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Genetic Basis Of Congenital Malformations

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ABSTRACT:

Congenital malformations, a diverse group of structural abnormalities present at birth, significantly impact a child's health and well-being. While environmental factors play a role, the genetic basis of these anomalies remains largely unknown. This review aims to shed light on the complex interplay between genes and congenital malformations. We will employ an approach to investigate the genetic underpinnings of congenital malformations in a cohort of malformations. We explore the diverse spectrum of genetic contributions, including ***Mendelian Inheritance:*** *We examine the role of single-gene mutations causing well-defined malformation syndromes.* ***Polygenic Inheritance:*** *We discuss the complex interplay of multiple genes with environmental factors in the common congenital malformations development.* ***Copy Number Variations (CNVs):*** *We explore the impact of duplications or deletions of chromosomal segments on birth defects.*

Keywords: *Congenital malformations, genetics, whole-exome sequencing, genetic variants, prenatal diagnosis*

INTRODUCTION:

Congenital malformations, and structural abnormalities present at birth, cast a long shadow on human health. Affecting roughly 3% of newborns globally [1], these birth defects encompass a vast spectrum, ranging from subtle facial anomalies to complex malformations of internal organs. While the causes of congenital malformations are often multifaceted, the intricate dance between genes and the developing embryo plays a pivotal role in their origin. This essay delves into the fascinating world of genetic influences on congenital malformations, exploring chromosomal abnormalities, single-gene defects, and the complex interplay between genes and the environment.

One well-defined category of genetic contribution involves chromosomal abnormalities. Chromosomes, the thread-like structures housing our genetic code, come in specific pairs. Errors in chromosome number, such as having an extra copy of chromosome 21 (Down syndrome) or missing a portion of chromosome 18 (Edwards syndrome), can have profound consequences on embryonic development, leading to various malformations [2]. These chromosomal abnormalities can arise spontaneously during cell division or be inherited from a parent carrying a balanced translocation, where chromosomal material is rearranged without causing health problems in the carrier but potentially impacting offspring.

Beyond chromosomal imbalances, mutations in individual genes can also orchestrate the development of congenital malformations. These single-gene defects can be inherited in a dominant or recessive way. In dominant inheritance, a gene single altered copy from one parent is sufficient to cause the malformation. Examples include achondroplasia, a type of dwarfism, and Apert syndrome, characterized by craniofacial malformations and fused fingers and toes [3, 4]. Recessive inheritance requires mutations in both gene copies, one from each parent. Cystic fibrosis, a debilitating lung disease, and phenylketonuria, a metabolic disorder, are classic examples of recessive inheritance in congenital malformations [5, 6].

However, the story of genetics and congenital malformations extends beyond simple inheritance patterns. Many birth defects likely arise from a combination of factors, with genetic susceptibility interacting with environmental exposures. For instance, maternal folate deficiency during pregnancy it is a known factor of risk for neural tube defects, and spine and brain malformations that can be influenced by genetic variations in folate metabolism genes [7]. Similarly, teratogens, environmental agents like certain medications or consumption of alcohol at the time of pregnancy, can disrupt development and exacerbate the effects of underlying genetic predispositions.

OBJECTIVE:

To elucidate the genetic factors contributing to the development of congenital malformations in congenital malformation or birth defects.

THE STATEMENT OF PROBLEM / RESEARCH QUESTION:

Do mutations in specific genes or chromosomal abnormalities contribute to the development of congenital malformations?

PICO Format for Genetic Basis of Congenital Malformations

P: Population Population/individuals with birth defects
I: Intervention Mutations in specific genes or chromosomal abnormalities
C: Comparison Unaffected controls (without the malformation)
O: Outcome Increased risk of congenital malformations
THE NULL HYPOTHESIS:

Disruptions in normal developmental gene function due to mutations in genes or chromosomal abnormalities cannot lead to an increased risk of congenital malformations.

THE HYPOTHESIS:

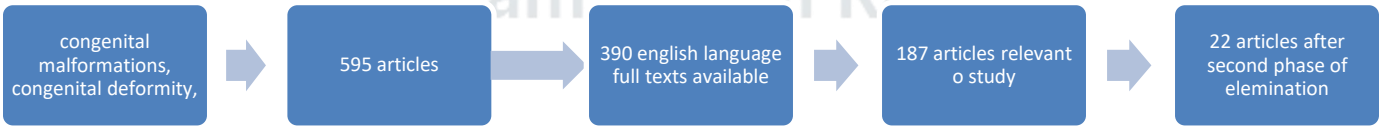
Disruptions in normal developmental gene function due to mutations in genes or chromosomal abnormalities can lead to an increased risk of congenital malformations.

RESEARCH METHODOLOGY:

During the initial phase of the research, a comprehensive search was conducted specifically focusing on congenital malformations. A comprehensive analysis of congenital malformations was conducted. The articles pertaining to the aspect of definition were the main focus. An analysis was conducted on the factors contributing to congenital malformations. The study encompassed all the articles that make reference to these. Subsequently, in the subsequent phase of the study, we have directed our attention towards examining each cause in isolation. The search strategy has been altering to individual causes. The genetic basis or the genetic cause of congenital malformations was then dealt with in detail. The most commonly occurring congenital malformations were reviewed.

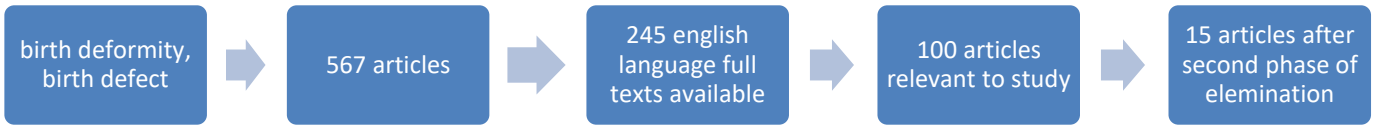
PRISMA SEARCH PROTOCOL:

Priority was placed on review articles pertaining to the specified topics in this section of the study.



A total of 595 articles were obtained using the aforementioned keywords. The 390 articles were subsequently included in the analysis, taking into account their availability of full text and the language utilized.

A uniform approach to article screening was implemented for all keywords.



When we searched for the words 'birth defects/birth deformity a list of 567 articles was found. After conducting a preliminary screening based on the availability of full text and the language used, only 245 articles were deemed eligible for inclusion. The initial stage of elimination was executed. 100 articles were chosen based on the abstract.

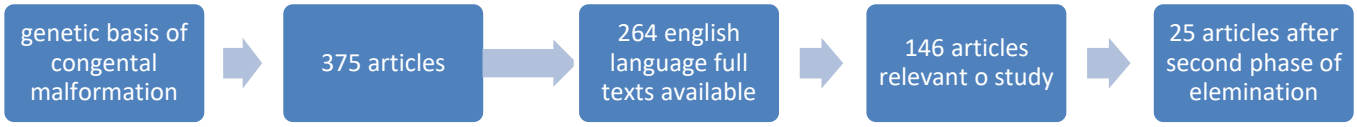
Part 2 of the search:

The same screening procedure was utilized in part 1.

However, the keywords utilized were "genetic basis of congenital malformation."

The studies that conducted comparisons between two or more approaches were also taken into account.

Only the articles specifically related to India were considered in this section.



LITERATURE REVIEW/ANALYSIS:

The complex multicellular human being is formed from the fusion of unicellular ovum and sperm. This leads to the formation of a zygote which then undergoes a series of well-coordinated and complex divisions to form a multicellular organism (1). The process though complex is very coordinated. The entire sequence of divisions is regulated by the genes. The timely expression and unexpression of these genes are important for the proper formation of humans (2).

CONGENITAL ANOMALIES:

The WHO defines congenital disorders as structural or functional anomalies, such as metabolic disorders, that arise during fetal development and can be identified either before birth, at the time of delivery, or sometimes only later in infancy. In a general sense, congenital means present at or before birth. The synonyms for this term are congenital abnormalities, congenital malformations, or birth defects. (4)

Birth defects can be varied. They can range from the simple deformation of an organ to the complete absence of one. These can be lethal. Some are so dangerous as to cause abortions during the initial period of pregnancy itself. While on the other hand, some of the defects go unnoticed till later in life. The defects present in internal organs are only discovered when they become symptomatic. (2)

TYPES OF CONGENITAL MALFORMATIONS:

Major malformation: We can find single major malformation in 3% of births, whereas 0.7 % show the presence of multiple major deformations. These are defects that occur in the early phase of organogenesis. They cause significant impairment of normal structure and /or function of the affecting organ so as to cause spontaneous abortions or subsequent mortality or morbidity in later life. Examples include Meningocele, posterior urethral valve, ventricular septal defect, and cleft lip (02).

Minor malformation: single or multiple minor deformities can be seen in 14 or 3% of cases respectively. Minor malformations are those that only cause esthetic disturbances. they can however be of great use to determine the etiology of the defect and also be a sign of the presence of an underlying major malformation. The examples are Polydactyly, ear tag, Single palmar crease (5)

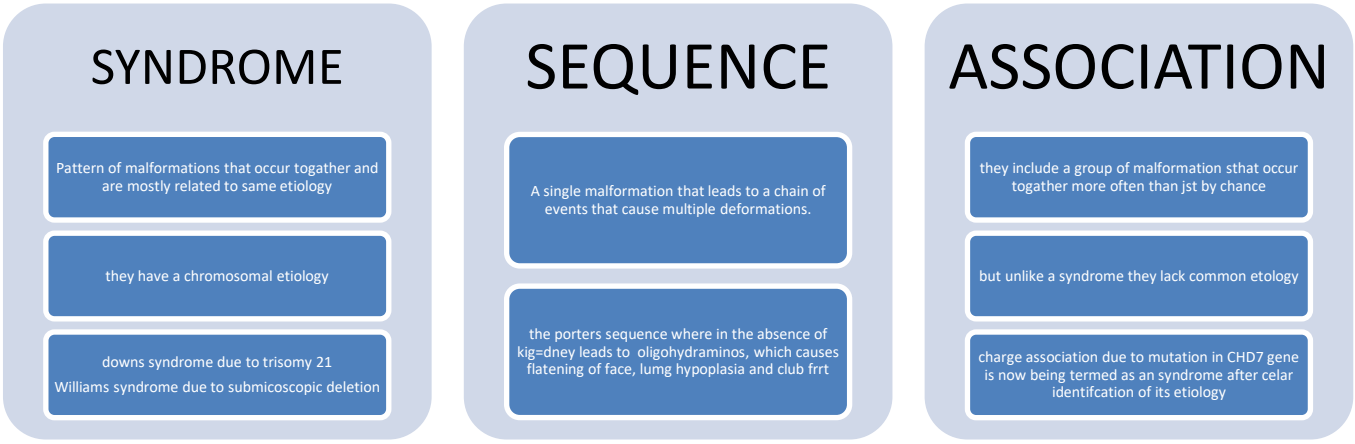
3. Normal variants Clinical features which are at the far end of normal distribution Low set ears, hypertelorism. May be present in normal individuals but in association with other birth defects can be of help in the diagnosis of a syndrome(5).

4. Deformation: these are abnormalities of the shape of the normally formed organ due to mechanical stress. Talipesequinovarus in a child with amyoplasia or congenital myopathy due to oligohydramnios or intrauterine crowding are good examples. They usually have a good prognosis with postnatal intervention. The risk of recurrence in OTHER generations is minimal if the causative stress factor is removed timely(6)

5. Disruption: it is the Damage or dissolution of a part following normal development The examples include Amputation of digits due to damage by constricting amniotic band or thrombo-embolic phenomenon. Usually do not recur in the family (5)

6. Dysplasia: Morphological defects caused by abnormal maturation and organization of cells into tissue Achondroplasia (involvement of bones), Ectodermal dysplasia (hair, teeth, sweat glands, and nails are involved) Involvement of multiple organs in the body where the particular tissue is present. Most are single-gene disorder (6)

PATTERNS OF CONGENITAL MALFORMATION (7)



CAUSES OF CONGENITAL MALFORMATIONS:

various authors have put forward five categories of causes of congenital deformations (6-10):

(1) Single gene defects (mutant genes);

(2) Chromosome abnormalities;

(3) Multifactorial disorders that occur as an outcome of the interaction between the underlying genetic cause and the environmental predisposition.

(4) Teratogenic factors; and

(5) Those of unknown cause. (12)

Owing to the technological advances in genetic sequencing and determination of mutations the knowledge in genetics has increased enormously in the past decades. This however still does not change the fact that more than 50% of congenital malformations still lack a proper etiology (7,8,9). Genetic mutations, chromosomal abnormalities, and known teratogens could be blamed for around 7-8percent of malformations/ the other 20-25% can be attributed to multifactorial disorders. (6)

Depending upon the time when the genetic mutation occurs the congenital malformations can be subdivided as follows: (11-13)

1. pregenesis: Here the genetic mutation is early enough to cause damage to the gamets leading to gametogenesis or is preexisting in the gonads to cause gonadogenesis,

2. blastogenesis : the mutations occur in the first four embryonic weeks. This leads to damage to the blastocyst stage of embryonic development.

3. Organogenesis: this included the mutations in the fifth to eighth weeks of embryonic life. they cause damage to the forming organs pof the future human

4. phenogenesis : the damage occurring roughly in the fetal period.

GENETIC DISORDERS

Chromosomal Abnormalities(14)

Humans develop from a set of 23 pairs of chromosomes. this complement of chromosomes need to be complete and perfect in order for a human to survive without and deformations or abnormalities. The set consists of 22 pairs of homologous autosomes as well as 1 pair of sex chromosomes (Fig.). Typically, one member of each pair is passed down from either parent. Currently, we have the ability to distinguish each chromosome individually using banding technology and, more recently, FISH (fluorescence in situ hybridization).

Chromosomal malformations occur when there is excess or deficiency of the material chromosome in the complement set. (Fig.). It is estimated that around 1 in every 200 live human births chromosomal anomaly is present (7). Chromosomal anomalies can be one of the major causes of first-trimester miscarriages accounting for around 60%. Out of the total perinatal deaths that are reported, the frequency of chromosomal anamoliesvaries between 5 and 10%, (8).

Excessive or deficient chromosomal material can be a result of either increase or decrease in the chromosome structure or number. Variations in the chromosome number have been of 2 kinds:

(1) polyploidy: Where the abnormality takes place only in a single chromosome of the pair that is in haploid state such as triploidy with chromosome number 21. Triploids can be seen in around 6% of all pregnancies. It mostly occurs due to errors of fertilization where 1 ovum is fertilized by 2 spermatozoa.

(2) aneuploidy: Here, the occurrence of the loss or gain of an entire pair of chromosomes is observed, known as monosomy and trisomy, respectively.

Except for a small percentage of monosomy X cases, both of these conditions are fatal in humans.

Chromosome gain is more prevalent than chromosome loss. Autosomal trisomy has been observed in the majority of autosomes, with varying frequency.

Trisomy of chromosome 16 is the most prevalent, but it is uncommon because it typically leads to spontaneous abortion during the first trimester of pregnancy (13). Down syndrome (trisomy 21) is the most frequent chromosomal abnormality observed in live births. It is followed by trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome). Down syndrome has been 1st explained by Down in 1866, while Edwards et al. and Patau et al. reported on Edwards syndrome as well as Patau syndrome respectively in 1960.

Among the karyotypes presented in the table above, miscarriage is the most commonly occurring outcome (13).

Down syndrome

It is characterized by

1. mental deficiency,
2. The individual exhibits a distinctive facial expression characterized by the eyes upward slanting along with the prominent skin folds that extend from the nose base to the eyebrows' inner aspect.
3. congenital heart malformations.

Down syndrome is caused by three types of chromosomal abnormalities: (1) trisomy 21, which happens when there is a failure of chromosomes to separate during meiosis (this accounts for 95percent of affected individuals); (2) translocation type or partial trisomy 21; and (3) mosaicism for trisomy 2. In 95% of cases, the additional chromosome comes from the mother (14). Trisomy 21 arises from an unbalanced translocation in fewer than 5% of cases. Mosaicism for trisomy 21 is an exceptionally uncommon condition, found in less than 1–2% of cases. Trisomy 21 is a prevalent complication associated with advanced maternal age. It accounts for approximately 50% of all maternal age-related abnormalities (15): at ages 35, 40, and 45, the risk is approximately 1 in 270, 1 in 135, and 1 in 50, respectively.

When Down syndrome is suspected due to the age of the mother as foreseen in the early sonogram results like measurement of nuchal translucency thickness show positive signs the “cytogenetic prenatal diagnosis of Down syndrome has been formed using chorion villus sampling”. The test has been conducted between 10 as well as 12 gestational weeks. Amniocentesis can also be used. However, the test takes place later between 14 and 16 weeks. (16)

The measurement of nuchal translucency thickness is conducted during the initial trimester of pregnancy. It exhibits a superior detection rate compared to invasive techniques. The brains of individuals with Down syndrome exhibit distinct characteristics, including reduced size, a rounded shape, and a foreshortened appearance. The brain displays a pronounced increase in the occipital lobes and a major decrease in the superior temporal gyri size. The opercularization is not fully developed, resulting in the exposure of the insular cortex. Additionally, there is a decrease in the development of secondary sulcal. (17)

The primary factor responsible for these abnormalities is the reduced and distorted development of the frontal as well as temporal lobes. These secondary effects occur due to impaired neuronal differentiation, as documented by Lubec and Engidaworkin in 2002. (18)

The brain weight of individuals with Down syndrome typically falls within the lower end of the normal range. The relative size of the brain stem along with the cerebellum is smaller compared to the cerebral hemispheres (19).

The majority of individuals with Down syndrome develop pathology similar to Alzheimer's disease by the age of 40. (20)

STRUCTURAL CHROMOSOME ABNORMALITIES

These involve

1. translocations: that is exchange of material from one chromosome in the pair to another,
2. inversions,
3. deletions
4. duplications (Fig. 4). (21)

They can occur spontaneously or as a consequence of a chromosomal rearrangement in one of the parents. Robertsonian translocation, which involves fusion at or near the centromere of the 5 acrocentric chromosomes, is a frequently observed type of balanced structural rearrangement. (21) In a simple reciprocal translocation, two chromosomes exchange material. Although balanced carriers are perfectly normal, they run the risk of miscarriages or chromosomally unbalanced progeny as a result of meiotic malsegregation. Duplications (partial trisomy) and deletions (partial monosomy) are the outcomes of unbalanced structural chromosome rearrangements. (21)

An increasing number of microdeletion syndromes are being identified, including DiGeorge & Shprintzen syndromes (chromosome 22), Prader-Willi and Angelmann syndromes (chromosome 15), and Miller-Dieker syndrome (chromosome 17; Chapter 10). Numerous clinical phenotypes are linked to chromosome 22q11 deletion (del22q11) (5). Genomic imprinting plays a key role in some microdeletion syndromes. A chromosomal subregion receives a sex-specific mark from both the male and female parents, allowing only the maternal or paternal allele of a gene to be active in the progeny. As a result, the expression of some genes in the progeny will depend on the transmitting parent sex. (5) The phenotype of Prader-Willi and Angelmann syndromes depends on whether the microdeletion is inherited from the mother (in the case of Angelmann syndrome) or the father (in the case of Prader-Willi syndrome).

Defects in a Single Gene These conditions are caused by a single mutant gene and are classified as X-linked, autosomal dominant, or autosomal recessive traits according to Mendelian principles. Numerous disorders out of the over 8,000 that have been identified are uncommon, and some might not exhibit morphological defects (24). At term, known single gene defects cause about 8percent of congenital malformations. In heterozygous individuals, autosomal dominant gene defects result in noticeable effects, typically resulting in an equal distribution of sex in roughly 50percent of the offspring. While some of these conditions—like Huntington's disease along with some autosomal dominant cerebellar ataxias—do not manifest symptoms until adulthood, others—like thanatophoric dysplasia as well as achondroplasia—show symptoms from birth and can even be identified during pregnancy through ultrasonography examination. (25) Siblings of an autosomal disorder with unaffected parents are unlikely to experience a new mutation. Reduced penetrance, variable expression, and gonadal mosaicism could indicate a slight but actual recurrence rate. Contiguous gene syndromes are caused by small deletions, which can segregate as dominant mutations. For instance, the deletion of 22q11 causes velocardiofacial syndrome (VCFS); however, when this deletion is sufficiently extensive, other conditions such as DiGeorge sequence (25), become more severe. Males along with females have been equally affected by autosomal recessive gene defects, which only show clinical symptoms in homozygotes with a 25% chance of recurrence. As a result, the parents of affected people are heterozygous but in good health. There is frequently a history of consanguineous marriage unless there is an “autosomal recessive disorder that is common in a particular population, like Tay-Sachs disease in Ashkenazi Jews. Meckel-Gruber syndrome, a trio of CNS malformations including occipital encephalocele, prosencephalic dysgenesis, and rhombic roof dysgenesis combined with the multicystic, dysplastic kidneys and polydactyly, is an example of a recessive inherited disorder that affects the CNS(26-27).

If 50% of the mothers have the recessive gene defect, X-linked recessive gene defects usually only affect males. Daughters of healthy female carriers are similarly likely to carry the gene and to pass on the disorder. He would never pass on the X-linked recessive trait to his male progeny because fathers generally do not pass on an X chromosome to their sons. Haemophilia and Duchenne muscular dystrophy are two examples. The fragile X mental retardation syndrome is not straightforwardly X-linked (Gardner and Sutherland 1996; Hamel 1999; Warren and Sherman 2001; O’Donnell and Warren 2002). Affected individuals have a prevalence of 1 in 4,000–6,000 males and 1” in 8–10,000 females with this type of inherited mental retardation. These chromosomes are easily broken at Xq27.3, an unstable, fragile site caused by the FMR1 gene on the X chromosome long arm. DNA analysis can be used to identify the locations. (28-30)

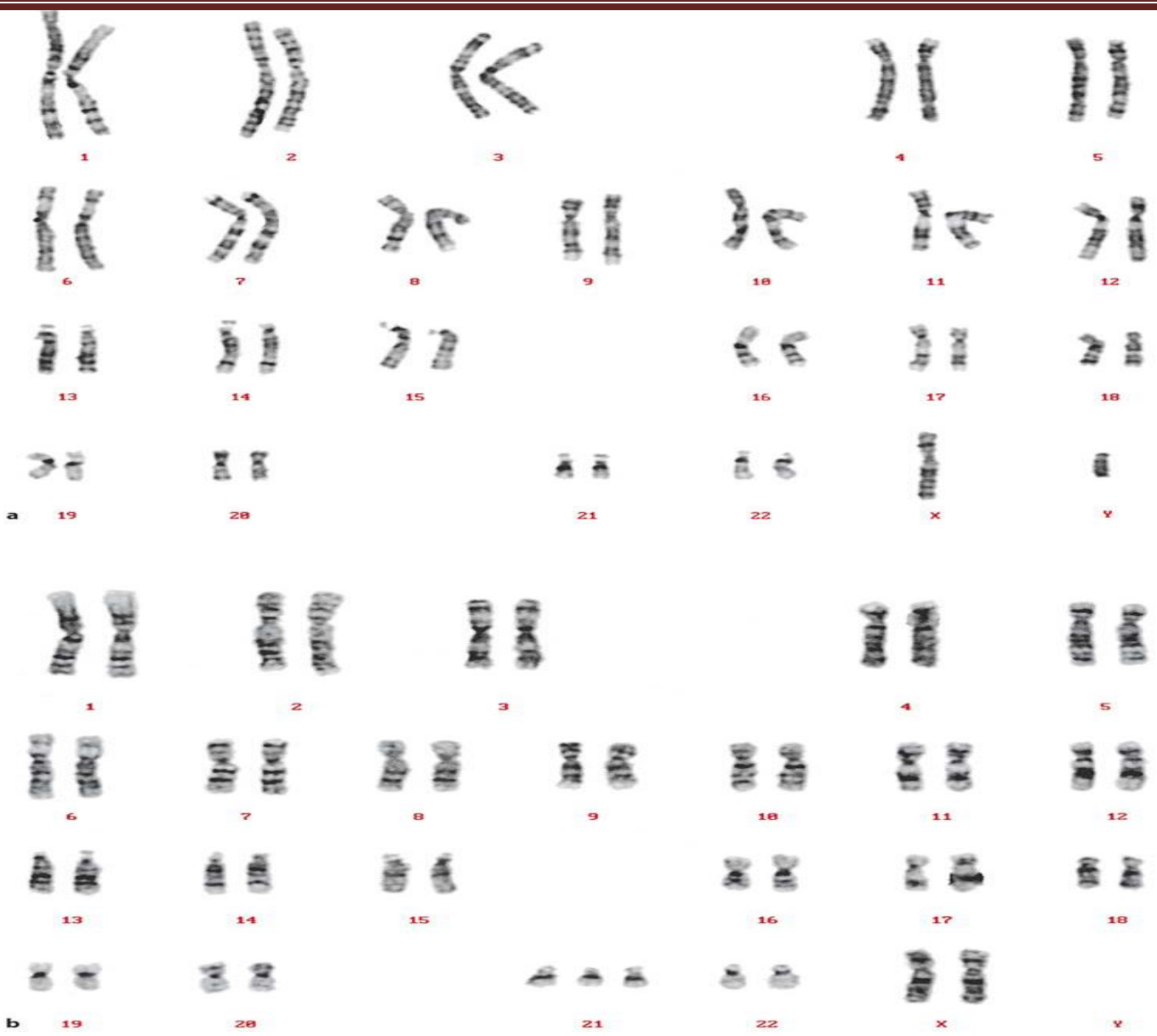
Genetic mutations in mitochondria The majority of metabolic disorders and diseases that appear to be degenerative are the known consequences of mother-transmitted mitochondrial DNA (mtDNA) mutations. Since mitochondria are found in all nucleated cells, mtDNA mutations may affect any tissue or organ. Since the heart, brain, and skeletal muscles are most commonly impacted, these conditions have been typically referred to as mitochondrial encephalomyopathies. Since oxidative phosphorylation (OXPHOS) defects may affect all tissues

as well as organs, that term might be more appropriate (31-32). A lot of patients experience their first symptoms before turning two years old. OXPHOS defects are typically fatal disorders that progress over time. Although the clinical characteristics of individuals with OXPHOS defects vary greatly, Leigh syndrome is a well-known phenotype that actually serves as the prototype for this broad category of disorders (32–33). The progressive subcortical disorder known as Leigh syndrome (33) or subacute necrotizing encephalomyopathy has been categorized by bilateral, subtotal necrosis multifocal areas in the brain stem tegmentum, basal ganglia, and cerebellum, as well as to a certain extent in the spinal cord (9). Any kind of movement disorder, such as chorea, myoclonus, dystonia, or hypokinetic-rigid syndrome, maybe the most noticeable. (8)

Differential Disorders The familial distribution of common congenital malformations, like defects of the neural tube and cleft lip with or without cleft palate, is consistent with the multifactorial inheritance, indicating that the disease results from several genes and environmental factors interaction. (31) In direct proportion to their relationship, family members of an affected person experience these disorders more frequently. It is possible to build a mathematical "liability" model with a threshold effect and determine the likelihood of recurrence in family members' offspring. In order to find out the recurring risks for genetic counseling of families having congenital anomalies which have been find out by multifactorial inheritance, empirical risks are utilized. These risks are based on the anomaly frequency in the general population as well as in various categories of relatives. (32) Since these estimates are typically population averages rather than exact probabilities for a given family, they may be erroneous in individual cases. (33)A growing number of human diseases, involving deafness, retinitis pigmentosa, Usher syndrome, Hirschsprung disease, holoprosencephaly, and Waardenburg syndrome type 2, have been shown to be inherited in a genetic manner. 34, 35

Environmental Factors Between fertilization and delivery, teratogenic factors can negatively and disruptively impact an embryo or fetus. Typically, the term "teratogen" refers only to environmental contaminants like medications, radiation, and viruses. Congenital defects, fetal and embryonic death, intrauterine growth retardation (IUGR), and mental impairment are among the disruptive effects. While changes in morphology are less likely to occur in a fetus than in an embryo, they can nonetheless affect cognitive ability, reproduction, and renal function. Vascular disruptions and the amnion disruption sequence may be the cause of mechanical effects.36)

figure 1:



CONCLUSION:

In this review, we delved into the complex world of genetics and its role in congenital malformations, specifically focusing on congenital malformations or birth defects. By meticulously analyzing existing research, we aimed to elucidate the potential link between genetic factors and the development of these malformations.

In conclusion, this review underscores the significant role genetics plays in [specific congenital malformation]. However, a more complete picture likely involves a complex interplay between genes and other factors. Further research is necessary to fully unravel this intricate dance and ultimately improve our understanding of these birth defects.

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