Systematic Review

Gene polymorphism in oral health condition associated with coal dust exposure: a systematic review

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ABSTRACT

Introduction: South Kalimantan, known as the second largest coal supplier in Indonesia, is associated with the presence of significant quantities of coal dust in the environment. Coal dust contains various substances that are carcinogenic and cytotoxic. Direct contact of coal dust to the oral cavity is at risk of gene polymorphism resulting in the manifestation of diseases in the mouth. The study aimed to explore the relationship between gene polymorphisms affecting oral health conditions and coal dust exposure through a systematic review. **Methods**: A systematic search of PubMed, Google Scholar, Crossref, Scopus, Web of Science, Lens, and Semantic Scholar databases was conducted for English peer-reviewed articles (1/1/2004–15/9/2024) on oral-related gene polymorphisms from coal dust exposure in humans, animals, and cells. The review followed PRISMA 2020 guidelines, with a narrative synthesis of the findings. Bias was assessed using the Newcastle-Ottawa Scale (NOS), SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) and Quality Assessment Tool for In Vitro Studies (QUIN). **Result**: Overall 17 studies were included. From all 6.703 case-control, 136 in vivo participants and 60 cell samples showed that gene polymorphisms were more frequent in the coal dust-exposed group compared to the non-exposed group and the healthy group. Predisposing factors such smoking, length of time, and age contribute to triggering oral gene polymorphisms. The limitation of this research was the limited number of studies discussing gene polymorphisms due to coal dust exposure directly to the oral cavity, which affected the representativeness of the articles. **Conclusion**: There are polymorphisms in 11 oral-related genes (AhR, CYP1A1, GSTM1, GSTT1, hOGG1, IL6, IL1B, NQO1, TNF, TP53, and XRCC1) after coal dust exposure, presenting genotoxic and mutagenic potential.

KEYWORDS

Genetic polymorphism, dna damage, oral manifestation, coal

INTRODUCTION

Coal dust is a solid particle produced during the underground and open pit exploitation of coal mining. Top five coal mine producers around the world are India, Australia, China, United States, and Indonesia. As of 2021, India reported coal production from 442 active mines.[1] In 2022, Australia operated 93 black coal mines, 3 brown coal mines, and identified over 200 known coal deposits.[2] By December 2018, China had 3,373 fully licensed coal mines.[3] The number of coal producing mines in the United States increased from 548 to 560 by 2023.[4] In 2021, Indonesia recorded a total of 1,567 coal mines.[5] Coal dust exposure contains large amounts of metals (silica, aluminium, cadmium), aluminium silicon crystals,

quartz, and polycyclic aromatic hydrocarbons (PAHs). Coal dust content can cause gene polymorphism.[6,7]

Quartz or crystalline silica (SiO2) can induce DNA mutations that lead to the release of oxidants, proteolytic enzymes and inflammatory factors (TNF-α and IL-1β), causing interstitial lung diseases such as silicosis and sarcoidosis.[8] Silica (Si) metal can damage DNA as in pneumoconiosis.[9] Cadmium (Cd) can damage mitochondria, which can trigger the formation of reactive oxygen species (ROS) and has a high risk of liver and kidney cancer.[10,11] Other components of coal dust, such as PAHs, also have carcinogenic, mutagenic and cytotoxic properties and can increase the risk of cancer through the formation of DNA adducts. DNA adducts induce mutations that activate proto-oncogenes or inactivate tumour suppressor genes.[12,13]

The oral cavity has the potential to be exposed to coal dust due to its anatomical aspects, which are connected to the nose. This creates a risk of disease in the oral cavity due to coal dust exposure. Some diseases in the oral cavity that occur due to coal dust exposure are Burton's line, periodontal disease, dental caries and oral cancer.[14–16]

As with the risk of gene polymorphisms in the lungs, liver and kidneys due to coal dust exposure, gene polymorphisms in the oral cavity are also at high risk. This will be a complication for dentists in providing therapy. The lack of information on gene polymorphism due to coal dust exposure is the basis for us to conduct this systematic review. To date, there has been no systematic review that comprehensively examines the relationship between coal dust exposure and genetic polymorphisms that affect oral health.

This study provides a new synthesis by combining findings from human, in vitro, and in vivo studies, with a particular focus on genes expressed in the oral cavity. Therefore, the aim of this study is to explore the relationship between gene polymorphisms affecting oral health conditions and coal dust exposure through a systematic review.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 criteria were followed in the construction of a key question in accordance with the population, intervention, control, and outcomes procedure. "Is there a correlation between gene polymorphisms and oral health conditions associated with coal dust exposure?" was the inquiry.[17]

An automated comprehensive literature search was conducted using different combinations of corresponding descriptors and free text terms, such as *oral genetic polymorphism, oral dna damage, coal dust exposure, coal dust disease* in PubMed, Google Scholar, Crossref, Scopus, Web of Science, Lens, and Semantic Scholar (using Harzing's Publish or Perish) databases. The search was restricted to English-language studies published between January 2004 and September 2024 in order to narrow down the results.

We looked through Prospero databases to see whether there were any registered protocols on related subjects. Furthermore, Prospero registered the systematic review as a protocol (PROSPERO 2025:CRD42025616976).

Using a standardized methodology, three reviewers (FHA, SNA, MHA) first assessed paper titles and abstracts according to inclusion and exclusion criteria created especially for this investigation (Table 1). Then independent reviews were conducted on the full texts of the studies that were deemed relevant. Only with the approval of all authors were the studies included in the review.

Table.1 Inclusion and exclusion criteria for study selection

Aspect considered	Inclusion Criteria	Exclusion Criteria
Type of publication	Original clinical research, such as cross-sectional, cohort, case-control studies, and experimental studies	Case reports, letters to the editor, guideline, conference paper, book and review articles.
Sample size	Studies with at least 40 cases	Studies with less than 40 cases
Study unit	Studies that analysed human, animals and cells exclusively	Studies that analysed plants
Type of evaluated genes	Genes present in oral anatomy	Genes that are not associated with oral anatomy
Result evaluation	studies that showed the risk of oral genes polymorphism through odds ratio adjusted at least by consumption of alcohol and tobacco, radiation, age, and gender	studies that showed the risk of other than oral genes
Language	English	Other than english

We included original clinical studies, such as cohort, case control, and cross-sectional studies, with at least 40 cases. We limited this review to human, animal, and cell studies that assessed only genes (including their cytokine products) associated with oral anatomy. Lastly, we restricted the review to articles written in English only. We only took into consideration research that used odds ratio to control for alcohol and tobacco intake, radiation exposure, age, and gender. The selection process is summarized following the PRISMA 2020 flow diagram (Diagram. 1).

The data from these pieces of research were carefully collected and compiled into evidence tables. Gene type, coal dust component, associated diseases, anatomical location of oral cavity-related gene alterations, risk of gene damage, study type, sample characteristics (number of cases, controls, age, and gender), and author identity were all included in the abstracted data. Table 2 summarises the characteristics of each study included in this review. This systematic review adopts a narrative methodology aimed at explaining phenomena and discovering the reasons behind them through natural and biomedical approaches, providing a structured framework to synthesize various literature meaningfully.

Risk of bias assessment was conducted by three reviewers (FHA, SNA, MHA) using the Newcastle-Ottawa Scale (NOS) for case-control studies, Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) for animal studies, and Quality Assessment Tool for In Vitro Studies (QUIN) for in vitro studies. An independent review was conducted on inclusion articles to determine low, medium or high risk of bias.

The risk assessment of NOS bias in case-control studies has the following scoring indicators: A score of 9-10 will be assessed as an excellent study and considered to have a low risk of bias. Studies with a score of 7-8 will be rated as good studies. Studies with a score of 5-6 will be classified as satisfactory studies and a score of 0-4 will be given to studies that have a high risk of bias or unsatisfactory studies.[18] In the SYRCLE assessment the risk of bias is determined from answers to a series of "signal questions" about the behaviour and conduct of the study.

Chen et al. (2014) outlined that SYRCLE's risk of bias tool includes 10 signalling questions with responses categorized as "yes", "no", or "unclear", corresponding respectively to low, high, or unclear risk of bias. A single "no" response indicates a high risk of bias for that item. Finally, the risk of bias in in vitro studies was performed using the QUIN assessment. QUIN consists of 12 criteria for which researchers who wish to use this tool are asked to rate each criterion under the specified heading by annotating "specified, inadequately specified, not specified, or not applicable". "Specified" specifies a score of 2,

"inadequately specified" indicates a score of 1, "not specified" is scored 0, and "not applicable" is excluded from the calculation.[19]

The scores obtained were then used to grade the in vitro studies as high, medium, or low risk (>70% = low risk of bias, 50% to 70% = medium risk of bias, and <50% = high risk of bias) using the following formula: Final score= (total score x 100)/ (2×number of criteria applicable)

RESULTS

A total of 17 studies that met the eligibility criteria were included in the review. Espitia, et al (2016), Espitia, et al (2018), Caballero, et al (2016), and Castilla, et al (2014) were conducted in Colombia. Yucesoy, et al (2008), Ghanem, et al (2009), Ghanem, et a (2006), and Ghanem, et al (2004) were from USA. Minina (2020), Minina (2022), and Volobaev, et al (2018) were conducted in Russia. Xu, et al (2022), Ji, et al (2012), and Wu, et al (2014) were from China. There are also Dey, et al (2014) from India; Ates, et al (2017) from Turkey; and Wang, et al (2005) from Japan. The majority of the studies that made up the systematic review employed the case-control approach, except for five studies, four of which used in vivo method and the other one used in vitro.

From all searches obtained, two studies examined liver sites, five studies in lung, two in oral buccal, seven in peripheral blood, two in peripheral lymphocytes, and one study each in kidney, spleen, and blood monocytes. From the search, we also included articles that only discussed changes in cytokine expression due to various coal dust components. Although the data (cytokines) we extracted do not belong to genes, we believe there is a relationship between the production of cytokine levels and the pro-inflammatory genes responsible.

A total of 11 genes (AhR, CYP1A1, GSTM1, GSTT1, hOGG1, IL6, IL1B, NQO1, TNF, TP53, and XRCC1) were reported to have polymorphisms due to coal exposure. Of the total inclusion studies, three articles evaluated the AhR gene with contradictory results. There were 6 articles evaluating the CYP1A1 gene with Espitia, et al (2016), Espitia, et al (2018), Caballero, et al (2016), Castilla, et al (2014) showing an increase in CYP1A1 expression while Ghanem, et al (2004) and Ghanem, et al (2009) articles reporting the opposite.

Three articles on the GSTM1 gene were identified: Espitia, et al (2016), Dey, et al (2014), and Minima (2022). The first two articles reported increased genetic damage due to its absence, while Minina (2022) found decreased damage linked to GSTM1 polymorphism.[6,20] Two studies on GSTT1 provoked conflicting results: Espitia, et al (2016) showed a lower risk with GSTT1 null, while Dey, et al (2014) reported a threefold increase in lung cell damage.[6,20]

Espitia, et al (2016) and Minina (2020) on the hOGG1 gene underlined its protective role against DNA damage.[6,21] Then, Xu, et al (2022) and Yucesoy, et al (2008) also found on IL-6 indicated its polymorphisms increase the risk of CWP and PMF.[22] Of the two IL-1B studies, only Volobaev, et al (2018) linked it to DNA damage.[23,24] Two articles on NQO1 showed opposing results: Caballero, et al (2016) stated coal dust exposure either reduced NQO1 expression, while Castilla, et al (2014) stated that coal dust exposure increased it 4.7-fold.[25,26]

Three studies on the TNFA gene showed TNFA-238 polymorphism linked to CWP in Wu, et al (2014) and Ates, et al (2017), while Wang, et al (2005) implicated the TNFA-308 polymorphism (allele A) as a significant contributor.[27,28] Minina (2020) article on tp53 found its polymorphisms led to increased DNA damage.[21] Lastly, Espitia, et al (2016) and Minina (2020) on XRCC1 linked its polymorphisms to reduced DNA repair, greater DNA damage, and apoptosis activation.[6,21]

In addition to the association between coal dust exposure and the presence of gene polymorphisms, we also analysed the influence of predisposing factors on gene polymorphisms. Based on all the studies we reviewed, there are five predisposing factors: tobacco, alcohol, exposure time, age and sex. Dey, et al (2014), Minina (2020), Minina (2022), Xu, et al (2022), Yucesoy, et al (2008), Ji,

et al (2012), and Wu, et al (2014) explain the relationship between tobacco and gene polymorphisms. Dey, et al (2014), Minina (2020), and Ji, et al (2012) showed a positive association between gene polymorphisms and smoking risk factors. Minina (2022), Xu, et al (2022), Yucesoy, et al (2008), and Wu, et al (2014) showed no significant association between polymorphisms and smoking risk factors. The next predisposing factor is alcohol.

Espitia, et al (2016) and Espitia, et al (2018) mentioned the association between alcohol consumption and gene polymorphisms, and these did not show a significant association. Exposure time is also a predisposing factor for gene polymorphisms, as shown Espitia, et al (2016) and Xu, et al (2022) articles. Xu, et al (2022) showed a positive association between the time of exposure and the occurrence of gene polymorphisms. On the other hand, Espitia, et al (2016) showed the opposite result. Espitia, et al (2016), Minina (2020), Minina (2022), Xu, et al (2022), Yucesoy, et al (2008), and Espitia, et al (2018) discuss the relationship between age and gene polymorphisms.

Minina (2022) supported age as a predisposing factor contributing to gene polymorphisms, while Espitia, et al (2016), Minina (2020), Xu, et al (2022), Yucesoy, et al (2008), and Espitia, et al (2018) reported no significant association between age and changes in gene variation. For the last predisposing factor, only Espitia, et al (2018) mentioned sex and gene polymorphisms, and the article reported an insignificant association.

Table.2 Summary of included studies on gene polymorphism and coal dust exposure

No	Article Identity	Origin	Purpose	Research design	Target Population	Conceptual Framework	Finding	Limitation	Conclusion
					Human Population				
1	Polymorphisms in metabolism and repair genes affects dna damage caused by open – cast coal mining exposure (Espitia, *et* al., 2016)	Guajira, Colombia	The purpose of this study was to determine whether important polymorphisms in the metabolism genes CYP1A1Msp1, GSTM1Null, GSTT1Null, and DNA repair genes XRCC1Arg194Trp and hOGG1Ser326Cys could alter an individual's susceptibility to harmful effects of coal exposure.	Case control	• Cases: 100 cases • Control: 100 controls • Mean age: cases= 44.0±7.5 y, control= 43.7± 7.8 y • sex: men only	1. CYP1A1 Exposure to coal dust produces reactive oxygen species (ROS), which in turn suppresses the expression of genes susceptible to oxidative stress. This leads to a negative feedback control of the expression of the CYP gene. Production inside cells may be restricted by this negative autoregulation. 2. GSTM1 GSTM1null gene can reduce the ability to detoxify harmful compounds from coal exposure 3. GSTT1 Induced by GSTT1 genes damage pathway The rates of karyolysis and karyorrhexis were likewise markedly elevated in exposed GSTM1Null and GSTT1Null allele carriers. 4. hOGG1 hOGG1 acts as a protective gene, triggering genetic damage repair pathways hOGG1 is associated with low BMNCY micronuclei 5. XRCC1 XRCC1Arg194Trp is associated with low BMNCY micronuclei and karyorrhectic/ pyknotic cells The protective effect of XRCC1 is associated with Arg/Trp and Trp/Tpr alleles	1. CYP1A1 significantly increased micronuclei frequency (FR: 1.34, P=0.01). 2. The GSTM1 null gene polymorphism was significantly higher in the exposed workers (FR: 1.28, P = 0.03). 3. GSTT1null showed lower micronuclei frequency compared to GSTT1 carriers (FR: 0.83; P=0.04). 4. hOGG1Ser326Cys (Ser/Cys, Cys/Cys) has a protective effect against gene polymorphims (FR: 0.93; P=0.06). 5. XRCC1Arg194Trp carriers also showed lower levels of cariolytic cells (FR: 0.62; P=0.03) 6. Associated disease: not reported	The study did not prove whether or not the control group had been exposed to coal.	• Individuals with CYP1A1Msp1(m1/m2, m2/m2) gene carriers show a significant frequency of gene damage. • GSTM1null variants have reduced detoxification capacity. • The GSTT1 gene is more susceptible to genotoxicity than GSTT1 null variants exposed to coal. • Protective effect of hOGG1 Ser326Cys polymorphism against DNA damage due to toxic environmental exposure • XRCC1Arg194Trp polymorphism shows a decrease in BMNCyt frequency.

						XRCC1 polymorphisms are associated with reduced protective effects against DNA damage.	7. Coal dust component: C,H,N,S, Si, Al, Cr, Cu, Mn, Ni. Zn, Pb. SiO2, Al2O3, K2O, Ti2O, P2O5, SO3, CaO, MgO, Na1O, MnO, Fe2O3,K2O, Quartz, Kaolinite, Pyrite, Illite, PAH 8. Study anatomical site: Buccal epithelial cell		
2	Genetic Damage in Environmentally Exposed Populations to Open-pit Coal Mining residues: analysis of buccal Micronucleus Cytome (bmn-cyt) Assay and Alkaline, Endo III and FPG High-throughput Comet assay (Espitia-Pérez et al., 2018)	Guajira, Colombia	This study evaluated DNA damage in individuals exposed to coal mining residues in northern Colombia using a cytomic assay (BMN-cyt) in buccal cells and its correlation with primary and oxidative DNA damage in lymphocytes, as determined by the high-performance alkaline and modified Comet assay (FPG-ENDO III).	case-control	• Case: 98 cases • Control: 41 • Mean age: cases= 35.20±13 .34 y, control= 30.69±11 .56 y • Sex: men (n=41). woman (n=98)	CYP1A1 • A xenobiotic compound's in situ activation is suggested by the highly expressed genes CYP1A1, which is associated to PAH metabolism. • CYP1A1 polymorphisms have been shown to be significantly associated with genetic damage in buccal mucosa cells, indicating that they may be able to modify the consequences of PAH exposure in this epithelial tissue.	1. CYP1A1 The DNA damage observed in individuals exposed to environmental coal dust was caused by mainly due to oxidative damage (P<0.001) 2. Associated disease: not reported 3. Coal dust component: PAH 4. Anatomical site: Buccal epithelial cell	This study does not directly prove the presence of gene polymorphisms, only the presence of DNA damage through biomarkers	CYP1A1 polymorphism significantly associated with genetic damage to buccal mucosal cells
3	Role of Glutathione S Transferase Polymorphism in COPD with	Ledo, in Assam, India	The purpose of this study was to assess the contribution of GST	Case control	• Case: 70 cases • control: 85 controls	1. GSTM1 • Smokers with the GSTM1 (null genotype) allele were more likely to develop COPD, and respirable coal	1. There was a significant association between the GSTM1 null	The study did not explicitly state whether the interviews	• GSTM1 null genotype is significantly associated

	Special Reference to Peoples Living in the Vicinity of the Open Cast Coal Mine of Assam (Dey, T *et al*. 2014)		polymorphism, a detoxifying enzyme, to the pathophysiology of COPD in relation to the contaminated environment in which the population resides.		(healthy non smoker= 35, healthy smoker= 50) • Mean age: Case=47 y, Control= 49 y • Sex: Men (n=116), Women (n=39)	dust from coal mines had a further role. • In the course of COPD development, either (GSTM1/GSTT1) appeared to have a protective effect. 2. GSTT1 • Subject to the fact that nonsmokers with non-null GSTT1 genotypes are three times more likely to be sick than nonsmokers with non-null genotypes. In the course of COPD development, either GSTM1/GSTT1 appeared to have a protective effect.	genotype and COPD at $p<0.05$. 2. GSTT1 null genotype was significantly associated with COPD ($p<0.203$). 3. Associated disease: Chronic Obstructive Pulmonary Disease (COPD) 4. Coal dust component: Silicone and aliphatic C-F compounds 5. Anatomical site: Peripheral blood	were blind or not.	with reduced lung function • The GSTT1null genotype in the non-smoker group showed an approximately three-fold increased risk of COPD
4	Chromosomal Instability and Genetic Polymorphism in Miners and Workers of Coal Thermal Power Plants (Minina, 2020)	Kemerovo oblast, Russia	This study compares the levels of gene polymorphism and chromosomal instability in coal-mining and coal-fired power plant personnel.	Case control	• Cases: 653 cases • control: 642 controls • Mean age: coal miner=48 .4 ± 0.5 y, power plant worker= 51.5 ± 0.4 y, control= 49.8 ± 0.2 y	1. hOGG1 • Variant polymorphisms of hOGG1 are associated with decreased enzyme activity or repair ability 2. TP53 • Polymorphism variations of genes (TGFβ1, TP53) that regulate proliferation, differentiation, and apoptosis have a substantial influence. 3. XRCC1 • There was a strong correlation found between reduced levels of BMNCy and genetic polymorphisms in base-excision repair route (BER)	1. hOGG1 2. TP53 3. XRCC1 4. The frequency of the gene polymorphism was significantly higher in the group of miners than in the group of people who did not work in the mine ($p < 0.00001$).	The control group did not have a series of health checks that are evidence of a person's good health.	• The hOGG1 gene polymorphism has a significant effect on DNA damage. • TP53 polymorphism increases risk of chromosome breakage damage • XRCC1 polymorphic variants result in reduced

					• Sex: men (n=1.118), women (n=177)	genes, such as XRCC1Arg194Trp (Arg/Trp, Trp/Tpr) and hOGG1Ser326Cys (Ser/Cys, Cys/Cys). • The protective effect of XRCC1Arg194Trp may be related to the (Arg/Trp, Trp/Tpr) alleles' reduced ability to repair the BER pathway. • The polymorphism may impact XRCC1's capacity to bind to poly (ADP-ribose) polymerase or POL β. Therefore, a diminished capacity for DNA repair may result in a greater build-up of DNA damage, which amplifies cell cycle arrest and death. • People with the XRCC1Arg194Trp (Arg/Arg) genotype than those without, those with the genotype showed reduced amounts of karyorrhectic and pyknotic cells.	5. Associated disease: not reported 6. Coal dust component: not reported 7. Anatomical site: Peripheral blood		DNA repair capacity
5	Polymorphisms in DNA Repair and Xenobiotic Biotransformation Enzyme Genes and Lung Cancer Risk in Coal Mine Workers (Minina, 2022)	Kuzbass, Western Siberia, Russian Federation	The purpose of this study was to look at the relationship between LC risk in patients who worked in coal mines and the gene polymorphisms for GSTM1 (deletion), APEX1 (rs1130409), XPD (rs13181), and NBS1 (rs1805794).	Case control	• Cases: 208 cases • control: control I=187, control II=244 • sex: all subject were men	GSTM1 • GSTM1 involved in antioxidant activity • Research has demonstrated that individuals with a deletional genotype of GSTM1 had lower amounts of 8-oxoguanine, which can be generated by the mutagenic effects of benzo(a)pyrene and benz(a)anthracene PAHs. • A lower likelihood of LC formation was associated with the significant deletion l in GSTM1.	1. GSTM1 Large deletion of GSTM1 was associated with lower risk of lung cancer (ORadj = 0.59) Associated disease: lung cancer 2. Coal dust component: PAH 3. Anatomical site: Peripheral blood	Although it was stated that lung cancer is never diagnosed in healthy patients, the study did not explain that the healthy group had undergone a number of lung cancer screenings.	Coal mine workers with deletions in the GSTM1 gene have a lower risk of developing lung cancer

6	Association between the IL-6 polymorphisms and coal workers' pneumoconiosis in a Chinese Hui population(Xu X, Yin J, Zhang J, et al. 2022)	Ningxia Hui, China	The purpose of this study was to assessthe safety and effectiveness of high frequency oscillatory ventilation in the treatment of coal workers' pneumoconiosis (CWP) in a Chinese Hui community, as well as to ascertain whether polymorphisms in IL-6 and IL-12 contribute to the genesis of CWP.	Case control	• Case: 160 cases • control: 150 controls • age: cases=63.6 ± 8.1 y, controls =64.6 ± 9.6 y	IL6 • The IL-6-634C/G polymorphism in CWP patients may be linked to altered blood IL-6 levels, a crucial sign of the patients' immune systems.	1. IL6 Carrying the IL-6-634C/G allele (rs1800796) was associated with a decreased risk of CWP ($p<0.05$). 2. Associated disease: Pneumoconiosis 3. Coal dust component: Silica 4. Anatomical site: Peripheral blood	The study did not explicitly state that the interview questions would make participants aware of their case or control group allocation.	IL-6-634C/G polymorphism is associated with CWP risk.
7	Genetic susceptibility to progressive massive fibrosis in coal miners (Yucesoy, B., *et al.* 2008)	National Institute for Occupational Safety and Health, 1095 Willowdale Road, WV 26505-2888, USA	To investigate the theory that single nucleotide polymorphisms (SNPs) in genes related to fibrotic and inflammatory processes influence the development risk of PMF, a case-control research was carried out.	Case-control	• Case: 304 cases • Control: 344 controls • Average age: ase=69.9±8.9 y, control=69.9±9.0 y • Sex: male	1. IL6 • IL-6-634C/G polymorphism is associated with the risk of CWP • The IL-6-634C/G polymorphism in CWP patients may be linked to altered blood IL-6 levels, a crucial sign of the patients' immune systems.	1. A higher risk of PMF was associated with the polygenotype of VEGF +405/ICAM-1 +241/IL-6 -174 (C-A-G) (odds ratio 3.4, 95% CI 1.3–8.8). 2. Associated diseases: Progressive Massive Fibrosis (PMF) 3. Coal dust component: Not reported 4. Anatoical site: Lung tissue	No gene polymorphism examination before the intervention (coal dust exposure) in the case group	The IL-6-634C/G polymorphism in CWP patients can be seen through changes in serum IL-6 levels as an important indicator of the immune function of CWP patients

8	Associations of polymorphisms in the cytokine genes IL1β (rs16944), IL6 (rs1800795),IL 12b (rs3212227) and growth factor VEGFA (rs2010963) with anthracosilicosis in coal miners in Russia and related genotoxic effects (Volobaev, V. P. et al. 2018)	Kemerovo Region of the Russian Federation	In Russian coal miners with anthracosilicosis (AS), this study examined the genotoxic effects and polymorphism variations of certain cytokine genes.	Case control	• Case: 78 cases • Control: 56 controls • Age: cases=57.61 ± 8.30 y, control= 49.61 ± 7.66y. • Sex: not reported	IL1B • Patients with anthracosilicosis (AS) who possess the IL1β (rs16944) TT genotype have a higher frequency of dicentric chromosomes than AS patients who carry the CC genotype. This difference may be due to an overall increase in oxidative damage in the AS group. • In patients with AS, the T allele causes an increase in the production of the cytokine IL1, which exacerbates oxidative stress and resulting in more chromosomal abnormalities.	1. AS was linked to the IL1β gene T/T genotype (rs16944) (odds ratio = 4.77, P < 0.01). 2. Associated diseases: Anthracosilicosis 3. Coal dust component: Quartz 4. Anatoical site: Lymphocytes peripheral	No gene polymorphism examination before the intervention (coal dust exposure) in the case group	The IL1B (rs 16944) polymorphism with TT allel results in increased levels of IL1 cytokine expression leading to exacerbation of oxidative stress
9	Polymorphisms in Inflammasome Genes and Risk of Coal Workers' Pneumoconiosis in a Chinese Population (Ji, X., *et al.* 2012)	Xuzhou, China	The study evaluated whether common single nucleotide polymorphisms (SNPs) in inflammasome genes are linked with CWP	Case-control	• Cases: 697 cases • Control: 694 control • Average age: Cases= 68 y, Control= 67.1 y	IL1B • Has a pro-fibrotic effect and is crucial to the pathophysiology of lung fibrosis brought on by inflammation.	1. IL1B 2. Associated diseases: Coal worker's pneumoconiosis (CWP) 3. Coal dust component: Silica 4. Anatoical site: Lymphocytes peripheral	No gene polymorphism examination before the intervention (coal dust exposure) in the case group	Polymorphism on IL1B genes resulting in inflammatory response
10	GITR promoter polymorphism contributes to risk of coal workers' pneumoconiosis: A case–control study from China (Wu, B., *et al.* 2014)	China	This study looked at the relationship in a Chinese population between the functional polymorphisms in GITR and the risk of CWP.	Case-control	• Cases: 693 • Control: 690 • Sex: Men only • Mean age: cases=68.0 ± 11.1 y, control=	TNF • The CG/GG genotypes' greater risk for CWP was considerably increased by the promoter polymorphism TNFA-238 (rs3753348). • Genetic variants in GITR, a protein linked to TNF receptor that is triggered by glucocorticoids, may have a role in the development of CWP and can serve as a genetic	1. The risk of CWP was considerably increased by the GITR rs3753348 GG/GC genotypes (adjusted OR = 1.32, 95%CI = 1.02–1.71).	• No gene polymorphism examination before the intervention (coal dust exposure) in the case group • The sample size of this	The TNFA-238 polymorphism with CG/GG genotypes significantly enhanced expression for developing CWP

					67.1 ± 8.4 y		biomarker for those who are sensitive.	2. Associated diseases: Coal worker's pneumoconiosis (CWP) 3. Coal dust component: Not reported 4. Anatoical site: Peripheral blood	study is moderate,thus the statistical power is limited especially among some subgroups • Except for cigarette smoke and occupational exposure, this study may need other information on environmental exposure that may have an interaction with GITR gene.	
11	A Genotyping and Phenotyping Study Concerning the Possible Effects of Some Inflammatory Cytokine Gene Polymorphisms on the Development of Coal Workers' Pneumoconiosis (Ates, I., *et al*. 2017)	Kozlu/Zonguldak region of Turkey	The objective of this research was to determine the cytokine gene profiles of Turkish coal workers by the investigation of genotyping and phenotyping of three key proinflammatory cytokines associated with CWP: TNF-alpha, IL1-alpha, and IL1-beta.	Case-control	• Cases: 67 cases • Control: 92 control • Sex: Not reported • Average age: cases= 58.60 ± 4.41 y, control= 48.75 ± 5.21 y	TNF • This study discovered that TNFA-238 variation is a potent CWP risk factor. • TNF-alpha and IL1 cytokine releases from the monocytes in CWP patients were considerably higher than those in healthy workers, according to the phenotyping analysis.		1. A TNFA-238 gene polymorphism was shown to be associated with an increased chance of developing CWP (OR=3.79) 2. Associated diseases: Coal worker's pneumoconiosis (CWP) 3. Coal dust component: Crystalline silica	• No gene polymorphism examination before the intervention (coal dust exposure) in the case group • limited sample size of the studied groups, so they need to comment these findings cautiously as precursors.	Polymorphism in TNFA-238 A stimulates the release of TNF-α from monocytes induced by coal dust and lipopolysaccharide (LPS).

								4. Anatomical site: Blood monocytes		
12	Antithetical Effect of Tumor Necrosis Factor-a Gene Polymorphism on Coal Workers' Pneumoconiosis (CWP) (Wang, X.T. *et al*. 2005)	Iwamizawa Rosai Hospital (Hokkaido, Japan)	The following two theories were investigated in this study. CWP patients who have been exposed to a lot of dust are associated with TNF-a polymorphisms and vulnerability to nodular CWP and PMF is determined by distinct genetic pathways.	Case-control	• Case: CWP cases=84, PMF cases=44 • Control: 122 controls • Mean age: CWP case=66,8 y, control= 46,1 +/- 4,3 • Sex: men and women	TNF • The TNF-a 308 G/G allele were linked to the development of PM • TNF-a 308 A gene is linked to the development of nodular CWP. • One of the mechanisms that promote PMF in those with the 308 G allele may be increased susceptibility to respiratory infections like TB.	1. Compared to PMF, the 308 G/A genotype was 3.8 times more likely to be linked to nodular CWP (P=0.036). 2. Associated diseases: Coal worker's pneumoconiosis (CWP) 3. Coal dust component: Quartz 4. Anatomical site: Peripheral blood	No gene polymorphism examination before the intervention (coal dust exposure) in the case group	the A allele of TNFA-308, together with smoking, increased the risk of nodular CWP without contributing to the development of PMF
					Animal Population					
13	(Caballero-Gallardo, K., & Olivero-Verbel, J., 2016)	La Loma, Cesar, Colombia, South America,	To assess the harmful consequences of being exposed to sand that has coal dust particles smaller than 38 µm in diameter. This sand was acquired from a mineral sample that was taken from La Loma, the biggest coal mine in South America, located in Cesar, Colombia.	Experimental studies (In vivo)	• Number of subjects: 36 mice • Age: 6 weeks • Sex: female	1. AhR • The way that PAHs control the transcription of the Cyp1a1 gene is through the ligand-dependent activation of the aryl hydrocarbon receptor (AhR). • In mice, AhR activation adversely controls the expression of genes involved in fatty acid production, including Scd1. 2. CYP1A1 • The expression of Cyp1a1, a gene involved in the metabolism and activation of many procarcinogens, including PAHs, was clearly	1. AhR 2. CYP1A1 3. NQO1 4. Damage index (DI) values were significantly higher in groups exposed to 2 and 4% coal dust in sand than in the control group (P<0.05). 5. Associated diseases: Coal Worker's	This article is unclear of some information like there is no statement about the subjects were randomly allocated, housed, were the caregivers and/or investigators, outcome assessor blinded, or was the study free from other problems that could result in high risk of bias	Coal dust exposure increases AhR and CYP1A1 which negatively affect human body and decreasing NQO1 which further preventing human body response to oxidative stress and xenobiotic detoxification

						elevated in response to coal dust exposure. 3. NQO1 ● Coal dust exposure in mice leads to a decrease in NQO1 mRNA expression at higher coal dust concentrations (2-4%). ● NQO1 is an enzyme involved in the response to oxidative stress and xenobiotic detoxification metabolism	Pneumoconiosis (CWP) 6. Coal dust component: PAH 7. Anatomical site: Peripheral blood cells, tissue samples from lung, liver, kidney, and spleen		
14	(Ghanem, M., Battelli, L.A., Law, B.F., Castranova, V., & Kashon, M.L., 2009)	National Institute for Occupational Safety and Health, Morgantown, USA	Examining how CD affects AhR's nuclear translocation caused by PAHin AT-II cells taken from rats exposed in vivo.	Experimental studies (In vivo)	● Number of subjects: 16 rats ● Sex: Male ● Age: Not reported	1. AhR ● In rats exposed to CD, BNF had no discernible effect on the location of AhR in AT-II cell nuclei, as shown by a proportionate expression of AhR in the nucleus. BNF had no discernible effect on the proportion of AT-II cells in CD-exposed rats expressing nuclear AhR. These results imply that the inability of the CD-exposed cells to translocate AhR following PAH exposure may be one of the mechanisms behind CD-induced suppression of CYP1A1 induction. 2. CYP1A1 ● As pulmonary inflammation is linked to CD exposure, proinflammatory mediators that are known to affect CYP1A1 activity are probably involved in the mechanism of reduced PAH-induced CYP1A1 activity in the lung exposed to particles.	1. AhR 2. CYP1A1 BNF substantially ($P < 0.036$) enhanced the overall expression area (in nucleus and cytoplasm) of AhR (measured as square micrometer per AT-II cell) in rats who received IT saline. 3. Associated diseases: Pneumoconiosis 4. Coal dust component: PAH 5. Anatomical site: Alveolar type II cells	This article is unclear of some information such as there is no statement whether the subjects were randomly housed, were the outcome assessor blinded, investigators, outcome assessor blinded, or was the study free from other problems that could result in high risk of bias	CD modifies nuclear translocation of AhR in AT-II cells after subsequent BNF exposure. This provides an explanation for at least some of the diminished CYP1A1 induction observed in the partide-exposed lung upon subsequent BNF exposure.

15	Apoptosis and bax expression are increased by coal dust in the polycydic aromatic hydrocarbon-exposed lung. (Ghanem, *et al.,* 2006)	National Institute for Occupational Safety and Health, Morgantown ,West Virginia, USA	Examining the ways in which down-regulation of CYP1A1 induction and lung damage are related to apoptosis in combined exposures to CD and PAHs	Experimental studies (In vivo)	• Number of subjects: 64 Rats • Sex: Male • Age: Not reported	Suppresses CYP1AI induction by PAH through apoptosis	1. Coal dust exposure dramatically decreased the proportionate CYP1A1 expression in alveolar type II cells in rats given BNF injections (p = 0.0028). 2. Associated diseases: Pneumoconiosis 3. Coal dust component: PAH 4. Anatomical site: Lung	This article is unclear of some information such as there is no statement about the subjects allocatian were adequately concealed, or was the outcome assessor blinded, the study free from selective outcome reporting and other problems that could result in high risk of bias	CYP1A1 induction suppressed by PAH
16	Respirable coal dust partides modify cytochrome P4501A1 (CYP1A1) expression in rat alveolar cells. (Ghanem, *et al.,* 2004)	Ntional Institute for Occupational Safety and Health, Morgantown ,West Virginia, USA	Examine how exposure to coal dust (CD) modifies CYP1A1 induction to affect lung carcinogenesis.	Experimental studies (In vivo)	• Number of subjects: 20 rats • Sex: Male Sprague-Dawley rats • Age: Not reported	Alters lung carcinogenesis by altering CYP1A1 induction	1. Rats subjected to 20 mg (P = 0.005) and 40 mg (P = 0.003) coal dust and BNF showed substantially lower proportionate CYP1A1 expression in AT-II of PA regions than control. 2. Associated diseases: Not reported 3. Coal dust component: Silica and iron 4. Anatomical site: Lung	It is unclear that the allocation of the subject were adequately concealed and free of other problems that could result in high risk of bias	CYP1A1 induction altering, alters lung carcinogenesis

						Cell Sample			
17	Altered gene expression in HepG2 cells exposed to a methanolic coal dust extract (Castilla, A.G., & Verbel, J.O. 2014)	La Loma, Colombia	Examine the impact of a methanolic extract from coal dust on the human liver hepatocellular carcinoma cell line HepG2.	Experimental studies (In vitro)	• Cases: 40 cell sample • Controls: 20 cell sample	1. AHR • The aryl hydrocarbon receptor (AhR) is activated in response to ligands, which is how PAHs control the transcription of the Cyp1a1 gene. 2. CYP1A1 • The overexpression of CYP1A1 in this study may indicate that the coal extract has the potential to be genotoxic, even at low doses, as it is likely to cause PAH oxidation to reactive metabolites. 3. NQO1 • The activation of the Keap1/Nrf2/ARE pathway, which results in an increase in NQO1 expression, is thought to be an adaptive reaction that happens when chemicals that are electrophilic or oxidative are exposed.	1. AHR 2. CYP1A1 3. NQO1 4. Associated diseases: Not reported 5. Coal dust component: PAH 6. Anatomical site: Hepatocellular carcinoma HepG2 cell line	Operator details, cell sample randomization, and outcome assessor details are not specified	HepG2 cells exposed to non-cytotoxic concentrations of coal dust extract showed genotoxic damage and activation of AhR and DNA repair signaling pathways.

The majority of the included studies had a moderate to low risk of bias, according to the quality of the article. Ten studies (58%) were considered to be at low risk of bias, three studies (17%) were considered to be at moderate risk of bias, and another four studies (23%) were considered to have an unclear risk of bias due to insufficient data details. Result assessment risk of bias could be seen in the table 3-5.

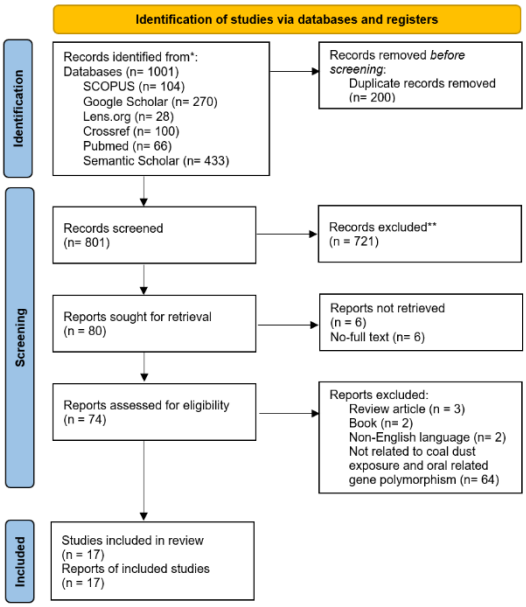

Diagram 1. PRISMA 2020 Flowchart of study selection

Table 3. Newcastle-ottawa scale for assessing quality of case-control study

References	Selection	Comparability	Exposure	Overall grade
Espitia-Pérez et al. (2016)	**	**	***	7
Espitia-Pérez et al. (2018)	**	**	**	6
Dey, T et al. (2014)	***	**	***	8
Minina, V. et al. (2020)	**	**	**	6
Minina, V. I. et al. (2022)	***	**	***	8
Xu, X. et al. (2022)	****	**	***	9
Yucesoy, B. et al (2008)	***	**	**	7
Volobaev, V. P. et al (2018)	***	**	**	7
Ji, X. et al. (2012)	***	**	**	7
Wu, B. et al. (2014)	***	**	***	8
Ates, I. et al. (2017)	**	**	***	7
Wang, X.T. et al. (2005)	***	**	**	7

Gene polymorphisms associated with coal dust exposure have been identified in various organs, with the lungs being the most frequently affected site (Table 6). Although the International Agency for Research on Cancer (IARC) classifies coal dust as non-carcinogenic, accumulating evidence of genetic alterations suggests a considerable risk of disease development, including in oral tissues. While the majority of mutations are reported in pulmonary tissues, similar polymorphic patterns observed in the oral cavity raise concerns about their potential to contribute to pre-malignant and malignant oral conditions.

Table 4. Systematic review centre for laboratory animal experimentation (SYRCLE) for assessing quality of In vivo study.

Domain aspect	Signaling question	Caballero-Gallardo, K., & Olivero-Verbel, J. (2016)	Ghanem, M., Battelli, L.A., Law, B.F., Castranova, V., & Kashon, M.L. (2009)	Ghanem, M. M., Battelli, L. A., Mercer, R. R., Scabilloni, J. F., Kashon, M. L., Ma, J. Y., & Hubbs, A. F. (2006)	Ghanem, M. M., Porter, D., Battelli, L. A., Vallyathan, V., Kashon, M. L., Ma, J. Y., ... & Hubbs, A. F. (2004)
Selection bias	Was the allocation sequence adequately generated & applied?	UC	Y	Y	Y
	Were the groups similar at baseline or were they adjusted for confounders in the analysis?	Y	UC	Y	Y
	Was the allocation adequately concealed?	UC	UC	UC	UC
Performance bias	Were the animals randomly housed during the experiment?	UC	Y	Y	Y
	Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	UC	Y	Y	Y
Detection bias	Were animals selected at random for outcome assessment?	Y	Y	Y	Y
	Was the outcome assessor blinded?	UC	UC	UC	Y
Attrition bias	Were incomplete outcome data adequately addressed?	UC	UC	Y	Y
Reporting bias	Are reports of the study free of selective outcome reporting?	Y	Y	UC	Y
Other	Was the study apparently free of other problems that could result in high risk of bias?	UC	UC	UC	UC
Overall grade		Some concern	Some concern	Some concern	Some concern

Table 5. QUIN for assessing quality of in vitro study.

Criteria no.	Assessment criteria	Castilla, A.G., & Verbel, J.O. (2014)
1.	Clearly stated aims/objectives	2
2.	Detailed explanation of sample size calculation	2
3.	Detailed explanation of sampling technique	1
4.	Details of comparison group	2
5.	Detailed explanation of methodology	2
6.	Operator details	0
7.	Randomization	0
8.	Method of measurement of outcome	2
9.	Outcome assessor details	0
10.	Blinding	2
11.	Statistical analysis	2
12.	Presentation of results	2
Overall grade	Final score= (17x 100)/ (2×12) = 70% (medium risk of bias)	

Table 6. Lung diseases and related gene polymorphism from coal dust exposure

Coal-induced lung disease	Gene type	Coal dust component
Coal Worker's Pneumoconiosis (CWP)	AHR	PAH
	IL1B	Silica
	TNF	Not reported
		Crystaline Silica (Quartz)
Pneumoconiosis	AHR	PAH
	CYP1A1	PAH
Chronic Obstructive Pulmonary Disease (COPD)	GSYM1	Silicone and aliphatic C-F compounds
	GSTT1	silicone and aliphatic C-F compounds
Lung cancer	GSTM1	PAH
Progressive Massive Fibrosis (PMF)	IL6	Not reported
	TNF	Not reported
Anthracosilicosis	IL1B	Quartz

The association between coal dust exposure and alterations in genes expressed in oral tissues highlights potential risks for various oral health conditions. A summary of oral manifestations potentially linked to specific gene polymorphisms and coal-related chemical components is presented in Table 7.

Table 7. Oral manifestations linked to gene polymorphisms from coal dust exposure

Affected oral genes	Oral manifestation	Coal dust component
AHR & CYP1A1	Oral Squamous Cell Carcinoma (OSCC)	PAH
		Trace mineral
		Quartz
		Kaolinite
		Pyrite
		Illite
GSTM1null	Oral Submucous Fibrosis (OSF)	PAH
		Trace mineral
		Silicone and aliphatic C-F compounds
		Quartz
		Kaolinite
		Pyrite
		Illite
GSTT1null	Oral Submucous Fibrosis (OSF)	PAH
		Trace mineral
		Silicone and aliphatic C-F compounds
		Quartz
		Kaolinite
		Pyrite
		Illite
hOGG1	Oral Squamous Cell Carcinoma (OSCC)	PAH
		Trace mineral
		Quartz
		Kaolinite
		Pyrite
		Illite
IL6	Periodontitis	Silica
IL1B	Periodontitis	Quartz
		Silica
NQO1	Oral Submucous Fibrosis (OSF)	PAH
TNFA	Chronic Periodontitis	Quartz
	Oral lichen planus	
	Odontogenic keratocysts	
TP53	Salivary gland tumor	Not reported
XRCC1	Oral Squamous Cell Carcinoma (OSCC)	PAH
		Trace mineral
		Quartz
		Kaolinite
		Pyrite
		Illite

DISCUSSION

This review synthesizes current evidence on coal dust–related gene polymorphisms and their relevance to oral health. The study selection followed strict inclusion criteria to ensure adequate sample size and control of major confounders (Table 1), increasing internal validity, although the focus on oral-related genes may have excluded systemic polymorphisms that still influence oral pathology.[17] Considerable heterogeneity was evident across studies in terms of geographic setting, gene targets, anatomical sources, and research design, with most using a case-control approach. CYP1A1 was the most frequently investigated gene, reflecting a scientific emphasis on detoxification pathways, yet direct evaluation of oral mucosa remained limited and most conclusions were extrapolated from systemic tissues.[6,25,36]

Quality assessment showed that case-control studies were generally of moderate to good quality, though many lacked adequate control for confounders (Table 3).[18] In vivo studies demonstrated some unclear risk of bias due to insufficient reporting on randomization and blinding (Table 4), while the single in vitro study exhibited moderate bias but still provided mechanistic insights into coal-related toxicity (Table 5).[19] Overall, outcome measurements were consistent with the biological plausibility of coal-induced genotoxicity.

Most identified polymorphisms were originally described in the context of pulmonary diseases such as CWP, COPD, PMF, and lung cancer, offering useful parallels because the oral cavity shares similar exposure routes and molecular vulnerabilities.[22,28,40,47] Several polymorphisms, particularly in CYP1A1, GSTM1, GSTT1, NQO1, hOGG1, XRCC1, IL1B, IL6, and TNFA have also been associated with oral outcomes such as chronic inflammation, periodontitis, oral potentially malignant disorders, and OSCC, further indicating that the oral cavity may be an important site affected by coal dust–related genotoxic pathways.[34-37,49-51]

Based on analysis of the entire article, eleven genes were polymorphised due to coal dust exposure, each participating in interconnected pathways that govern xenobiotic metabolism, oxidative defense, DNA repair, and inflammatory regulation.[6,21,25,53] Together, these pathways help explain how inhaled coal particles can generate systemic and oral vulnerability through cumulative biological stress.

AhR normally regulates xenobiotic metabolism by activating CYP1A1 following PAH binding.[29] Polymorphic or dysregulated AhR signaling causes excessive CYP1A1 induction, up to 163-fold, leading to oxidative stress and DNA adduct formation.[25,26] AhR also affects metabolic genes like *Scd1*,25 while β-naphthoflavone exposure can suppress AhR nuclear translocation and reduce CYP1A1 activity, indicating pathway overload.[29,30] These disruptions potentially increase oral epithelial susceptibility to toxic metabolites.

CYP1A1 metabolizes PAHs into reactive intermediates under AhR control.[31] Coal dust markedly elevates CYP1A1 expression in vitro and in vivo, particularly in high-risk variants such as *Msp1* (m1/m2, m2/m2), which produce higher micronucleus formation[6,21,25] Additional alterations such as telomere shortening and hypermethylation further amplify CYP1A1 expression.[32] Reduced induction under AhR suppression increases apoptotic signaling.[33] These mechanisms explain the association of CYP1A1 variants with buccal DNA damage and OSCC-related changes.[34–37]

GSTM1 normally detoxifies electrophilic compounds through glutathione conjugation.[20] The GSTM1 null genotype abolishes this function and, while systemic studies show variable effects, oral studies consistently link GSTM1null to increased BMNCyt abnormalities.[6,38–41] Reduced detoxification allows accumulation of reactive metabolites, elevating risk for OSF and other mucosal precancerous changes.[6,42]

GSTT1 performs a similar role in eliminating electrophilic carcinogens.[43] Its null variant increases COPD risk and DNA instability although some evidence suggests adaptive reductions in micronucleus frequency.[6,39,43] Combined GSTM1null–GSTT1null genotypes, however, severely impair detoxification and markedly increase OSF and precancer risk due to carcinogen buildup.[42,44]

hOGG1 repairs 8-oxoguanine lesions in the base-excision repair pathway. The Ser326Cys variant alters repair efficiency, with some studies reporting reduced DNA

damage, while others show greater chromosomal instability due to weaker glycosylase activity.[6,21,45] The Cys allele also appears more frequently in OSCC-susceptible individuals, linking impaired oxidative repair to carcinogenesis.[46]

IL-6 regulates inflammatory and fibrotic responses triggered by coal or silica via ROS-dependent NF-κB activation.[28,47] Promoter polymorphisms (−174 G/C, −634 C/G) heighten susceptibility to PMF, CWP, and cancer.[22,48] In the oral cavity, these variants increase periodontitis risk through enhanced osteoclast and MMP activity.[49–51]

IL-1β, activated through the NLRP3 inflammasome, rises after coal dust exposure. Polymorphisms at −31 T/C and +3954 C/T increase IL-1β expression, oxidative stress, and chromosomal abnormalities.[23,52] In oral tissues, the +3954 T and TT genotypes are associated with more severe periodontitis due to stronger inflammatory and bone-resorptive effects.[53,54]

NQO1 detoxifies quinones and supports antioxidant defense. Coal dust produces bidirectional expression—suppression at higher concentrations and induction at lower levels through Keap1/Nrf2/ARE signaling.[25,55] The C609T polymorphism, especially TT genotypes, significantly reduces enzyme activity, increasing OSF susceptibility as oxidative and electrophilic intermediates accumulate.[56,57]

TNFA regulates pro-inflammatory cytokine production. Polymorphisms at −238 and −308 elevate TNF-α levels and increase CWP susceptibility.[27,28] The −308 A allele also intensifies oral inflammatory disorders, including chronic periodontitis, oral lichen planus, and odontogenic keratocysts, through enhanced epithelial proliferation and connective-tissue remodeling..[8,58–62]

TP53 maintains genome stability through cell-cycle regulation and DNA repair. Coal-induced oxidative stress promotes the Arg72Pro polymorphism, reducing repair efficiency and increasing chromosomal damage.[63] This variant raises lung cancer risk and is enriched in malignant salivary gland tumors, linking TP53 dysfunction to oral oncogenic transformation.[21]

XRCC1 repairs single-strand DNA breaks in the BER pathway. The Arg194Trp variant disrupts interactions with PARP and POL β, reducing repair capacity and increasing apoptosis.[6,21] This instability corresponds with a higher risk of OSCC, further connecting DNA repair impairment to oral carcinogenesis.[64]

Several predisposing factors were evaluated alongside coal dust exposure, yet their influence on gene polymorphisms was generally inconsistent. Alcohol intake showed no meaningful association across studies; although Espitia-Pérez et al. reported a near-significant increase in exposed individuals, the overall DNA damage markers such as Tail%DNA and Damage Index remained unaffected, likely due to low-to-moderate consumption levels.[6,36]

Findings regarding smoking varied widely. Some studies observed higher frequencies of polymorphisms such as GSTM1 null, APEX1, XPD, and TGFβ in smokers, suggesting increased oxidative stress and impaired DNA repair, while the NLRP3 rs1539019 variant showed a synergistic effect with smoking in elevating genetic injury.[20,21,39] Conversely, other studies reported no significant differences between smokers and non-smokers among CWP or PMF groups, and certain variants like GITR rs3753348 were even more harmful in non-smokers with prolonged exposure.[22,27] These discrepancies reflect complex interactions between genetic susceptibility and environmental exposures.

Duration of exposure also produced mixed results. BMN-cyt analyses did not show a clear relationship between longer exposure and DNA damage, while Xu et al. found that IL-6 polymorphisms remained significantly associated with CWP even after adjusting for exposure duration.[27,36] Differences in sampling methods and micronucleus scoring may explain these inconsistencies, alongside the multifactorial nature of chronic oxidative stress.[30,49,65]

Sex as a modifying factor was rarely assessed, with one study reporting no significant association despite higher BMN-cyt markers in exposed individuals.[36] Age

also showed conflicting evidence: one study suggested age-related declines in DNA repair capacity, whereas five others found no significant link with DNA damage or polymorphism frequency.[6,21,22,30,36,66] Although age-related telomere shortening may increase vulnerability, its effect appears strongly dependent on interactions between genotype, exposure intensity, and general health status.[66,67] Overall, these findings indicate that no single predisposing factor consistently explains genetic susceptibility, reinforcing the multifactorial nature of coal dust–related genotoxicity.

From a public health perspective, the presence of coal dust–related gene polymorphisms with potential oral manifestations highlights the importance of continued monitoring, improved dust suppression, and strengthened occupational safety standards for miners. Moreover, based on preliminary evidence, this appears to be the first review identifying gene polymorphisms potentially expressed in the oral cavity following coal dust exposure. This knowledge may support future studies aimed at characterizing oral-specific polymorphisms, assessing lesion development, and developing preventive and therapeutic strategies—including targeted gene-based approaches.

The limitation of this review is that, although the review was carried out by three independent reviewers, the results of this review may be biased by the quality assessment of individual studies. From a total of seventeen studies, two case-control studies and one in vitro study were found to have a moderate risk of bias, and four in vivo studies had an unclear risk of bias due to insufficient data details. The moderate risk of bias in two case-control studies was caused by low scores on the selection and exposure quality scale, while in one in vitro study, the moderate risk of bias was caused by low scores on the operator, randomization, and outcome assessor details scale. The unclear risk of bias status in the in vivo study was due to low scores on the quality scale of the selection, detection, and "other" aspects domains.

Furthermore, there are limitations in the content of the articles we obtained. Only a few studies discussed gene polymorphisms caused by coal dust exposure directly affecting the oral cavity, which limits the representativeness of the review. Some articles did not directly demonstrate the presence of gene polymorphisms but only indicated DNA damage through biomarkers. Additionally, many articles did not explicitly state in their methods whether the participants were fully blinded to being in the case or control groups. Almost all the articles also failed to confirm that the control group was completely free of the polymorphism gene.

CONCLUSION

The overall review showed eleven oral-related genes had changes in gene structure variation: AhR, CYP1A1, GTSM1, GSTT1, hOGG1, IL6, IL1B, NQO1, TNF, TP53, and XRCC1. These variations result in changes in the normal activity and function of each gene, leading to increased genotoxicity and tissue mutagenicity. We also found that predisposing factors, such smoking, length of time, and age, contribute to triggering oral gene polymorphisms.

The implications of this review are expected to improve the early detection of susceptible individuals, allowing for a more personalized approach to prevention and treatment. From a policy perspective, the findings may lead to stricter regulations on mine worker safety and improved coal dust management to protect public health. Future research is needed to explore the relationship between gene polymorphisms in the oral cavity and the presence of oral lesions, aiming to develop effective treatment strategies.

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and M.H.A.; data curation, F.H.A., S.N.A., and M.H.A.; writing original draft preparation, F.H.A., S.N.A., and M.H.A; writing review and editing, F.H.A., S.N.A., and M.H.A.; visualization, M.H.A.; supervision, A.N.C. and S.R.P.; project administration, F.H.A. All authors have read and agreed to the published version of the manuscript."

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