From the Genetic Mutation to the Specific Pathologies

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Abstract. Translational bioinformatics has been a new science that uses to transform huge volumes of molecular targets into therapeutic therapies. The bioinformatical approach pinpoints a better understanding of disease processes by combining genetic, phenomic, and environmental data. Our summary integrates several explanations from diverse publications were combined to construct pathways that depict the expression of gene mutations in driving a variety of diseases. The study involves literatures indexed by Scopus and Pub Med, the search uses a combination of the following keyword variants; "HaploReg" AND "genomic", "HaploReg" AND "repurposing drug". This study only used original articles in English which were peer reviewed journals published in 2022. Thus, the screening results of library sources were narrowed to 10 original articles that met the inclusion criteria. Here in, we list 16 genes which have driven nine special diseases, two of which (JAK, CD207) encode atopic dermatitis, two genes trigger vitiligo (IFIH1, TICAM1), two genes role in multiple sclerosis (CD80, CD86), a pathway of three genes activate ankylosing spondylitis (HLA-B27-ERAP1), a gene link to breast cancer (EMSY), a gene associate with gastric cancer (MMP-7), two genes relate to colorectal cancer (miR-143/145, KRAS), three genes play the role in chronic prostatitis/chronic pelvic pain syndrome (IFNG, IFNGR1, AR), and a gene rule on arterial hypertension (TBX2). Last, our discovery provides new insight into the development of novel medications that act on specific druggable target genes that have not previously been investigated.

Keywords: Gene Mutation, Bioinformatic, HaploReg.

1 Introduction

Pharmacogenetics is the study of human variability in response to medication interventions, and it is a rapidly emerging field in molecular biology and clinical medicine [1]. Clinical practitioners will increasingly rely on informatic technologies to support in the discovery and understanding of genetic drivers of disease as they attempt to implement personalized treatment [2]. HaploReg was applied to investigate the possibility of SNPs having any transcriptional regulatory function [3].

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Biomedical sciences are confronted with a significant rise in the quantity and diversity of data available from public sources, referred to as biomedical big data. Translational bioinformatics is a new field that uses bioinformatic techniques to transform massive amounts of biological data into therapeutic actions [4]. Translational bioinformatics will allow for a better understanding of disease processes by combining genetic, phenomics, and environmental data [5], [6]. Randomized medical trials for a number of drug-gene combinations have indicated that performing pharmacogenetic testing prior to the treatment administration can enhance patient health outcomes. As a result, there is an urgent need to standardize genomic medicine and pharmacogenetics in clinical practice [7].

Related to the bioinformatical approach pinpoints a better understanding of disease processes by combining genetic, phenomics, and environmental data. Our summary integrates several explanations from diverse publications were combined to construct pathways that depict the expression of gene mutations in driving a variety of diseases

2 Method

The study involves literatures indexed by Google Scholar, Scopus, and Pubmed databases, and the search uses a combination of the following keyword variants; "HaploReg AND Genomic", "HaploReg AND Repurposing Drug". This study only used original articles in English which were peer-reviewed journals published all year (Fig. 1).

Each literature was extracted by identifying author's name, year, title, research purpose, method, and conclusion. It also includes the identity types of diseases, organ systems, number and types of genes involved.

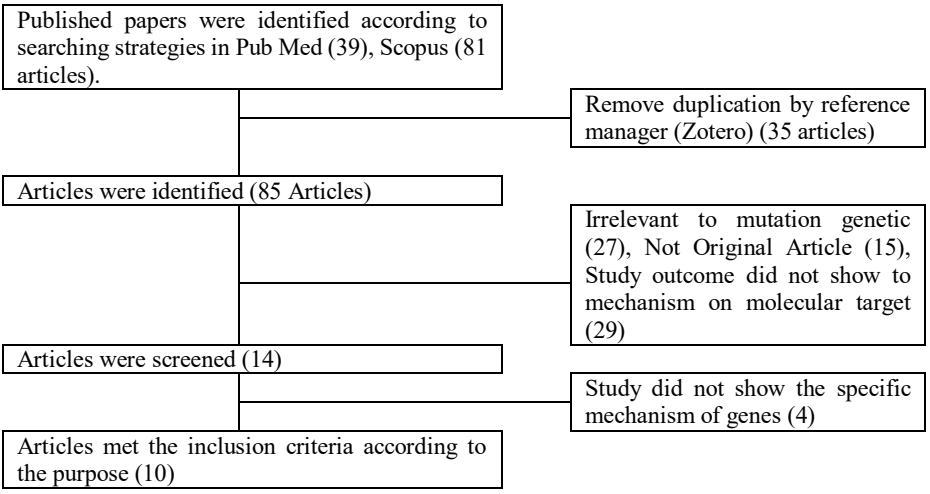

Fig. 1. The literatures study of workflow

3 Result and Discussion

Our finding lists 16 genes which have driven nine special diseases, two of which (JAK, CD207) encode atopic dermatitis, two genes trigger vitiligo (IFIH1, TICAM1), two genes role in multiple sclerosis (CD80, CD86), a pathway of three genes activate ankylosing spondylitis (HLA-B27-ERAP1), a gene link to breast cancer (EMSY), a gene associate with gastric cancer (MMP-7), two genes relate to colorectal cancer (miR-143/145, KRAS), three genes play the role in chronic prostatitis/chronic pelvic pain syndrome (IFNG, IFNGR1, AR), and a gene rule in arterial hypertension (TBX2) (**Error! Reference source not found.**).

According to deal with immune responses associated with atopic disease (AD), Janus kinase 1 (JAK1) was identified as a target of the novel drugs blocked signaling in immunopathology [8]. JAK1 lead activation signal transducer and activator of transcription proteins (STAT) through mobilized the cytokines such as IL3, IL4, IL13, IL31. Thus, over the accumulation of cytokines in blood that extend to skin promote the phenotype of AD [9].

JAK is responsible for transcribing STAT. Several cytokines, including IL 4, IL3, IL13, and IL 31, are activated when STAT is translated. These cytokines can produce atopic dermatitis symptoms if they disseminate and enter blood vessels through the skin [8] [9].

Table 1. Main Result of Literature Review

No.	Topic	Disease	Gene	Ref.
1.	Integument	Atopic Dermatitis	JAK, CD207	[3], [8]
2.	Integument	Vitiligo	IFIH1, TICAM1	[10]
3.	Musculoskeletal	Multiple Sclerosis	CD80, CD86	[11]
4.	Musculoskeletal	Ankylosing Spondylitis	HLA-B27-ERAP1	[12]
5.	Oncology	Breast Cancer	EMSY	[13]
6.	Oncology	Gastric Cancer	MMP-7	[14]
7.	Oncology	Colorectal Cancer	miR-143/145, KRAS	[15]
8.	Neurology	Chronic Prostatitis/Chronic Pelvic Pain Syndrome	IFNG, IFNGR1, AR	[16]
9.	Cardiovascular	Arterial Hypertension	TBX2	[17]

IL-4 mediators stimulate the JAK STAT pathway. JAK activation is followed by STAT phosphorylation, which translocate to the cell nucleus in an active state to target certain genes. JAK-STAT activation regulates Th2 differentiation and so has a function in atopic dermatitis [18]. However, in some cases, atopic dermatitis can be caused by the CD207 gene, which is involved in antigen uptake, internalization, Birkbeck granule production, processing, lymph node transfer, and Langerhans cell maturation, all of which are important in regulating body immunity. The CD207 gene can be overexpressed in the skin of certain persons under abnormal situations. In this case, CD207 will play a role in the maturation of Langerhans cells, which are required for IgE mobilization in response to allergen assault [3].

Lebrikizumab is a subcutaneous medication that inhibits IL-13. Lebrikizumab can neutralize cytokines and block IL-13 and IL-4 binding and heterodimerization [19]. The main mediators of the inflammatory response in atopic dermatitis are IL-4 and IL-13 via their heterodimer receptors. The binding of IL-4 and IL-13 to their respective receptor subunit leads subunit dimerization, which activates the JAK-STAT pathway [20]. Tralokinumab is a subcutaneously given IL-13 receptor antagonist. Canakinumab is a monoclonal anti-interleukin 1 (IL-1) the antibody that inhibits IL-1-mediated pathway [21].

The interferon-induced helicase C domain 1 (IFIH) a missense variant at 2q24.2 produces the IFIH1 protein, which can activate the innate immune response by binding to damage-related molecular patterns. IFIH dysfunction can hinder immune response activation. SNPs rs4807000 and rs6510827 at 19p13.3 are 140 bp upstream and split intron TICAM1. TICAM1 modulates innate immune responses to viruses by stimulating IFN production via recognition receptors. TICAM1, also known as IFN-b, is an IFN-b that activates adaptors with TIR domains, such as Toll molecule 1, and promotes immunological response to the virus, and may have a role in the etiology of vitiligo [22] The SNP rs4822024 at 22q13.2 is located 6 kb upstream of TEF, which encodes the protein thyrotroph embryonic factor (TEF), and is associated with TEF expression levels in blood. TEF is a component of the leucine zipper transcription factor, which is high in amino acids and contains the amino acid proline, which is vital in the regulation of circadian rhythms. These genes may have a role in the pathophysiology of vitiligo via immunological or other processes [10].

CD80 and CD86 have been identified as potential targets for MS (Multiple Sclerosis) therapy [11]. CD80, the major B7 family coreceptor expressed in acute MS, promotes a Th1 cell-mediated inflammatory response, whereas CD86 causes a Th2 humoral response [23]. Belatacept, which targets the genes, could be considered therapy, hence the novel drug needs more preclinical and clinical evidence [11]. Activated T-cells have a significant function in the inflammatory cascade that leads to inflammation, tissue injury/damage, and rejection in autoimmune disorders and organ transplant grafts, making them an attractive target for immune modulation therapy. T-cells require specific antigen and costimulatory signals to fully activate. CD28 is a costimulatory protein produced by T-cells that interact with antigen-presenting cell receptors CD80 and CD86 (APCs). T-cell activation requires the CD28 pathway, which leads in T-cell cytokine production and proliferation. CD86 is constitutively expressed on APC and rapidly upregulates following stimulation, whereas surface the expression of CD80 is typically raised much later after stimulation [24].

Belatacept (LEA29Y) is a second-generation cytotoxic T-lymphocyte antigen 4 (CTLA-4) immunoglobulin (Ig) variation designed to offer the immunosuppressive qualities required to avoid graft rejection following transplantation. It is a kind of therapy known as a selective costimulation inhibitor. Belatacept is a human-only the fusion protein made up of a human CTLA-4 extracellular domain that binds to CD80 and CD86 and suppresses CD28 signaling (5-7) and a human IgG1 Fc domain fragment. The CTLA-4 moiety of Belatacept has two amino acid modifications that result in increased binding of CD80 and CD86 relative to the parent molecule, resulting in effective CD28 signaling prevention and T-cell activation suppression [24].

Ankylosing spondylitis (AS) associated mutations were discovered, as well as the HLA-B27-ERAP1 linkage [12]. The long-established publication had connected the polygenic chronic inflammatory illness with HLA-B27. The ERAP1 rule produces peptides for loading onto and stabilizing HLA-B27, altering NK cell interactions with receptors, and initiating the unfolded protein response [25]. The class I human leukocyte antigen gene (HLA-B27) is the most powerful risk factor for ankylosing spondylitis [26]. Endoplasmic reticulum aminopeptidase 1 (ERAP1) (also known as the TNFR1 shedding regulator aminopeptidase 1 or ARTS1) is a key non-MHC gene associated with AS in genetic study. By trimming fragmented antigen peptides to adequate lengths for peptide/MHC I complex (pMHC I) formation, ERAP1 increases antigen peptide loading onto MHC I, which is necessary for effective immunization. ERAP1 also participates in the production of pro-inflammatory cytokine receptors for TNFa, IL-1, and IL-6 SNPs. ERAP1 has been related to AS in several ethnic groups [27].

The BRCA1 and BRCA2 mutations increase the likelihood of getting hereditary breast cancer. Surprisingly, the EMSY gene codes for a BRCA2-interacting protein [13]. The EMSY gene, also known as C11orf30, encodes a nuclear protein that interacts with and inactivates the BRCA2 gene [28]. The BRCA gene, which is involved in DNA repair and transcription control, is mutated in breast and ovarian cancer. After DNA damage, EMSY can inhibit the potential activation of BRCA 2 exon 3, connect with the chromatin regulators HP1 and BS69, and relocate to the repair site. The MC is located on chromosome 11q13.5, which has been linked to breast and ovarian cancer [29].

The MMP-7 181 A/G polymorphism has been associated with gastric cancer. The MMP-7, the member of a family of proteolytic enzymes, promotes a wide range of biological processes related to cellular function. However, the -181 A to G transition increases transcriptional activity due to the G allele is more overexpression in transcription than A allele [14]. Because the G allele of MMP7 A-181G may serve as an early predictor of gastric cancer risk, other indications of gastric cancer are critically needed [30]. The MMP-7 was discovered to have a considerable negative prognostic influence on gastric cancer survival in previous research. It was also associated with a more aggressive clinical phenotype [31]. MMP7 expression in gastric cancer is not linked to mTOR, on the other hand, the expression of MMP7 in the gastric mucosa can be induced by H. pylori-driven inflammation, which is mediated by tissue macrophages [32].

The rs74693964 C/T and rs41291957 G/A mutations in the miR-143/145 cluster increase rectal cancer risk, while Rs712 G/T in KRAS associated with worse survival [15]. MiR-143 and miR-145, which are both present on 5q23, are likely to be derived from the same donor miRNA. MiR-143 and miR-145 consistently lowered the expression of mature miRNAs in colorectal neoplasms when compared to healthy colorectal mucosa. When compared to neighboring non-neoplastic colon mucosa, MiR-143/145 expression is reduced in rectal cancer. KRAS is one of the most often mutated genes linked to CRC risk, and KRAS mutations play an important role in CRC carcinogenesis [15]. When KRAS is mutated, GTP hydrolysis decreases and nucleotide exchange increases, leading KRAS to accumulate in an active state and contribute to the continuing activation of downstream signaling pathways, resulting in tumor cell proliferation. Colorectal cancers with KRAS mutations are therefore linked with advanced disease state,

poor tumor differentiation, distant metastases, and worse survival in these individuals [33].

Genetic variations in IFNG, IFNGR1, and AR have been linked to CP/CPPS, indicating a hereditary predisposition to the disease. IFN-, a proinflammatory and immunomodulatory cytokine generated by the natural killer (NK), T cells, and NKT, activates the innate immune system against invading pathogens by binding to its receptors. AR (encoded by the AR gene) is a transcription factor that regulates androgen target genes [16].

4 Conclusion

Our finding lists 16 genes which has driven nine special diseases, two of which (JAK, CD207) encode atopic dermatitis, two genes trigger vitiligo (IFIH1, TICAM1), two genes role in multiple sclerosis (CD80, CD86), a pathway of three genes activate ankylosing spondylitis (HLA-B27-ERAP1), a gene link to breast cancer (EMSY), a gene associate with gastric cancer (MMP-7), two genes relate to colorectal cancer (miR-143/145, KRAS), three genes play role in chronic prostatitis/chronic pelvic pain syndrome (IFNG, IFNGR1, AR), and a gene rule on arterial hypertension (TBX2). Last, our discovery provides new insight into the development of novel medications that act on specific druggable target genes that have not previously been investigated.

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