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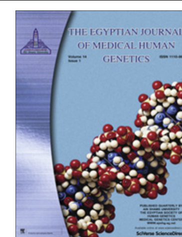

REVIEW

Single nucleotide polymorphism in genome-wide association of human population: A tool for broad spectrum service

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Abstract Genome-wide patterns of variation across individuals provide most powerful source of data for uncovering the history of migration, expansion, and adaptation of the human population. The arrival of new technologies that type more than millions of the single nucleotide polymorphisms (SNPs) in a single experiment has made SNP in genome-wide association (GWA) assay a prudent venture. SNPs represent the most widespread type of sequence variation in genomes, and known as valuable genetic markers for revealing the evolutionary history and common genetic polymorphisms that explain the heritable risk for common diseases. Characterizing the nature of gene variation in human populations and assembling an extensive catalog of SNPs in candidate genes in association with particular diseases are the major goals of human genetics. In this article we explore the recent discovery of SNP–GWA to revolutionize not only the process of genetic variation and disease detection but also the convention of preventative and curative medicine for future prospects.

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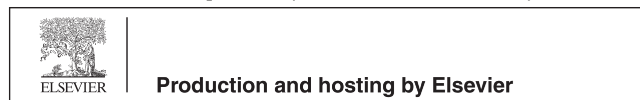

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1. Introduction

Genome-wide data sets are increasingly being used to identify biological pathways and networks underlying complex diseases and in drug development process (Fig. 1). In particular, analyzing genomic data through sets defined by functional pathways offers the potential of greater power for discovery and natural connections to biological mechanisms. Much of genetic variation in the human genome is in the form of SNPs which is the result of point mutations that produce single base-pair differences (substitutions or deletions) among chromosome sequences. There are many laboratories and computational approaches to finding single nucleotide polymorphisms (SNPs) within a genome, but all involve some form of comparative analysis of the same DNA segment from different individuals or from different haplotypes. SNP identification can be based on expressed sequence tags (ESTs), which are generated by single-run sequencing of cDNAs obtained from different individuals and assembly of overlapping sequences for the same region permits novel SNP discoveries. The non-coding SNPs can be classified according to whether they are found in gene regulating segments of the genome. Many complex diseases may arise from quantitative, rather than qualitative, differences in gene products. Coding SNPs can be classified as to whether they alter the sequence of the protein encoded by the altered gene. Changes that alter protein sequences can be classified by their effects on protein structure [1].

GWA studies have become an important tool for discovering susceptibility genes for complex diseases. Information, including genotype frequencies, linkage disequilibrium (LD), and recombination rates, across populations help researchers to conduct GWA analysis using millions of SNP markers. The differences in association results among populations for phenotypes of interest are partially explained by HapMap information such as population specific common variants and linkage disequilibrium blocks [2,3]. Moreover, the phased haplotypes of HapMap samples are used as a reference for imputing untyped markers. One million SNPs can be increased to up to 2.5 million by imputing haplotypes from HapMap phased haplotypes based on the pattern of observed genotypes [4].

2. SNPs in human population and concerning issues

GWA studies build directly on recent efforts to map the patterns of inheritance for the most common form of genomic variation by the use of SNPs [5]. An estimated 10 million common SNPs, those with a minor-allele frequency of at least 5%, are transmitted across generations in blocks, allowing a few

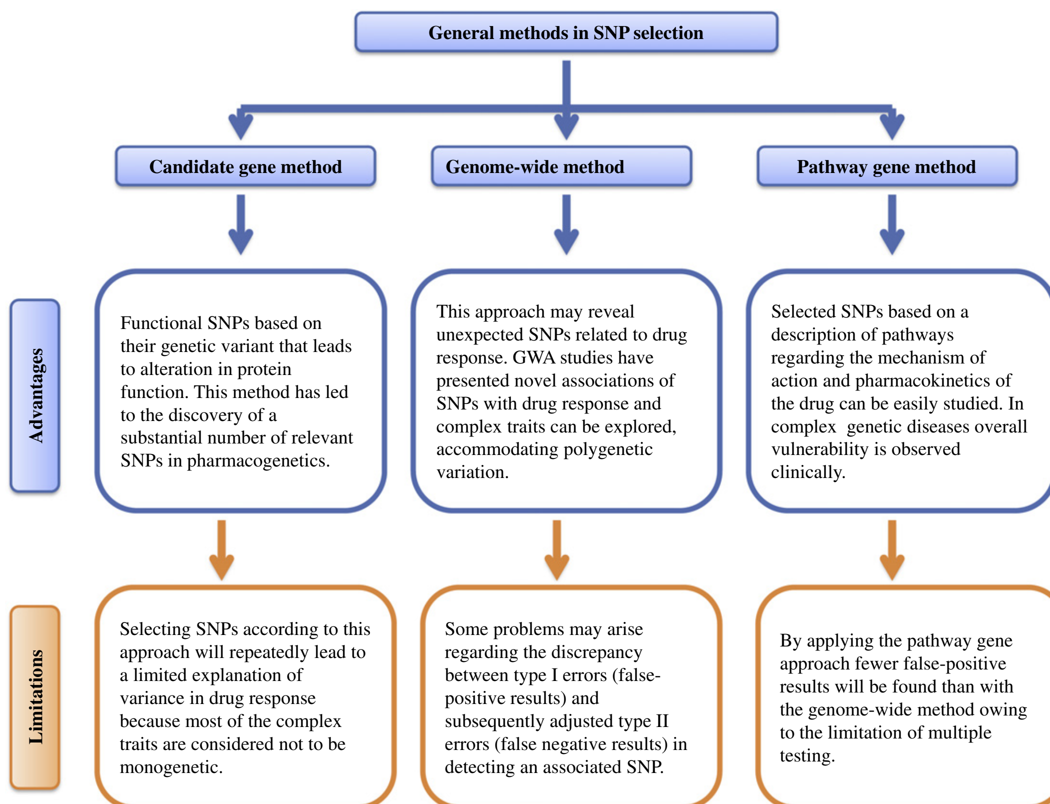

Figure 1 Selection of SNP made through three different pathways (approaches) exploring the mechanism of genome variation and drug development with some advantages and limitations [105–113].

particular, or tag, SNPs to capture the great majority of SNP variation within each block [6]. Rapid advances in technology and quality control now permit affordable, reliable genotyping of up to 1 million SNPs in a single scan of a person's DNA [7]. Genotyping hundreds of thousands of SNPs has led to a great accuracy with new models and approaches in inferring population structure, thus reconstructing population histories from given SNPs data [8].

A complication of genome wide association studies is the enormous number of tests of association required (at least one per SNP); thresholds of statistical significance are stringent, making it necessary to work with very large samples [9]. One frequently used approach to managing size is the tiered design, in which a subset of SNPs found to be significant in the GWA study (sometimes called the discovery set) is genotyped in a second tier (a replication set), yielding a smaller subset of significantly associated SNPs that are then tested in a third tier (a second replication set), and so on [10,11]. This process helps to identify false positive associations. Carrying forward a large number of SNPs identified through a GWA study into a test of replication also minimizes false negative results [12], while raising the bar for the establishment of true positive results. The pooling of results obtained in GWA studies (Fig. 2) under the auspices of large consortia is often required for the detection of variants with small effects on the risk of disease. Such pooled studies, like all genetic association studies, must be examined and controlled for differences in allele frequency between groups that can lead to spurious (false positive) associations [13].

3. SNPs reveal functional polymorphism

Regulatory polymorphisms at DNA level can potentially cause variations in gene expression. A SNP in a regulatory DNA binding site may alter the affinity with the regulatory protein, resulting in different gene expressions as shown in Fig. 2. SNPs in the osteopontin promoter have been shown to modify DNA binding affinity to transcription factors SP1/SP3 [14]. A GWA study revealed a G-to-A substitution in the 5_ untranslated region (5_-UTR) of the FOXE1 gene to associate with thyroid cancer susceptibility [15]. The T-to-C substitution located in the 5_-UTR of the GDF5 gene causes a different interaction with DEAF-1, a trans-acting factor for GDF5, leading to a reduced gene expression [16].

Opioid receptors (mainly μ-, δ- and κ-receptors) in the endogenous opioid system regulate neuronal activity via neurotransmission or neuromodulation. Variation in opioid receptor genes may change the expression level or activity of opioid

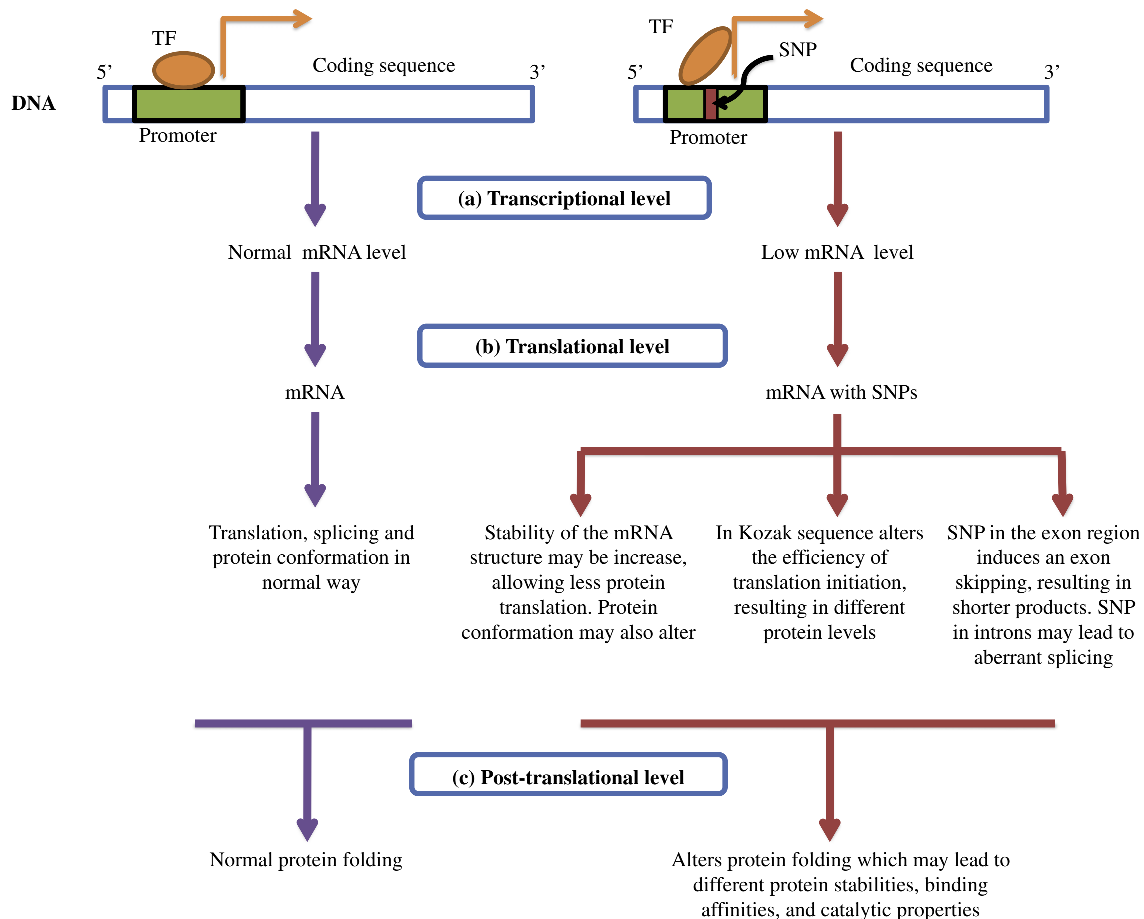

Figure 2 SNP in a regulatory DNA binding site may alter the affinity of the regulatory protein such as transcription factor (TF) resulting into different mRNA levels. The SNP in promoter region leads to decreased affinity as shown above, resulting in low gene expression. Several examples of the effects of SNPs on mRNA, translational levels and post-transcriptional levels [114–118] are there.

receptors, leading to increased risk for drug or alcohol dependence. The minor G-allele of SNP rs569356 may enhance transcription factor binding and increase δ-opioid receptor gene (*OPRD1*) expression [17].

At the protein and post-translational levels, variation in protein stability due to SNPs in coding sequences can cause different levels of enzyme activities. Thiopurine S-methyltransferase (TPMT) catalyzes the S-methylation of thiopurine drugs. Several human TPMT variant alleles that alter the encoded amino acid sequence of the enzyme generate less stable proteins [18]. Therefore, patients with those alleles have very low TPMT activity and suffer severe, life-threatening drug toxicity when treated with "standard" doses of thiopurine drugs [19]. The μ opioid receptors (MOPRs), belonging to the seven transmembrane receptor (7TMR) family [also called the G protein-coupled receptor (GPCR) family], mediate the pharmacological effects of morphine and other μ-preferring compounds. Activation of the MOPRs produces analgesia, reward, mood changes, sedation, respiratory depression, immunosuppression, decreased gastrointestinal motility, increased locomotor activity, tolerance and dependence. A common A118G SNP reduces MOPR N-glycosylation and protein stability [20].

Non-synonymous SNPs can affect post-translational modifications. Because protein phosphorylation is one of the key elements in signal transduction, an altered phosphorylation pattern can cause different responses to the environment. The human ether-a-go-go-related gene 1 (ERG1) protein channel polymorphism is associated with cardiac arrhythmias [21]. A SNP leading to a Lys897Thr substitution creates a phosphorylation site in ERG1, which in turn inhibits channel activity for the downstream signal transduction [22].

4. GWA study in human disease

GWA studies in which hundreds of thousands of single-nucleotide polymorphisms (SNPs) are tested for association with a disease in hundreds or thousands of persons have revolutionized the search for genetic influences on complex traits [23,24]. Such conditions, in contrast with single-gene disorders, are caused by many genetic and environmental factors working together, each having a relatively small effect and few if any being absolutely required for a disease to occur. Although complex conditions have been referred to as the geneticist's nightmare [25], in recent years GWA studies have identified SNPs implicating more than hundreds of robustly replicated loci for common diseases such as cancer, infectious diseases and many other traits shown in Tables 1–3 respectively.

GWA studies use dense maps of SNPs covering the human genome to look for allelic frequency differences between the cases (patients with a specific disease or individuals with a certain trait) and controls. Linkage disequilibrium (LD) mapping, recognizes that a mutation which is shared by affected individuals through common descent is surrounded by other alleles at nearby loci, thus representing the haplotype of the ancestral chromosome region where the mutation first occurred. Two polymorphic sites are said to be in LD when their specific alleles are correlated in a population. High LD means that the SNP alleles are almost always inherited together; information about the allele of one SNP in an individual is strongly

Table 1 GWA studies showing SNPs association with cancer.

Disease	Chromosomal location	Gene	Strongest SNPs-risk allele	*P*-value	Reference
Breast cancer	10q26.13	*FGFR2*	rs2981582-G	2×10^{-76}	[11,36-38]
	16q12.1	*TNCR9/LOC643714*	rs3803662-C	1×10^{-36}	
	5q11.2	*MAP3K1*	rs889312-A	7×10^{-20}	
	11p15.5	*LSP1*	rs3817198-T	3×10^{-9}	
	8q24.21	Intergenic	rs13281615-T	5×10^{-12}	
	2q34	*ERBB4*	rs13393577-C/T	8.8×10^{-14}	
	10q26.13	*FGFR2*	rs1219648-G	1×10^{-10}	
	2q35	Intergenic	rs13387042-A	1×10^{-13}	
Basal cell carcinoma	1q42.13	*RHOU*	rs801114-G	6×10^{-12}	[39-44]
	1p36.13	*PADI4, PADI6, RCC2, ARHGEF10L*	rs7538876-A	4×10^{-12}	
	12q12.13	*KRT5*	rs11170164-A	2×10^{-9}	
	9p21	*CDKN2A/B*	rs2151280-C	7×10^{-9}	
	8q24.21	Intergenic	rs16901979-A	1×10^{-12}	
	8q24.21	Intergenic	rs6983267-G	9×10^{-13}	
	17q12	*TCF2*	rs4430796-A	1×10^{-11}	
	11p15	*IGF2, IGF2A, INS, TH*	rs7127900-A	3×10^{-33}	
Colorectal cancer	8q24.21	*ORF, DQ515897*	rs10505477-A	3×10^{-11}	[45,46]
	18q21.1	*SMAD7*	rs4939827-T	1×10^{-12}	
Lung cancer	15q25.1	*CHRNA3, CHRNA5, CHRNB4, PSMA4, LOC123688*	rs8034191-C	5×10^{-20}	[47]
	6p22.1	*TRNAA-UGC*	rs4324798-A	2×10^{-8}	[48]
Melanoma	20q11.22	*CDC91L1*	rs910873-T	1×10^{-15}	[49,50]
	22q13.1	Intergenic	rs2284063-G	2×10^{-9}	
Neuroblastoma	6p22.3	*FLJ22536, FLJ44180*	rs6939340-G	9×10^{-15}	[51,52]
	2q35	*BARD1*	rs6435862-G	9×10^{-18}	
Ovarian cancer	9p22.2	Intergenic	rs3814113-T	5×10^{-19}	[53]
Thyroid cancer	9q22.23	*FOXE1*	rs965513-A	2×10^{-27}	[15]
	14q13.3	*NKX2-1*	rs944289-T	2×10^{-9}	

Table 2 SNPs significantly associated with infectious disease phenotypes in genome-wide studies.

Disease	SNP location	Strongest SNPs-risk allele	*P*-value	Reference
Creutzfeldt–Jakob disease	PRNP	rs1799990	2.0×10^{-27}	[54]
Dengue shock Syndrome	MICB	rs3132468	4.4×10^{-11}	[55]
Hepatitis B	HLA-DPA1	rs3077	2.3×10^{-38}	[56]
	HLA-DPB1	rs9277535	6.3×10^{-39}	
Hepatitis C	IL28B	rs8099917	6.1×10^{-9}	[57]
HIV-1 and AIDS	HLA-C	rs9264942	5.9×10^{-32}	[58–64]
	HLA-B, HCP5	rs2395029	4.5×10^{-35}	
	HLA-B	rs2523608	5.6×10^{-10}	
	HLA-C	rs9264942	2.8×10^{-35}	
	MICA	rs4418214	1.4×10^{-34}	
	HLA-B, HCP5	rs2395029	9.7×10^{-26}	
	PSORS1C3	rs3131018	4.2×10^{-16}	
	HLA-B	rs2523608	8.9×10^{-20}	
	Intergenic	rs2255221	3.5×10^{-14}	
	HLA-B	rs2523590	1.7×10^{-13}	
	Intergenic	rs9262632	1.0×10^{-8}	
	ZNRD1, RNF39	rs9261174	1.8×10^{-8}	
	PARD3B	rs11884476	3.4×10^{-9}	
	HLA-B, HCP5	rs2395029	6.8×10^{-10}	
	CXCR6	rs2234358	9.7×10^{-10}	
Leprosy	LACC1	rs3764147	3.7×10^{-54}	[65]
	NOD2	rs9302752	3.8×10^{-40}	
	RIPK2	rs42490	1.4×10^{-16}	
	CCDC122	rs3088362	1.4×10^{-31}	
	TNFSF15	rs6478108	3.4×10^{-21}	
Meningococcal disease	CFH	rs1065489	2.2×10^{-11}	[66]
Severe malaria	HBB	rs11036238	3.7×10^{-11}	[67]
Tuberculosis	18q11.2 GATA6, TAGE1, RBBP8, CABLES1	rs4334126	6.8×10^{-9}	[68]

predictive of the allele of the other SNP on that chromosome. The first example of LD between a DNA polymorphism and a disease mutation was provided by an association between an allele of an RFLP in the β-globin gene and the sickle-cell form of hemoglobin [26].

Next-generation sequencing projects are revolutionizing our understanding of genetic variation. The quality of data from the next-generation technology and the availability of analysis tools are both rapidly increasing. Just considering the pilot data from the 1000 Genome Projects, this new resource has provided the location, allele frequency, and local haplotype structure of approximately 15 million SNPs [27]. Successful GWA studies are the most visible and exciting outcome of HapMap which has also been invaluable in developing genotyping and analytic methods to realize advances in the prevention and treatment of common diseases. The tool of sequencing enables scientists to pinpoint functional variants from association studies and improve the knowledge available to researchers interested in evolutionary biology, and hence may lay the foundation for predicting disease susceptibility and drug response.

5. Role of SNPs in drug development

GWAS have uncovered many genetic loci that are associated with human diseases, but two fundamental limitations have hampered our ability to translate these results into clinically useful predictors of disease and drug targets [28]. The U.S. Food and Drug Administration's Adverse Event Reporting System (AERS) allows us to develop an initial understanding of the context within which molecular level drug-target interactions can lead to distal effectors that results in adverse phenotypes at the organ and organismal levels [29]. Targeting drugs for complex diseases and predicting therapeutic efficacy and adverse risk for individuals with allelic variation (like SNPs) are the major goals of pharmacology. The allelic variants of the genes can lead to adverse effect of drugs and open new ways to drug development. Some of the genes related to severe diseases with pharmacogenomic targets and recommended drug therapy are shown in Table 4.

Drug transporters are now widely known as important determinants governing drug absorption, excretion, and, in many cases, extent of drug entry into target organs. Transporters of the solute carrier (SLC) and ATP-binding cassette (ABC) superfamilies are considered to be of major importance in drug therapy and outline how understanding the expression, function, and genetic variation in such drug transporters will result in better strategies for optimal drug design and tissue targeting as well as reduce the risk for drug–drug interactions and adverse drug responses. SNPs in genes encoding Organic cation transporters (OCTs) have been identified and characterized [30].

Aldehyde oxidase (AO) is a complex molybdoflavoprotein that belongs to the xanthine oxidase family. Human aldehyde oxidase (hAOX1) encoded by *AOX1* gene has an important role in the metabolism of drugs, based on its broad substrate specificity oxidizing aromatic aza–heterocycles, e.g., N1-methylnicotinamide and N-methylphthalazinium, or aldehydes, such as benzaldehyde, retinal and vanillin. SNP based functionally inactive hAOX1 allelic variants and also variants coding for enzymes with different catalytic activities are well

considered for the design of future drugs [31]. *VKORC1* encodes the vitamin K-epoxide reductase protein, the target enzyme of warfarin. *VKORC1* catalyzes the conversion of vitamin K-epoxide into vitamin K, which is the rate-limiting step

Table 3 SNP-GWA association studies in various traits.

Disease/trait	Chromosomal location	Gene	Strongest risk allele	*P*-value	References
Autoimmune diseases					
Rheumatoid arthritis	2p14	SPRED2	rs934734-A	3.2×10^{-7}	[69–71]
	5q11	ANKRD55, IL6ST	rs6859219-C	2.5×10^{-9}	
	3p14	PXK	rs13315591-T	3.7×10^{-7}	
	4p15	RBPJ	rs874040-G	1.9×10^{-7}	
	3 6q27	CCR6	rs309302-G	3.3×10^{-7}	
	31 7q32	IRF5	rs104886-T	2.8×10^{-6}	
	9q34	*TRAF1-C5*	rs3761847-G	1×10^{-14}	
	6q23.3	Near *TNFAIP3*, *OLIG3*	rs10499194-C	1×10^{-9}	
Systemic lupus erythematosus	4q24	*BANK1*	rs10516487-G	4×10^{-10}	[72]
Cardiovascular conditions					
Atrial fibrillation/atrial flutter	4q25	Intergenic	rs2200733-T	3×10^{-41}	[73]
		Near *PITX2*	rs10033464-T	7×10^{-11}	
Coronary disease	9p21.3	*CDKN2A/B*	rs1333049-C	1×10^{-13}	[74,75]
	9p21.3	*CDKN2A/B*	rs1333049-C	3×10^{-19}	
	6q25.1	*MTHFD1L*	rs6922269-A	3×10^{-8}	
	2q36.3	Pseudogene	rs2943634-C	2×10^{-7}	
Coronary heart disease (CHD)	9q33	DAB2IP	rs7025486-?	0.003	[76]
Myocardial	9p21.3	*CDKN2A/B*	rs10757278-G	1×10^{-20}	[77]
Diabetes					
Type 1 diabetes	19q13.33	*FUT2*	rs601338A > G	4.3×10^{-18}	[74,78–80]
	12q24.13	*C12orf30*	rs17696736-G	2×10^{-16}	
	12q13.2	*ERBB3*	rs2292239-A	2×10^{-20}	
	16p13.13	*KIAA0350*	rs12708716-A	3×10^{-18}	
	18p11.21	*PTPN2*	rs2542151-C	1×10^{-14}	
	18q22.2	*CD226*	rs763361-A	1×10^{-8}	
	12q13.2	*ERBB3*	rs11171739-C	1×10^{-11}	
	16q13.13	*TRAFD1*, *PTPN11*, *KIAA0350*	rs12708716-A	5×10^{-7}	
	16p13.13	*KIAA0350*	rs2903692-G	7×10^{-11}	
Type 2 diabetes	11p15	*KCNQ1*	rs151290-?	0.002	[25,81–84]
	8q24.11	*SLC30A8*	rs13266634-C	6×10^{-8}	
	16q12.2	*FTO*	rs8050136-A	1×10^{-12}	
	10q23.33	*HHEX*	rs5015480-C	6×10^{-10}	
	6p22.3	*CDKAL1*	rs10946398-C	4×10^{-11}	
	9p21.3	*CDKN2B*	rs10811661-T	8×10^{-15}	
	3q27.2	*IGFBP2*	rs4402960-T	9×10^{-16}	
	9p21.3	*CDKN2A/B*	rs10811661-T	8×10^{-15}	
	3q27.2	*IGF2BP2*	rs4402960-T	9×10^{-16}	
	6p22.3	*CDKAL1*	rs7754840-C	4×10^{-11}	
	6p22.3	*CDKAL1*	rs7754840-C	4×10^{-11}	
	9p21.3	*CDKN2A/B*	rs10811661-T	8×10^{-15}	
	3q27.2	*IGF2BP2*	rs4402960-T	9×10^{-16}	
	11p12	Intergenic	rs9300039-C	4×10^{-7}	
Gastrointestinal disorders					
Celiac disease	4q27	*KIA1109*, *TENR*, *IL2*, *IL21*	rs6822844-G	1×10^{-14}	[85]
Crohn disease	5p13.1	Intergenic	rs1373692-?	2×10^{-12}	[74,86-88]
	1q24.3	Intergenic	rs12035082-?	2×10^{-7}	
	18p11.	*PTPN2*	rs2542151-?	3×10^{-8}	
	3p21.31	Many genes	rs9858542-?	5×10^{-8}	
	5q33.1	*IRGM*	rs13361189-?	2×10^{-10}	
	21q22.2	Intergenic	rs2836754-?	5×10^{-7}	
	10q24.2	*NKX2–3*	rs10883365-?	4×10^{-18}	
	1q31.2	Intergenic	rs10801047-?	3×10^{-8}	
	2q37.1	*ATG16L1*	rs2241880-G	1×10^{-13}	
	3p21.31	*BSN*, *MST1*	rs9858542-A	4×10^{-8}	
	5q33.1	*IRGM*	rs1000113-T	3×10^{-7}	
	10q24.2	*NKX2–3*	rs10883365-G	6×10^{-8}	
	18p11.21	*PTPN2*	rs2542151-G	2×10^{-7}	

Table 3 (*contiued*)

Gallstones	2p24.2	*ABCG8*	rs11887534-C	1×10^{-14}	[89]
	12q24.13	*SH2B3/LNK*	rs17696736-G	2×10^{-14}	
Inflammatory bowel disease	1p31	*IL23R*	rs11209026-A	4×10^{-11}	[90]
Lipid metabolism					
HDL-cholesterol	1q42.13	*GALNT2*	rs4846914-G	2×10^{-13}	[91,92]
	12q24.11	*MVK/MMAB*	rs2338104-G	3×10^{-8}	
LDL-cholesterol	1p13.3	*CELSR2, PSRC1*	rs599839-G	1×10^{-7}	[91,93]
	1p13.3	*CELSR2, PSRC1, SORT1*		3×10^{-29}	
	19p13.11	*CILP2, PBX4*	rs16996148-G	3×10^{-8}	
Triglycerides	7q11.23	*BCL7B, TBL2, MLXIPL*	rs17145738-T	7×10^{-22}	[91,92,94]
	19p13.11	*CILP2, PBX4*	rs16996148-G	4×10^{-9}	
	8q24.13	*TRIB1*	rs17321515-A	4×10^{-17}	
	1q42.13	*GALNT2*	rs4846914-G	7×10^{-15}	
	1p31.3	*ANGPTL3, DOCK7, ATG4C*	rs12130333-C	2×10^{-8}	
	2p23.3	*GCKR*	rs780094-T	6×10^{-32}	
	8q24.13	*TRIB1*	rs17321515-A	7×10^{-13}	
	19p13.3	*NCAN/CILP2*	rs16996148-G	3×10^{-9}	
	7q11.23	*MLXIPL*	rs17145738-C	2×10^{-12}	
	1p31.3	*ANGPTL3*	rs1748195-C	2×10^{-10}	
	7q11.23	*MLXIPL*	rs3812316-C	1×10^{-10}	
Neuropsychiatric conditions					
Amyotrophic lateral sclerosis	7q36.2	*DPP6*	rs10260404-C	5×10^{-8}	[95]
*APOE**e4* with late-onset Alzheimer disease	11q14.1	*GAB2*	rs2373115-G	1×10^{-10}	[96]
Bipolar disorder	13q14.11	*DGKH*	rs1012053-A	2×10^{-8}	[74,97]
	16p12.1	*PALB2, NDUFAB1, DCTN5*	rs420259-A	6×10^{-8}	
Multiple sclerosis	16p13	*KIAA 0350*	rs6498169-?	?	[98,99]
	10p15.1	*IL2RA*	rs12722489-C	3×10^{-8}	
	5p13.2	*IL7RA*	rs6897932-C	3×10^{-7}	
Restless legs syndrome	6p21.2	*BTBD9*	rs3923809-A	1×10^{-17}	[100,101]
	2p14	*MEIS1*	rs2300478-G	3×10^{-28}	
	6p21.2	*BTBD9*	rs9296249-T	4×10^{-18}	
	15q23	*MAP2K5, LBXCOR1*	rs12593813-G	1×10^{-15}	
Schizophrenia	Xp22.33/Yp11.32	*CSF2RA*	rs4129148-C	4×10^{-7}	[102]
Sporadic amyotrophic lateral sclerosis	10q26.13	Intergenic	rs4363506-?	7×10^{-7}	[103]

N/R = not reported, ? = not described.

in vitamin K recycling. A common non-coding variant (−1639G > A, rs9923231) is significantly associated with warfarin sensitivity and its polymorphism alters a *VKORC1* transcription factor binding site, leading to lower protein expression [32].

Fig. 3 represents allelic variants associated with drug-induced liver injury (DILI). Pharmacogenomic study reveals the associations between DILI susceptibility and several polymorphisms in various genes, such as specific alleles in manganese superoxide dismutase glutathione peroxidase, and glutathione *S*-transferase that are significantly more frequent in DILI patients than in controls and shared across multiple drugs [33–36]. In the context of large genetic variation, GWA studies help us in identifying SNPs as pharmacodynamic models which can lead to develop a mechanistic understanding of drug action in the context of population as well as an individual's genomic status.

6. Conclusion

Natural selection exerts its influence by changing allele frequencies of polymorphic markers to eliminate a deleterious phenotype from a population or otherwise fix a beneficial one. The human complex traits as a matter of fact, show variation with SNPs having adverse effects on drug exposure which could be lethal. Many SNPs have been explored as a high-resolution marker for accelerating the pace of gene mapping related to diseases or traits. The GWA–SNPs have been studied in different human populations and their quantification for population structure within and between the populations has been attempted for association studies. Inter-individual variability in drug response is influenced by variation in genes that control the absorption, distribution, metabolism and excretion of drugs. The Wellcome Trust Case Control Consortium (WTCCC) is engaged in exploring the utility, design and analysis of GWA studies. The International HapMap resource, documents patterns of genome-wide variation and linkage disequilibrium in population samples and greatly facilitates both the design and analysis of association studies. The availability of advance genotyping chips, containing sets of large number of SNPs provides good coverage of the human genome, to which means that GWA studies can be used for thousands of cases and controls for exploring the basis of complex traits.

Identification of the genetic basis for polymorphic expression of a gene is done through intronic or exomic SNPs which abolishes the need for different mechanisms for explaining the variability in drug metabolism. SNPs based variations in membrane receptors lead to multidrug resistance (MDR) and the drug–drug interactions. Even drug induced toxicity and many adverse effects can be explained by GWA studies. The aim of

Table 4 Some genes identified by Genome-wide studies which are pharmacogenomic targets with recommended drug therapy.

Therapeutic area	Gene/marker	Drug involved
Allergy	*CYP2D6*	Desloratadine, Pseudoephedrine
Analgesics	*CYP2D6*	Codeine, Tramadol, Acetaminophen
	CYP2C9	Celecoxib
Antiarrhythmics	*CYP2D6*	Quinidine
Antifungals	*CYP2C19*	Voriconazole
	CYP2D6	Terbinafine
Antiinfectives	*NAT1; NAT2*	Rifampin, Isoniazid, Pyrazinamide
Antivirals	*CCR5*	Maraviroc
	IL28B	Boceprevir
Cardiovascular	*ApoE2*	Pravastatin
	CYP2C19	Ticagrelor, Clopidogrel
	CYP2D6	Metoprolol, Carvedilol, Propranolol
Dermatology and dental	*PML/RARα*	Tretinoin
	DPD	Fluorouracil
	CYP2D6	Cevimeline
Gastroenterology	*UCD NAGS; CPS; ASS; OTC; ASL; ARG*	Sodium Phenylacetate, Sodium Benzoate
	CYP2C19	Rabeprazole, Esomeprazole, Pantoprazole, Dexlansoprazole,
Hematology	*VKORC1*	Warfarin
	CYP2C9	Warfarin
Metabolic and Endocrinology	*LDL* receptor	Atorvastatin
Musculoskeletal	*CYP2C19*	Carisoprodol
Neurology	*CYP2D6*	Dextromethorphan, Quinidine, Tetrabenazine, Galantamine
	CYP2C19	Clobazam
	*HLA-B*1502*	Carbamazepine
Oncology	*PDGFR*	Imatinib
	PML/RARα	Arsenic Trioxide
	CYP2D6	Gefitinib
	CD20 antigen	Tositumomab
	KRAS	Cetuximab, Panitumumab
	Her2/neu	Lapatinib, Trastuzumab
	CD30	Brentuximab Vedotin
	C-Kit	Imatinib
	DPD	Capecitabine
	TPMT	Mercaptopurine, Thioguanine, Cisplatin
	FIP1L1-PDGFRα	Imatinib
	ER &/PgR receptor	Exemestane
	ER receptor	Fulvestrant, Tamoxifen
	Ph Chromosome	Nilotinib, Dasatinib, Busulfan, Imatinib
	BRAF	Vemurafenib
	ALK	Crizotinib
	EGFR	Panitumumab, Cetuximab
Psychiatry	*UCD NAGS; CPS; ASS; OTC; ASL; ARG*	Valproic Acid
	CYP2C19	Diazepam, Citalopram, Fluvoxamine, Modafinil
	CYP2D6	Citalopram, Clomipramine, Desipramine, Aripiprazole, Iloperidone, Fluoxetine, Pimozide, Doxepin, Protriptyline, Chlordiazepoxide, Amitriptyline, Modafinil, Nefazodone, Nortriptyline, Thioridazine, Trimipramine, Venlafaxine, Clozapine, Risperidone, Fluoxetine, Olanzapine
Pulmonary	*CFTR G551D*	Ivacaftor
Reproductive and urologic	*CYP2D6*	Tolterodine
Rheumatology	*TPMT*	Azathioprine
	CYP2C9	Flurbiprofen

Compiled from Food and Drug Administration, 2012 [104].

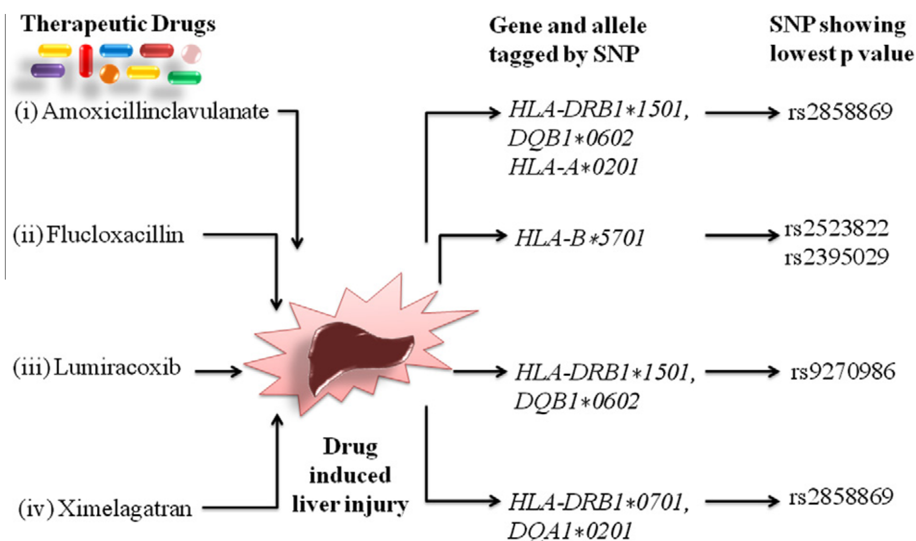

Figure 3 GWA approach to uncover SNPs for drug induced hepatotoxicity. The study has shown statistically significant associations with particular HLA class I or II alleles, suggesting that T cell responses contribute to the liver injury. The adverse reactions by the corresponding SNPs against HLA genes in response to drugs are shown on the right hand side of the above figure which is compiled from the data of some recent studies [119–122] based on GWA studies.

this review is to throw fresh light on human genetic variation using SNPs to predict drug response and its wide applications in medical, health and pharmacogenetic studies. The tool of SNPs can help understand the alteration in the amino-acid sequence of the encoded protein and make a common cause of pharmacologically relevant functional variation. The multitude of SNPs help in understanding gene pharmacokinetic (PK) or pharmacodynamic (PD) pathways. The association of a wide range of human diseases like cancer, infectious diseases (AIDS, leprosy, hepatitis, etc.) autoimmune, neuropsychiatric and many other diseases (Tables 1–4) with different SNPs can be made as relevant pharmacogenomic targets for drug therapy.

Disclosure statement

The authors declare that there is no conflict of interest.

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