Potential Risk Factors in Enhancing the Occurrence of Genetic Disorders in Humans

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Abstract

Genetic disorders (GD) are diseases caused by changes in DNA that can be from a single gene to multiple genes and external conditions. Although mutations are the main cause, other factors also enhance the effects of these disorders in areas such as Pakistan. This chapter examines key risk factors associated with GD: Family factors such as parental consanguinity, advanced parental age, nutrition, and family history. These are frequent in some communities and increase the risk of recessive GD due to consanguinity and increased regions of homozygosity. Also, maternal age greater than 35 years and paternal age greater than 44 years are associated with an increased risk of GD, especially chromosomal ones. Nutritional factors like folic acid deficiency can also lead to neural tube defects and heart malformations, emphasizing the value of prenatal folate supplements. Family history remains essential in risk assessment and genetic counseling, aiding in preventative strategies and advancing healthcare to reduce the burden of GD globally.

Keywords: Chromosomal abnormalities, Family history, Genetic counseling, Genetic disorders, Parental consanguinity, Preventive strategies, Public health

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Introduction

Genetic disorders (GD) are a wide range of conditions that can significantly impact individuals and families. A GD happens when there's a change in the DNA sequence from its usual form, which can lead to disease. This change could be due to a mutation in just one gene (monogenic disorder), in several genes (multifactorial inheritance disorder), a mix of gene changes and environmental factors, or even issues within chromosomes (Kazantzidou et al., 2025). Common types of GD include familial hypercholesterolemia, hereditary breast, ovarian cancer syndrome, Lynch syndrome diabetes mellitus, thrombosis, cardiovascular disorders, celiac disease, Alzheimer's disease, Down syndrome and Turner syndrome, sickle-cell disease, thalassemia, glucose-6-phosphate dehydrogenase deficiency, hemophilia, coronary artery disease, arteriosclerosis, diabetes mellitus, hypertension, and obesity (Patel et al., 2020).

While genes play a critical role, environmental factors and socioeconomic status also influence the expression of GD (Mandal et al., 2015). Certain non-genetic factors are also linked to a higher prevalence of GD, such as intellectual disability (ID), in developing countries like Pakistan. These factors include advanced maternal age, limited maternal education, low socioeconomic status, rural backgrounds, poor access to healthcare, inadequate antenatal care, maternal malnutrition, and infections. Together, these conditions contribute to increased risks for GD, especially in regions where healthcare resources are limited (Huang et al., 2016).

1.1 Potential Risk Factors Contributing to Human Genetic Disorders

In this chapter, we will discuss some of the major risk factors that increase the likelihood of GD in humans. In the following sections, there is a detailed discussion of each risk factor and its importance, providing a deeper understanding of how they influence the occurrence and severity of GD.

1.1.1 Parental Consanguinity

There is a strong connection be parental consanguinity and the occurrence of GD (Table. 1 and 2). Consanguineous unions (CU) are more commonly practiced in developing countries, specifically in the Muslim world (Al-Gazali & Hamamy, 2014). Pakistan is referred to as a highly consanguineous country, with more than 50% consanguineous marriages (Perez, 2023). Different countries have different rates of

this kind of familial marriage, which are impacted by things including socioeconomic level, religion, local customs, and educational attainment (Götmark & Andersson, 2020). Because consanguinity increases the risk of acquiring autosomal recessive disorders from shared ancestry, research suggests that consanguinity may increase the incidence of certain genetic abnormalities and birth malformations. For clarity, children born to closely related parents are more likely to inherit two copies of a defective gene, which can result in genetic diseases and congenital abnormalities (CA) (Karami Matin et al., 2020).

Several studies show that children born to first-degree relatives are at a significantly higher risk of developing several GD. For example, a study conducted in Hong Kong revealed that people, who were born from consanguineous marriage, had OR of 8.70 for recessive diseases and 4.55 for structural abnormalities compared with people with non-consanguineous marriage (Siong et al., 2019).

The study also found that the Regions of Homozygosity (ROH) should also be considered as possible sources of recessive disorders. In populations that engage in consanguineous marriages, the ROH rates are higher, and this is associated with higher risk of GD. Non-Jewish populations in Israel with high consanguinity rates had ROH rates above the cutoffs for prenatal testing (Gafni-Amsalem et al., 2024).

1.1.2 Advanced Maternal Age

Advanced maternal age (AMA) is defined as age 35 years and older at the time of delivery of a newborn and it has been associated with various GD (Table 1 and Table 2). The relationship between maternal age and the risk of GD is complex and has been the subject of numerous studies. Systematic research indicates that AMA is associated with a higher risk of having children with congenital disorders compared to younger mothers (ages 20-34). The odds ratio for any congenital abnormalities in older mothers was found to be 2, which suggests a significant increase in risk. The risk of chromosomal anomalies was notably higher, with an odds ratio of 6 for older mothers compared to younger ones (Ahn et al., 2022). Some studies also suggest that AMA is correlated with a decreased risk of major fetal abnormalities and certain structural abnormalities (Goetzinger et al., 2016).

AMA impacts oocyte quality and embryo competence, primarily through post-transcriptional mechanisms. While germinal vesicle oocytes show similar transcript abundance across age groups, metaphase II oocytes exhibit divergent transcriptomes following in vitro maturation (Reyes et al., 2017). As growing women age, there is a significant increase in oxidative stress within the ovaries. This is characterized by an imbalance between reactive oxygen species and the body's antioxidant defenses. Studies indicate that after the age of 37, levels of malondialdehyde, a marker of lipid peroxidation, increase, while antioxidant enzyme activities such as superoxide dismutase and catalase decrease (Debbarh et al., 2021). This oxidative environment can lead to cellular damage in oocytes, impairing their quality and developmental potential. Mitochondria play a crucial role in energy production and metabolic regulation in oocytes. In women of AMA, mitochondrial metabolism becomes impaired, which negatively affects meiotic progression and oocyte maturation (Pietroforte et al., 2023). Poor mitochondrial function is linked to high rates of aneuploidy and reduced maturation capacity, further contributing to infertility risks associated with AMA. These findings collectively suggest that advanced maternal age significantly impacts genetic stability in offspring, highlighting the importance of understanding and potentially mitigating these effects.

1.1.3 Advanced Paternal Age

Research indicates that advanced paternal age (APA) is also associated with an increased risk of GD in offspring (Table. 1, 2). This relationship between APA and GD is highlighted by various studies and outcomes. A recent study examined more than 17 million live births in the United States from 2016 to 2021 found that fathers over the age of 44 have a significantly higher likelihood of having children with CA, especially chromosomal abnormalities. The adjusted odds ratio (aOR) was 1.59 when compared to fathers aged 25–34. Additionally, the study highlighted that advanced paternal age is linked to a higher risk of preterm birth and low birth weight in newborns (Bu et al., 2023).

1.1.4 Folic Acid Deficiency

Folic acid is the synthetic form of folate (vitamin B9) which plays a role in many metabolic processes in the body such as DNA synthesis, repair and methylation. It has a crucial function in cell division and growth, and therefore is important for embryonic development and other cellular processes (Abbasi et al., 2018). Folic acid is a pre-cursor of tetra-hydrofolic acid which is a carrier of one carbon units in enzymatic reactions required for DNA synthesis and methylation. This process is important for cell division and growth and is especially important during embryonic development and in rapidly dividing cells. The administration of exogenous folic acid during oocyte maturation increases blastocyst yields and decreases intracellular ROS levels, suggesting better cell proliferation and less cellular (Saini et al., 2022).

GD for example neural tube defects (NTDs) and congenital heart problems, are significantly influenced by folic acid deficiency. Research has demonstrated that folic acid supplementation at important times during organogenesis can prevent many diseases, including anencephaly and spina bifida, as well as structural heart defects, particularly conotruncal malformations (Crider et al., 2022). To lower the chance of NTDs and other congenital abnormalities, guidelines advise women who are capable of becoming pregnant to take 0.4 mg of folic acid daily through supplements, multivitamins, or fortified meals (Bibbins-Domingo et al., 2017). Higher doses under medical supervision may be advised for women with particular risk factors or a history of NTD-affected pregnancies to further reduce the risk (Kerr et al., 2017). Several studies found that taking folic acid daily reduced the risk of NTDs in women without a history of the condition by 40 to 100% (Viswanathan et al., 2017).

Research also suggests that maternal periconceptional folic acid supplementation may reduce the risk of limb defects in offspring. Studies have found decreased prevalence of limb defects, particularly clubfoot, among women who took folic acid supplements compared to non-users (Zhang et al., 2021). In northern China, a population-based study revealed that folic acid supplementation was associated with a significantly lower risk of upper limb reduction defects (Liu et al., 2019). Genetic factors may also play a role, as the MTHFR 677T variant in offspring was linked to increased limb reduction defect risk among non-supplementing mothers (Cleves et al., 2011). Multivitamin use containing folic acid was associated with a 30-35% reduced risk of conotruncal heart defects and limb deficiencies (Elizabeth et al., 2017; Mao

et al., 2017). While the specific role of folic acid remains unclear, these findings suggest that periconceptional folic acid supplementation may help prevent certain limb defects, especially in populations with low folate status (Moulik et al., 2017).

1.1.5 Environmental Exposures and Teratogens

Environmental exposures and teratogens significantly contribute to the risk factors associated with GD, particularly during critical developmental periods such as pregnancy (Table. 1). Teratogenic agents such as retinoic acids, valproic acid, diethylstilbestrol, and cyclopamine interfere with the regulation of genes controlling embryonic development (Garry & Truran, 2017).The effects of teratogens depend on the dose, route, and timing of exposure during pregnancy. The concept that any substance can be teratogenic at a high enough dose is known as Karnofsky's law (Kugler, 2017).

Neural tube defects have been associated with exposure to organic solvents, pesticides, water nitrates, heavy metals, and ionizing radiation (Rana et al., 2017). Maternal exposure to certain pharmaceuticals, such as thalidomide, retinoids, and valproic acid, can lead to birth defects through various molecular mechanisms (Mazzu-Nascimento et al., 2017). Other environmental risk factors include air pollution, parental smoking, maternal obesity, and infectious diseases during pregnancy (Lee et al., 2021). Genetic factors, including variations in genes like MTHFR, GATA4, and CFTR, also contribute to CA (Lee et al., 2021).

Prenatal Alcohol Exposure (PAE) is acknowledged as one of the commonest teratogens – environmental agents that cause birth defects, resulting in a range of disorders collectively referred to as Fetal Alcohol Spectrum Disorders (FASD). They can cause structural and neurological abnormalities of the body such as craniofacial abnormalities. Previous studies suggest that genetic factors can influence the effects of PAE, and that certain genetic pathways, including the Hedgehog signaling pathway, are involved in increasing the vulnerability to teratogenic effects of both alcohol and other environmental chemicals like piperonyl butoxide (PBO), which is used in pesticides (Everson et al., 2020). The same applies to schizophrenia in which genetic susceptibility is combined with other factors like cannabis use and childhood trauma. These interactions demonstrate how some people can be born with genes that make them susceptible to developing psychiatric diseases when they come across certain environmental factors (Guloksuz et al., 2019). Understanding these gene-environment interactions is crucial for developing preventive strategies and safer pharmaceutical compounds to reduce the incidence of preventable birth defects (Kwabi-Addo, 2017). Fig. 1 and Table 1 show the risk factors associated with GD.

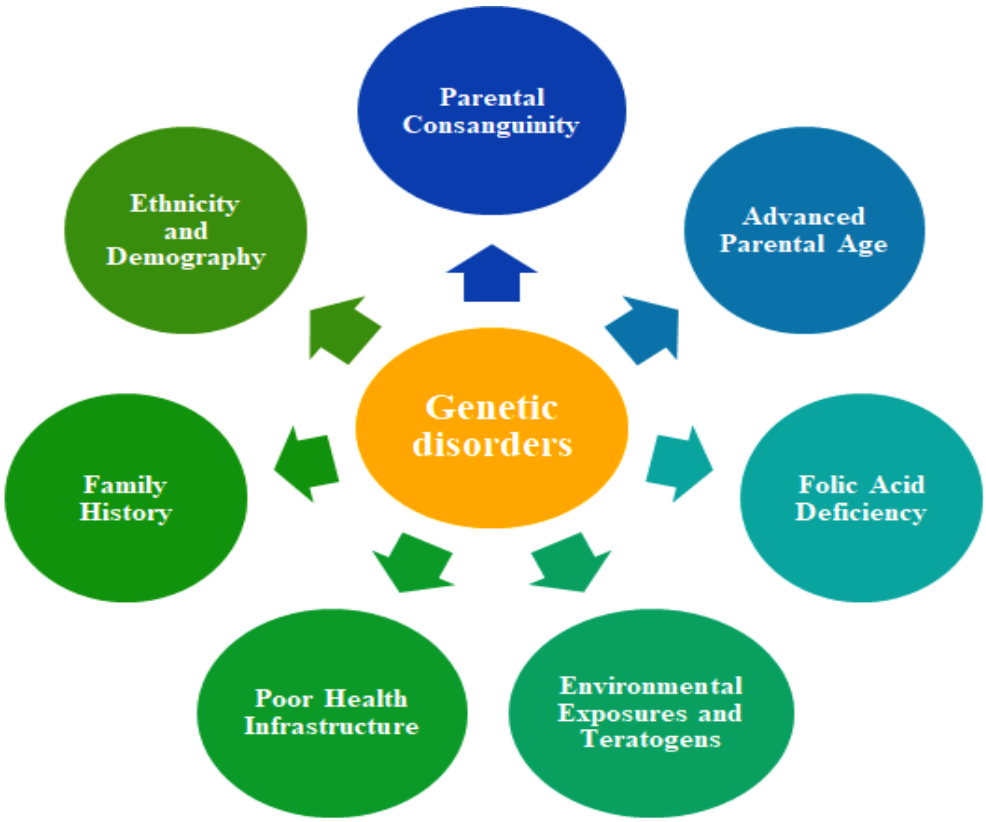

Fig. 1: Risk Factors in enhancing genetic disorders in humans

1.1.6 Family History

GD are influenced by both inherited genetic factors and family history (Table. 2). Family history is a valuable tool for assessing genetic risk factors in complex diseases. A comprehensive family history can stratify risk for multiple preventable, chronic conditions, with 5-15% of individuals having moderately increased risk and 1-10% having high risk for specific diseases (Griffith et al., 2017). In an internal medicine

setting, approximately 80% of patients were found to be at increased risk for at least one disease category based on family history, with 20% having risks not documented in their charts (Carroll et al., 2017). As knowledge of human genetics expands, the role of family history in risk assessment continues to evolve, particularly for common disorders with complex etiologies (Leung et al., 2017).

Family history and polygenic risk scores (PRS) provide complementary information for assessing inherited disease susceptibility. Family history captures shared genetic and environmental factors, while PRS offers a direct measure of genetic risk (Mars et al., 2022). Risk Stratification: Combining family history with PRS can significantly enhance risk stratification. For instance, a high PRS can elevate risk even in individuals without a family history, and a low PRS can mitigate risk in those with a positive family history (Mars et al., 2022) . Family history remains a valuable tool in primary care for assessing risk of common chronic diseases, even when the molecular cause is unknown. It integrates genetic susceptibilities and environmental exposures. Knowledge of family history can motivate behavior changes, such as increased adherence to screening recommendations for diseases like breast cancer (Talley et al., 2017). The accuracy of family history information can vary, and it is often misreported or misunderstood, particularly for conditions with subtle distinctions like different types of cardiac disease, in these conditions Genetic testing offers utility as a supplement to traditional family health history intake over certain conditions, such as cardiomyopathy, arrhythmia, and malignant hyperthermia (May et al., 2023).

Table 1: Link of congenital anomalies with non-genetic risk factors

Exposure	Outcomes	Reference
Toxic chemicals	CA	(Kyung-Shin et al., 2021)
Parental smoking	CHD, Oral clefts, Digestive system, Nervous system, Musculoskeletal system, Eye, ear, face and neck, Cryptorchidism, Brain tumors	
Maternal infectious health	CHD, Neural tube defects, Orofacial clefts, Digestive system, Limb reduction defects	
Maternal Fever	CHD	
Gestational diabetes mellitus	CA, Anorectal malformations	
Pre-gestational diabetes mellitus	CA, Anorectal malformations	
Maternal overweight	CHD, Anorectal malformations	
Maternal drug intake	Congenital malformation, CHD, Cleft lip, Neural tube defects, Urogenital anomalies, Musculoskeletal anomalies	
Artificial reproductive technologies	Nervous system, Genitourinary system, Digestive system, Musculoskeletal system, Ear, face, and neck, CHD, Congenital malformation	
Socioeconomic status	CHD, Cleft Lip	
Consanguineous marriages	Congenital malformation	
Paternal age (45+)	Congenital malformation, CHD	

Table 2: Summary of risk factors associated with genetic disorders

Factor	Description	Impacts on Individuals	References
Age	Increased risk GD with maternal age, especially after 35; paternal age over 50 also contributes.	Higher likelihood of conditions like GD can cause many problems to infants like chromosomal abnormalities; emotional stress due to potential health implications for offspring.	(Cao et al., 2023)
Family history	A family history of genetic abnormalities raises the risk for future generations.	Increased anxiety about health risks in relatives; potential for genetic counseling and testing decisions.	(Yoon et al., 2022)
Genetic variants	Presence of rare deleterious variants or specific common variants can significantly influence health.	Can lead to chronic conditions, impacting quality of life and increasing healthcare needs.	(Jukarainen et al., 2022)
Environmental interactions	Interaction between genetic predispositions and environmental factors (e.g., lifestyle, toxins).	May exacerbate genetic conditions, leading to an increased burden of disease and disability-adjusted life years (DALYs).	(Zhang et al., 2024)
Ethnicity and ancestry	Certain GD are more prevalent in specific ethnic groups (e.g., sickle cell disease).	Impacts access to targeted healthcare resources may lead to stigmatization or discrimination within communities.	(Lee et al., 2019)
Previous pregnancy complications	History of miscarriages or stillbirths increases the risk of GD in subsequent pregnancies.	Heightened anxiety and stress for future pregnancies; potential for increased medical interventions.	(Vu et al., 2022)
Psychosocial Factors	Emotional responses to genetic diagnoses can vary widely among individuals.	May lead to feelings of guilt, fear, or helplessness; can affect family dynamics.	(Billingsley et al., 2018)

Families with hereditary cancer syndromes collectively. The psychological response and risk management behaviors of mutation carriers are influenced by family dynamics and communication patterns. Families, especially parents, need support in disclosing genetic information to children and managing the emotional impact of hereditary risk (Gomes et al., 2022). Understanding and addressing the personal and familial dimensions of genetic risk can enhance patient care and disease prevention strategies.

1.1.7 Ethnic Background and Geographic Distribution

Ethnic background and geographic distribution play significant roles in the prevalence and risk of GD (Table. 2). Studies have shown that while cancer risk alleles may be broadly consistent across ethnic groups, reproducing clinical findings in different populations is challenging due to confounding genomic architecture (Jing et al., 2014). Populations like Arabs have high consanguinity rates, contribute to increased autosomal recessive disorders, with many novel mutations identified (Tadmouri et al., 2014). Geographic distribution of GD can be influenced by immigration patterns and ancestral contributions, as demonstrated in the French Canadian population of Saguenay-Lac-Saint-Jean, where certain regions show higher incidences of autosomal recessive disorders (Drift, 2017). Ethnic and geographic differences in cancer incidence and outcomes are influenced by variations in both germline and somatic genomes. For instance, prostate cancer is more common and more aggressive in African and African American people than in whites because of genetic risk factors (Rebbeck, 2017). These findings emphasize the importance of considering ethnic and geographic factors in genetic research and clinical practice.

Many genetic researches have been done on the White people, thus making a research gap on other people of other origins. Population- and multi-ethnicity based biobanks are crucial for identifying genetic factors for diseases worldwide and for the subsequent therapies (Gurdasani et al., 2019). Understanding the interplay between ethnicity, geography, and GD risk is crucial for advancing personalized medicine and improving health outcomes across diverse populations.

1.1.8 Poor Health Infrastructure

Lack of health facilities may greatly affect the occurrence and control of GD. The ethnic minorities could be genetically predisposed to adverse effects of environmental toxins than the other groups of people. Lack of adequate health facilities in these societies exposes these people to these toxins hence increasing the rate of GD (Olden & White, 2005; Shao et al., 2017).

Research indicates that a number of rural health care services in countries like Pakistan relies on a combination of personnel including untrained personnel, traditional and faith healers, Unani medicine practitioners and semi-trained personnel like medical assistants and community health workers. These providers are not affiliated with the conventional health care systems but play a crucial role in the provision of health care to the poor in the rural areas where qualified health care providers are scarce. This situation captures the dynamics of the Pakistan rural health care system and how people try to seek help from available resources when they have a health issue (Kumar & Bano, 2017). Lebanon also suffers from similar problems; there is a shortage of genetic services, and the majority of healthcare professionals and the community remain ignorant of the situation (Nakouzi et al., 2015). To achieve good control of GD, there is need to have a good epidemiological background, early diagnosis and proper utilization of resources.

Conclusion

Understanding risk factors for GD provides a valuable foundation for improving healthcare outcomes. In regions like low- and middle-income countries, acknowledging these factors is crucial for developing targeted strategies to reduce the prevalence and impact of GD. By improving public awareness, promoting genetic counseling, and implementing policies that address healthcare gaps, can help mitigate the impact of these disorders. Furthermore, fostering a comprehensive approach that includes both genetic and environmental considerations will be essential in improving healthcare outcomes and enhancing the quality of life for affected individuals.

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