Patau Syndrome: Genetic and Epigenetic Aspects

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Abstract. Patau syndrome, also known as trisomy 13 syndrome, is a syndrome caused by a chromosomal abnormality. This rare syndrome is a lethal disease, where the life expectancy more than 1 year after birth is only less than 15%. The cause of Patau Syndrome is an abnormality on chromosome 13, where the possibilities that can occur are complete trisomy 13, translocation trisomy 13, partial trisomy 13 and mosaic trisomy 13. In addition to genetic factors, it was revealed that epigenetic factors have also played an important role in this syndrome, after it was discovered that DNA methylation occurring in a number of CpGs could be used as a potential biomarker to detect trisomy 13. The aim of this paper is to discuss the genetic and epigenetic factors involved in Patau Syndrome.

Keywords: Patau syndrome · Genetic · Epigenetic · DNA Methylation

1 Introduction

The human body consists of millions of cells, each cell has spesific function. Chromosomes are sub-cellular structures that found in the nucleus of every cell that forms the human body. There are 23 pairs of chromosomes, which are 22 pairs of autosomes and 1 pair of sex. These chromosomes have the responsibility to transfer genetic information from one generation to the next [1].

Chromosomes consist of very dense DNA structures, which contain information that will be needed to control production of proteins. DNA will determine which protein will be produced in what quantity and the time. Proteins are molecules that have important role in determining the structure and function of body's cell. Proteins consists of amino acids. Genes are spesific lengths of DNA that determine the sequence of amino acids used to make protein. The dysfunctional behaviour of a gene is known as a mutation. Based on gene mutation level, diseases are categorised into the following: chromosomal diseases, single-gene disorders, multifactorial disorders, and mitochondrial disorders [1, 2].

1.1 Definition

Genetic disorders in fetus can be caused by chromosomal abnormalities (aneuploidy). Aneuploidy is a condition in which there are missing or extra chromosomes, which is the cause of the syndrome [3].

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Trisomy 13 syndrome was first revealed by researchers Dr. Patau in 1960. There were several synonyms of this syndrome: Chromosome 13, Trisomy 13 Complete, Complete Trisomy 13 Syndrome, D Trisomy Syndrome, and Patau Syndrome [4, 5].

Patau syndrome is a lethal disease, the possibility of survival more than 1 year of birth is less than 15%. Most causes of death are brain and heart problems, mainly due to septal defects that cause by altered of gene regulation [6, 7].

Patau's syndrome is a syndrome that caused by an abnormal chromosome. Patient with this syndrome has 3 copies of chromosome 13, when he should have just 2 copies. This extra copy of chromosome 13 can occur in all cells or just in a portion of cells. Patau syndrome is a genetic disorder that are rarely happen [5, 8].

1.2 Classification

Majority cases of patau syndrome is Complete Trisomy 13 or Full Trisomy 13, have three copies of chromosome 13 in each cell of the body. Also known as Trisomy 13 or simple trisomy 13 [9].

Trisomy 13 can also develop when a portion of chromosome 13 gets rearranged (translocated) to other chromosomes during the creation of eggs and sperm, or during the early stages of fetal development. This disorder is known as Trisomy Translocation 13, and it is characterized by two normal chromosomes 13 and an additional copy of chromosome 13 connected to another chromosome. Trisomy Translocation 13 can be inherited [9, 10].

In rare cases, there is a type of Partial Trisomy 13, where only part of chromosome 13 has 3 copies in each cell. The last one Trisomy 13 is Mosaic Trisomy 13, a condition where additional copies of chromosome 13 are found in only some cells of the body [9].

2 Patau Syndrome

2.1 Symptoms and Features

Patau syndrome can cause a variety of health issues in babies. Because their growth in the womb is restricted, they will be born with low weight, and eight out of ten will have significant heart problems. Holoprocencephaly is a condition in which the brain is not divided into two halves. Cleft lip and palate, abnormally small eyes (microphthalmia), micrognathia, absence of one or both eyes (anophthalmia), shortened distance between the eyes (hypertelorism), and issues with the development of nasal passages are all anomalies that can occur when this disease develops. Other facial and head anomalies include: decreased head size (microcephaly), Cutis aplasia, ear deformity or deafness, and red birthmarks (capillary haemangiomas) [11].

Patau syndrome can produce a variety of issues, including an abdominal wall defect, abnormal cysts in the kidneys, an unusually tiny penis in boys, and an enlared clitoris in girls. Polydactily and rocker-bottom feet are two examples of deformities of the hands and feet [11].

Patients with patau syndrome who can save and live through infancy accompanied severe psychomotor disorders, failure to develop, mental retardation, and seizures [5].

2.2 Patau Syndrome's Prevalence

Patau syndrome (trisomy 13) is a third frequent trisomy, with ratio af 1:5000 total births. This frequency is less when compared to Down syndrome (Trisomy 21), which is 1: 700 total births.While for Edward syndrome (Trisomy 18) the frequency is relatively the same, which is about 1: 5000 total births [5].

Studies at the Neonatal care unit of Dokkyo University Hospital, Japan during 22 years from 1989–2010 reported 183 of 6.230 total births who have external malformations or organ malformations that were taken clinical checks and chromosome analysis were detected chromosomal anomalies. A total of 138 patients (2.2%) were found to have numerical autosomal aberration. Trisomy 21 is the most common trisomy, affecting 83 patients (1.33%), Trisomy 18 is the second most common trisomy, affecting 39 patients (0.63%), and Trisomy 13 is the third most common trisomy, affecting 16 patients (0.26%). The remaining 45 patients had other chromosomal abnormalities [12].

Studies from Denmark and United Kingdom informed that prevalence of birth in live born of trisomy 13 as about 1:20.000 to 1:29.000. Meanwhile, studies from Hawaiian notified the prevalence about 1: 12.048 in live born infants [12]. Patau syndrome affects about 1 in every 8,000–12,000 live births in the United States. Springett et al. discovered that the incidence of trisomy 13 was 1.9 per 10,000 total births in a study of 25 population-based registries in 16 European nations [13].

2.3 Causes of Patau Syndrome

Patau syndrome can be diagnosed in prenatal stage or at birth. Trisomy 13 is often caused by nondisjunction in meiosis, and commonly occurs in women aged over 35 years. While mosaicism results from error in mitotic nondisjuntion and is not connected to the age of the pregnant mother. In patients with mosaicism and unbalanced translocation have better prognosis [5, 13].

After the first or second meiotic division, nondisjunction occurs when one or more pairs of chromosomes fail to separate. Autosomal trisomies are caused by nondisjunction. Nonodisjunction occurs during meiosis of the egg or sperm during the prefertilization phase. As a result, that gamete has 24 chromosomes (normal = 23). All cells have 47 chromosomes as a result of fertilization with a gamete carrying 24 chromosomes and a normal gamete. The earlier nondisjuction occurs, the bigger the number of cells affected [14].

In the postfertilization, nondisjunction occurs in early mitotis phase, so the baby has mixure cells. The mixture cells is called as mosaicism, where there are a variety of different cell lines, cell with normal chromosomes, cells with 45 chromosomes, and cells with 47 chromosomes [14].

Whereas the other type of trisomy 13 is trisomy translocation, usually called Robertsonian translocation. This type of trisomy 13 occurs as a result of translocation on the chromosomes, and it can be inherited. For more detail, it will be discussed in the inheritance pattern.

2.4 Inheritance Pattern

Patau syndrome cause by coincidental and majority do not run in families (not inherited). Trisomy 13 syndrome is generally caused by random events during eggs and sperm formation in healthy parents (prior to conception). This error happens when the cells divide, producing an extra copy or a part of copy chromosome 13, that affects development of baby in the womb [11].

Between 1989 and 2010, researchers at Dokkyo University Hospital's Neonatal Care Unit monitored 16 newborn infants who were diagnosed with Trisomy 13, none of them had a family history of chromosomal abnormalities. The chromosomal karyotypes were determined using the G-band approach, and full trisomy 13 was found in 14 individuals, mosaic trisomy 13 in one patient, and Robertsonian translocation in one patient [12].

Less than 20% of trisomy 13 happens bacause of chromosomes translocation, called as Robertsonian translocation. The long arms of the two acrocentric chromosomes will unite at the centromere after translocation, whereas the two short arms will disappear. Robertsonian translocation is most commonly found on chromosomes 13, 14, 15, 21, and 22. Robertsonian translocation can result in offspring who are normal, carrier, trisomic, or monosomic. The chance of recurring translocation is roughly 5% -10% when a parent has a 13:14 Robertsonian translocation. If a parent has a 13:13 Robertsonian translocation, all of their children will have Trisomy 13 [14].

2.5 Screening for Patau Syndrome

A screening test of Patau syndrome is carried out from 10 to 14 weeks of pregnancy, like test of Down syndrome and Edward syndrome. The screening test involves a blood test and ultrasound scan, so it is known as combined test [11].

Karyotyping is a test that carried out to check chromosomes in a test sample. This test is intended to help identify genetically related to disease. Karyotyping test can be done on almost all tissues, including: amniotic fluid, blood, bone marrow, and tissue from organs that develop during pregnancy. To test amniotic fluid, is check with amniocentesis [15].

If the results of the screening test show that you have a higher chance of having a baby with Patau syndrome, you will be offered a diagnostic test. The chromosomes of the newborn will be tested in a sample of cells collected from him or her during this examination. Amniocentesis or chorionic villus sampling are two methods for obtaining a cell sample (CVS). These are invasive tests that involve removing a sample of tissue or fluid in order to check for the existence of an extra copy of chromosome 13 [11].

A novel test has recently been created. Non-invasive prenatal testing is a type of non-invasive prenatal testing that is only available privately. A sample of the mother's blood is obtained for this test, and the DNA of the baby found within it is examined [11].

If the woman is unable to undergo a combined screening test, she will be offered a scan to search for physical abnormalities associated with Patau syndrome. This scan is known as a mid-pregnancy scan, and it is performed between 18 and 21 weeks of pregnancy [11].

Malformation that occurs in patau syndrome can detected by prenatal ultrasound, like holoprocencephaly anomalies, skeletal anomalies, renal or cardial defects, and other

growth limitation that usually happen. Ultrasound that takes after 17 weeks of gestation is most sensitive in finding patau syndrome abnormalities [5].

2.6 Patau Syndrome's Genetics

The largest human chromosome with an acrocentricity is chromosome 13. The short arm of chromosome 13 is heterochromatic and contains families of repetitive sequences, including the ribosomal RNA gene arrays, as are the other acrocentric autosomes (14,15,21, and 22). The euchromatic long arm, which contains most or all of the chromosome's protein-coding genes, is euchromatic [16].

Patau syndrome is a fatal congenital disorder characterized by various congenital defects. Central nervous system (CNS) problems and cardiac abnormalities, particularly septal defects, are the leading causes of death. Septal abnormalities are a complicated condition involving hundreds of genes that are found on numerous chromosomes, including chromosomes 13 and 14. Chromosome 13 is 114,364,328 bp long and encodes 308 proteins, accounting for over 4% of total DNA. 343 protein-coding genes, 622 non-coding RNA genes, and 481 pseudogenes are found on chromosome 13 [6, 10].

Molecular pathway and gene ontology research of chromosome 13 revealed that a number of important genes, including FOXO1, Col4A1, HMGBB1, FLT1, EFNB2, EDNRB, GAS6, TNFSF1, STARD13, TRPC4, TUBA3C, TUBA3D, are linked to cardiovascular problems, including atrial and ventricular septal abnormalities. FOXO1 is a strong transcription factor that interacts with and regulates a number of other genes that are not on chromosomes 13 but affect septal defects, including (GATA4 (8p23.1), GATA6 (18q11.2), GJA1 (6q22.31), JAG1 (20p12.2), CITED2 (6q24.1), RYR2 (1q43), NKX2–5 (5q35.1), RARA (17q21.2), CXCL Several genes have been linked to Patau syndrome, including NODAL, FPR1, AFP, AGO2, UROD, and ZIC2, but none of these genes are found on chromosome 13 [6].

The gene forkhead box O1 (FOXO1), which belongs to the forkhead box O family of transcription factors and is found at 13q14.11, has to be discussed in detail. FOXO1 functions by binding to downstream gene promoters or interacting with other transcription factors; its up- or downregulation has major consequences. Several studies have concluded that FOXO1 plays a key role in the control of cellular functions such as proliferation, survival, cell cycle, metabolism, muscle differentiation, and myoblast fusion. FOXO1 is likely to be the major regulator of cardiac abnormalities in Patau syndrome. Survival can be enhanced by suppressing elevated FOXO1, according to certain studies. This is become a motivation for Adel Abuzenah et al. to examine the rate of FOXO1 expression which is considered to play an important role in patau syndrome and to observe its inhibitors by checking molecular docking with certain drugs [6].

2.7 Patau Syndrome's Epigenetics

Several research groups have been working for more than a decade to develop non-invasive prenatal testing (NIPT) of fetal illness caused by specific chromosome aneuploidies using circulating free fetal DNA (cffDNA) in maternal plasma. NIPT techniques that can be given to all pregnant women without danger of miscarriage. The finding of cffDNA in maternal plasma was made possible by the establishment of NIPT. Recent

research has found that fetal DNA contents in maternal circulation are remeasured at around 10% during the first semester [17].

The addition of the cytosine found in CpG dinucleotides to a methyl group on carbon 5 is an epigenetic marker known as DNA methylation. The levels of methylation in distinct tissues have been shown to differ significantly. Furthermore, the introduction of next-generation sequencing (NGS) has transformed the production of NIPT, opening up new avenues for the detection of fetal aneuploidy and other genetic aberrations [17].

Lotte Hatt et al. extended their previous study by examining the placental DNA methylation landscapes of the three common aneuploidies T21, T13, and T18 and comparing it to the DNA methylation landscapes of normal placentas and maternal blood cell (MBC) DNA in an attempt to demonstrate possible methylation differences that are better suited for NIPT, especially for T13 and T18 [18].

Research which conducted by Kimberly Bunce et al. using The HumanMethylation27 DNA Analysis Beadchip to classify DNA methylation in samples of CVS (Chronic Villus) and MBC, then picked a subset of differentially methylated CpG sites on chromosom 13, and used the Epityper tool to analyze them using mass spectrometry. All samples of de-identified tissues used in this analysis were discarded. During gestational weeks 11 and 13 CVS was collected from the Cytogenic Screening Laboratory at Magee Womens Hospital. All samples were confirmed using standard cytogenic techniques to bear typical euploid karyotypes. Samples were dissected under a microscope, distinguishing them from any decidual tissue or blood flecks. The culture media was extracted and before use the tissue was preserved in 1,5 ml centrifugal tubes at -80 °C [19].

The HumanMethylation27 DNA Analysis beadchip (Illumina) allows researchers to investigate 27,578 CpG sites based on the NCBI CCDS database (Genome Construct 36), as well as the promoter regions of 110 miRNA genes. The EZ DNA Methylation TM Kit (Zymo Research Corp) was used to convert unmethylated cytosine nucleotides to uracil utilizing bisulfite conversion. Transformed DNA samples in a proprietary amplification reaction mix were amplified by incubation at 37 °C for 20 h after denaturation with 0.1N NaOH. Denatured DNA samples were introduced to the infinium arrays and hybridized for 16–24 h at 48 °C with rocking. Unhybridized and non-specifically hybridized DNA was washed away from the Beadchip, and single base extension of labeled nucleotide binding primers was done. The data was processed using Bead Studio 2.0 after the completed array was scanned with an Illumina BedArray Reader. The MassArray Compact (Sequenom) method was used to do the quantitative methylation study. 1 ug genomic DNA was bisulfite converted using EZ DNA Methylation (Zymo Research) according to the manufacturer's instructions [19].

In this research, they performed a genome-wide study of DNA methylation using the Infinium "Human Methylation27" platform in first trimester CVS samples and gestational age matched MBC, this platform is targeted to 27,578 CPGs. Since the infinium microarray includes CpG loci probes on all human chromosomes, the researchers filtered the data to identify differentially methylated regions (DMRs) located on chromosomes 13, 18, 21 and X.

As the result of this research, 718 differentially methylated regions (DMRs) unique to the tissue were found between MBC and CVS. 563 of these sites had MBC hypermethylated and CVS hypomethilated while 155 sites had MBC hypomethylated and CVS hypermethylated [19].

Epityper's further investigation of 13 DMRs on chromosome 13 confirmed the misroarray results and provided further information on the methylation patterns of nearby CpG sites. Based on the findings, a large number of GpGs have been identified as prospective biomarkers for selective amplification of fetal DNA from maternal plasma and subsequent non-invasive trisomy 13 identification. The major goal of this study was to define CpG sites in the human genome that are differently methylated in DNA from CVS and gestationally matched MBC samples [19].

3 Conclusion

Patau syndrome is a lethal disease due to abnormalitiesin the structure of chromosome 13. There are several types chromosomal abnormalities that occur in this syndrome including: complete trisomy 13, translocation trisomy 13, partial trisomy 13, and mosaic trisomy 13. Babies with patau syndrome will experience serious health problems and generally with poor prognosis. Infants who can save and survive infancy experience psychomotor disorders, fail to develop, menal retardation and seizures.

Patau syndrome is not inherited disease, except translocation trisomy 13, this type could be inherited to the offspring. Various method have been developed to be able to identify patau syndrome, ranging from invasive tests to non-invasive tests.

Based on research that conducted by Kimberly Bunce et al., analysis of the resulting data which get from a genome-wide study of DNA methylation between gestational weeks 10 and 13 in CVS and MBC samples, identifies a significant number of CpG which are potential biomarkers for selective amplification of maternal plasma fetal DNA and subsequent non-invasive detection of trisomy 13.

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