The Influence of Environmental and Genetic Factors on Various Disorders and Diseases

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Abstract
Both genetic and environmental factors have been implicated in the mechanism of various disorders. Epidemiological data have shown that environmental factors can also cause and/or exacerbate the pathogenesis of these diseases. However in this article, we provide a summary of evidence for environmental and genetic factors influencing the diseases. The review also incorporates the major findings categorizing the common diseases on the basis of genetic profiles and ethnic information and in establishing personalized disease diagnosis, drug responses and treatment modalities based on the genetic determinants. These studies provide important insights into the interplay between environmental and genetic factors leading to human diseases. Overall an attempt has been made to highlight the importance of studying the genetic profiles of an individual with many factors.

Keywords: Epidemiology; Genome; Genetic disorder; Environmental; Triggers; Disorders

Introduction
Basic biology of genetic syndromes
A genetic syndrome is any disease that is caused by an abnormality in an individual’s genome. The abnormality can range from minor to major from a discrete mutation in a single base in the DNA of a single gene to a gross chromosome abnormality involving the addition or subtraction of an entire chromosome or set of chromosomes. A genetic disorder is an illness caused by abnormalities in genes or chromosomes. While some diseases, such as cancer, are due in part to genetic disorders, they can also be caused by environmental factors. Some types of recessive gene disorders confer an advantage in the heterozygous state in certain environments. Environmental factors such as the weather affect business interests. If a disease process is concluded to be the result of a combination of genetic and environmental factor influences, its etiological origin can be referred to as having a multifactorial pattern. Many cancers along with a plethora of other diseases, are thought to be a result of environmental triggers (Figure 1).

Various genetic diseases and its genetic factors
Sickle cell disease is a collective term for a group of blood diseases resulting from the inheritance of haemoglobin S. The pathological process in sickle cell disease is caused by the sickling phenomenon. In the deoxy state hemoglobin S molecules aggregate into long polymers that are aligned to form liquid crystals called tactoids. In the presence of tactoids the normal disc shaped, easily deformable red cell is transformed into the characteristic sickle shaped cell that gives this condition its name. The sickling phenomenon damages the red cell membrane so that it becomes increasingly rigid. Such cells are sequestered in the reticulo endothelial system and rapidly destroyed, causing hemolytic anemia. A second major disturbance in sickle cell disease arises as a result of altered flow properties of sickled red cells. There is an increase in blood viscosity associated with small vessel stasis and obstruction, which eventually lead to vasocclusive crises and ultimately to permanent organ damage. Furthermore, patients suffering from sickle cell disease have a propensity to bacterial infection owing to a combination of asplenia, defective opsonisation, and other, as yet ill defined factors [1]. Besides the impact of direct environmental factors, the occurrence of non-communicable adult disease is determined by non-genetic and genetic developmental factors [2]. Attention deficit hyperactivity disorder (ADHD) is a developmental disorder. It is primarily characterized by “the co-existence of attentional problems and hyperactivity. ADHD is the most commonly studied and diagnosed psychiatric disorder in children, affecting about 3 to 5 percent of children globally. Heterogeneity in attention deficit hyperactivity disorder with complex interactive operations of genetic and environmental factors, is expressed in a variety of disorder manifestations: severity, co-morbidities of symptoms, and the effects of genes on phenotypes. Neurotrophic factors that participate in the neurogenesis, survival, and functional maintenance of brain systems, are involved in neuroplasticity alterations underlying brain disorders, and are implicated in the genetic predisposition to ADHD, but not obviously, nor in a simple or straightforward fashion. In the context of intervention, genetic linkage studies of ADHD pharmacological intervention have demonstrated that associations have fitted the “drug response phenotype,” rather than the disorder diagnosis [3]. Chronic neutrophilic leukemia (CNL) is an extremely rare myeloproliferative disorder characterized by persistent mature neutrophilia. Because this disease entity is very rare, and because it is typically a diagnosis of exclusion, it is important for pathologists and hematologists to be familiar with CNL when approaching the patient with a myeloproliferative clinical picture [4]. Preoperative Iron deficiency anemia (IDA) is common and associated with poor postoperative outcomes. Standard treatment includes allogenic blood transfusion or oral iron supplementation, but new intravenous iron strategies have shown promise in the perioperative setting. This trial demonstrates that intravenous iron is both a feasible and effective treatment for IDA in anemic colorectal cancer patients [5]. Arterial thrombosis is responsible for heart attacks, strokes and peripheral vascular disease (thrombosis in leg arteries). The only funded etiology of arterial
thrombosis is the recent plasmapheresis donation. Although this technique is known to be safe, this report is the third one published about a life threatening arterial thrombosis due to apheresis donation, raising the interrogation about it harmlessness [8]. Asymptomatic microfilariaemia is relatively common in India and the larvae have long been described the bone marrow. The coexistence of parasitic and neoplastic illnesses in some cases is purely incidental, although the richly vascular leukemic bone marrow was an optimal site to yield the diagnostic larval forms. Filaria is in association with solid malignancies is well described in literature [7]. Huntington’s disease is a genetic disorder (inherited due to a faulty gene) which usually affects people in their 40s and 50s. It primarily affects the brain, with a gradual loss of control of movement, memory and mental ability. The gene for Huntington disease on the fourth chromosome has been characterized in recent years [8]. Monogenic forms of Parkinson’s disease account for ~3% of all “idiopathic” Parkinson’s disease [9]. Oral-facial-digital syndrome (OFDS) type 1 (OFD1) is an X-linked dominant condition associated with embryonic male lethality. It almost always affects the oral cavity, face, and digits [10]. Breast cancer represents a heterogeneous group of tumors that are diverse in behavior, outcome, and response to therapy. Currently, breast cancer patients are managed according to algorithms based on the clinical and histopathological parameters. One study shows the possibility of using ANXA7 as both a clinically relevant indicator of disease progression and a prognostic biomarker for survival in the patients with triple negative breast cancer. So the ANXA7 may serve as a promising target for triple negative breast cancer therapy [11]. Gastrointestinal diseases are recognized, as being dominant in women (Irritable bowel diseases, chronic constipation), but others, as being more common in men (Anal fistulae). The pathogeneses of gastrointestinal diseases are unclear. Steroid sex hormones play crucial role in the pathogenesis of several gastrointestinal diseases [12]. Defective Fas function causes the autoimmune lymphoproliferative syndrome, but it is also involved in common autoimmune disorders [13]. Diabetes has been associated with a net loss of bone with reduction of new bone formation and decreased bone mineral density. In diabetic mice the up-regulation of specific transcription factors is attenuated, resulting in deficiency in conversion of mesenchymal cells to osteoblasts. Bone growth in diabetes which is disturbed is also not enhanced to the same extent by hormone replacement therapy and might be the result of lower hip BMD in young women due to their type 1 diabetes therefore the use of the specific phytoestrogens and their synthetic derivatives that we use in this study, might provide an alternative solution [14]. Protein p21, member of the Cip/Kip family of cyclin kinase inhibitors, is a physiological regulator of cell cycle, differentiation and apoptosis in various cell types. Its role in regulation of secretory activity of both non-ovarian and ovarian tissues is unknown [15]. Type 1 diabetes, known as insulin dependent diabetes mellitus (IDDM) is well documented as an autoimmune disease in which pancreatic islet cells are progressively destroyed. The high degree of fluorescence sensitivity and enzyme specificity indicate that enzyme inhibition assay is simpler, more accurate and sensitive enough for screening of a large number of serum samples for the presence of anti-GAD antibodies for identification of people who are at risk for insulin dependent diabetes mellitus (IDDM.) [16]. Schizophrenia is a complex psychiatric disorder characterized by perceptual abnormalities including hallucinations and delusions, conceptual disorganization, cognitive impairment, and frequently, the presence of negative symptoms such as alogia, affective flattening, and avolition. In conclusion, our results support the idea that the Angiotensin-converting enzyme, DD genotype and its ACE levels are important risk factors for schizophrenia. However; further investigations are required to elucidate the increased frequency of the D allele among schizophrenia patients and to understand the mechanism behind the suggested protective effect of the L allele against schizophrenia [17]. Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) coexist in some patients. Specific tests for genetic

![Figure 1: Genetic Disorders in Humans.](image-url)
interactions between loci revealed potential association of genes that influence neural, barrier, or mast cell function with colonic transit. Conclusions & Inferences genetic variations that may influence local mucosal immune functions are univariately associated with altered colonic transit in lower functional gastrointestinal disorders [18]. Pier pont syndrome is a multiple congenital anomaly syndrome with learning disability first described in 1998. Mutations in the FERMT1 gene (also known as KIND1), encoding the focal adhesion protein kindlin-1 underlie the Kindler syndrome, an autosomal recessive skin disorder with an intriguing progressive phenotype comprising skin blistering, photosensitivity, progressive poikiloderma with extensive skin atrophy, and propensity to skin cancer. Environmental factors and yet unidentified modifiers may play a role. Better understanding of the molecular pathogenesis of KS should enable the development of prevention strategies for disease complications [19]. Periodontal disease could be a risk factor for several systemic conditions such as a heart/vertebrate disease, diabetes, pneumonia and premature birth [20]. Gastrointestinal diseases are recognized, as being dominant in women (Irritable bowel diseases, chronic constipation), but others, as being more common in men (Anal fistulae). These observations raise concerns about the involvement of sex steroid hormones in the pathogenesis of these diseases [21]. This prospective, non-randomized study assessed toxicity and potential efficacy of low-dose granulocyte macrophage colony-stimulating factor (GM-CSF), interferon alpha (IFN) and interleukin 2 (IL-2) postoperatively in patients with high-risk renal cell carcinoma (RCC) [22]. Prostate cancer (PC) is the second leading cause of cancer deaths in men in America and Western Europe. Epidemiological studies suggest that prostate cancer incidence increased in last few years in Asian population [23]. Liposomas are recognized as important vehicles for cytotoxic drugs because they can protect the drugs from degradation in circulation, thereby protecting healthy cells and tissues from exposure to lethal drug doses [24]. In the aetiology of HIV-1 infection, some genetic factors may be important, for example the gene variants, which encode chemokine receptors: CCR5, CCR2 and CXCR4 - SDF-1 ligand receptor. This finding might be useful for epidemiological researches of HIV infections and other diseases like diabetes [25]. Asthma and chronic obstructive pulmonary disease (COPD) show similarities and substantial differences. It is stipulated that asthma and COPD have common genetic and environmental risk factors, which ultimately lead to clinical disease depending on the timing and type of environmental exposures. Thus, a particular group of shared genetic factors may lead to asthma when combined with specific environmental factors, whereas combination with other environmental factors, will lead toward COPD. The genetic predisposition to certain pathways may further help to define the development of either asthma or COPD. In the end this may lead to stratification of patients by their genetic make-up and open new therapeutic prospects [26]. Juvenile Myelomonocytic Leukemia (JMML) is a relentlessly progressive myeloproliferative/myelodysplastic (MPD/MDS) hematopoietic disorder more common in patients with any one of at least three distinct genetic lesions, specifically NFI gene loss and PTPN11 and NRAS mutations [27]. Metabolic syndrome is defined as a cluster of multiple risk factors, including central obesity, dyslipidemia, hypertension and impaired glucose tolerance, that increase cardiovascular disease morbidity and mortality. Genetic factors are important in the development of metabolic syndrome, as are environmental factors [28]. Ovarian cancer is the fourth leading cause of cancer-related death in women in the U.S. and the leading cause of gynecologic cancer death. Specifically, epithelial ovarian cancer (EOC) is characterized by few early symptoms, presentation at an advanced stage, and poor survival. There are more than 190,000 new cases of epithelial ovarian cancer (EOC) each year worldwide and this malignancy represents the leading cause of death from gynecological cancers. The possibility of using ANXA7 as both a clinically relevant indicator of disease progression and a prognostic biomarker for survival in the patients with ovarian cancer [29]. Chronic infantile neurological cutaneous and articular syndrome (CINCA), also known as neonatal-onset multisystem inflammatory disease (NOMID), is dominantly-inherited systemic auto inflammatory disease. Some Neuroendocrine tumours (NET) occur in hereditary-familial neoplastic syndromes such as MEN (multiple endocrine neoplasias) or neuroectodermal dysplasias (neurofibromatosis-NF1, von Hippel Lindau disease, pheochromocytoma-chemodectoma familial syndrome, etc.) while others arise as solitary-isolated tumours such as those of gastrointestinal tract, pancreas, lung, skin, genitourinary system [30]. HNF1B nephropathy is typically responsible for bilateral renal cystic hypodysplasia in childhood One findings have provided data that are useful for recognition and diagnosis of HNF1B disease in adulthood and might help in renal management and genetic counseling [31]. Genetic defects of platelet function give rise to mucocutaneous bleeding of varying severity because platelets fail to fulfill their haemostatic role after vessel injury [32]. Mendelian inheritance has been demonstrated for some disorders, others are associated with mutations and polymorphisms in susceptibility genes [33]. If stable gene transfer is desired, non-integrating vector systems may be combined with transposon-or phage integrase-based systems or future site-specific systems to achieve integration into the host B cell genome [34]. First time a de novo chromosomal abnormality which produced the phenotype of a female with primary ovarian failure and subsequent osteopenia in early adult life [35]. Mutations in several multidrug resistance proteins (MRPs) are associated with human genetic disorders [36]. Dravet syndrome, also called severe myoclonic epilepsy of infancy (SMEI), is a severe form of epilepsy. It appears during the first year of life with frequent febrile seizures – fever-related seizures. Dravet syndrome depends on a series of independent factors including seizure control, behavior, cognitive, and motor problems [37]. Fanconi Anemia (FA). FA is a model disease in cancer research, yet there are no contemporary data on carrier frequency or prevalence in the general United States (US) population or elsewhere [38]. Genetic, hormonal and life-style related factors determine SHBG levels and low sex hormone-binding globulin levels are a known risk factor for the development of the metabolic syndrome, diabetes and cardiovascular diseases [39].

Environmental factors influencing diseases in different ways

During the past few years, experimental evidence has emerged to suggest that environmental factors may influence cellular proliferation attrition in an organ-specific manner. Mostly, transmission rates were significantly lower than expected. In such cases, and in disorders with no genetic background, environmental factors seem to influence and/or cause disease onset, progression, and outcome [40]. Traditional risk factors for breast cancer explain only a fraction of cases. Causes for trends in breast cancer incidence are not fully understood. Breast cancer incidence and mortality rates decrease with environmental conditions that promote Vitamin D synthesis in human skin including lower latitude and higher personal exposure to sunlight [34]. Environmental factors are threats to health, and controlling them is public environmental health. They include [41].

- Environmental conditions favoring disease vectors (endemic and exotic vectors)
Invasive biota (viruses, bacteria, etc), their hosts and vectors

- Environmental disruptions: floods, droughts, storms, fires, earthquakes, volcanoes
- Air quality: pollen and pollution leading to respiratory diseases or cancers
- Water quality: biotic and abiotic contaminants; integrity of water transport and treatment infrastructure
- Monitoring and management of municipal, agricultural, industrial outflows to the environment (gases, liquids, solid wastes)

**Gene therapy and other diagnosis factors in cure of diseases**

In gene therapy the integration process of the viral DNA genome into the host cell genome is a necessary step for virus integration. Just a few years ago, retrovirus integration was believed to be random and the chance of accidentally activating a gene was considered remote. Tumorigenesis associated to some studies in gene therapy is suspected to be caused by insertion process. Depending on whether the provirus integrates into or in the vicinity of genes normal transcription can be enhanced or disrupted thus inducing oncogenic mutations. This is called "insertional mutagenesis". Investigating whether an area over the genome could be favoured by retrovirus integration is a crucial aspect in gene therapy. These area are called "Common Integration Sites" (CIS)or "hotspots" [42]. Recombinant adeno-associated virus (rAAV)-based gene therapy represents a promising approach for the treatment of heart muscle diseases, but the molecular mechanisms that direct rAAV transduction remain unclear. It is concluded that a calcium-dependent pathway regulates rAAV vector transduction at a number of stages that may include vector mobilization, conversion, and transcription activity. Modulating this pathway through β-adrenergic signaling enhances rAAV-mediated gene delivery to cardiomyocytes, and may be valuable when considering therapeutic approaches for heart muscle diseases [43]. Liposomes are recognized as important vehicles for cytotoxic drugs because they can protect the drugs from degradation in circulation, thereby protecting healthy cells and tissues from exposure to lethal drug doses. Liposomes have been touted as tumor-specific and effective carriers of cytotoxic drugs. However, they are not devoid of significant problems including premature destruction to cause toxicity to healthy tissues or in the other extreme, undesirably long stability to prevent effective delivery to the tumor cells [44]. Plasma B-type natriuretic peptide (BNP) values have been evaluated as predictors of outcome and are helpful in determination of therapeutic options in patients with both acute and chronic heart failure [45]. Early and increased amounts of plasma have been associated with improved survival after penetrating and blunt injury. However, no studies involving burn patients demonstrate the effects of Intraoperative plasma administration on postoperative resuscitation requirements. This study examined perioperative transfusion ratios and the role of early, aggressive plasma administration in a contemporary burn center [46]. Therapeutic fluids used in intensive care can have profound effects on coagulation, not only by dilution itself but also by other more complicated interactions. The aim of some study was to monitor the extent of dilutive coagulopathy induced by the most common therapeutic fluids and to attempt normalization of haemostasis by fibrinogen addition [47]. Currently a number of countries including United States screen all donations for anti HBc which is not mandatory in some other countries such as Iran. Nevertheless it has been argued that the exclusion of anti-HBC positive donors is impractical in countries where HBV infection is prevalent and more than 20 percent of the populations are positive for anti-HBc [48]. There has been recent findings on cobalamin deficiencies due to food-cobalamin malabsorption or nondissociation of vitamin B12 from its carrier proteins syndrome [49]. The quality platelets concentrate plays an important role in transfusion therapy [50]. It has been provided that the evidence of the expression profile of GR proteins in the human myometrium and have demonstrated a pregnancy related down-regulation. Further research is needed to understand the physiological significance of this observation and to clarify the role of glucocorticoids and GR in pregnancy maintenance and the onset of labour [51]. Metabonomics is formally defined as "the quantitative measurement of the multi-parametric metabolic response of living systems to pathophysiological stimuli or genetic modification". This approach is complementary to proteomics and genomics and is applicable to a wide range of problems in diverse biomedical research areas [52]. Development of nanoparticles as agents for targeted detection of cancer cells through imaging has been an exciting area of investigation in recent years. Accurate targeting is of critical importance particularly when these agents are also used for shuttling therapeutic molecules to treat specific tumors or cancer. Magnetic resonance imaging (MRI) remains an attractive imaging platform due to its high spatial resolution [53]. Molecular tumor profiling has potential importance in identifying the tissue of origin in patients with cancer of unknown primary [54]. There have been several mutations identified in the apoB-100 gene leading to premature truncation of protein synthesis or to amino acid substitution within the protein such changes can influence the metabolism of plasma lipoprotein and may therefore be important in the development of hyperlipidemia and coronary heart disease [55]. Previously, It has been reported that normal ovaries lack neutrophil gelatinase associated lipocalin (NGAL) expression and that NGAL expression occurs in benign tumours and increases in early grade ovarian tumours [56]. Continuous subcutaneous insulin infusion (CSII) therapy is widely accepted for brittle type 1 diabetes, since it has the benefit of less frequency of hypoglycemia and better management of the dawn phenomenon compared to multiple daily insulin injection (MDI) therapy [57]. Comparative studies between African and European populations suggest that total lymphocyte count (TLC), including CD4+ count, is likely to vary significantly by ethnicity, in both, healthy and HIV-infected Individuals [58]. Natural killer (NK) cell function was investigated in Malaysian HIV patients beginning antiretroviral therapy (ART) with advanced immunodeficiency. Some patients experienced immune restoration disease (IRD) presenting as exacerbations of pre-existing infections. Whilst most IRD are attributed to interferon-gamma produced by T-cells, NK cells may also contribute [59]. In recent years particular attention has been drawn to the effect of antiretroviral (ARV) therapies on the incidence of serious non-AIDS events (SNAEs), including cardiovascular disease (CVD), end-stage renal disease, liver failure and fractures Of particular interest is the effect of individual ARVs or ARV classes on these events [60]. Immune Recovery Inflammatory Syndrome (IRIS) is characterized by a paradoxical deterioration of clinical status after initiation of Anti-Retroviral Therapy (ART), despite improved immune function. It is caused by inflammatory response against the infectious antigen [61]. It follows a previously asymptomatic man who presented with common, non-specific symptoms and was diagnosed with a rare complication of non-typhi Salmonella infection. This serves as a clear reminder to all clinicians to have a low threshold for testing for HIV and highlights the need to introduce an opt-out system for HIV testing in all acute healthcare settings with a high prevalence of HIV infection [62].
Concomitant antiretroviral therapy (ART) can be a factor leading to a lower efficacy of pegylated interferon (peg-IFN) plus ribavirin (RBV) in human immunodeficiency virus (HIV)/hepatitis C virus (HCV)-infected patients. In this study, HIV/HCV-infected patients who were treated with a three-drug regimen including TDF plus 3TC or FTC along with NVP responded better to peg-IFN plus RBV than those who took LPV/r, a finding that has not been previously reported [63]. Even with combination antiretroviral therapy (cART) regimen, the durability of HIV control is limited by many factors (adherence to treatment, drug toxicity, bioavailability, among the most important). When salvage therapy is considered, better outcome is expected if antiretroviral regimen includes a class to which the patient has not been exposed previously. Therefore classes of antiretroviral drugs directed at targets other than reverse transcriptase or protease are of potential great interest [64]. Studies aimed to assess the effects of drugs in patients with immune failure, as well as on the incidence on AIDS and non-AIDS events, liver fibrosis and atherosclerosis progression are clearly needed [65]. Histoplasma is a dimorphic pathogenic fungus which causes human infection worldwide, mainly in equatorial countries [66]. Infectious organisms, most likely viruses, have long been a suspect for triggering the autoimmune response in people genetically susceptible to MS. Although many infectious microorganisms have been investigated, no particular organism has emerged as a proven trigger. The AIDS virus is a neurotropic virus and CNS involvement as the presenting complaint is seen in approximately ten percent of cases of HIV infection [67]. Osteopontin (OPN) is a secreted phosphoprotein which plays a critical role in metastasis of colon, liver, and breast cancers [68]. Epigenetic regulation of gene expression, through covalent modification of histones, is a key process controlling growth and development. Accordingly, the transcription factors regulating these processes are important targets of genetic diseases [69].

Conclusion and Future Directions

This review is aimed to focus on the influence of host and genetic factors in the pathogenesis of disease and its diagnosis. These studies have to be replicated in different populations for interpreting the mechanism of pathogenesis of the disease. Future studies should explore the mechanism of gene alteration targeting the disease progression from healthy state. Despite recent advances in the understanding of the pathophysiology of human diseases acquired aplastic anemia and idiopathic pulmonary fibrosis, the possible causes of these diseases remain enigmatic. Numerous studies have documented environmental factors (e.g., benzene exposure in AA and cigarette smoking in IPF) to be highly associated with the diseases, the mechanisms of which are unknown.

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