Heliyon 10 (2024) e33003

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Immunomodulatory gene polymorphisms in non-small cell lung carcinoma susceptibility and survival

Vithiya Dewarajan [a], Nourhan Elsayed [b], Jhi Biau Foo [b,c], Yin Sim Tor [a,c,*], Sze Shin Low [d], Wai Siong Chai [e]

[a] School of Biosciences, Faculty of Health and Medical Sciences, Taylor's University, 1, Jalan Taylors, 47500, Subang Jaya, Selangor, Malaysia
[b] School of Pharmacy, Faculty of Health and Medical Sciences, Taylor's University, 1, Jalan Taylors, 47500, Subang Jaya, Selangor, Malaysia
[c] Digital Health and Medical Advancement Impact Lab, Taylor's University, Subang Jaya 47500, Selangor, Malaysia
[d] Nottingham Ningbo China Beacons of Excellence Research and Innovation Institute, University of Nottingham Ningbo China, Ningbo, PR China
[e] Department of Chemical and Environmental Engineering, The University of Nottingham Ningbo China, Ningbo 315100, PR China

ARTICLE INFO

Keywords:
Single nucleotide polymorphism
Non-small cell lung carcinoma
Immune markers
Cancer susceptibility
Cancer survival
Prognosis

ABSTRACT

Lung cancer is the leading cause of cancer-associated mortality and non-small cell lung carcinoma (NSCLC) constitutes 85 % of all lung cancer cases. This malignancy is characterized by multi-factorial risk factors, poor prognosis, and deplorable clinical outcome. Considerable evidence indicates that there is inter-individual variability in the lung cancer predisposition and survival due to genetic variations introduced by genetic polymorphisms between individuals, indirectly affecting the lung cancer susceptibility and the patient survival. In the past decades, immune landscape in the tumour environment and host immune response are constantly implicated as determining factor in NSCLC development and patients' survival. With the change of paradigm in NSCLC treatment to immunotherapy and increasing recognition of the role of the immune system in cancer development and survival, the inspection of single nucleotide polymorphisms (SNPs) in immunomodulated markers associated with the risk and prognosis for NSCLC is crucial. Despite extensive studies reported the implication of SNPs in predicting the risk and survival of NSCLC. SNPs in the genes that modulate immune response in NSCLC have not been reviewed before. Hence, this review uncovers the evidence on the genetic polymorphisms of immunomodulatory markers which include immune checkpoints, immune checkpoint inhibitors, chemokines, interleukins, human leukocyte antigen and its receptors, and antigen presenting machinery genes, and their significance in the susceptibility, prognosis and survival in NSCLC. The identification of genetic factors associated with NSCLC risk and survival provides invaluable information for a greater comprehension of the pathogenesis and progression of the disease, also to refine prognosis and personalize clinical care in early and advanced-stages disease.

1. Introduction

Lung cancer is the leading form of cancer, causing over 1.8 million cases yearly [1] and 1 in 4 cancer deaths [2]. Lung cancer is a heterogeneous disease, including two major histologic categories: Small-Cell Lung Cancer (SCLC) and Non-Small-Cell Lung Cancer

* Corresponding author. School of Biosciences, Faculty of Health and Medical Sciences, Taylor's University, 1, Jalan Taylors, 47500, Subang Jaya, Selangor, Malaysia
E-mail addresses: yinsim.tor@taylors.edu.my (Y.S. Tor), sze-shin.low@nottingham.edu.cn (S.S. Low).

https://doi.org/10.1016/j.heliyon.2024.e33003
Received 8 April 2024; Received in revised form 12 June 2024; Accepted 12 June 2024
Available online 13 June 2024

(NSCLC). The latter accounts approximately for 80–85 % of all lung cancer with adenocarcinoma (AC) (60 %), squamous cell carcinoma (SCC) (25 %), large cell carcinoma (LCC) (10 %) and other less common histologic subtypes [3]. AC is the most frequent type in men and women of all ages, including smokers and non-smokers [4]. It originates from glandular-like epithelial cells with excretory properties. SCC develops from squamous cell precursors in airway epithelial cells of the bronchial tubes and is reported to strongly linked to cigarette smoking [5].

Genetic polymorphism, known as single nucleotide polymorphism (SNP), significantly impacts development and progression of cancer. It is estimated that 1.42 million SNPs are distributed throughout the human genome, approximately 60,000 SNPSs within the coding region [6]. Polymorphisms in immune-related genes can affect the balance between the pro-inflammatory and anti-inflammatory networks. Moreover, genetic variations in various immune-related markers have been associated with cancer risk and overall survival (OS). Although a clear association has been shown between the tumour immune response and clinical outcome in many cancers, the genetic polymorphisms of immune markers for stratifying susceptibility and clinical outcomes in NSCLC is less defined. This is the first review to our knowledge to assess the implication of SNPs in immunomodulatory markers in regard to NSCLC susceptibility and survival (Fig. 1).

2. Immunomodulatory markers

In recent years, the immune system has become more implicated in cancer genesis and progression [7]. Tumour cells can upregulate immune checkpoints expression [8] and downregulate surface Major Histocompatibility Complex (MHC) class I/tumour antigen expression, in particular NSCLC tumour cells, allowing these cells to evade the immune system [9]. In addition, elevated chemokines [10,11] and interleukins [12,13] have also been linked to worse prognosis and survival in NSCLC patients. This review explores the immunomodulatory markers on the susceptibility and survival of NSCLC. This review focuses on selected categories of immunomodulatory markers such as the immune checkpoints, chemokines and their receptors, interleukins, human leukocyte antigen (HLA)

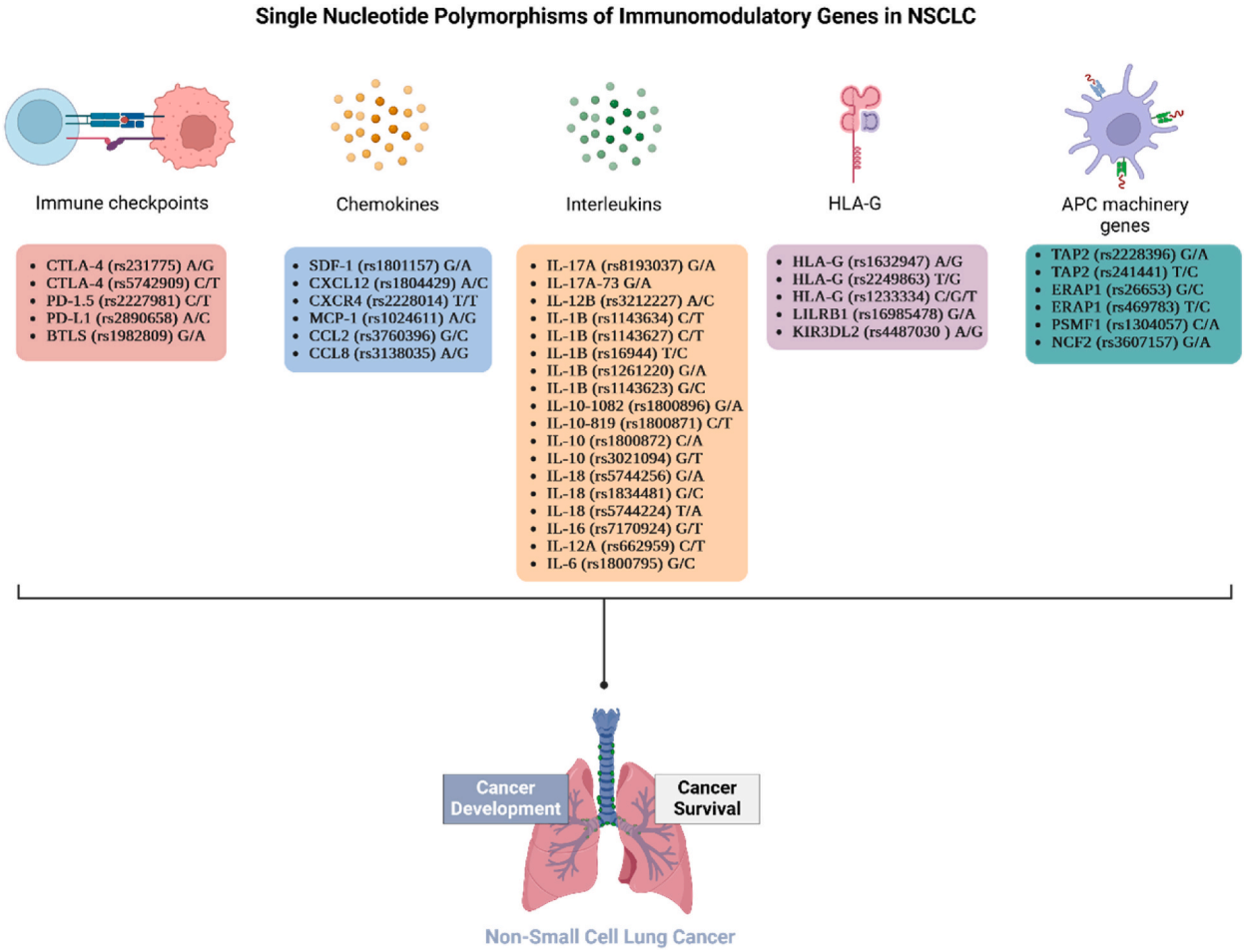

Fig. 1. Immunomodulatory genes and their single nucleotide polymorphisms. The figure shows the respective restriction sites and alleles of single nucleotide polymorphisms of immunomodulatory genes associated with the susceptibility and survival in non-small cell lung carcinoma (created with BioRender.com).

and its receptors as well as antigen presenting cells (APCs).

Immune checkpoints are receptor-based signal cascades that negatively regulate T cells and cause immune tolerance, allowing tumours to evade immune surveillance [14]. Key inhibitory immunoreceptors includes Cytotoxic T-lymphocytes-associated antigen-4 (CTLA-4) and Programmed Death-Ligand-1 (PD-L1). CTLA-4 is an immunoglobulin-like receptor expressed on regulatory T (Treg) cells and activated $CD4^+$ and $CD8^+$ T cells [14]. PD-1/PD-L1 is an important pair of immune checkpoints, expressed on peripheral T cells, Natural Killer (NK) cells, B cells, and monocytes [15]. PD-1 binds to its ligands, PD-L1 and PD-L2, which are not only expressed on APCs but also on the exterior of tumour cells [14].

Chemokines are pro-inflammatory cytokines that regulates cell migration, adhesion, and cell-cell interactions [16]. Cancer cells and recruited immune cells shape tumorigenesis through chemokine ligands and receptors [17]. Genetic polymorphism in chemokines expression or function may attenuate immune responses against various cancers. Among cytokines, several interleukins (ILs) can also interact with a variety of cells that alter the immune system and act on a wide range of cancers [18]. It was discovered that cytokines are also produced by cancer cells [19], and its receptors to escape immune attack [20]. Recent genetic susceptibility studies focus on SNPs in candidate genes, including chemokine and interleukins due to their critical roles in invasion, migration, and metastasis [21].

In order to avoid immune elimination, tumours have adopted loss of human leukocyte antigen (HLA) molecules and dysregulation of antigen presenting machinery (APM) genes or proteins as a strategy. HLA molecules and Killer-cell immunoglobulin-like receptor (KIR) serve as ligands and receptors, respectively, and their interplay is important for transmitting activating or inhibitory signals which plays a role in the defence against tumour cells [22]. Defects in APM may enable tumour cells to evade T lymphocyte-mediated recognition and lysis [23] and abrogates T cell-mediated antitumor immunity [9]. Genetic variation of genes or proteins involved in HLA, KIR and APM facilitates immune evasion which is known to be associated with the risk of occurrence of several malignancies [24].

3. Genetic polymorphisms of immunomodulatory markers on NSCLC susceptibility and prognosis

3.1. Immune checkpoint and immune checkpoint inhibitors genes 3.1.1 CTLA-4

Among the polymorphisms of CTLA-4, +49 Adenine (A)/Guanine (G) (rs231775) and −318 Cytosine (C)/Thymine(T) (rs5742909) are widely studied functional polymorphisms. Results from a study [25] indicated that individuals carrying +49 GG-allele exhibits 2.23-fold increased lung cancer susceptibility (OR = 2.23; 95 % CI = 1.17–4.48; P = 0.015) and individuals carrying +49 AG-allele exhibits 1.16-fold increased lung cancer susceptibility (OR = 1.16; 95 % CI = 0.62–2.21; P = 0.74), but it is not significant. However [25], also indicated that individuals carrying the homozygote +49 AA-allele exhibits decreased likelihood of cancer susceptibility by 0.41-fold (OR = 0.41; 95 % CI = 0.21–0.78; P = 0.02) as depicted in Table 1. Additional testing also identified +49 AA-genotype as an independent prognostic indicator for NSCLC prognosis by 1.6-fold (HR = 1.6; 95 % CI = 1.3–1.9; P = 0.001) [26] as depicted in Table 2.

Antczak et al. [25], showed that individuals carrying −318 CC-allele (OR = 0.96; 95 % CI = 0.91–1.82; P = 0.15) exhibits decreased likelihood of lung cancer susceptibility by 0.96-fold. Besides, −318 CT-allele (OR = 0.66; 95 % CI = 0.34–1.28; P = 0.97) also exhibits decreased likelihood of lung cancer susceptibility by 0.66-fold. However, the results indicated that individuals carrying the homozygote −318 TT-allele exhibits an increased likelihood of cancer susceptibility by 1.53-fold (OR = 1.53; 95 % CI = 0.81–2.89; P = 0.41), but it is not significant. However, Ma et al. [27] revealed that the +49 G-genotype exhibited 1.15-fold increased cancer risk (OR = 1.15; 95 % CI = 0.97–1.36; P = 0.118) and the T-genotype of −318 polymorphism exhibited 0.74-fold decreased cancer risk (OR = 0.74; 95 % CI = 0.53–1.04; P = 0.085), which is deemed non-significant.

3.1.1. PD-1/PD-L1

Among the polymorphisms of PD-1, the identified functional polymorphism is PD-1.5 (+7785) C/T polymorphism (rs2227981) while PD-L1 is the (8293) A/C polymorphism (rs2890658). Both AC-genotype and C-allele carriers exhibits increased risk of lung cancer susceptibility by 1.55-fold (OR = 1.55; 95 % CI = 1.13–2.13; P = 0.006) and by 1.52-fold (OR = 1.52; 95 % CI = 1.14–2.04; P = 0.004), respectively [27]. Moreover, it was also reported that the homozygote CC-genotype increases the likelihood of lung cancer susceptibility by 1.85-fold (OR = 1.85; 95 % CI = 0.52–6.59; P = 0.345), however it is not significant based on the p-value.

Statistical significance on (CC + CT) versus TT-genotype of PD-1.5 (+7785) C/T polymorphism has been observed by 2.34-fold (OR = 2.34; 95 % CI = 1.35–4.06; P = 0.003) [28]. The CC-genotype is strongly linked to NSCLC risk by 2.40-fold (OR = 2.40; 95 % CI = 1.37–4.24; P = 0.002). Meanwhile, the CT-genotype has also significantly increased the risk of advanced NSCLC by 2.22-fold (OR = 2.22; 95 % CI = 1.23–4.02; P = 0.008). The results depicted in Table 1 suggests that PD-1.5 C/T was potentially related to NSCLC susceptibility in Asian population, in particular Chinese Han population. In contrast to Ref. [28], other studies have indicated no association between PD-1.5 C/T (+7785) polymorphism with NSCLC [27,29].

3.1.2. B and T lymphocyte Attenuator (BTLA)

BTLA garnered significant attention emerging as the newest immune checkpoint. BTLA (rs1982809) was found to reduce the risk of NSCLC for GA vs GG genotype by 0.81-fold (OR = 0.81; 95 % CI = 0.66–0.99; P = 0.043) [30]. In contrast to Ref. [30], another study revealed that genotypes distribution analysis in Polish population showed AG + GG genotypes were more frequent in the NSCLC group, indicating G allele increases susceptibility to NSCLC by 1.304-fold (OR = 1.304; 95 % CI = 0.99–1.71; P = 0.057) [31]. Allele distribution analysis also confirmed that G allele (rs1982809) is significantly associated with increased NSCLC risk by 1.254-fold (OR = 1.254; 95 % CI = 1.01–1.57; P = 0.046). Moreover, the (rs1982809) AA genotype was found to be an independent risk factor for OS by

1.52-fold (HR = 1.52; 95 % CI = 1.12–2.07; P = 0.01) in the multivariate analysis stratified for smokers.

3.2. Chemokine and chemokine receptors

3.2.1. Stromal cell-derived factor-1 (SDF-1) and C-X-C- chemokine receptor 4 (CXCR4)

The SDF-1 G801A G/A polymorphism (rs1801157) can be regarded as a potential risk factor of increasing LC probability [10]. Individuals with SDF1-3′AA-genotype had a 1.95-fold increased cancer risk (OR of 1.95; 95 % CI = 1.08–3.50; P = 0.018) whereas individuals with CXCR4-138 TT-genotype had a 4.71-fold increased cancer risk (OR = 4.71; 95 % CI = 1.99–11.2; P < 0.0001) for NSCLC susceptibility [32]. Ma et al. [11], also revealed consistent results that SDF-1 (rs1804429) remained as a significant prognostic marker of NSCLC with an increased risk of death. After adjusting for age, gender, histology, stage and treatment status, CC-genotype (HR = 6.03; 95 % CI = 1.44–25.24) and AC-genotype (HR = 1.23; 95 % CI = 0.88–1.73) genotype were significantly associated with unfavorable prognosis of NSCLC for CXCL12 (rs1804429).

Contradictory to Refs. [11,32] findings, another study has revealed that SDF-1 G801A polymorphism was not a risk factor for NSCLC in Chinese Han population [33]. NSCLC patients with homozygote AA-allele carriers exhibit 1.328-fold cancer risk (OR = 1.328; 95 % CI = 0.542–3.784; P = 0.523) and heterozygote GA-allele carriers exhibit 1.268-fold cancer risk (OR = 1.268; 95 % CI = 0.811–2.583; P = 0.361). Hence, it can be deduced that both the AA and GA-genotype may have an association to NSCLC susceptibility as the results are deemed not significant [33].

3.2.2. Monocyte chemoattractant protein-1 (MCP-1)

−2518 MCP-1 is a biallelic G/A polymorphism in the MCP-1 gene. Yang et al. [34] indicates that the distributions of AA, AG and GG-genotypes of −2518 MCP-1 were significantly different in NSCLC patients compared to controls (P = 0.006). A significant increase in the frequency for AA-genotype (OR = 3.138; 95 % CI = 1.480–6.652; P = 0.003) and a significant decrease in the frequency for the GG-genotype (OR = 0.516; 95 % CI = 0.282–0.944; P = 0.032) was observed in the NSCLC patients. Meanwhile, the A-genotype exhibited increased cancer risk by 1.963-fold (OR = 1.963; 95 % CI = 1.301–2.962; P = 0.001) and G-genotype exhibited decreased cancer risk by 0.509-fold (OR = 0.509; 95 % CI = 0.337–0.768; P = 0.001). Based on these results, it is suggestible that the −2518 MCP-1 G/A polymorphism is associated with genetic susceptibility to NSCLC. In another study [35], MCP-1 expression in cancer cells showed an independent prognostic factor for OS by 0.256-fold (HR = 0.256; 95 % CI = 0.106–0.616; P = 0.002), indicating that MCP-1 is overexpressed, its expression is associated with better survival in NSCLC patients.

3.2.3. C–C motif ligand 2 (CCL2) and C–C motif ligand 8 (CCL8)

A study conducted in Chinese population established that variant genotypes of CCL2 (rs3760396) and CCL8 (rs3138035) were associated with a significantly decreased risk of death for NSCLC [11]. The CC-genotype of CCL2 exhibited 0.80-fold decreased NSCLC mortality risk (HR = 0.80; 95 % CI = 0.25–2.62) whereas the CG-genotype exhibited 0.64-fold decreased NSCLC mortality risk (HR = 0.64; 95 % CI = 0.47–0.88). Meanwhile, the CC/CG-genotype displayed 0.65-fold decreased mortality risk (HR = 0.65; 95 % CI = 0.48–0.89) for CCL2 (rs3760396). Besides, the AA-genotype of CCL8 exhibited 0.99-fold decreased NSCLC mortality risk (HR = 0.99; 95 % CI = 0.36–2.70) whereas the AG-genotype exhibited 0.63-fold decreased NSCLC mortality risk (HR = 0.63; 95 % CI = 0.47–0.85). Meanwhile, the AA/AG-genotype displayed 0.65-fold decreased NSCLC mortality risk (HR = 0.65; 95 % CI = 0.49–0.86) for CCL8 (rs3138035).

Further analysis indicated that only CCL8 was an independent prognostic factor of NSCLC, suggesting CCL8 as a potential NSCC biomarker [11]. However, in another study [36], it has been established that CCL2 expression levels could serve as potential prognostic biomarker for NSCLC patients. Based on this study, CCL2 overexpression in lung SCC patients was associated with beneficial OS (P = 0.048) and progression-free survival (PFS) (P = 0.012). Meanwhile, lung AC patients with higher CCL2 expression had unfavorable OS (P = 6.7e-08) and PFS (P = 0.00098) as depicted in Table 2.

3.3. Interleukins (IL)

3.3.1. IL-17

IL-17A, commonly referred as IL-17 plays critical roles in cancer immunity including NSCLC. Cheng et al. [37] identified that IL-17A G/A (rs8193037) SNP was associated with increased NSCLC susceptibility, especially to AC in Han Chinese population. The data revealed that the prevalence of (rs8193037) GA-genotype (OR = 2.20; 95 % CI = 1.53–3.16; P < 0.001) and AA-genotype (OR = 3.19; 95 % CI = 1.42–7.15; P = 0.003) were significantly higher in the patients. This data indicates that both the GA and AA-genotypes significantly increases the likelihood of NSCLC susceptibility by 2.20-fold and 3.19-fold, respectively. Further analyses showed significantly higher percentage of A-allele (rs8193037) in AC by 1.72-fold (OR = 1.72; 95 % CI = 1.12–2.64; P = 0.013). These data indicates that IL-17A polymorphism is associated with increased risk of NSCLC probably by elevating gene expression [37].

Similar to Ref. [37], Ma et al. [38] revealed that IL-17A −73 G/A polymorphism is also associated with increased NSCLC susceptibility, especially to AC in the Chinese population. −73 GA-genotype carriers exhibited 2.09-fold increased risk of NSCLC (OR = 2.09; 95 % CI = 1.46–2.98; P < 0.001) whereas the AA-genotype carriers exhibited 2.52-fold increased risk of NSCLC (OR = 2.52; 95 % CI = 1.30–4.88; P = 0.005), as depicted in Table 1. In addition, IL-17 was also displayed as an independent prognostic factor for disease-free survival (DFS) in NSCLC by 2.345-fold (HR = 2.345; 95 % CI = 1.012–5.435; P = 0.047) [39]. These results may also possibly suggest that IL-17 plays a role in the metastasis of lung cancer by promoting lymphangiogenesis.

3.3.2. IL-16

Studies in several types of solid malignancies have reported strong association between IL-16 levels and cancer progression. A study conducted in Spanish population revealed a trend toward overrepresentation of GG-genotype with high risk of NSCLC clinical outcomes [40]. IL-16 (rs7170924) GG-genotypes predicted higher mortality risk in NSCLC patients by 1.82-fold (HR = 1.82; 95 % CI = 1.13–2.94; P = 0.0139). Besides, GG-genotype carriers also presented a trend towards higher risk of progression by 1.42-fold (HR = 1.42; 95 % CI = 0.97–2.09; P = 0.073), but it was reported as not significant based on the p-value. This result was supported by Woods et al. [41], revealing that the GG-genotype (rs7170924) was significantly associated with DFS by 0.65-fold (HR = 0.65; 95 % CI = 0.50–0.83), as depicted in Table 2.

3.3.3. IL-12

Perez-Ramirez et al. [40] established that IL-12A (rs662959) SNP predicted higher risk of progression in patients with NSCLC. TT-genotype carriers presented higher risk of progression in the non-resected NSCLC patient subgroup by 4.49-fold (HR = 4.49; 95 % CI = 1.06–18.99; P = 0.0412). Besides, another study [42] reported that the IL-12B (+1188) A/C (rs3212227) SNP was associated with NSCLC risk. The minor G-allele was correlated with elevated NSCLC with the GG-genotype exhibiting 1.80-fold increased NSCLC risk (OR = 1.80; 95 % CI = 1.26–2.55; P = 0.003) and GT-genotype exhibiting 1.16-fold increased NSCLC risk (OR = 1.16; 95 % CI = 0.86–1.57; P = 0.003).

3.3.4. IL-1β

IL-1β plays an important role in various inflammatory diseases including lung cancer [43]. IL-1β-31 C/T (rs1143627), IL-1β-511 T/C (rs16944), IL-1β-1464 G/C (rs1143623) and IL-1β-3893 G/A (rs1261220) were among the several SNPs that have been identified and widely investigated. The genotypic logistic regression model adjusted by smoking status showed that IL-1β-31 (rs1143634) TT-genotype was associated with a 0.22-fold lower risk of NSCLC (OR = 0.22; 95 % CI = 0.05–0.68; P = 0.013) and the CT-genotype was also associated with a 0.69-fold lower risk of NSCLC (OR = 0.69; 95 % CI = 0.46–1.02; P = 0.013) [44]. In another study, the −31 T-allele was positively associated with NSCLC risk [45]. The TT-genotype was associated with a 3.247-fold increased risk (OR = 3.247; 95 % CI = 1.794–5.878, P = 0.01) whereas the CT-genotype was associated with a 2.157-fold increased cancer risk (OR = 2.157; 95 % CI = 1.295–3.593; P = 0.003).

A study on Norwegian population revealed that −31 C/T (rs1143627) and −511 T/C (rs16944) were significantly associated with NSCLC [46]. The results indicated that T-allele at the −31 SNP and C-allele at −511 SNP were overrepresented in NSCLC. The homozygotes were particularly at higher risk of NSCLC by 2.39-fold for −31 T/T-genotype (OR = 2.39; 95 % CI = 1.29–4.44; P = 0.01) and by 2.51-fold for −511 C/C genotype (OR = 2.51; 95 % CI = 1.47–4.58; P < 0.01). Moreover, the heterozygotes were at 1.89-fold increased risk of NSCLC for −31 C/T genotype (OR = 1.89; 95 % CI = 1.03–3.46; P = 0.01) and by 1.91-fold increased risk of NSCLC for −511 C/T genotype (OR = 1.91; 95 % CI = 1.06–3.40; P < 0.01).

The results from Ref. [46] was consistent with Li et al. [47] who detected significant associations between NSCLC and IL-1β SNPs. The GA-genotype (rs1261220) for IL-1β-3893 exhibited 0.96-fold decreased NSCLC risk (OR = 0.96; 95 % CI = 0.77–1.20; P = 0.74) whereas the AA-genotype (rs1261220) exhibited 1.01-fold increased NSCLC risk (OR = 1.01; 95 % CI = 0.75–1.37; P = 0.95), but it is not significant based on the p-value. For IL-1β-1464, GC-genotype (rs1143623) exhibited 0.90-fold decreased NSCLC risk (OR = 0.90; 95 % CI = 0.72–1.12; P = 0.32) and the CC-genotype (rs1143623), exhibited 0.99-fold decreased NSCLC risk (OR = 0.99; 95 % CI = 0.74–1.34; P = 0.96), but it is also not significant. CC-genotype (rs16944) of IL-1β-511 exhibits 1.05-fold increased NSCLC risk (OR = 1.05; 95 % CI = 0.79–1.38; P = 0.75) while TC-genotype (rs16944) exhibits 0.95-fold decreased NSCLC risk (OR = 0.95; 95 % CI = 0.74–1.23; P = 0.71), but it is not significant based on the p-value. For IL-1β-31, TT-genotype (rs1143627) shows a 1.09-fold increased NSCLC risk (OR = 1.09; 95 % CI = 0.82–1.46; P = 0.54) and the CT-genotype (rs1143627) shows a 0.98-fold decreased NSCLC risk (OR = 0.98; 95 % CI = 0.75–1.26; P = 0.85), but it is also not significant.

In addition, Metwally et al. [48] conducted a study on Egyptian population that has revealed IL-1β (rs16944) patients with heterozygous CT genotype were less prone to NSCLC by 0.16-fold (OR = 0.16; 95 % CI = 0.05–0.56; P = 0.004) in a codominant model. Decreased risk of NSCLC was also observed in dominant model for TT + CT genotypes by 0.17-fold (OR = 0.17; 95 % CI = 0.05–0.59; P = 0.005) and in the overdominant model for TT + CC genotypes by 0.15-fold (OR = 0.15; 95 % CI = 0.05–0.44; P = 0.001), respectively.

3.3.5. IL-10

IL-10 polymorphisms include IL-10-1082, IL-10-819 and IL-10-592. Shih et al. [49] reported that IL-10-1082 G-allele, IL-10-819 C-allele and IL-10-592 C-allele frequency was independently higher in NSCLC patients. Higher susceptibility for NSCLC were observed in individuals with G-allele of IL-10-1082 by 5.26-fold (OR = 5.26; 95 % CI = 2.65–10.4, P < 0.0001), C-allele of IL-10-819 by 1.57-fold (OR = 1.57; 95 % CI = 1.15–2.16, P = 0.005) and C-allele of IL-10-592 by 1.59-fold (OR = 1.59; 95 % CI = 1.15–2.19, P = 0.005). These results were also supported by Hart et al. [50], revealing a significant association of IL-10-592 SNP (rs1800872) with increased risk of NSCLC by 1.35-fold (OR = 1.35; 95 % CI = 1.01–1.81, P = 0.019) in the Norwegian population.

A study on South Indian population revealed that IL-10-1082 G/G polymorphism was significantly associated with NSCLC [51] as depicted in Table 1. The GG-genotype was correlated with 1.68-fold increased NSCLC risk (OR = 1.68; 95 % CI = 1.11–2.29; P = 0.01). Furthermore, the IL-10-1082 G/G polymorphisms showed two-fold increased risk among patients who were smokers. However, (rs3021094), an intronic SNP of IL-10 was examined in a study [42] that showed a decreased susceptibility towards NSCLC. The GG-genotype (rs3021094) was associated with a 0.46-fold decreased risk of NSCLC (OR = 0.46; 95 % CI = 0.29–0.72; P < 0.001).

3.3.6. IL-18

IL-18-607 A/C polymorphism has established a significant association with the risk of NSCLC in Chinese population [52]. The results showed that the AA/AC-genotype distribution in NSCLC patients was significantly higher (P = 0.02). On the other hand, the minor G-allele of IL-18 (rs5744256) and (rs1834481) were correlated with decreased risk of NSCLC (P < 0.05), whereas, in contrast, the minor T-allele (rs5744224) was correlated with an increased risk of NSCLC (P < 0.05) [42]. GG-genotype (rs5744256) exhibited a 0.59-fold decreased NSCLC risk (OR = 0.59: 95 % CI = 0.37–0.95; P = 0.040) and AG-genotype exhibited a 0.79-fold decreased NSCLC risk (OR = 0.79; 95 % CI = 0.61–1.02; P = 0.040). The GG-genotype (rs1834481) exhibited a 0.56-fold decreased NSCLC risk (OR = 0.56; 95 % CI = 0.34–0.93; P = 0.022) and CG-genotype exhibited a 0.76-fold decreased NSCLC risk (OR = 0.76; 95 % CI = 0.59–0.99; P = 0.022). Besides, TT-genotype (rs5744224) exhibited a 1.45-fold increased NSCLC risk (OR = 1.45; 95 % CI = 1.01–2.08; P = 0.014) whereas the AT-genotype exhibited a 0.89-fold decreased NSCLC risk (OR = 0.89; 95 % CI = 0.67–1.19; P = 0.014).

3.3.7. IL-6

Metwally et al. [48] also investigated on IL-6 (rs1800795) to the risk of NSCLC in genetic models. It is revealed that (rs1800795) CC + GC genotypes amplified the NSCLC risk in the dominant model (adjusted, OR = 2.34, 95 % CI = 1.17–4.6; P = 0.015), and GC genotype raised the NSCLC risk in the overdominant model (adjusted, OR 2.1 95 % CI = 1.06–4.27; P = 0.033). Under the allele model, the mutant C allele significantly increased NSCLC risk by 2.28-fold (adjusted, OR 2.28, 95 % CI = 1.2–4.33; P = 0.011).

3.4. HLA and receptors

HLA-G has recently gained popularity among the immunosuppressive molecules expressed by various cancer cells contributing to their immune escape [53]. The HLA-G gene contains at least 35 SNPs [54] with three polymorphisms, −716 T/G (rs2249863), −725 C/G/T (rs1233334), −964 G/A (rs1632947) that are widely known as functional polymorphisms. Wisniewski et al. [55] reported that only −964 A/G demonstrated a significant difference where GG-genotype increases the NSCLC likelihood by 1.31-fold (OR = 1.31; 95 % CI = 0.88–1.95; P = 0.0392) while GA-genotype reduces the NSCLC likelihood by 0.84-fold (OR = 0.84; 95 % CI = 0.59–1.2; P = 0.03892).

Nevertheless, no significant correlations were found between NSCLC and −725 C/G/T or −716 T/G among Polish patients [56]. −716 GG and GT-genotype decreases the likelihood of NSCLC by 0.75-fold (OR = 0.75; 95 % CI = 0.42–1.34; P = 0.2998) and by 0.74-fold (OR = 0.74; 95 % CI = 0.46–1.19; P = 0.2998), respectively. But it is regarded as not significant based on the p-values. Besides, the −725 GG/GT-genotype increases the risk of NSCLC by 2.62-fold (OR = 2.62; 95 % CI = 0.69–9.96) whereas the CT/CG-genotype also increases the NSCLC risk by 1.06-fold (OR = 1.06; 95 % CI = 0.68–4.09). However, the p-value for all comparisons of HLA-G polymorphisms was non-significant (P = 0.3623).

This result was supported by Wisniewski et al. [55], where the global P value for −716 and −725 HLA-G polymorphisms was non-significant (P = 0.062) in Polish population. The −716 GT-genotype exhibits a 0.86-fold decreased NSCLC risk (OR = 0.86; 95 % CI = 0.61–1.23) whereas TT-genotype exhibits a 1.29-fold increased NSCLC risk (OR = 1.29; 95 % CI = 0.87–1.93), but both genotypes are not significant (P = 0.0681). Besides, −725 GG-genotype exhibits a 2.5-fold increased NSCLC risk (OR = 2.5; 95 % CI = 0.59–10.57) while the GT-genotype exhibits a 4.5-fold increased NSCLC risk (OR = 4.5; 95 % CI = 0.47–43.54), but both genotypes are also not significant (P = 0.4641). −725 CG-genotype exhibited increased risk of NSCLC by 1.01-fold (OR = 1.01; 95 % CI = 0.66–1.55), CT-genotype exhibited increased risk of NSCLC by 1.5-fold (OR = 1.5; 95 % CI = 0.70–3.21) and GC-genotype exhibited decreased risk of NSCLC by 0.96-fold (OR = 0.96; 95 % CI = 0.60–1.54). All these three genotypes are deemed to be non-significant (P = 0.4641).

The inhibitory receptor for HLA-G is killer cell immunoglobulin-like receptor 2DL4 (KIR2DL4) leukocyte immunoglobulin-like receptor B member 1 (LILRB1). LILRB1 (5724) G/A polymorphism was found to influence the risk of NSCLC [55]. GA-genotype exhibited 0.71-fold lower susceptibility of NSCLC (OR = 0.71; 95 % CI = 0.51–1.00; P = 0.0491). Similarly, AA-genotype exhibited a 0.67-fold lower susceptibility of NSCLC (OR = 0.67; 95 % CI = 0.17–2.70; P = 0.0491). A slight difference was also observed in the probability of patients' survival in LILRB1 (5724) G/A-genotypes, but the result was non-significant.

Furthermore, Wisniewski et al. [55] also studied the 9620 9A/10A (rs11410751) KIR2DL4 polymorphism. However, there were no effect observed to prove the prevalence of NSCLC with this polymorphism. This result was also supported by Falco et al. [57] where no correlation among individual KIR genes with NSCLC susceptibility was detected. In contrast to Ref. [57], KIR3DL2 (rs4487030) A/G SNP was found to be associated with better NSCLC survival by 0.84-fold (HR = 0.84; 95 % CI = 0.76–0.92, P < 0.001) [58]. Additional analyses suggested that genetic variants of KIR3DL2 may be potential prognostic marker for NSCLC survival.

3.5. APM genes

In recent years, transporter associated with antigen processing 1 (TAP1) and 2 (TAP2) have been reported to be associated with multiple cancer risks [59]. Liu et al. [60] investigated TAP1 and TAP2 SNPs association with NSCLC in Han Chinese population. Based on his results, none of the SNPs investigated in TAP1 was associated with NSCLC risk (P > 0.0038). However, TAP2 (rs2228396) alleles were found to be significantly different between NSCLC patients and healthy controls. The A-allele might be associated with an increased NSCLC risk by 1.65-fold (OR = 1.65; 95 % CI = 1.23–2.21; P = 0.001). These suggests A-allele and G/A-genotype as a potential risk factor for NSCLC. Additionally, TAP2 (rs241441) T/C-genotype was strongly linked to NSCLC with T-allele displaying increased NSCLC risk by 1.30-fold (OR = 1.30; 95 % CI = 1.06–1.60; P = 0.013) [60] as depicted in Table 1.

Three independent functional SNPs, endoplasmic reticulum aminopeptidase protein 1 (ERAP1) (rs469783) T/C, proteasome inhibitor subunit 1 (PSMF1) (rs13040574) C/A and neutrophil cytosolic factor 2 (NCF2) (rs36071574) G/A was found to remain

Table 1
Summary of the single nucleotide polymorphisms of immunomodulatory markers on the susceptibility of non-small cell lung carcinoma.

Gene	SNPs	Genotype/ Allele	Type of study	Study population	Type of specimen	Genotyping method	Odds Ratio (Confidence interval)	Cancer Risk	References
CTLA-4	+49 (rs231775) A/G	AA	Case-control study	Polish (Poland)	Lung tissue and peripheral blood	TaqMan PCR	0.41 (95 % CI = 0.21–0.78; p = 0.02)	DECREASED	[25])
		AG					1.16 (95 % CI = 0.62–2.21; p = 0.74)	NS	
		GG					2.23 (95 % CI = 1.17–4.48′ p = 0.015)	INCREASED	
	-318 (rs5742909) C/T	CC					0.96 (95 % CI = 0.91–1.82; p = 0.15)	NS	
		CT					0.66 (95 % CI = 0.34–1.28; p = 0.97)	NS	
		TT					1.53 (95 % CI = 0.81–2.89; p = 0.41)	NS	
	+49 (rs231775) A/G	G	Case-control study	Chinese (China)	Peripheral blood leukocytes	PCR-RFLP	1.15 (95 % CI = 0.97–1.36; p = 0.118)	NS	[27]
	−318 (rs5742909) C/T	T					0.74 (95 % CI = 0.53–1.04; p = 0.0085)	DECREASED	
PD-1	PD-1.5 + 7785 (rs2227981) C/T	CC	Population-based case-control study	Chinese Han (China)	Peripheral venous blood	PCR	2.40 (95 % CI = 1.37–4.24; p = 0.002)	INCREASED	[28]
		CT					2.22 (95 % CI = 1.23–4.02; p = 0.008)	INCREASED	
		CC + CT					2.34 (95 % CI = 1.35–4.06; p = 0.003)	INCREASED	
PD-L1	+8923 (rs2890658) A/C	AC	Case-control study	Chinese (China)	Peripheral blood leukocytes	PCR-RFLP	1.55 (95 % CI = 1.13–2.13; p = 0.006)	INCREASED	[27]
		CC					1.85 (95 % CI = 0.52–6.59; p = 0.345)	NS	
		C					1.52 (95 % CI = 1.14–2.04; p = 0.004)	INCREASED	
BTLA	rs1982809 G/A	AG + GG	Case-control study	Polish (Poland)	Blood	Taqman Probes - ViiA 7 Real-Time PCR System	1.304 (95 % CI = 0.99–1.71; p = 0.057)	INCREASED	[31]
		G					1.254 (95 % CI = 1.01–1.57; p = 0.046)	INCREASED	
		GA or GG		Chinese (China)	Peripheral blood	SNPscan kit	0.81 (95 % CI = 0.66–0.99; p = 0.043)	DECREASED	[30]
CXCL12/ SDF-1	SDF-1 G801A (rs1801157) G/A	AA	Hospital-based case-control study	Chinese Han (China)	Peripheral blood	RFLP	1.328 (95 % CI = 0.542–3.784; p = 0.0523)	NS	[33]
		GA					1.286 (95 % CI = 0.811–2.583; p = 0.361)	NS	
CXCR4	CXCR4-138 (rs2228014) T/T	AA	Case-control study	Chinese (Taiwan)	Venous blood	PCR-RFLP	1.95 (95 % CI = 1.08–3.50; p = 0.018)	INCREASED	[32]
		TT					4.71 (95 % CI = 1.99–11.2; p = <0.0001)	INCREASED	

(*continued on next page*)

Table 1 (*continued*)

Gene	SNPs	Genotype/ Allele	Type of study	Study population	Type of specimen	Genotyping method	Odds Ratio (Confidence interval)	Cancer Risk	References
MCP-1	MCP-1-2518 (rs1024611) A/G	AA	Case-control study	Chinese Han (China)	Peripheral blood leukocytes	PCR-RFLP	3.183 (95 % CI = 1.480–6.652; p = 0.003)	INCREASED	[34]
		GG					0.516 (95 % CI = 0.282–0.944; p = 0.032)	DECREASED	
		A					1.963 (95 % CI = 1.301–2.962; p = 0.001)	INCREASED	
		G					0.509 (95 % CI = 0.337–0.768; p = 0.001)	DECREASED	
IL-17A	IL-17A(rs8193037) G/A	GA	Case-control study	Chinese Han (China)	Whole blood	Primer-introduced restriction analysis–polymerase chain reaction (PIRA-PCR) assay	2.20 (95 % CI = 1.53–3.16; p = <0.001)	INCREASED	[37]
		AA					3.19 (95 % CI = 1.42–7.15; p = 0.003)	INCREASED	
	IL-17A-73 G/A	AA	Case-control study	Chinese (China)	Whole blood	NR	2.52 (95 % CI = 1.30–4.88; p = 0.005)	INCREASED	[38]
		GA					2.09 (95 % CI = 1.46–2.98; p = <0.001)	INCREASED	
IL-12B	IL-12B (+1188) (rs3212227) A/C	GG	Case-control study	Chinese Han (China)	Blood	Sequenom MassARRAY RS1000 (Sequenom, SanDiego, CA).	1.80 (95 % CI = 1.26–2.55; p = 0.003)	INCREASED	[42]
		GT					1.16 (95 % CI = 0.86–1.57; p = 0.003)	INCREASED	
IL-1B	IL-1B-31 (rs1143634) C/T	TT	Retrospective Case-control study	South Spanish Caucasians (Spain)	Blood and Saliva	TaqMan PCR	0.22 (95 % CI = 0.05–0.68; p = 0.013)	DECREASED	[44]
		CT					0.69 (95 % CI = 0.46–1.02; p = 0.013)	DECREASED	
	IL-1B-31 (rs1143627) C/T	TT	Case-control study	Chinese (China)	Peripheral blood	PCR-RFLP	3.247 (95 % CI = 1.794–5.878; p = 0.001)	INCREASED	[45]
		CT					2.157 (95 % CI = 1.295–3.593; p = 0.003)	INCREASED	
		TT	Observational study	Norwegian (Norway)	Whole blood or normal lung tissue	TaqMan-PCR	2.39 (95 % CI = 1.29–4.44; p = 0.01)	INCREASED	[46]
		CT					1.89 (95 % CI = 1.03–3.46; p = 0.01)	INCREASED	
	IL-1B-511 (rs16944) T/C	CC					2.51 (95 % CI = 1.47–4.58; p = <0.01)	INCREASED	
		CT					1.91 (95 % CI = 1.06–3.40; p = <0.01)	INCREASED	
		TT + CT	Case-control study	Egyptians (Egypt)	Blood	ARMS-PCR	0.17 (95 % CI = 0.05–0.59; p = 0.005)	DECREASED	[48]
		TT + CC					0.15 (95 % CI = 0.05–0.44; p = 0.001)	DECREASED	

(*continued on next page*)

Table 1 (*continued*)

Gene	SNPs	Genotype/ Allele	Type of study	Study population	Type of specimen	Genotyping method	Odds Ratio (Confidence interval)	Cancer Risk	References
		CT					= 0.16 (95 % CI = 0.05–0.56; p = 0.004)	DECREASED	
	IL-1B-3893 (rs1261220) G/A	GA	Case-control study	Chinese (China)	Peripheral blood	SNPscanTM Genotyping system	0.96 (95 % CI = 0.77–1.20; p = 0.74)	NS	[47]
		AA					1.01 (95 % CI = 0.75–1.37; p = 0.95)	NS	
	IL-1B-1464 (rs1143623) G/C	GC					0.90 (95 % CI = 0.72–1.12; p = 0.32)	NS	
		CC					0.99 (95 % CI = 0.74–1.34; p = 0.96)	NS	
	IL-1B-511 (rs16944) T/C	CC					1.05 (95 % CI = 0.79–1.38; p = 0.75)	NS	
		TC					0.95 (95 % CI = 0.74–1.23; p = 0.71)	NS	
	IL-1B-31 (rs1143627) C/T	TT					1.09 (95 % CI = 0.82–1.46; p = 0.54)	NS	
		CT					0.98 (95 % CI = 0.75–1.26; p = 0.85)	NS	
IL-10	IL-10-1082 (rs1800896) G/A	G	Case-control study	Chinese (Taiwan)	Venous blood	PCR-RFLP	5.26 (95 % CI = 2.65–10.4; p = <0.0001)	INCREASED	[49]
	IL-10-819 (rs1800871) C/T	C					1.57 (95 % CI = 1.15–2.16; p = 0.005)	INCREASED	
	IL-10-592 (rs1800872) C/A	C	Case-control study	Norwegian (Norway)	Whole blood or normal lung tissue	TaqMan genotyping assays	1.59 (95 % CI = 1.15–2.19; p = 0.005)	INCREASED	[50]
		A					1.35 (95 % CI = 1.01–1.81; p = 0.019)	INCREASED	
	IL-10-1082 (rs1800896) G/A	GG	Case-control study	South Indian (India)	Whole blood	Amplification refractory mutation system polymerase chain reaction (ARMS PCR)	1.68 (95 % CI = 1.11–2.29; p = 0.01)	INCREASED	[51]
	IL-10 (rs3021094) G/T	GG	Case-control study	Chinese Han (China)	Blood	Sequenom MassARRAY RS1000 (Sequenom, SanDiego, CA)	0.46 (95 % CI = 0.29–0.72; p = <0.001)	DECREASED	[42]
IL-18	IL-18 (rs5744256) G/A	GG	Case-control study	Chinese Han (China)	Blood	Sequenom MassARRAY RS1000 (Sequenom, SanDiego, CA).	0.59 (95 % CI = 0.37–0.95; p = 0.040)	DECREASED	[42]
		AG					0.79 (95 % CI = 0.61–1.02; p = 0.040)	DECREASED	
	IL-18 (rs1834481) G/C	GG					0.56 (95 % CI = 0.34–0.93; p = 0.022)	DECREASED	
		CG					0.76 (95 % CI = 0.59–0.99; p = 0.022)	DECREASED	
	IL-18 (rs5744224) T/A	TT					1.45 (95 % CI = 1.01–2.08; p = 0.014)	INCREASED	
		AT					0.89 (95 % CI = 0.67–1.19; p = 0.014)	DECREASED	
IL-6	rs1800795	CC + GC	Case-control study	Egyptians (Egypt)	Blood	ARMS-PCR	2.34 (95 % CI = 1.17–4.6; p = 0.015)	INCREASED	[48]
		GC					2.1 (95 % CI = 1.06–4.27; p = 0.033	INCREASED	

(*continued on next page*)

Table 1 (*continued*)

Gene	SNPs	Genotype/ Allele	Type of study	Study population	Type of specimen	Genotyping method	Odds Ratio (Confidence interval)	Cancer Risk	References
		G					2.28 (95 % CI = 1.2–4.33; p = 0.011	INCREASED	
HLA-G	−964 (rs1632947) A/G	GG	Case-control study	Polish (Poland)	Venous blood	Applied Biosystems (Foster City, CA) ready-made Assay-on Demand	1.31 (95 % CI = 0.88–1.95; p = 0.0392)	INCREASED	[55]
		GA					0.84 (95 % CI = 0.59–1.2; p = 0.0392)	DECREASED	
	−716 (rs2249863) T/G	GT				TaqMan PCR	0.86 (95 % CI = 0.61–1.23; p = 0.0681)	NS	
		TT					1.29 (95 % CI = 0.87–1.93; p = 0.0681)	NS	
	−725 (rs1233334) C/G/T	GG					2.5 (95 % CI = 0.59–10.57; p = 0.4641)	NS	
		GT					4.5 (95 % CI = 0.47–43.54; p = 0.4641)	NS	
		CG					1.01 (95 % CI = 0.66–1.55; p = 0.4641)	NS	
		CT					1.5 (95 % CI = 0.70–3.21; p = 0.4641)	NS	
		GC					0.96 (95 % CI = 0.60–1.54; p = 0.4641)	NS	
	−716 (rs2249863) T/G	GG	Case-control study	Polish Caucasian (Poland)	Whole blood leukocytes	PCR	0.75 (95 % CI = 0.42–1.34; p = 0.2998)	NS	[56]
		GT					0.74 (95 % CI = 0.46–1.19; p = 0.2998)	NS	
	−725 (rs1233334) C/G/T	GG or GT					2.62 (95 % CI = 0.69–9.96; p = 0.3623)	NS	
		CT or CG					1.06 (95 % CI = 0.68–4.09; p = 0.3623)	NS	
LILRB1	LILRB1 (5724) (rs16985478) G/A	GA	Case-control study	Polish (Poland)	Venous blood	NR	0.71 (95 % CI = 0.51–1.00; p = 0.0491)	DECREASED	[55]
		AA					0.67 (95 % CI = 0.17–2.70; p = 0.0491)	DECREASED	
TAP 2	(rs2228396) G/A	A	Case-control study	Chinese (China)	Peripheral blood	TaqMan - PCR	1.65 (95 % CI = 1.23–2.21; p = 0.001)	INCREASED	[60]

(*continued on next page*)

Table 1 (*continued*)

Gene	SNPs	Genotype/ Allele	Type of study	Study population	Type of specimen	Genotyping method	Odds Ratio (Confidence interval)	Cancer Risk	References
	(rs241441) T/C	T					1.30 (95 % CI = 1.06–1.60; p = 0.013)	INCREASED	
ERAP1	rs26653 G/C	GC (smokers)	Case-control study	Polish (Poland)	Whole blood	TaqMan SNP Genotyping Assay - PCR	1.01 (95 % CI = 0.69–1.47; p = 0.011)	INCREASED	[59]
		CC (smokers)					2.56 (95 % CI = 1.07–10.1; p = 0.011)	INCREASED	
		GC (non-smokers)					0.51 (95 % CI = 0.25–0.97; p = 0.011)	DECREASED	
		CC (non-smokers)					0.42 (95 % CI = 0.06–1.17; p = 0.011)	DECREASED	

Table 2
Summary of the single nucleotide polymorphisms of immunomodulatory markers on the survival of non-small cell lung carcinoma.

Gene	SNPs	Genotype/ Allele	Type of study	Study population	Type of specimen	Genotyping method	Treatment	Survival (OS/PFS/ DSS) – Hazard Ratio	Cancer survival	References
CTLA-4	NA	AA	Observational study	Northen Chinese (China)	Peripheral blood	PCR-RFLP	Platinum-based chemo-therapy (270), Radiotherapy [20], Radiotherapy and chemo-therapy [23], Treatment by other methods or no treatment [15]	1.6 (95 % CI = 1.3–1.9; p = 0.001)	DECREASED	[26]
BTLA	rs1982809 G/ A	AA	Case-control study	Polish (Poland)	Blood	Taqman Probes - ViiA 7 Real-Time PCR System	NA	OS - 1.52 (95 % CI = 1.12–2.07; p = 0.01)	INCREASED	[31]
CXCL12/ SDF-1	rs1804429 A/ C	CC	Prospective study	Chinese (China)	Venous blood leukocytes	Illumina GoldenGate Assay	NA	6.03 (95 % CI = 1.44–25.24)	NC	[11]
		AC						1.23 (95 % CI = 0.88–1.73)	NC	
CCL2	−972 (rs3760396) G/C	CC				PCR-RFLP genotyped by using the Illumina GoldenGate platform		0.80 (95 % CI = 0.25–2.62)	NC	
		CG						0.64 (95 % CI = 0.47–0.88)	NC	
		CC or CG						0.65 (95 % CI = 0.48–0.89)	NC	
	NA	NA	Case-control study	Chinese (China)	NSCLC tissue specimens	NA	No treatment received	SCC (OS) – p = 0.048 AC (OS) – p = 6.7e08 SCC (PFS) – p = 0.012 AC (PFS) – p = 0.00098	INCREASED INCREASED DECREASED DECREASED	[36]
CCL8	rs3138035 A/ G	AA	Prospective study	Chinese (China)	Venous blood leukocytes	Illumina GoldenGate Assay	NR	0.99 (95 % CI = 0.36–2.70)	NC	[11]
		AG						0.63 (95 % CI = 0.47–0.85)	NC	
		AA or AG						(95 % CI = 0.49–0.86)	NC	
IL-16	rs7170924 G/ T	GG	Prospective cohort study	South Spanish Caucasian (Spain)	Blood	TaqMan RT-PCR	No treatment received	OS – 1.82 (95 % CI = 1.13–2.94; p = 0.0139) PFS – 1.42 (95 % CI = 0.97–2.09; p = 0.073)	DECREASED NS	[40]
			Prospective study	Hispanic/Latino	Peripheral blood	Illumina GoldenGate Assay	Surgery and adjuvant chemo-therapy	DFS – 0.65 (95 % CI = 0.50–0.83)	NC	[41]
IL-12A	rs662959 C/T	TT	Prospective cohort study	South Spanish Caucasian (Spain)	Blood	TaqMan RT-PCR	No treatment received	PFS – 4.49 (95 % CI = 1.06–18.99; p = 0.0412)	INCREASED	[40]

(*continued on next page*)

Table 2 (*continued*)

Gene	SNPs	Genotype/ Allele	Type of study	Study population	Type of specimen	Genotyping method	Treatment	Survival (OS/PFS/ DSS) – Hazard Ratio	Cancer survival	References
KIR3DL2	rs4487030 A/ G	A/G	GWAS genotyping dataset of (PLCO) (HLCS)	PLCO – United States HLCS (Caucasian)	Whole blood	Illumina HumanHap240Sv1.0 and HumanHap 550v3.0	Intervention arm: Trial Screening for PLCO cancers Control arm: Routine medical care	OS – 0.84 (95 % CI = 0.76–0.92; p = <0.001)	INCREASED	[58]
ERAP1	rs469783 T/C	C	GWAS genotyping dataset of (PLCO)	PLCO (European descent) - United States	Whole blood	Illumina HumanHap240Sv1.0 and HumanHap 550v3.0	Intervention arm: Trial Screening for PLCO Control arm: Routine medical care	OS – 0.65 (95 % CI = 0.52–0.80; p = <0.001) DSS – 0.64 (95 % CI = 0.51–0.81; p = 0.0002)	INCREASED DECREASED	[61]
PSMF1	rs1304057 C/ A	A						OS – 0.75 (95 % CI = 0.61–0.92; p = 0.007) DSS – 0.76 (95 % CI = 0.61–0.95; p = 0.015)	INCREASED DECREASED	
NCF2	rs3607157 G/ A	A						OS – 2.35 (95 % CI = 0.87–6.38; p = 0.093) DSS – 2.68 (95 % CI = 0.99–7.29; p = 0.053)	NS NS	

NC indicates not conclusive as the p-value is not provided.
NS indicates not significant.
*Indicates P is less than 0.05.
**Indicates P is less than 0.01.

significant for OS [61]. Patients with ERAP1, C-genotype was associated with better survival by 0.65-fold (HR = 0.65; 95 % CI = 0.52–0.80; P < 0.0001) and by 0.64-fold (HR = 0.64; 95 % CI = 0.51–0.81; P = 0.0002) for disease-specific survival (DSS). PSMF1 A-genotype carriers was also associated with better survival by 0.75-fold (HR = 0.75; 95 % CI = 0.61–0.92 and P = 0.007) and by 0.76-fold (HR = 0.76; 95 % CI = 0.61–0.95, P = 0.015) for DSS. In contrast, NCF2 A-genotype was associated to poor survival by 2.35-fold (HR = 2.35; 95 % CI = 0.87–6.38; P = 0.093) and by 2.68-fold (HR = 2.68; 95 % CI = 0.99–7.29; P = 0.053) for DSS as depicted in Table 2.

Wisniewski et al. [59] discovered that GC-genotype had the same risk with GG-genotype carriers which showed increased NSCLC risk by 1.01-fold (OR = 1.01; 95 % CI = 0.69–1.47; P = 0.011) in the smokers' group for ERAP1 (rs26653). However, individuals with CC-genotype exhibited a 2.56-fold higher risk of NSCLC (OR = 2.56; 95 % CI = 1.07–10.1; P = 0.011). In never-smokers group, CC-genotype carriers exhibited a 0.42-fold decreased NSCLC risk (OR = 0.42; 95 % CI = 0.06–1.17; P = 0.011) and GC-genotype carriers exhibited a 0.51-fold decreased NSCLC risk (OR = 0.51; 95 % CI = 0.25–0.97; P = 0.011). This concludes that there is a significant relationship between (rs26653) GC-genotype with NSCLC and is dependent on the smoking status.

4. Implication and clinical relevance

This review delves into the intricate landscape of immunomodulatory gene polymorphisms in NSCLC, revealing noteworthy insights into their association with both susceptibility to NSCLC and prognosis outcomes. The concise findings outlined in this review, as elucidated through Tables 1 and Table 2 quantifies the magnitude of these associations. Moreover, it also emphasizes the clinical relevance of the identified genetic variations, shedding light on their potential implications for understanding and managing NSCLC.

The meticulous analysis of existing literatures has pinpointed significant associations with immune checkpoints, chemokines and interleukins towards NSCLC risk. The identification of SNPs in immunomodulatory markers, as highlighted in this review, emerges as a promising avenue for the exploration of potential predictive biomarkers for NSCLC [62]. Certain genetic variations in *CTLA-4 (rs231775), PD-1.5 (rs2227981), PD-L1 (rs2890658), SDF-1 (rs1801157), CXCR4 (rs2228014), MCP-1 (rs1024511), IL-17A (rs8193037), IL-17A-73, IL-12B (rs3212227), IL-1B-31 (rs1143627), IL-1B-511 (rs16944), IL-10-1082 (rs1800896), IL-10-819 (rs1800871), IL-10-592 (rs1800872), IL-18 (rs5744224), IL-6 (rs1800795), HLA-G (rs1632947), TAP 2 (rs2228396), TAP 2 (rs241441)* and *ERAP 1 (rs26653)* may potentially act as biomarkers associated with an increased risk of developing NSCLC (Fig. 2).

By studying these polymorphisms, researchers can identify specific markers indicating susceptibility to the disease, therefore facilitating early detection. Moreover, the comprehension of these markers also aids in stratifying individuals into distinct risk groups. Individuals with an elevated genetic risk can be subjected to more vigilant monitoring, allowing for earlier detection through imaging or alternative screening techniques. Additionally, individuals in this high-risk category can also be advised and receive guidance on lifestyle modifications or interventions aimed at diminishing their overall risk or detecting the disease at an earlier, more treatable stage. These biomarkers serve as valuable indicators for risk stratification and preventive strategies, providing clinicians with insights for more efficacious patient management [63].

Immunomodulatory gene polymorphisms can impact the response to specific treatments, including immunotherapies and targeted

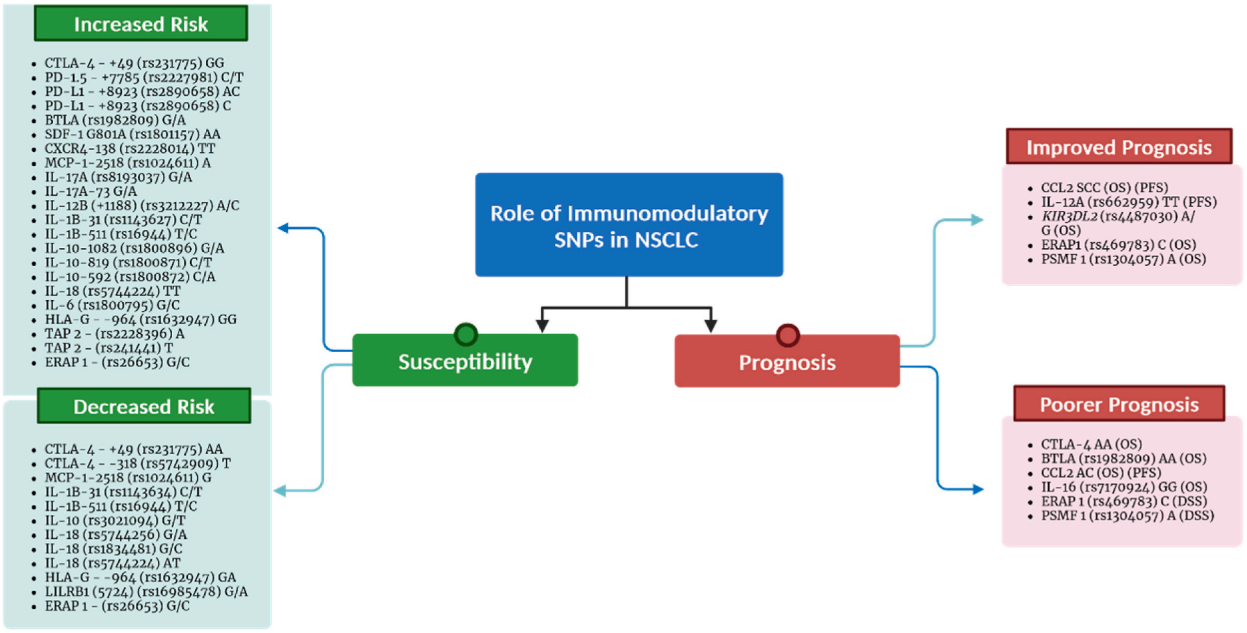

Fig. 2. Role of immunomodulatory single nucleotide polymorphisms in NSCLC. The figure shows respective restriction sites and alleles of immunomodulatory single nucleotide polymorphism associated with susceptibility and prognosis of NSCLC (created with BioRender.com).

therapies. Knowledge of these polymorphisms allows for more accurate and precise predictions regarding how an individual patient might respond to various treatment modalities. This review underscores certain genetic variations in *CTLA-4, BTLA (rs1982809), CCL2, IL-12A (rs662959), IL-16 (rs7170924), KIR3DL2 (rs4487030), ERAP 1 (rs469783)* and *PSMF1 (rs1304057)* displayed significant association to OS, PFS and DSS rates in NSCLC (Fig. 2). Patients harbouring specific polymorphisms may experience a more favourable or unfavorable prognosis, offering valuable information for clinicians to tailor their treatment plans for patients. In early-stage disease, the identification of specific polymorphisms facilitates personalized medical care by guiding treatment decisions based on the patient's genetic profile. For advanced-stage NSCLC, this knowledge guides the selection of targeted therapies, optimizing the likelihood of a more effective response and ultimately improving overall patient outcomes. The integration of genetic information into clinical care enhances precision and individualization in managing both early and advanced stages of NSCLC. Customising treatment measures based on individual genetic profiles may optimise therapeutic outcomes, marking a significant advancement in precision medicine for NSCLC.

5. Conclusion and future perspectives

The human genome is highly polymorphic, and a vast number of genetic polymorphisms have been identified as potential biomarkers for lung cancer susceptibility and prognosis. The analysis of available literatures depicted that some of the SNPs in the immunomodulatory genes, especially *CTLA-4, PD-1.5, PD-L1, SDF-1, IL-17, IL-1B, IL-10, IL-8, HLA-G* and *TAP 2* are associated with higher susceptibility towards NSCLC. Conversely, SNPs in *IL-12A, KIR3DL2, ERAP 1,* and *PSMF 1* demonstrate a correlation with better survival and prognosis. While this review sheds light on the crucial role of immunomodulatory gene polymorphisms in NSCLC, further research avenues beckon for more comprehensive and improved understanding of clinical applications.

In light of the inconclusive results of some investigations, future studies with larger sample sizes and stringent methodologies are needed to replicate, validate and minimize the lack of uniformity and bias in the study design and results analysis. Besides, it is crucial to acknowledge that genetic variations may serve as risk factors for a disease in one population but not necessarily in others, as the genotype and allele frequencies vary across different ethnic and geographical populations. Given the relevance of association between specific immunomodulatory SNPs and cancer risk to populations, there is an urgent imperative to conduct well-designed, large-scale studies across diverse populations. This becomes particularly essential in elucidating variants that play a significant role in risk estimation and the selection of patients for immunotherapy based on the genetic variation in specific ethnicities. It is crucial for investigators to conduct a thorough analysis of SNPs spanning the entire genes of interest. This comprehensive SNP analysis will facilitate the evaluation of phenotypic effects of specific haplotypes on immunomodulatory genes, allowing for an assessment whether a particular haplotype is linked to a higher or lower risk of NSCLC development and survival.

Future investigations could possibly delve into elucidating the functional consequences of identified gene variations and SNPs, aiming to explore their impact on immune responses, dynamics within the TME and potential interactions with emerging therapeutic modalities. Additionally, the integration of high-throughput technologies such as, genomics, transcriptomic and proteomics, holds the potential to unveil intricate molecular networks among these gene variation as well as uncover novel genes and SNPs contributing to NSCLC heterogeneity. These prospective endeavours carry the promise of refining risk stratification, enhancing personalized treatment strategies, and improving patient outcomes. It is also important to highlight that genetic predisposition to NSCLC constitute just one facet of the disease's risk factor. The interplay among genetic, environmental and lifestyle factors can influence the susceptibility and survival to the NSCLC.

In conclusion, this review underscores the critical role of genetic polymorphisms in immunomodulatory markers within NSCLC. Recognizing the interplay between individual genetic variations and immune response is essential, particularly in the context of the evolving landscape of NSCLC treatment towards immunotherapy. The exploration of genetic polymorphisms in genes modulating the immune response offers vital insights into the associated risk, prognosis, and survival outcomes in NSCLC. Despite the wealth of studies on NSCLC risk and survival, this review is the first to comprehensively examine SNPs in genes influencing the immune response in NSCLC. Uncovering evidence on genetic factors associated with NSCLC not only enhances our understanding of disease pathogenesis and progression but also holds promise for refining prognosis and tailoring clinical care for both early and advanced-stage NSCLC. This comprehensive analysis contributes to the broader initiatives aimed at advancing personalized medicine in the realm of lung cancer.

Disclosure statement

The authors declare no conflict of interest.

Funding

This study was funded by Fundamental Research Grant Scheme (FRGS/1/2019/SKK02/TAYLOR/03/2) from Ministry of Higher Education Malaysia.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Vithiya Dewarajan: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Nourhan Elsayed:** Validation, Investigation, Data curation. **Jhi Biau Foo:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Yin Sim Tor:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Sze Shin Low:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Wai Siong Chai:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Fundamental Research Grant Scheme (FRGS/1/2019/SKK02/TAYLOR/03/2) for the funding. This work was supported by Taylor's University through Taylor's Research Scholarship programme and Taylor's University Publication Fee Funding.

References

[1] J. Jia, B. Huang, Z. Zhuang, Sen Chen, Circulating tumor DNA as prognostic markers for late stage NSCLC with bone metastasis, Int. J. Biol. Markers 33 (2) (2018) 222–230, https://doi.org/10.1177/1724600817753576.
[2] M. D'Arcangelo, A. D'Incecco, C. Ligorio, S. Damiani, M. Puccetti, S. Bravaccini, L. Terracciano, C. Bennati, G. Minuti, S. Vecchiarelli, L. Landi, M. Milesi, A. Meroni, S. Ravaioli, M.M. Tumedei, M. Incarbone, F. Cappuzzo, Programmed death ligand 1 expression in early stage, resectable non-small cell lung cancer, Oncotarget 10 (5) (2019) 561–572, https://doi.org/10.18632/oncotarget.26529.
[3] A.R. Gibbs, F. Thunnissen, Histological typing of lung and pleural tumours: Third edition, J. Clin. Pathol. 54 (7) (2001) 498–499, https://doi.org/10.1136/jcp.54.7.498.
[4] S. Couraud, G. Zalcman, B. Milleron, F. Morin, P.J. Souquet, Lung cancer in never smokers – a Review, Eur. J. Cancer 48 (9) (2012) 1299–1311, https://doi.org/10.1016/j.ejca.2012.03.007.
[5] S.A. Kenfield, E.K. Wei, G.A. Colditz, M.J. Stampfer, B.A. Rosner, Comparison of aspects of smoking among four histologic types of lung cancer, Tobac. Control 17 (3) (2008) 198–204, https://doi.org/10.1136/tc.2007.022582.
[6] R. Sachidanandam, D. Weissman, S.C. Schmidt, J.M. Kakol, L.D. Stein, G. Marth, S. Sherry, J.C. Mullikin, B.J. Mortimore, D.L. Willey, S.E. Hunt, C.G. Cole, P. C. Coggill, C.M. Rice, Z. Ning, J. Rogers, D.R. Bentley, P.Y. Kwok, E.R. Mardis, D. Altshuler, A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms, Nature 409 (6822) (2001) 928–933, https://doi.org/10.1038/35057149.
[7] Y. Liu, G. Zeng, Cancer and innate immune system interactions, J. Immunother. 35 (4) (2012) 299–308, https://doi.org/10.1097/cji.0b013e3182518e83.
[8] S. Marwitz, S. Scheufele, S. Perner, M. Reck, O. Ammerpohl, T. Goldmann, Epigenetic modifications of the immune-checkpoint genes CTLA4 and PDCD1 in non-small cell lung cancer results in increased expression, Clin. Epigenet. 9 (1) (2017), https://doi.org/10.1186/s13148-017-0354-2.
[9] K. Dhatchinamoorthy, J.D. Colbert, K.L. Rock, Cancer immune evasion through loss of MHC class I antigen Presentation, Front. Immunol. 12 (2021), https://doi.org/10.3389/fimmu.2021.636568.
[10] M. Razmkhah, A.-R. Talei, M. Doroudchi, T. Khalili-Azad, A. Ghaderi, Stromal cell-derived factor-1 (SDF-1) alleles and susceptibility to breast carcinoma, Cancer Lett. 225 (2) (2005) 261–266, https://doi.org/10.1016/j.canlet.2004.10.039.
[11] H. Ma, Y. Shu, S. Pan, J. Chen, J. Dai, G. Jin, Z. Hu, H. Shen, Polymorphisms of key chemokine genes and survival of non-small cell lung cancer in Chinese, Lung Cancer 74 (2) (2011) 164–169, https://doi.org/10.1016/j.lungcan.2011.03.005.
[12] E.M. Silva, V.S. Mariano, P. Pastrez, M.C. Pinto, A.G. Castro, K.J. Syrjanen, A. Longatto-Filho, High systemic IL-6 is associated with worse prognosis in patients with non-small cell lung cancer, PLoS One 12 (7) (2017) e0181125, https://doi.org/10.1371/journal.pone.0181125.
[13] A. Dutkowska, B. Szmyd, M. Kaszkowiak, D. Domanska-Senderowska, D. Pastuszak-Lewandoska, E. Brzezianska-Lasota, J. Kordiak, A. Antczak, Expression of inflammatory interleukins and selected mirnas in non-small cell lung cancer, Sci. Rep. 11 (1) (2021), https://doi.org/10.1038/s41598-021-84408-1.
[14] R. Park, M. Winnicki, E. Liu, W.M. Chu, Immune checkpoints and cancer in the immunogenomics ERA, Briefings in Functional Genomics 18 (2) (2018) 133–139, https://doi.org/10.1093/bfgp/ely027.
[15] A.H. Sharpe, E.J. Wherry, R. Ahmed, G.J. Freeman, The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection 8 (3) (2007) 239–245, https://doi.org/10.1038/ni1443.
[16] M. Locati, K. Otero, T. Schioppa, P. Signorelli, P. Perrier, S. Baviera, S. Sozzani, A. Mantovani, The chemokine system: Tuning and shaping by regulation of receptor expression and coupling in polarized responses, Allergy 57 (11) (2002) 972–982, https://doi.org/10.1034/j.1398-9995.2002.02166.
[17] N. Nagarsheth, M.S. Wicha, W. Zou, Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy, Nat. Rev. Immunol. 17 (9) (2017) 559–572, https://doi.org/10.1038/nri.2017.49.
[18] D. Briukhovetska, J. Dorr, S. Endres, P. Libby, C.A. Dinarello, S. Kobold, Interleukins in cancer: from biology to therapy, Nat. Rev. Cancer 21 (8) (2021) 481–499, https://doi.org/10.1038/s41568-021-00363-z.
[19] S. Setrerrahmane, H. Xu, Tumor-related interleukins: Old validated targets for new anti-cancer drug development, Mol. Cancer 16 (1) (2017), https://doi.org/10.1186/s12943-017-0721-9.
[20] J. Wolf, S. Rose-John, C. Garbers, Interleukin-6 and its receptors: a highly regulated and Dynamic System, Cytokine 70 (1) (2014) 11–20, https://doi.org/10.1016/j.cyto.2014.05.024.
[21] A.M. Fulton, The chemokine receptors CXCR4 and CXCR3 in cancer, Curr. Oncol. Rep. 11 (2) (2009) 125–131, https://doi.org/10.1007/s11912-009-0019-1.
[22] Y. Li, S. Liu, C. Hong, Q. Ma, F. Tan, C. Liu, P. Kusnierczyk, C. Li, L. Shi, Y. Yao, The association of *HLA/kir* genes with non-small cell lung cancer (adenocarcinoma) in a Han Chinese population, J. Cancer 10 (20) (2019) 4731–4738, https://doi.org/10.7150/jca.33566.
[23] P. Leone, E.C. Shin, F. Perosa, A. Vacca, F. Dammacco, V. Racanelli, MHC class I antigen processing and presenting machinery: organization, function, and defects in tumor cells, J. Natl. Cancer Inst. 105 (16) (2013) 1172–1187, https://doi.org/10.1093/jnci/djt184.
[24] A.M. Mehta, E.S. Jordanova, T. van Wezel, H.W. Uh, W.E. Corver, K.M. Kwappenberg, W. Verduijn, G.G. Kenter, S.H. van der Burg, G.J. Fleuren, Genetic variation of antigen processing machinery components and association with cervical carcinoma, Gene Chromosome Cancer 46 (6) (2007) 577–586, https://doi.org/10.1002/gcc.20441.
[25] A. Antczak, D. Pastuszak-Lewandoska, P. Gorski, D. Domanska, M. Migdalska-Sek, K. Czarnecka, E. Nawrot, J. Kordiak, E. Brzezianska, CTLA-4 expression and polymorphisms in lung tissue of patients with diagnosed non-small-cell lung cancer, BioMed Res. Int. (2013) 1–8, https://doi.org/10.1155/2013/576486.
[26] B. Song, Y. Liu, J. Liu, X. Song, Z. Wang, M. Wang, Y. Zhu, J. Han, CTLA-4 +49A>G polymorphism is associated with advanced non-small cell lung cancer prognosis, Respiration 82 (5) (2011) 439–444, https://doi.org/10.1159/000329345.

[27] Y. Ma, X. Liu, J. Zhu, W. Li, L. Guo, X. Han, B. Song, S. Cheng, L. Jie, Polymorphisms of co-inhibitory molecules (CTLA-4/PD-1/PD-L1) and the risk of non-small cell lung cancer in a Chinese population, Int. J. Clin. Exp. Med. 8 (9) (2015) 16585–16591.

[28] L. Yin, H. Guo, L. Zhao, J. Wang, The programmed death-1 gene polymorphism (PD-1.5 C/T) is associated with non-small cell lung cancer risk in a Chinese han population, Int. J. Clin. Exp. Med. 7 (12) (2014) 5832–5836.

[29] Z. Piredelkhosh, T. Kazemi, M. Haghshenas, M. Ghayumi, N. Erfani, Investigation of programmed cell death-1 (PD-1) gene variations at positions PD1.3 and PD1.5 in Iranian patients with non-small cell lung cancer, Middle East Journal of Cancer 9 (1) (2018) 13–17, https://doi.org/10.30476/mejc.2018.42095.

[30] J. Wang, Z. Chen, R. Cao, Q. Zhang, T. Chen, C. You, W. Tang, S. Chen, Association of *BTLA* polymorphisms with susceptibility to non-small-cell lung cancer in the Chinese population, BioMed Res. Int. (2021) 9121824, https://doi.org/10.1155/2021/9121824.

[31] A. Andrzejczak, A. Partyka, A. Wisniewski, I. Porebska, K. Pawelczyk, K. Ptaszkowski, P. Kusnierczyk, M. Jasek, L. Karabon, The Association of BTLA gene polymorphisms with non-small lung cancer risk in smokers and never-smokers, Front. Immunol. 13 (2023), https://doi.org/10.3389/fimmu.2022.1006639.

[32] Y.L. Lee, W.H. Kuo, C.W. Lin, W. Chen, W.E. Cheng, S.C. Chen, C.M. Shih, Association of genetic polymorphisms of CXCL12/SDF1 gene and its receptor, CXCR4, to the susceptibility and prognosis of non-small cell lung cancer, Lung Cancer 73 (2) (2011) 147–152, https://doi.org/10.1016/j.lungcan.2010.12.011.

[33] W. Xu, R. Cui, H. Yu, The association between SDF-1 G801A polymorphism and non-small cell lung cancer risk in a Chinese Han population, Int. J. Clin. Exp. Med. 8 (8) (2015) 14065–14069.

[34] L. Yang, G.L. Shi, C.X. Song, S.F. Xu, Relationship between genetic polymorphism of MCP-1 and non-small-cell lung cancer in the Han nationality of North China, Genet. Mol. Res. 9 (2) (2010) 765–771, https://doi.org/10.4238/vol9-2gmr740.

[35] X.W. Zhang, X. Qin, C.Y. Qin, Y.L. Yin, Y. Chen, H.L. Zhu, Expression of monocyte chemoattractant protein-1 and CC chemokine receptor 2 in non-small cell lung cancer and its significance, Cancer Immunol. Immunother. 62 (3) (2013) 563–570, https://doi.org/10.1007/s00262-012-1361-y.

[36] L. Li, Y.D. Liu, Y.T. Zhan, Y.H. Zhu, Y. Li, D. Xie, X.Y. Guan, High levels of CCL2 or CCL4 in the tumor microenvironment predict unfavorable survival in lung adenocarcinoma, Thoracic Cancer 9 (7) (2018) 775–784, https://doi.org/10.1111/1759-7714.12643.

[37] S. Cheng, Z. Shao, X. Liu, L. Guo, X. Zhang, Q. Na, X. Chen, Y. Ma, J. Zheng, B. Song, J. Liu, Interleukin 17A polymorphism elevates gene expression and is associated with increased risk of non-small cell lung cancer, DNA Cell Biol. 34 (1) (2015) 63–68, https://doi.org/10.1089/dna.2014.2628.

[38] Q.Y. Ma, J. Chen, S.H. Wang, N. Wu, Z.H. Hao, X.F. Chen, Interleukin 17a genetic variations and susceptibility to non-small cell lung cancer, APMIS 123 (3) (2015) 194–198, https://doi.org/10.1111/apm.12341.

[39] X. Chen, J. Wan, J. Liu, W. Xie, X. Diao, J. Xu, B. Zhu, Z. Chen, Increased IL-17-producing cells correlate with poor survival and lymphangiogenesis in NSCLC patients, Lung Cancer 69 (3) (2010) 348–354, https://doi.org/10.1016/j.lungcan.2009.11.013.

[40] C. Perez-Ramirez, M. Canadas-Garre, A. Alnatsha, M.A. Molina, A.I. Robles, E. Villar, J.R. Delgado, M.J. Faus-Dader, M.A. Calleja-Hernandez, Interleukins as new prognostic genetic biomarkers in non-small cell lung cancer, Surgical Oncology 26 (3) (2017) 278–285, https://doi.org/10.1016/j.suronc.2017.05.004.

[41] N.T. Woods, A.N. Monteiro, Z.J. Thompson, E.K. Amankwah, N. Naas, E.B. Haura, A.A. Beg, M.B. Schabath, Interleukin polymorphisms associated with overall survival, disease-free survival, and recurrence in non-small cell lung cancer patients, Mol. Carcinog. 54 (S1) (2015) E172–E184, https://doi.org/10.1002/mc.22275.

[42] W. Zhang, S. Dang, G. Zhang, H. He, X. Wen, Genetic polymorphisms of IL-10, IL-18 and IL12B are associated with risk of non-small cell lung cancer in a Chinese Han population, Int. Immunopharm. 77 (2019) 105938, https://doi.org/10.1016/j.intimp.2019.105938.

[43] I.A. Bhat, N.A. Naykoo, I. Qasim, F.A. Ganie, Q. Yousuf, B.A. Bhat, R. Rasool, S.A. Aziz, Z.A. Shah, Association of Interleukin 1 beta (IL-1β) polymorphism with mrna expression and risk of non-small cell lung cancer, Meta Gene 2 (2014) 123–133, https://doi.org/10.1016/j.mgene.2013.12.002.

[44] C. Perez-Ramirez, A. Alnatsha, M. Canadas-Garre, E. Villar, J. Valdivia-Bautista, M.J. Faus-Dader, M.A. Calleja-Hernandez, 'Cytokine single-nucleotide polymorphisms and risk of non-small-cell Lung Cancer', Pharmacogenetics Genom. 27 (12) (2017) 438–444, https://doi.org/10.1097/fpc.0000000000000307.

[45] K.S. Wu, X. Zhou, F. Zheng, X.Q. Xu, Y.H. Lin, J. Yang, Influence of interleukin-1 beta genetic polymorphism, smoking and alcohol drinking on the risk of non-small cell lung cancer, Clin. Chim. Acta 411 (19–20) (2010) 1441–1446, https://doi.org/10.1016/j.cca.2010.05.035.

[46] S. Zienolddiny, D. Ryberg, V. Maggini, V. Skaug, F. Canzian, A. Haugen, Polymorphisms of the interleukin-1 β gene are associated with increased risk of non-small cell lung cancer, Int. J. Cancer 109 (3) (2004) 353–356, https://doi.org/10.1002/ijc.11695.

[47] Y. Li, W. Zhao, Z.H. Zhao, J. Wu, L. Chen, Y. Ma, Q. Li, D. Lu, L. Jin, J. Wang, IL1B gene polymorphisms, age and the risk of non-small cell lung cancer in a Chinese population, Lung Cancer 89 (3) (2015) 232–237, https://doi.org/10.1016/j.lungcan.2015.06.009.

[48] Y.F. Metwally, A.M. Elsaid, R.R. Elsadda, S. Refaat, R.F. Zahran, Impact of IL-6 and il-1β gene variants on non-small-cell lung cancer risk in Egyptian patients, Biochem. Genet. (2023), https://doi.org/10.1007/s10528-023-10596-2.

[49] C.M. Shih, Y.L. Lee, H.L. Chiou, W.F. Hsu, W.E. Chen, M.C. Chou, L.Y. Lin, The involvement of genetic polymorphism of IL-10 promoter in non-small cell lung cancer, Lung Cancer 50 (3) (2005) 291–297, https://doi.org/10.1016/j.lungcan.2005.07.007.

[50] K. Hart, N.E. Landvik, H. Lind, V. Skaug, A. Haugen, S. Zienolddiny, A combination of functional polymorphisms in the CASP8, MMP1, IL10 and SEPS1 genes affects risk of non-small cell lung cancer, Lung Cancer 71 (2) (2011) 123–129, https://doi.org/10.1016/j.lungcan.2010.04.016.

[51] V. Peddireddy, S.P. Badabagni, S. Sulthana, V.K. Kolla, S.D. Gundimeda, H. Mundluru, Association of TNFA−308, IFNΓ+874, and IL10−1082 gene polymorphisms and the risk of non-small cell lung cancer in the population of the South Indian state of Telangana, Int. J. Clin. Oncol. 21 (5) (2016) 843–852, https://doi.org/10.1007/s10147-016-0972-2.

[52] Y. Jia, A. Zang, S. Jiao, S. Chen, Y. Fu, The interleukin-18 gene promoter -607 A/C polymorphism contributes to non-small-cell lung cancer risk in a Chinese population, OncoTargets Ther. 9 (2016) 1715–1719, https://doi.org/10.2147/ott.s99581.

[53] M. Loustau, F. Anna, R. Dréan, M. Lecomte, P. Langlade-Demoyen, J. Caumartin, HLA-G Neo-Expression on tumors, Front. Immunol. 11 (2020) 1–15, https://doi.org/10.3389/fimmu.2020.01685.

[54] E.C. Castelli, J. Ramalho, I.O. Porto, T.A.H. Lima, L.P. Felacio, A. Sabbagh, E.A. Donadi, C.T. Mendes-Junior, Insights into HLA-G genetics provided by worldwide haplotype diversity, Front. Immunol. 5 (2014), https://doi.org/10.3389/fimmu.2014.00476.

[55] A. Wisniewski, A. Kowal, E. Wyrodek, I. Nowak, E. Majorczyk, M. Wagner, E. Pawlak-Adamska, R. Jankowska, B. Slesak, I. Frydecka, P. Kusnierczyk, Genetic polymorphisms and expression of HLA-G and its receptors, KIR2DL4 and LILRB1, in non-small cell lung cancer, Tissue Antigens 85 (6) (2015) 466–475, https://doi.org/10.1111/tan.12561.

[56] A. Kowal, A. Wisniewski, P. Kusnierczyk, R. Jankowska, Human leukocyte antigen (HLA)-G gene polymorphism in patients with non-small cell lung cancer, Thoracic Cancer 6 (5) (2015) 613–619, https://doi.org/10.1111/1759-7714.12232.

[57] M. Falco, S. Sivori, R. Meazza, D. Pende, Report from the Eleventh Killer Immunoglobulin-like receptor (KIR) workshop: novel insights on KIR polymorphism, ligand recognition, expression and function, HLA 94 (2) (2019) 100–110, https://doi.org/10.1111/tan.13608.

[58] Y. Wu, S. Yang, H. Liu, S. Luo, T.E. Stinchcombe, C. Glass, L. Su, S. Shen, D.C. Christiani, Q. Wang, Q. Wei, Novel genetic variants of *KIR3DL2* and *PVR* involved in immunoregulatory interactions are associated with non-small cell lung cancer survival, Am. J. Cancer Res. 10 (6) (2020) 1770–1784.

[59] A. Wisniewski, M. Sobczynski, K. Pawelczyk, I. Porębska, M. Jasek, M. Wagner, W. Niepieklo-Miniewska, A. Kowal, J. Dubis, N. Jędruchniewicz, P. Kusnierczyk, Polymorphisms of antigen-presenting machinery genes in non-small cell lung cancer: different impact on disease risk and clinical parameters in smokers and never-smokers, Front. Immunol. 12 (2021), https://doi.org/10.3389/fimmu.2021.664474.

[60] W. Liu, Q. Ma, C. Li, Y. Li, S. Liu, L. Shi, Y. Yao, The association of tap polymorphisms with non-small-cell lung cancer in the Han Chinese population, Hum. Immunol. 82 (12) (2021) 917–922, https://doi.org/10.1016/j.humimm.2021.07.014.

[61] S. Yang, D. Tang, Y.C. Zhao, H. Liu, S. Luo, T.E. Stinchcombe, C. Glass, L. Su, S. Shen, D.C. Christiani, Q. Wang, Q. Wei, 'Potentially functional variants of ERAP1, PSMF1 and NCF2 in the MHC-I-related pathway predict non-small cell lung cancer survival', Cancer Immunol. Immunother. 70 (10) (2021) 2819–2833, https://doi.org/10.1007/s00262-021-02877-9.

[62] J.C. Restrepo, D. Dueñas, Z. Corredor, Y. Liscano, Advances in genomic data and biomarkers: revolutionizing NSCLC diagnosis and treatment, Cancers 15 (13) (2023) 3474, https://doi.org/10.3390/cancers15133474.

[63] A. Bodaghi, N. Fattahi, A. Ramazani, Biomarkers: promising and valuable tools towards diagnosis, prognosis and treatment of Covid-19 and other diseases, Heliyon 9 (2) (2023) e13323, https://doi.org/10.1016/j.heliyon.2023.e13323.