Karyotype analysis to detect cancer

Abstract

A complete set of metaphase chromosomes is called a 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 introduced to analyze the human karyotype. These karyotype analyse are widely used in genetic counselling to minimize the risk of having unfortunate abnormalities that can cause serious limitation on quality of life. So, nowadays individual and families are realized the necessity to implement the genetic testing.

Introduction

In genetic counselling, knowledge of karyotype analysis is greatly used to determine the heritable diseases including cancer. Moreover, pedigree construction based on Mendelian principles was used in days gone by the determinable pattern of inheritance. In recent years, FISH (fluorescence in situ hybridization), PCR (polymerase chain reaction), CGH (comparative genomic hybridization) and SNP (single nucleotide polymorphism) arrays have been developed and hold a promising future for 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 carried out all the approaches towards chromosome analysis. On the other hand, with the high risk society is greatly interested to do pre pregnancy counselling to reduce the heritable defective genes for the next generation. Therefore, use of karyotype analysis has been more and more

improved in genetic counselling for the screening and diagnosis as well as for treatment and prevention.

Karyotyping

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

There are 46 chromosomes in humans (22 autosome pairs and sex chromosomes). Karyotypes 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 observe smaller alterations (Klein and Tibboel, 2010).

Chromosomes in all human karyotype are divided into seven categories depending on their size and 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, any defect in chromosome region can be described as accurately. For example; 1q2. 4 defines 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 chorionic villus cells. Then the cells are prepared to enter mitosis and arrested in the stage of metaphase. Moreover, these preparations are treated with trypsin and staining to obtain the banding pattern. After that, a video camera attached microscope directly sends the images to the computer to generate the karyotypes (Yang et al., 2000).

Generally, the karyotype can be used to determine if chromosome of an adult has an abnormality or defect that can be passed on to a child. The origin of complex chromosomal defects is identified by using standard G-banding procedures, fluorescent staining, FISH and CGH. FISH is a recent technology to detect the specific chromosome structure by using particular DNA probes. This method is more accurate and enables the detection of micro-deletions and exact break points involved in each chromosome (Ligon et al., 2007).

The karyotype analysis is of benefit to pregnant women at the age of 35 and having the history of a previous child with a defect. Because the risk of chromosome abnormalities is 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 pregnant women who are older than 35 years and those with family history of chromosomal abnormalities. Different tests are done in different stages of pregnancy. In first trimester, these high risk mothers are conducted by non-

invasive procedures like high resolution ultrasound for nuchal translucency and PAPP-A (pregnancy associated plasma protein A) for trisomy 21 to exclude the major chromosomal abnormalities. Then “ triple test” consisting of a serum Î±-fetoprotein, unconjugated oestradiol and human chorionic gonadotrophin is usually carried out in second trimester. If the abnormalities are detected, it is necessary to continue some invasive procedures like chorionic villus sampling and amniocentesis for cytogenetic testing.

Chorionic villus sampling is offered at 11-13 weeks of pregnancy, Amniocentesis is done at 15 weeks and fetal blood sampling is carried out at 18-22 weeks of pregnancy. Although all these procedures carry the risk of miscarriage, they are suitable for chromosomal and DNA analysis (Callen et al., 1988). Particularly for the detection of trisomies in chromosome 13, 18, 21, X and Y because which account for more than 85% of all fetal aneuploidies.

As a benefit, if a couple has a known risk to offspring, they can choose options to avoid or plan further pregnancy. If the male partner is affected, the couple has the option for artificial insemination of sperm from a donor. If the female is affected with a dominant condition or is an X-linked carrier, the couple has the option for egg donation from another female. Moreover, a relatively new procedure is pre-implantation genetic diagnosis. Initially, this process requires in vitro fertilization. If fertilization occurred, one cell is removed from the stage of the 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 genetic counselling, 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 individuals 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 of value for autosomal dominant condition because of having a chance is of 50% if one parent is affected. Familial adenomatous polyposis, colon cancer and Huntington disease are the examples of autosomal dominant (Bodmer et al., 1991).

Chromosomal aberrations

Abnormalities of the chromosomes which are large enough to be visible under the light microscope are termed chromosomal aberrations. They are usually classified into numerical and structural aberrations. A numerical aberration is the disordering of chromosomes due to error in separation of the chromosome in cell division. Aneuploidy represents gain or loss of a specific whole chromosome due to failure of a paired chromosome in meiosis. The one with an extra copy of a chromosome is called trisomy and the one with a missing copy of that chromosome is called monosomy. These can be seen in either autosomes or sex chromosomes. 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. Triplody occurs in 2% of all conceptions but early spontaneous abortion is usual (Munne and Cohen, 1998).

Aneuploidy of the autosome

The most commonly seen autosomal aneuploidies are trisomy 21-Down's syndrome, trisomy 18-Edward's syndrome, trisomy 13-Patau's syndrome. Sex chromosomal aneuploidies are Klinefelter syndrome and XYY syndrome in male and Triple X syndrome and Turner syndrome in female. Autosomal monosomy is mostly lethal and autosomal trisomy is relatively common (Rodrigo et al., 2010).

The kayotype of Down's syndrome is 47, XX/XY, +21 that is an extra copy of chromosome at chromosome number 21. The disease incidence is 1 in 900 live births if the mother age is at 30 and is strongly correlation with advancing maternal age. More than 90 percent of cases are maternal in origin and are caused by non-disjunction in maternal meiosis 1. The affected children are born with sever hypotonia (floppy) and also show characteristic facies of upward sloping of eyes, small ears and protruding tongue. 40-45% of the patients are presenting with congenital cardiac abnormalities and serious limitation of IQ scores ranging from 25-75. The average life span is

50-60 year if the affected one does not have severe cardiac problems. Most of the patients suffer from Alzheimer disease in later life because of a gene dosage effect of amyloid precursor protein on chromosome 21(Wald et al., 1997).

The karyotype of Patau syndrome is 47, XX/XY, +13 and of Edward syndrome is 47, XX/XY, +18. Patau and Edward syndrome share many clinical features in common and are usually found at the time of doing cytogenetic analysis in malformed children. They both show the incidence of 1 in 50, 000 and convey a very poor prognosis, with most affected infants dying during the early life. Approximately 60% of cases are caused by non-disjunction and 10% of cases are resulted from mosiacism or unbalanced rearrangement. The recurrence risk is less than 1% if the parent is not a carrier of a balanced translocation (Massiah et al., 2008, Rasmussen et al., 2003).

Aneuploidy of the sex chromosome

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

The karyotype of Klinefelter syndrome is 47, XXY. The additional X chromosome of maternal origin is 56% and paternal is 44%. It usually arises from non-disjunction at either the first or second meiotic division (Lamb et al., 1996). For example, if the father produces XY sperm it can cross over

with the maternal X ovum to produce XXY. 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). This is the single commonest cause of hypogonadism and infertility in male. The other clinical findings include learning difficulties, gynecomastia and taller than average with long lower limbs. There is increased incidence of carcinoma breast and osteoporosis in adult life. But it can be treated with testosterone from puberty onwards and fertility has been achieved by using the techniques of testicular sperm aspiration and intracytoplasmic sperm injection in a small number of affected males.

Monosomy of the X chromosome results in Turner syndrome, 45, XO karyotype due to non-disjunction in either parent. It is estimated that 1% of all conception from which 95 to 99% of all 45, XO embryos die before birth. Therefore, the incidence of live birth is very low ranging from 1 in 5000 to 1 in 10, 000. It is being detected by routine ultrasound scan during second trimester showing the residue of intrauterine edema with neck webbing. They have significant defects in height, sexual development and fertility but there is no mental retardation (David et al., 1986). The short stature is apparent without growth hormone treatment and it is due to haploinsufficiency of the SHOX gene on the pseudoautosomal region. For the management of infertility, estrogen therapy should be started at adolescence for the development of secondary sexual characteristics and in-vitro fertilization using donor eggs offers the prospect of pregnancy.

The karyotype of the super female syndrome is 47, XXX which is also known as triple X syndrome. It usually appears as physically normal but 15- 25% are

mildly mentally handicapped and quite oppositional behavior. About three quarters of the affected females are fertile of which one- half of their offspring would expect to have this syndrome (Michalak et al., 1983). Many studies have shown that the additional X chromosome is of maternal in origin in 95% of the cases due to error in meiosis I.

Furthermore, another karyotype defect associated with personality disorder is 47, XYY syndrome. It was firstly noted in 1965 in a cytogenetic survey in males 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 the 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 disordering of the structure and shape of the chromosome resulting from chromosomal breakage and error in rejoining mechanisms. Translocation is the transfer of chromosomal material between non-homologous chromosomes but there is no DNA loss. Three recognizable translocations are reciprocal, centric fusion (Robertsonian) and insertion. The one important thing in translocation is the balanced reciprocal translocation which occurs in two non-homologus chromosomes (Michael and Malcolm, 1997). In a normal population, 1 in 500 is known balanced carriers 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

an unbalanced form that can lead to miscarriage and physical or developmental problems (Munne et al., 2000).

Deletion is the loss of a part of a chromosome that can cause multiple dysmorphic features because of the loss of one or more 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 with a large deletion.

Angelman syndrome

Deletion of the terminal portion of chromosome 4 causes the Wolf-Hirschhorn syndrome. Cri du chat syndrome is caused by a deletion in the short arm of chromosome 5. Both conditions are very rare and the incidence is 1 in 100, 000 live births (Cerruti, 2001). Wolf-Hirschhorn syndrome usually presents with variable phenotypic features. A characteristic feature of the Cri-du-chat syndrome is having a sound of cat like cry (Niebuhr, 1978). The phenotype is slightly different depending on their chromosome break point. There are two regions of break point in the short arm of chromosome 5 that 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 Angleman syndrome are caused by deletion in the region 15q11-13 or by uniparental disomy (Ledbetter, 1981). If both copies

of the 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). A characteristic feature of Prader-Willi syndrome is sleepiness and of Angelman's are bouts of laughter (Zori et al., 1992). The children with Prader-Willi syndrome develop marked obesity and learning difficulties in the later life. These cytogenetic microdeletions in the long arm of chromosome 15 can be visible by using either FISH (fluorescence in situ hybridization) or DNA analysis with probes from the deleted region (Nicholls, 1994).

Wilm's tumour is the one of the micro deletion syndromes and deletion occurs at chromosome 11p13. The affected child develops renal neoplasm (Wilm's tumour) together with aniridia (absent iris), genitourinary malformations and growth retardation. This combination is also known as WAGR syndrome. It is due to loss of several genes within this deletion. For example, loss of PAX6 is responsible for aniridia and loss of WT1 causes Wilm's tumour.

DiGeorge syndrome is caused by a mocro deletion in the proximal long arm of chromosome 22. The incidence is 1 in 400 live births and is presenting with heart abnormalities, thymic and parathyroid hypoplasia. The half of the affected has short stature and partial growth hormone deficiency. In adult life, 25% of the cases suffer from schizophrenia.

A micro deletion at the chromosome 7q11 causes Willam’s syndrome presenting with elf like face, hypercalcemia and supravalvular aortic stenosis. It is due to loss of one copy of the gene that encodes elastin.

With the improvement in the cytogenetic techniques and the use of FISH, additional rare micro deletion syndromes are identified, for example; deletion 1p36 syndrome and Smith-Magenis syndrome. The other structural abnormalities include duplication, inversion and mosiacism and the rare structural variants are fragile site, heteromorphisims, isochromosome and ring chromosome.

Cancer and chromosomal abnormalities

Some of the cancers can be detected by karyotype analysis. The connection between chromosome rearrangement and cancer is evident in hematological malignancies. The several chromosomal translocations are found in various types of leukemia. The specific chromosomal translocation between chromosome 9 and 22 occurs in ‘ chronic myeloid leukemia’ is called the Philadelphia chromosome. In this case, a part of the proto-oncogene, c-ABL on the chromosome 9 moves to the BCR gene on the chromosome 22. The resulting BCR-ABL gene codes for fusion protein that has tyrosine kinase activity in excess. Therefore, Philadelphia chromosome positive cases are prolonged survival with the treatment of tyrosine kinase inhibitor. Moreover, detection of BCR-ABL transcripts in the bone marrow by PCR analysis is also necessity for the clinical follow-up. So, it can be used as a well defined diagnostic tool and prognostic factor.

The most specific cytogenetic abnormality in childhood ‘ acute lymphoid leukemia’ is the translocation between chromosome 12 and 21 called TEL-AML1 translocation. Moreover, Philadelphia chromosome translocation also occurs in increasing age and carries a poor prognosis.

‘ Acute myeloid leukemia’ occurs in all age groups and is the common form of acute leukemia. The specific chromosomal abnormalities in acute myeloid leukemia are translocation between chromosome 15 and 17 and translocation between chromosome 8 and 21. In the chromosome 15 and 17 translocation, PML gene on the chromosome 15 is fused to the retinoic acid receptor Î± gene (RARÎ±). Therefore, acute myeloid leukemia associated with this type of translocation is well treated with all-trans retinoic acid and results in good prognosis. Furthermore, core binding transcription factor encoding genes CBFÎ± and CBFÎ² are involved in a translocation between chromosome 8 and 21. Another form of chromosome rearrangement in acute myeloid leukemia is inversion of the chromosome 16 in which CBFÎ² gene is also involved.

The four most common chromosome abnormalities in ‘ chronic lymphoid leukemia’ are trisomy 12, structural abnormalities of chromosome 17p, deletion at chromosome 13q14 and 11q23. These abnormalities carry the prognostic significance.

Likewise in leukemia, chromosomal abnormalities are also seen in lymphoma. Lymphoma is a group of diseases caused by malignant lymphocytes that accumulate in the lymph nodes. Burkitt’s lymphoma is caused by viral infection that induces the transfer of C-MYC oncogene on the

chromosome 8 to immunoglobulin gene on the chromosome 14. As a result, C-MYC gene is deregulated and the affected one clinically presents with massive lymhadenopathy of the jaw.

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 twins. The 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 others (Kelly, 1992).

Retinoblastoma is the well known childhood cancer that involves in the developing retina cells of the eyes. The disease onset is usually in the first five years with a white cat eye’s reflex or squint. Early diagnosis and treatment will have good long-term outcome. It can occur either hereditary or non-hereditary. In the heritable condition, the disease is an autosomal dominant in manner and is caused by the ‘ germline mutation’ that is the mutation in the RB1 gene. Approximately 5% of the cases reveal ‘ interstitial deletion’ involving the long arm of chromosome 13 in the cytogenetic analysis. In the non-heritable condition, the mutation in the RB1 gene arises as a post-zygotic event in early embryogenesis is also known as ‘ somatic mutation’.

Genetic counselling

Genetic counselling is a communication process that deals with the problems associated with the occurrence of a genetic disorder in a family. Genetic disorder is a considerable health and economic problem because there is no effective therapy. So, high risk population group often seek advices as to why it happened and about the risk of having further abnormal offsprings. Therefore, the realization of the need of the individuals and couples together with the awareness of the importance of the accurate information, has led to the widespread introduction of genetic counselling clinics in parallel with clinical genetics. The introduction of genetic counselling services has been

provided approximately 40 years ago. Thus, the genetic counselor provides the information related to the medical diagnosis, prognosis, complications and the possible treatment. Moreover, they have to explain the mode of inheritance of the disorder and also have to calculate the risk of the recurrence. Then, they have to bring out the options available for dealing with reducing the risks of having a disorder (Frets et al., 1991). .

The options are no further pregnancy, adoption, in vitro fertilization with pre implantation diagnosis, artificial insemination-AID by donor (egg donation), termination of pregnancy, or ignore and accept the risk (Zare et al., 1973). AID is performed for husband with AD trait or both are carriers for a serious AR (Taranissi, 2005).

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

In the setting of genetic counselling, interviews must be conducted with great sensitivity and psychological insight as the parents may feel guilty for their abnormal babies. Therefore, genetic counselling should be offered to both parents and must give adequate time under an appropriate situation. The depth of explanation should be matched to education background of the couples, outlining of the genetic basic of the condition with the aid of diagrams and recurrent risk calculations (Sermon, 2002).

The quality of the genetic counselling depends on the availability of facilities that ensure an accurate diagnosis can be made. If the diagnosis is incorrect, it will be totally misleading information. The important thing in genetic counselling must be non- judgemental and non-directive. The aim is to deliver a balanced version of the facts which will permit the parents to reach their own decision with regard to their reproductive future. Moreover, referral to an appropriate support group is also the essential integral component of the genetic counselling process.

The recurrence risk is usually calculated by using Baye's theorem that express probability of disease occurrence mathematically. Baye's theorem is also known as Bayesian analysis or Bayesian inference. But some of the limiting factors are delayed age of onset, reduced penetrance and use of DNA marker. These are more complex in the risk calculation.

Autosomal dominant trait is the risk to each child of an affected person at 1 in 2. However, the risk estimation in family counselling can be difficult because of the variable penetrance and expression. For example in case of " incomplete penetrance", although the parents have a dominant disorder but the disease does not manifest itself clinically. This gives the appearance of the gene having a " skipped" generation.

In Autosomal recessive trait, if one of the parents is carrier, the offspring have a 1 in 4 chance of being affected and a 2 in 3 chance of being carrier (Yoshikawa and Mukai, 1970). Recurrence risk of 1 in 4 chances does not mean that their next three children will be uneffected because of the tossed coin phenomenon and joint probability. Therefore, genetic counselor should

be explained that there are 3 chances out of 4 that their next baby will be affected. Autosomal recessive disorders are more severe and higher motality than autosomal dominant. In this case, there is usually no family history although the defective gene is passed from generation to generation.

Similarly the sex-linked disorder can be dominant or recessive as the autosomal genes. In an X-linked recessive trait, if females are obligate carriers, one half of her sons will be affected and one half of her daughter will be carriers. If an affected male reproduces, there will be normal sons and carrier daughters. An X-linked dominant condition is very rare and vitamin D-resistant rickets is the best known example.

Consanguineous marriage and incestuous relationship in the parents provides further support increases for the risk of recessive inheritance. Risk for consanguinity is common in Arab population. As for the carrier detection, some of the inborn errors of metabolism are autosomal recessive disorder like Tay Sachs disease and haemoglobinopathies but these can be detected only by biochemical analysis. But because of X inactivation, few of these are absolute and this information needs to be combined with the pedigree risk using Bayes’ theorem (Markova et al., 1984).

Fragile X syndrome is an X-inked dominant, single gene disorder rather than chromosome abnormalities. It is a common heritable cause of learning difficulties and affects 1 in 5000 males. The characteristic features are high forehead, large ears, long face, prominent jaw, large testes and repetitive speech. This is due to mutation of FMR1 gene encoding CGG repeats at the end of X chromosome’s long arm. It appears as a constriction in the X

chromosome in the chromosomal analysis called ‘ fragile site’. The more repeats, the more severe the disease. If this reaches greater than 200 CGG triplets, it becomes a full mutation. Each son of the carrier woman with full mutation will have a 50% chance of getting this disease. Moreover, 50% of the female carriers with full mutation also have mild learning difficulties and there will have a 25% chance of getting a daughter with learning difficulties.

Conditions needed for genetic counselling and investigation (Watson et al., 1992)

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

Gene therapy

The recent progress in molecular genetics is the prospect of successful gene therapy. Gene therapy is the genetic alteration of the cells of the affected persons for curing the genetic diseases. Somatic cell gene therapy consists of the alteration of genes in human somatic cells to treat a specific disorder, for example, X-linked severe combined immunodeficiency disease. In this case bone marrow stem cell has been a prime candidate for somatic therapy because it is a proliferating cell and has a long life span in the body.

Currently, the best source is believed to be embryonic stem cells and ethical consideration impinges on almost every aspect of clinical genetics.

On the other hand, gene replacement therapy has been used for loss of function mutation. This involves replacing a missing gene product by inserting a normal gene into somatic cells. There are many techniques for introducing of gene into cells but retrovirus and adenovirus are the most commonly used as gene therapy vectors.

Another method of gene therapy is the gene blocking therapy to encounter the effect of gain of function mutations. These include the use of antisense molecules and RNA cleaving riboenzymes.

Conclusion

The benefit of karyotype analysis in high risk populations provides the prevention and early management options to minimize the risk. As genetic science development, researchers and clinicians 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 translocations, uniparental disomy can only be detected by SNP arrays and high output sequencing. Despite the high cost, enormous benefit can be found for society to evaluate the superior treatment protocols and genomic technologies for the future.