NARRATIVE REVIEW

An insight into genetic landscape of inflammatory bowel disease

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Abstract

Inflammatory bowel disease has been regarded to be chronic intestinal inflammation characterised by a dsyregulatory immune response. The disease pathophysiology is known to be complex. Growing pieces of evidences underpin the involvement of various environmental and genetic determinants in the disease onset. The current narrative review was planned to manifest the contribution of genetic drivers for disease onset and to target signalling pathways that might present a therapeutic potential for further research. The factors of the disease that provide the genetic nature and understanding of the pathways involved have been researched in recent times. Also, numerous disease-developing factors have been studied and assessed. Among them genetic determinants of disease onset have further improved the understanding of disease development. Genetic contributors to the onset of disease as well as important therapeutic targets need to be understood as predictive genetic risk factors have a potential implication for personalised treatment.

Keywords: Crohn's disease, Gut microbiota, Inflammatory bowel disease.

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Introduction

Inflammatory bowel disease (IBD) is characterised by an abnormal immune response to the gut microbiome. This altered immune response leads to chronic intestinal inflammation. This inflammatory disease of the gastrointestinal tract (GIT) manifests genetic architecture comprising factors constituting a risk for disease susceptibility (Figure 1). Crohn's disease (CD) and ulcerative colitis (UC) are reported as common IBD subtypes. Others include IBD unclassified (IBD-U), also regarded as indeterminate colitis (IC), and microscopic colitis. Early onset and very early onset IBD are mostly found in the paediatric population, with most of them having a monogenic form of IBD. CD is characterised by an inflamed GIT and related immune disorders, whereas UC as an immune-mediated inflammatory disorder, is characterised by disrupted T-cell response to the gut microbiota. Strong pieces of evidence about disease risk have been collected through data from various genome-wide association studies (GWAS).[1]

The global prevalence of IBD has increased in recent years, mainly in the industrialised world, with poverty and lack of education generally being the contributory factors. The rising disease burden poses serious concerns to human health. Higher frequency of the disease has been reported from northern Europe, northern America, and the United Kingdom, while the number is continuing to rise in Asia, southern Europe, and many other developing regions and countries. The global incidence of disease increased from 3.7 million in 1990 to 6.8 million in 2017.[2] IBD epidemiology follows four stages, and it is estimated that by the year 2050, global life expectancy will be reduced with high mortality in IBD cases.[3] Ethnicity and racial global populations had been observed to have a link with a higher disease prevalence.[4, 5] A prospective study from the United Kingdom demonstrated higher incidence of UC among Indians compared to European

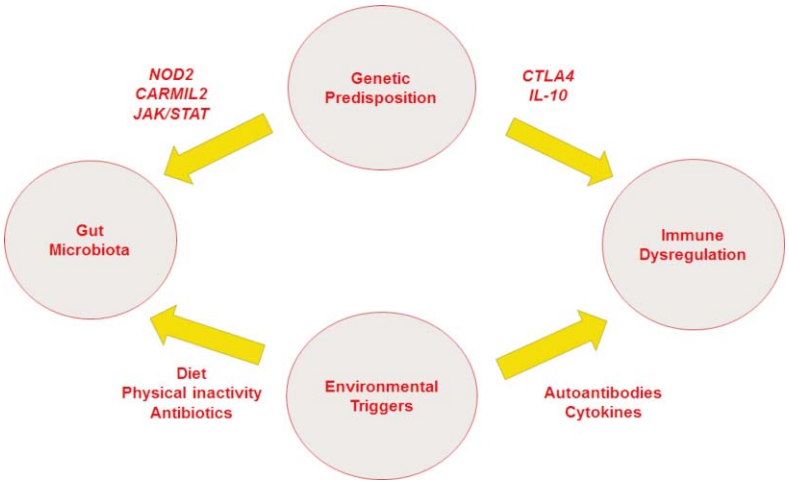

Figure-1: The interplay between genetic and environmental factors that contribute to disease development.

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and Pakistani ethnic groups.[6] A retrospective study revealed a higher incidence of IBD phenotypes among children of South Asian origin compared to non-Asians.[7] Similarly, the incidence of IBD was observed to be higher among the white race than in Hispanics, Blacks and Asians.[8] Though the pathological mechanism for the disease onset is complex and remains unclear, various studies have been conducted to explore the possible link of susceptible genes to that of IBD. They provide basis for the understanding of disease pathophysiology associated with genetic and environmental factors.

Methods

For the current narrative review, literature was searched on Google Scholar, Scopus and PubMed databases using key words, including "immune response in GIT", "IBD phenotypes", "signalling pathways in IBD", "gut microbiome", "genetics of IBD", "Crohn's disease", and "ulcerative colitis". Those included for detailed review were papers published in the English language about the association of genetic drivers with disease pathology. Studies on IBD patients with comorbidities and those in duplicates were excluded.

Disease pathogenesis

The accurate causative mechanism behind the onset of IBD is not that much clear, but data provides a more significant linkage of certain genetic factors to the early onset of IBD. The data from GWAS reports the identification of various gene loci conferring to the disease onset by a dysregulated immune response. IBD patients have also been observed with immunocyte-induced disrupted cytokine production. Further molecular genetic studies revealed the association of the genes encoding cytokines with the disease pathogenesis as well as mutations affecting T and B-cell immune response.[9] Apart from disruption in the immune system due to gene variations, other pathophysiological mechanisms have been studied to have insight into early-onset IBD, including epithelial barrier dysregulation, and signalling defects. Autoimmune response to friendly gut microbiota often causes intestinal inflammation and develops the disease course. The interplay between genetic predisposition and environmental stimuli often results in autoimmunity.[10] The intestinal physical barrier, separating the microbiome from the host, plays a crucial role in intestinal homeostasis as well. The intestinal epithelial cells have a short lifespan, so the epithelium has to be filled to protect the epithelial barrier from being disrupted. This balancing of the intestinal epithelium is regulated by constant cell proliferation and apoptosis. The intestinal tight junction proteins regulate the trafficking of biological molecules. These proteins provide a barrier between the gut tissue and microbiota to maintain homeostasis. Any molecular variation in these integral proteins may induce modification in the tight junction barriers and can enable the pathogen to invade the intestinal epithelial barrier through an increased intestinal permeability. A transcriptomic aberration of epithelial barrier genes induces dysregulated control of intestinal epithelial molecular machinery, resulting in the disease onset.[11]

This homeostasis disturbance results in abnormal inflammatory response and contributes to the pathogenesis of IBD (Figure 2). However, considering the

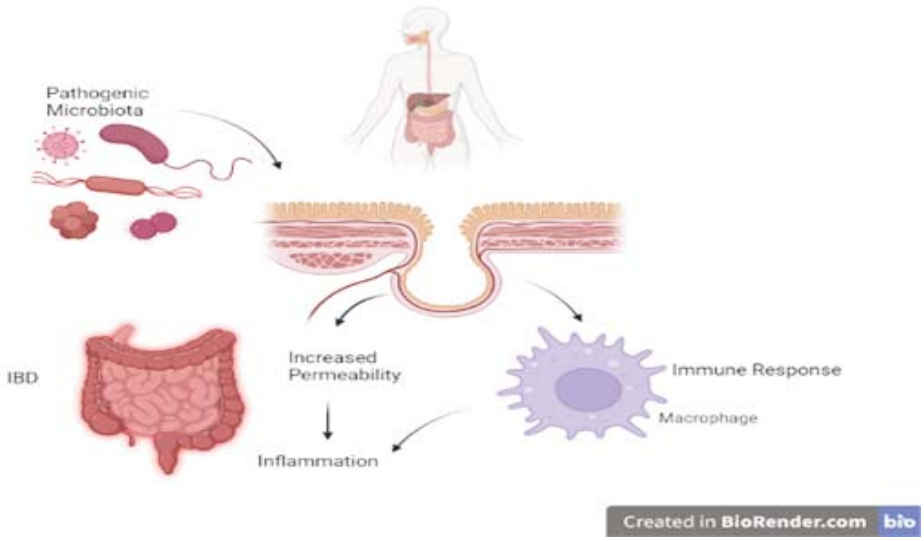

Figure-2: Pathogenic gut microbiota finds opportunity to invade the epithelial barrier due to molecular variations in the tight junction proteins, which disrupts the immune response and cause gut inflammation..

complexity of IBD to be diagnosed, it presents a bit difficult clinical way to rule out potential therapeutics.

Genetic determinants of monogenic IBD

Paediatric IBD is mostly caused in a monogenic pattern. Very early onset of IBD in children occurs due to monogenic mutations. The genes involved affect the regulatory immune mechanisms, conferring to developing intestinal inflammation. GWAS data has provided an underpinning of disease pathophysiology and molecular architecture through different gene loci. Most GWAS literature provides gene loci linking the disease susceptibility in the intronic region of the gene which manifests the transcriptional aberrations.[12] These studies have provided a roadmap to identify vital pathways governing the immune response and autophagy.[13] However, the large-size loci provide different disease phenotypes and affect the host response to the external stimulus, like pathogen invasion for infection.[14] Various genes have been studied for their possible role in the disease development. Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) is an immune checkpoint and is mainly expressed in regulatory T (Treg) cells. T-cell activation by its receptor and stimulatory proteins causes the overexpression of the gene. *CTLA4* gene mutations have been found to affect immune homeostasis, primarily the T-cell function. A range of immune-related health states develops as a result of these mutations, including inflammatory enteropathy and CD-like lesions. The interleukin (IL) family of receptor proteins has been reported to have an association with monogenic IBD. Loss of function mutations in the IL receptor genes, including *interleukin 10 receptor subunit alpha gene(IL-10RA)* and *interleukin 10 receptor subunit beta gene(IL-10RB)*, has been reported. These individuals develop colitis in the earlier years of their lives. Small bowel inflammation can be developed in later stages of life.[15] Capping protein regulator and myosin 1 linker (CARMIL2) is a cytoskeleton-associated protein that controls the regulation of actin assembly and signalling. Genetic analysis of the patients with early IBD onset from unrelated families manifested deleterious mutations in the *CARMIL2* gene. These patients show IBD-like symptoms, including abdominal pain and bloody or non-bloody diarrhoea. In addition to the function mutations, patients demonstrate a decreased level of T-cells, and depict hasty B-cell maturation. Further immunosuppression has been highlighted in early-onset IBD patients with various genetic anomalies of the related genes. In three IBD paediatric patients, *CARMIL2* gene variation was significantly observed. These gene variations were dominantly present in the studied patients.[16]

Genetic determinants of polygenic IBD

This immune-related complex disease can also be polygenic in nature. The onset of disease phenotypes can be characterised by interplay of several causative genes. The inherited predisposition of the disease exhibits clinical manifestations triggered by external stimuli or other genetic drivers. Several gene markers have been attributed to disease susceptibility. Genome scan analysis showed the association of chromosome 16 to disease susceptibility. One of the various polymorphisms associated with CD was observed to be an insertion of a nucleotide (cytosine) in exon 10 of the *nucleotide-binding oligomerisation domain protein 2(NOD2)* gene which was initially named as IBD1gene locus. The *NOD2* gene encodes the NOD2 protein, which is crucial in regulating immune response against foreign bacteria. As this protein is recognised as an intracellular microbe sensor, any defect to the protein may cause a loss in immune machinery, leading to disturbance in intestinal homeostasis. Other findings led to the identification of CD and UC susceptibility gene loci. The highest linking region was found on chromosome 12q.

In a study, the genetic data provided IBD-related genes' penetrance. *Wiskott-Aldrich syndrome (WAS), (IL-10RA), protein kinase deoxyribonucleic acid (DNA)-activated catalytic subunit (PRKDC) and NOD2* were found to be the genes with highest penetrance in the European cohorts.[17] A genome-wide association study on African-American individuals exhibited CD-associated gene variants at a locus adjacent to the prostaglandin E receptor 4 (PTGER4) region. The whole genome sequencing data provided the association of *Calbindin 2 (CALB2)* gene variants with UC in the studied subjects which was absent in the European cohorts.[18] CD is regarded to be one of the crucial polygenic sub-phenotypes of IBD characterised by inflammation in the digestive tract, diarrhoea, fatigue and weight loss. Gene polymorphisms have been reported to have an association with CD onset. In a family-based study done in Japan, two siblings affected with CD presented a mutation (Arg293Ser) in the *nuclear receptor subfamily 4 group a member 1 (NR4A1)* gene, using whole-exome sequencing.[19] In a case-control study conducted among Kuwaiti patients of CD, *NOD2* gene polymorphisms were observed to have a strong correlation with disease onset. The polymorphisms screened for association analysis included Gly908Arg, IVS8 (an intron variant), Leu100fs, Pro268Ser, and Arg702Trp.[20] In another study in Arab population, the *NOD2* gene variant Gly908Arg was found to be a strong predictor of CD development.[21] In a paediatric population, the gene clusters of NOD2 and *autophagy-related 16 like 1 (ATG16L)* demonstrated variants (rs2066844 and rs2241880), as strong risk factors for CD.[22] In a Malaysian

cohort, polymorphisms in the *autophagy-related 16 like 2 (ATG16L2)* gene and long intergenic non-protein coding ribonucleic acid (RNA) 8234 (LINC00824) were shown to have a high risk of CD development.[23] A study assessed the contribution of gene variants to the IBD among Arab Muslims, Ashkenazi Jews, and the Druze population. Variations in the non-coding region of the *NOD2* gene were observed in the Druze ancestry with CD. The other individuals showed homozygous variants of the genes influencing innate immunity.[24]

Role of gut microbiota in disease pathogenesis

The human gut microbiome consists of trillions of microbes, including bacteria (being most abundantly found), fungi and other microbes. The normal gut microbiota in humans provides an extensive approach to regulating certain metabolic pathways, affecting the quality of life in terms of health perspective. The aetiology of a disease course associated with these gut microbes can occur under the compromised and/or hyper-activated immune response. Various studies have been conducted to understand the pathophysiology of IBD, yet the causative mechanism remains unclear. Several factors, including environmental and genetic susceptibility, contribute to disease progression. One of the most crucial elements is dysfunctional immunomodulation influenced by genetic and environmental factors. Factors affecting the gut mucosal barrier, and normal gut microbiota imbalance pave the way for opportunistic pathogens. This can trigger the diversification of pathogenic microbes and hyperactivity of the immune response.[9] Nicotinamide adenine dinucleotide phosphate (NADPH) and NADPH oxidase complex 2 (NOX2) systems provide defence against microbial infections in the gut. NADPH oxidase produces reactive oxygen species *(ROS)*which have the ability to maintain intestinal homeostasis through phagocytes' regulatory action on invading microbes. The neutrophil cytosolic factor 2 protein (NCF2) is encoded by the *NCF2* gene. The protein is involved in making enzyme complex NADPH. The NOX2 protein-derived ROS are involved as key immune system-regulating compounds associated with inflammation. The gene cluster of NADPH complex has conserved sequences, and various polymorphisms of the gene constitute a high risk for immune-mediated disorders.[25] An exome sequencing approach-based study reported the involvement of 11 variants of *NADPH oxidase* complex, including the *NOX2* gene, in the early onset of IBD.[26] Another study of sequence analysis of NADPH oxidase complex exhibited an association of a novel missense variant in *NCF2* gene with very early-onset IBD.[27]

A germ-free animal model revealed the contribution of dysbiosis to IBD onset by provoking gene expression for pro-inflammatory immune cells. Diet consumption has a crucial effect on the overall gut microbiota in the intestines; a high-fat diet, for example, can affect the gut-microbiome interaction by altering the number. This influences the immunomodulation and can have T-lymphocytes triggered.[28] Furthermore, gene mutations regulating the gut's anti-fungal response have also contributed to IBD development. The gut microbiome produces metabolites in reaction to the diet consumed by the host, with which they establish their interactions. These metabolite-driven signals often impact immune homeostasis.[29]

Hedgehog signalling pathway

Hedgehog (Hh) signalling extends from epithelium to mesenchyma in the human intestine in a paracrine signalling pattern. Thus, it tends to maintain the homeostasis of mesenchymal cells. Hh signalling has been studied to have a crucial role in maintaining intestinal homeostasis. This signalling pathway has a role in inducing immune system activation through signalling mediators.[30] Many proteins are part of this signalling cascade, including sonic hedgehog (SH), Indian hedgehog (IH) and smoothened hedgehog (SmH). The gene variations in the transcriptional protein *glioma-associated oncogene (GLI1)* have revealed a significant risk of IBD development[31] and showed involvement in modulating chronic inflammation.[32] Evidence from various studies provides a strong implication of Hh signalling in the pathogenesis of IBD onset.[30] A study showed the elevated levels of circulating immune proteins upon inhibition of Hh proteins.[33] Antigen stimulation results in the polarisation of CD4+T-cells into T helper (Th) cells which further produce immune cells (cytokines). One of these helper cells includes Th17 cells. Certain transcription factors drive Th17 polarisation. These cells are significant in the immunomodulation of the intestinal barrier that drives the host defence mechanism in response to external immune-triggering factors (pathogens). These cells produce IL-17 (one of the important cytokines) which promotes epithelial cell proliferation in the intestine and enhances epithelial barrier function as well as stimulates antimicrobial peptide production. Hh signalling plays a role in Th17 cell polarisation through its mediators. Upregulation of Hh pathway expression induces high expression of Th17, driving immune response in the intestinal epithelium.[34]

Wingless/Integrated (Wnt) signalling

The wingless/integrated *(Wnt)signalling* pathway is a crucial evolutionary conserved pathway modulating cell fate and proliferation. Wnt proteins are glycoproteins, and this

family of proteins is primarily involved in cell communication, cell proliferation and differentiation. The extra-cellular Wnt signal induces several intracellular signal transduction cascades. These proteins bind to the N-terminal cysteine-rich extra-cellular domain of the Frizzled (Fz) receptor family. The binding of the Wnt ligand to the receptor complex induces a cytoplasmic phosphoprotein cascade, thus activating gene transcription. Wnt signalling induces differentiation of pluripotent stem cells into mesoderm and endoderm progenitor cells. Further, these progenitor cells differentiate into various other cell types, such as endothelial, cardiac, and vascular smooth muscle lineages. Wnt signalling also induces blood formation from stem cells. The activation of the Wnt pathway by a number of gene variations results in the hyper-proliferation of the intestinal epithelium. Abnormal switching of the Wnt pathway by receptor genes results in chronic inflammation in the intestinal epithelium, paving way for developing colon cancer.[35] Disrupted Wnt signalling has been observed to have a role in colorectal cancer. Recent studies have extensively shown the involvement of Wnt inhibitors as a potential therapeutic target against colorectal cancer.[36]

Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway

A wide range of cellular communication is mediated through Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. JAK/STAT signalling is a conserved pathway comprising a series of reactions of the proteins involved within a cell, conferring to play roles in cellular communication, cell death, tumorigenesis and immune regulation. JAK consists of four main proteins; JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), having a src homology 2 (SH2) domain, and a kinase domain which is involved in phosphorylation of certain proteins. The STATs are of seven subtypes (STAT1-STAT5A, STAT5B and STAT6). Of its domains, SH2 is important as it has a role in transcription. When a pro-inflammatory ligand binds the JAK receptor, it undergoes dimerization and JAK proteins come into closer proximity to induce kinase activity for tyrosine residues phosphorylation, which further transduce the intracellular signals. The activated JAKs then phosphorylate STATs which move to the nucleus to the enhancer elements to induce transcription of certain genes. The pathway is associated with cytokine receptors, which, upon binding of its ligand, induce STATs to be activated for transcribing immune-system genes (interferons). STAT5A protein has a crucial role in mediating intestinal homeostasis and mucosal repair. Human *JAK* mutations signalling dysregulation have been reported to cause various inflammatory and proliferative diseases, and cancer development. STAT5A loss of function drives autoimmune diseases, while the variations in *JAK/STAT* genes disrupt the production of their respective immune cells, and the immune response is compromised.[37]

Therapeutics

Various therapeutic strategies targeting IBD have been implicated. The drugs have been developed to influence the receptor proteins and signalling molecules involved. However, drug response varies from patient to patient. The idea of personalised medicine in drug efficacy and response has become an effective tool. Variations in the genetic makeup among different individuals affect the drug response. Various gene polymorphisms in response to drugs, like adalimumab (ADA) and infliximab (IFX), have been extensively studied in different populations. Effects of certain genotypes in individuals with CD on ADA or IFX drugs showed varying levels of C-reactive protein (CRP) and improvement. However, some alleles and genotypes were found to be non-responders to the drugs.[38] Natural-products-based nano-carrier systems, primarily from plants, have shown effective protection against drug premature release.[39] Many immuno-suppressants have been unresponsive in individuals with IBD. Recombinant technology has further improved drug efficacy. Avaximab (AVX-470) is a newly developed anti-tumour necrosis factor (TNF), and the risk of immunosuppression by this polyclonal antibody is rare. Various anti-integrin monoclonal antibodies, IL and JAK inhibitors have been approved for treating IBD.[40]

JAK inhibitors have been shown to have promising potential in treating CD. Various clinical trials have been observed as effective therapeutic options for treating disease severity.[41] Stem cell therapeutics has also shown significant potential in treating a number of diseases through animal models or clinical trials. The implication of mesenchymal stem cell transplantation (MSCT) has been studied in various inflammatory diseases. Mesenchymal stem cells release a glycoprotein having a role in tissue repair and immunomodulation. In a mice model of colitis, *TNF-alpha (TNF- α) stimulated gene 6 (TSG-6)*, carried by MSCs demonstrated a promising therapeutic approach through mucosal tissue repair.[42] In a mouse model of dextran-sulfate sodium-induced colitis, MSCT was shown to reduce the increased Treg levels. Observing stress in mice, autophagy was observed in the stem cells through STAT3 pathways. Autophagy-related genes were observed downregulated through blocking micro ribonucleic acid (miRNA) 7k (Mir7k).[43]

MSCT seems greatly promising, particularly for treating fistulising and perianal disease. Clinical studies using

autologous stem cell transplants (ASCT) showed encouraging results in which >50% of CD patients with fistulas achieved remission 1 year after transplantation. MSCs have the potential to induce the proliferation of the intestinal epithelial cells and up regulate the expression of the tight junction-associated protein, conferring to warrant integrity in the intestinal barrier. A study comprising 12 patients with anal fistula received adipose-derived MSCs. Following the injected dose, >60% patients showed improvement in their symptoms.[44]

Plant-based metabolites have been extensively studied in managing and treating various pathological events. Polyphenols have shown a profound potential against certain diseases, including inflammatory conditions, of the body. In contrast to already available pharmaceuticals treating IBD, a wide range of photochemical-based products help in mucosal healing. Inhibitors of JAKs that are considered to have the potential to affect multiple pro-inflammatory cytokine-dependent pathways are in clinical development for IBD treatment. Phytochemicals, like garlic, terpenoids, piceatannol-hydroxylated derivative of resveratrol, and phenolic compounds in grapes and berries, have been found to suppress STAT3 in colitis-induced mouse model.[45] Thymoquinone in black seed oil has potential effects on immunomodulatory signalling proteins, including TNF-α, IL-1-beta (IL-1β), and nuclear factor kappa B (NF-κB). A bioactive compound found in curcuma longa and ginger also has anti-inflammatory potential.[46] In a review of studies on green tea's potential in managing IBD, it was found that the naturally occurring metabolites in green tea downregulate the expression of various involved cytokines and pro-inflammatory elements.[47] Suppressing the immune modulators, including various cytokines, can present a therapeutic target in managing intestinal homeostasis.[48] G-protein coupled receptor 4 (GPR4) is a significant proton-sensitive GPR. Its expression has been found to be upregulated in various health conditions, including colorectal cancer. GPR4 antagonists have shown a promising way of reducing intestinal inflammation. Animal models with knock-out gene revealed a significant reduction in IBD-associated fibrosis.[49]

There are few limitations to the current narrative review. As the review aimed at exploring the molecular basis of the disease, it was limited by the depth and breadth of the studies focussing on gene variations involved in cellular pathways. The number of studies targetting the signalling mechanism of IBD was available in small numbers. There is a need to focus them in future research using animal models and/or human cell lines, and expand therapeutic-oriented studies.

Conclusion

Genome-wide scan studies have opened a new horizon in disease pathogenesis, demonstrating the involvement of numerous gene loci in disease onset. Further investigation of genetic loci associated with disease onset is needed to understand the mechanism causing inflammation. The interplay between environment and genes in relation to disease development is also vital to have a better understanding of disease pathogenesis and clinical implications. Understanding the genetic risk predictors may make personalised medicine an emerging therapeutic target against the disease phenotype. Data on the detection of various disease-related gene variants among global populations may help researchers in the field to develop such personalised therapies. However, further genetic evaluation is required through the pathways involved before applying genomics in clinical settings.

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