 1995).

Similarly, polyploidy represents a complete extra set of chromosomes due to fertilization by two sperms (dispermy) or failure in maturation divisions of either the eggs or the sperm. For examples, triploidy and tetraploidy depending on the number of extra sets of chromosomes. Triploidy occurs in 2% of all conception but early spontaneous abortion is usual (Munne and Cohen, 1998).

The most commonly seen autosomal aneuploidies are trisomy 21-Down's syndrome (47, XX, +21 or 47, XY, +21), trisomy 18-Edward's syndrome (47, XX, +18 or 47, XY, +18), trisomy 13-Patau's syndrome (47, XX, +13 OR 47, XY, +13). Sex chromosomal aneuploidies are Klinefelter syndrome (47, XXY), XYY syndrome (47, XYY), Triple X syndrome (47, XXX) and Turner syndrome (45, X).

Autosomal monosomy is mostly lethal and autosomal trisomy is relatively more common (Rodrigo et al., 2010). The commonest autosomal trisomies are Down's syndrome, Patau syndrome and Edwards syndrome. The karyotype of Down's syndrome is 47, +21, an extra copy of chromosome 21. It occurs in 1 in 900 live births and leading cause of childhood mental retardation and heart defect (Wald et al., 1997). Patau syndrome is usually found at the time of doing cytogenetic analysis in malformed children. It also revealed extra chromosome at chromosome number 13 (47, +13) (Rasmussen et al., 2003). Another trisomy is the Edwards syndrome (47, +18). It accounts for a frequency of 1 in 11, 000 live births (Massiah et al., 2008).

#### Aneuploidy of the sex chromosome

Aneuploidy of the sex chromosomes is more common than the autosomal aneuploidy but have less impact. Unlike the autosome, monosomy for Y chromosome is always lethal whereas monosomy for the X chromosome is a viable condition. The commonest syndromes that have ever seen in clinical setting are Turner syndrome, Klinefelter syndrome, Triple X syndrome and XYY syndrome (Smith et al., 1960).

Monosomy of X chromosome results in 45, X karyotype due to non-disjunction in either parent. It is estimated that 1% of all conception from which 95 to 99% of all 45, X embryos die before birth. They have significant defect in height, sexual development and fertility but there is no mental retardation (David et al., 1986).

The karyotype of Klinefelter syndrome is 47, XXY. The extra X chromosome of maternal origin is 56% and paternal is 44%. It is usually arise from non-disjunction at either the first or second meiotic division (Lamb et al., 1996). For example, if the father produces XY sperm that is cross over with maternal X ovum to produce XXY. This is the single commonest cause of hypogonadism and infertility in male. Overall the birth incidence of 47, XXY is 1 in 1000 male with an increased risk at maternal age and azoospermatic infertile males (Steinberger et al., 1965).

And the karyotype of super female syndrome is 47, XXX which also known as triple X syndrome. It is usually appears as clinically normal but 15- 25% are mildly mentally handicapped. About three quarter of the affected females is fertile of which one- half of their offspring would expect to have this syndrome (Michalak et al., 1983). Furthermore, another karyotype defect associated with personality disorder is 47, XYY syndrome. It is firstly noted in 1965 cytogenetic survey in male for violent and dangerous antisocial behavior and about 4. 5% of the males in this survey were shown as XYY karyotype. The frequency of having this characteristic karyotype in general population is 1 in 1000 birth according to the sub sequent studies. The recurrence risk for the offspring would be 2XXY : 2XY : 1XX : 1XYY due to production of YY sperm at the second meiotic division or post-fertilization non-disjunction of the Y (Staessen et al., 2003).

Structural aberration is the disordered in the structure and shape of the chromosome resulting from chromosomal breakage and error in rejoin mechanisms. Translocation is the transfer of chromosomal material between non-homologous chromosomes but there is no DNA loss. Three recognizable <https://assignbuster.com/use-of-karyotype-analysis-in-genetic-counseling-biology-essay/>



translocations are reciprocal, centric fusion (Robertsonian) and insertion. The one important thing in translocation is the balanced reciprocal translocation which occurs in two non-homologous chromosomes (Michael and Malcolm, 1997). In normal population, 1 in 500 are known balanced carrier and they are clinically healthy but they can give a problem when they reproduce. It is possible for the balanced translocation carrier to pass on the translocation in unbalanced form that can lead to miscarriage and physical or developmental problem (Munne et al., 2000).

Deletion is the loss of a part of chromosome that can cause phenotypic effect because of the loss of gene. For a deletion to be seen in karyotype analysis, the amount of deletion must be large. It may also occur as a result of an unbalanced translocation (Barber, 2005). Although deletion of a small piece of chromosome is not a serious problem, deletion of entire chromosome is lethal. Therefore, only a few viable conditions are found in large deletion. These are the listed below;

Adapted from Human Heredity Principles and Issues, seventh edition, 2006

Region of deletion

Related disease

5p-

Cri du chat syndrome

11q-

Wilm's tumour

13q-

Retinoblastoma

15q- (maternal uniparental disomy)

Prader-Willi syndrome

15q- (paternal uniparental disomy)

Angelman syndrome

Cri du chat syndrome is caused by deletion in short arm of chromosome 5 and incidence is 1 in 100,000 births (Cerruti, 2001). A characteristic feature of the affected child is having a sound of cat like cry (Niebuhr, 1978). The phenotype is slightly different depend on their chromosome break point. There are two regions of break point in the short arm of chromosome 5 have been identified in this syndrome. Loss of chromosome segment in 5p15.3 results in abnormal larynx development and deletion in 5p15.2 is associated with mental retardation (Overhauser et al., 1994; Simmons et al., 1995).

Prader-Willi syndrome and Angelman syndrome are caused by deletion in region 15q11-13 or by uniparental disomy (Ledbetter, 1981). If both copies of chromosome are inherited from the father, the child will have Angelman and from the mother, the child will have Prader-Willi syndrome (Horsthemke, 1996). The incidence of Prader-Willi is 1 in 10,000 whereas Angelman is 1 in 20,000 live birth (Clayton-Smith, 1993; Petersen et al., 1995). Characteristic

feature of Prader Willi syndrome is sleepiness and Angelman is bouts of laughter (Zori et al., 1992). These cytogenetic microdeletions in the long arm of chromosome 15 can be visible by using either FISH (fluoresce in situ hybridization) or DNA analysis with probes from the deleted region (Nicholls, 1994).

The others structural abnormalities include duplication, inversion and mosaicism and the rare structural variants are fragile site, heteromorphisms, isochromosome and ring chromosome.

### Cancer genetics

Some of the cancer can be detected by karyotype analysis. The connection between chromosome rearrangement and cancer is evident in leukemia. The specific chromosome translocation between chromosome 9 and 22 is called the Philadelphia chromosome. That can be used as well defined diagnostic tool and prognostic factor. Moreover, this specific translocation is associated with other forms of cancer including Burkitt's lymphoma and multiple myeloma.

### Chromosome translocation associated with haematological cancers

#### Translocation site

#### Type of cancer

t(9; 22)

Chronic myeloid leukemia (Rajasekariah et al., 1982)

t(8; 14), t(8; 22), t(2; 8)

Burkitt's lymphoma (Margrath, 1990)

t(8; 21)

acute myeloblastic leukemia (Oshimura et al., 1976)

t(4; 18)

follicular lymphoma (Fleischman and Prigogina, 1977)

t(4; 18)

acute lymphocytic leukemia (Oshimura et al., 1977)

The proportion of leukemia with a heritable component has been estimated as 25% in monozygotic twin. Risk to sibs in childhood leukemia is 2- 4 times higher than the population incidence. The risk of a relative developing Hodgkin's disease is seven fold higher than other (Kelly, 1992).

Genetic counseling

Genetic counseling should be offered to both parents and must give adequate time under appropriate setting. Depth of explanation should be matched to education background of the couples, outlining of clinical features, complication, natural history, prognosis and effective management (Frets et al., 1991). Simple Explanation of the genetic basic of the condition with the aids of diagram and recurrent risk calculation should be carried out (Sermon, 2002).

Furthermore, genetic counselor can give the suggestion to reduce the risk of having disorder. The options are no further pregnancy, adoption, in vitro fertilization with pre implantation diagnosis, artificial insemination-AID by donor (egg donation), termination pregnancy, OR ignore and accept the risk (Zare et al., 1973). AID is performed for husband with AD trait or both are carrier for a serious AR (Taranissi, 2005).

The important thing in genetic counseling must be non- judgemental and non-directive. The aim is to deliver a balanced version of the facts which will permit the consultants to reach their own decision with regard to their reproductive future.

In UK, congenital disabilities act of 1976 legal action can be brought against a person whose breach of duty to parent's results in a child being born disabled, abnormal or unhealthy. Prenatal diagnosis with selective termination of pregnancy became a reality in UK with the abortion ACT OF 1967 (Macintyre, 1973).

AD trait is the risk to each child of an affected person is 1 in 2. Disorder has high penetrance, most dominant trait shows variable expression. AR trait for the carrier parents, the risk recurrence risk is 1 in 4 diseases, 2 in 3 chance of being carrier (Yoshikawa and Mukai, 1970).

In X-linked recessive trait, if females are obligate carrier, one half of her sons will be affected and one half of her daughter will be carrier. If affected male reproduce, there will be normal sons and carrier daughters. Nowadays, biochemical tests may be available for carrier detection, but because of X inactivation few of these are absolute and this information needs to be <https://assignbuster.com/use-of-karyotype-analysis-in-genetic-counseling-biology-essay/>

combined with the pedigree risk using Bayes' theorem (Markova et al., 1984).

Conditions need for genetic counseling and investigation (Watson et al., 1992)

1. Infertility - one in ten of all couples are involuntarily infertile, such a couple need chromosomal analysis to exclude a balanced structural rearrangement and Klinefelter syndrome.
2. Recurrence miscarriage - one of six pregnancy ends as a spontaneous miscarriage. 3-5% of cases have a balanced structural rearrangement
3. Still birth
4. Perinatal death with multiple malformations

## Conclusion

The benefit of karyotype analysis in high risk population provides the prevention and early management options to minimize the risk. As the genetic science development, researchers and clinician have more advanced diagnostic tool like multiplex PCR, SNP microarray, CGH (comparative genomic hybridization) to identify the far more complex chromosome abnormalities. Although karyotyping by FISH can detect both balanced and unbalanced translocation, uniparental disomy can only be detected by SNP arrays and high output sequencing. Despite the high cost, enormous benefit can be found for the society to evaluate the superior treatment protocols and genomic technologies for the future.