Genetic Effects of Welding Fumes on the Development of Respiratory System Diseases

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Abstract

Background: Welding exposes a lot of gases, fumes and radiant energy that may be potentially hazardous for unsafe welder's health. Welding fumes (WFs) are a severe problem among all those exposed. WFs are an intricate composition of metallic oxides, fluorides and silicates that may effect to the progression of various health problems. If a welder inhales such fumes in large quantities over a long period, there is a risk of developing various respiratory system diseases (RSDs).

Methods: We developed quantitative frameworks to recognize the genetic effects of WFs on the development of RSDs. We analyzed Gene Expression microarray data from WFs exposed tissues and RSDs including Chronic Bronchitis (CB), Asthma (AS), Pulmonary Edema (PE), Lung Cancer (LC) datasets. We built disease-gene (diseasome) association networks and identified dysregulated signaling and ontological pathways, and protein-protein interaction sub-network using neighborhood-based benchmarking and multilayer network topology.

Results: We observed that WFs shares a massive number of differentially expressed genes, 34, 27, 50 and 26 with CB, AS, PE and LC respectively. Differentially expressed genes along with disease association networks, pathways, ontological analysis and protein-protein interaction sub-network insured that WFs are responsible for the development of respiratory system diseases, CB, AS, PE and LC.

Conclusion: Our developed network-based approach to analysis and investigate the genetic effects of welding fumes to the progression of CB, AS, PE and LC could be helpful to understand the causal influences of WFs exposure for the development of the RSDs.

Keywords: Welding fumes, Respiratory system diseases, Chronic Bronchitis, Asthma, Pulmonary Edema, Lung Cancer.

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1. Introduction

Welding is the process of joining metal at their contacting surface by using compatible heat and pressure. It is very hazardous because it exposes a lot of gases, fumes and radiant energy. WFs are the most dangerous components among all welding exposers [1]. WFs are an intricate composition of metallic oxides, fluorides and silicates include Beryllium, Aluminum, Cadmium, Chromium, Copper, Iron, Lead, Manganese, Magnesium, Nickel, Vanadium, and Zinc, etc. [2]. If a welder inhales welding fumes in large quantities over a long period, this may convey various RSDs [1, 3].

The human respiratory system consists of a series of organs involved in taking oxygen and expelling carbon dioxide. Nose, mouth, larynx, pharynx, bronchi, trachea and lungs are the most common parts of the respiratory system. The respiratory system can be attacked by a series of diseases such as bacterial pneumonia, emphysema, asthma, chronic bronchitis, and lung cancer [4]. We have studied on several RSDs include CB, AS, PE and LC to find the genetic effects of WFs on them.

Chronic bronchitis is the leading cause of death worldwide that reduces the functionality of lung. It damages the cilia of the breathing tubes and makes obstruction to airflow inside the lung [5]. Iron, Aluminum and Magnesium oxide of the welding fumes may be responsible for chronic bronchitis [6]. The Asthma is a pulmonary system disorder that narrows and inflames the airways. It can cause wheezing, shortness of breath, chest tightness and coughing [7]. Nitrogen oxides, Carbon dioxide and Phosgene of welding fumes may be work as culprits for asthma [6]. Pulmonary Edema is a chronic lung condition characterized by fluid buildup in the lung tissue that leads to serious breathing problems, coughing and chest pain [8]. Nickel, Beryllium and Cobalt oxide of the welding fumes may be responsible for the Pulmonary Edema disease and lung cancer [6]. Lung cancer is the most dangerous type of cancer and is a leading cause of death in the world. It can be characterized by uncontrolled cell growth in the lung tissue [9]. Welding fumes consist of several metallic oxides and silicates that can convey cancer in the lung tissue [6].

In this study, we developed a systematic and quantitative network-based approach to investigate the genetic effects of WFs to the development of RSDs. Thus, we studied the genetic effects for the progression of major RSDs including CB, AS, PE and LC. To find the genetic effects of WFs on RSDs, we analyzed differentially expressed gene, disease association network, signaling and ontology pathways, and protein-protein interaction networks. We also examined the validity of our study by employing the gold benchmark databases, (dbGAP and OMIM).

2. Materials and Methods

2.1. Datasets employed in this study

To understand the genetic effects of WFs on RSDs at the molecular level, we analyzed gene expression microarray data. In this study, we employed gene expression microarray data from the National Center for Biotechnology Information (NCBI) (*http://www.ncbi.nlm.nih.gov/geo/*). We analyzed 5 different datasets with accession numbers

GSE62384, GSE22148, GSE69683, GSE68610 and GSE10072 [10, 11, 12, 13, 14]. The WFs dataset (GSE62384) is a microarray data of fresh welding fumes influence on upper airway epithelial cells (RPMI 2650). This Data is collected from the people with spark-generated welding fumes at high (760 g/m3) and low (85 g/m3) concentrations. The donors inhaled welding fumes for 6 hours continuously, followed by zero hours or four hours post-exposure incubation. The CB dataset (GSE22148) is taken from the 480 ex-smokers and stage 2 - 4 chronic obstructive pulmonary disease patients from the United Kingdom. The AS dataset (GSE69683) is a microarray data collected from severe and moderate asthmatic patients with healthy subjects. The PE dataset (GSE68610) is an Affymetrix gene expression array of 25 acute lung injury patients. The LC dataset (GSE10072) is a microarray data where RNA was collected from 28 current smokers, 26 former smokers and 20 never smokers. In this data, final gene expression values have been reported by comparing between 58 tumor and 49 non-tumor lung tissues.

2.2. Overview of analytical approach

We applied a systematic and quantitative framework to investigate the genetic effects of WFs to the development of the RSDs by using several sources of available microarray datasets. The graphical representation of this approach is shown in figure 1. This approach uses gene expression microarray data to identify dysregulated genes, and identified commonly dysregulated genes for each RSD with WFs. Further, these common dysregulated genes are employed to analyze signaling pathway, gene ontology (GO) and protein-protein interaction (PPI) sub-networks. Gold benchmark data is also used in this approach to verify the validation of our study.

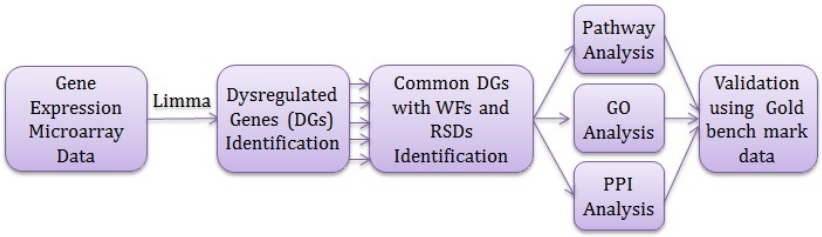


Figure 1: Flow-diagram of the analytical approach used in this study.

2.3. Analysis methods

Microarray based gene expression analysis is a global and sensitive method to find and quantify the human disorders at the molecular level [15]. We used these technologies to analyze the gene expression profiles of Chronic Bronchitis (CB), Asthma (AS), Pulmonary Edema (PE) and Lung Cancer (LC) to find the genetic effects of WFs on the development of respiratory system diseases. To uniform the mRNA expression data of different platforms and to avoid the problems of experimental systems, we normalized the gene expression data by using the Z-score transformation (Z_{ij}) for each RSD gene expression profile using $Z_{ij} = \frac{g_{ij} - mean(g_i)}{SD(g_i)}$,

where SD denotes the standard deviation, g_{ij} denotes the value of the gene expression i in sample j. After this transformation gene expression values of different diseases at different platforms can be directly compared. We applied two conditions for t-test statistic. We applied unpaired T-test to find differentially expressed genes of each disease over control data and selected significant dysregulated genes. We have chosen a threshold of at least 1 log_2 fold change and a p-value for the t-tests of $<= 1 * 10^{-2}$.

We employed neighborhood-based benchmark and the multilayer topological methods to find gene-disease associations. We constructed gene-disease network (GDN) using the gene-disease associations, where the nods in the network represent either gene or disease. This network can also be recognized as a bipartite graph. The primary condition for a disease to be connected with other diseases in GDN is they should share at least one or more significant dysregulated genes. Let D is a specific set of diseases and G is a set of dysregulated genes, gene-disease associations attempt to find whether gene $g \in G$ is associated with disease $d \in D$. If G_i and G_j, the sets of significant dysregulated genes associated with diseases D_i and D_j respectively, then the number of shared dysregulated genes (n_{ij}^g) associated with both diseases D_i and D_j is as follows [15]:

$$n_{ij}^g = N(G_i \cap G_j) \tag{1}$$

The common neighbours are the based on the Jaccard Coefficient method, where the edge prediction score for the node pair is as [15]:

$$E(i,j) = \frac{N(G_i \cap G_j)}{N(G_i \cup G_j)} \tag{2}$$

where G is the set of nodes and E is the set of all edges. We used R software packages "comoR" [16] and "POGO" [17] to cross check the genes-diseases associations.

To investigate the molecular determinants of WFs on several RSDs, we analyzed pathway and gene ontology using Enrichr ($https://amp.pharm.mssm.edu/Enrichr/$). We used KEGG, WikiPathways, Reactome and BioCarta databases for analyzing signaling pathway [18, 19, 20, 21]. We used GO Biological Process and Human Phenotype Ontology databases for ontological analysis [22, 23]. We also constructed a protein-protein interaction subnetwork for each RSD, using the STRING database ($https://string-db.org$), a biological database and web resource of known and predicted protein-protein interactions. Furthermore, we examined the validity of our study by employing two gold benchmark databases OMIM ($https://www.omim.org$) and dbGAP ($https://www.ncbi.nlm.nih.gov/gap$).

3. Results

3.1. Gene Expression Analysis

We analyzed the gene expressing microarray data from the National Center for Biotechnology Information (NCBI) ($http://www.ncbi.nlm.nih.gov/geo/$) for investigating the genetic effect of WFs to the development of RSDs. We observed that WFs have 903 differentially expressed genes obtained by adjusted $p <= .01$ and $|logFC| >= 1$. The differentially expressed genes of WFs contain 392 up and 511 down regulated genes. Similarly,

we identified the most significant dysregulated genes for each RSD after applying various steps of statistical analysis. We identified differentially expressed genes, 678 (463 up and 215 down) in CB, 602 (297 up and 305 down) in AS, 759 (404 up and 355 down) in PE and 890 (673 up and 217 down) in LC. We also performed cross-comparative analysis to find the common dysregulated genes between WFs and each RSD. We observed that WFs shares a huge number of differentially expressed genes 34, 27, 50 and 26 with CB, AS, PE and LC respectively. To investigate the significant associations among these RSDs with WFs, we built two separate gene-disease association networks for up and down-regulated genes, centered on the WFs as shown in figure 2 and 3. The essential condition for two diseases to be associated with each is they should have at least one or more common genes in between them [24]. Notably, two significant genes, PMAIP1 and SEC24A are commonly differentially expressed among WFs, PE, AS and LC; six significant genes, FGFR3, ID3, PROS1, AK4, TOX3 and MTHED2 are shared among WFs, PE and LC. Similarly, PECR, ALDH3A2 and TPD52L1 are commonly differentially expressed among WFs, PE and CB; one gene HSD17BB is commonly dysregulated among WFs, AS and CB.

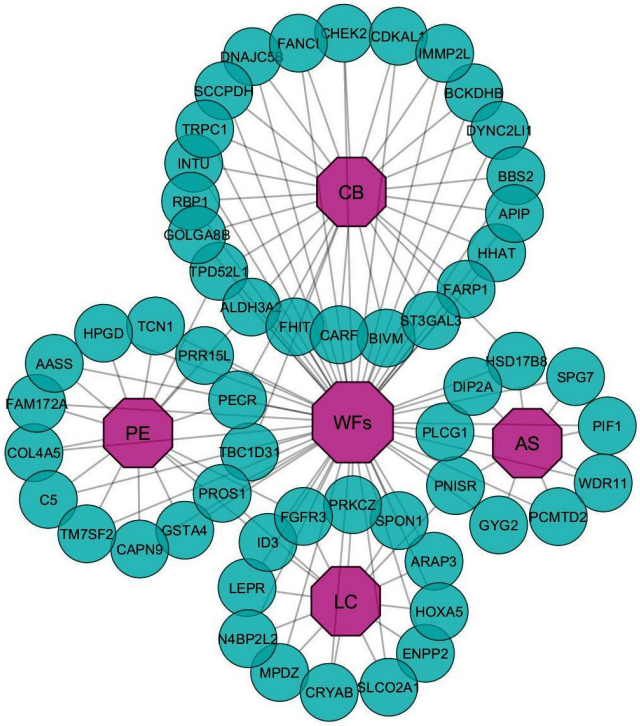


Figure 2: Gene-disease association network of Welding fumes (WFs) with Chronic Bronchitis (CB), Asthma (AS), Pulmonary Edema (PE) and Lung Cancer (LC). Octagon-shaped violet colored nodes represent different RSDs, and dark-cyan colored round-shaped nodes represent commonly up-regulated genes for WFs with the other respiratory system diseases. A link is placed between a disease and a gene if mutations in that gene lead to the specific disease.

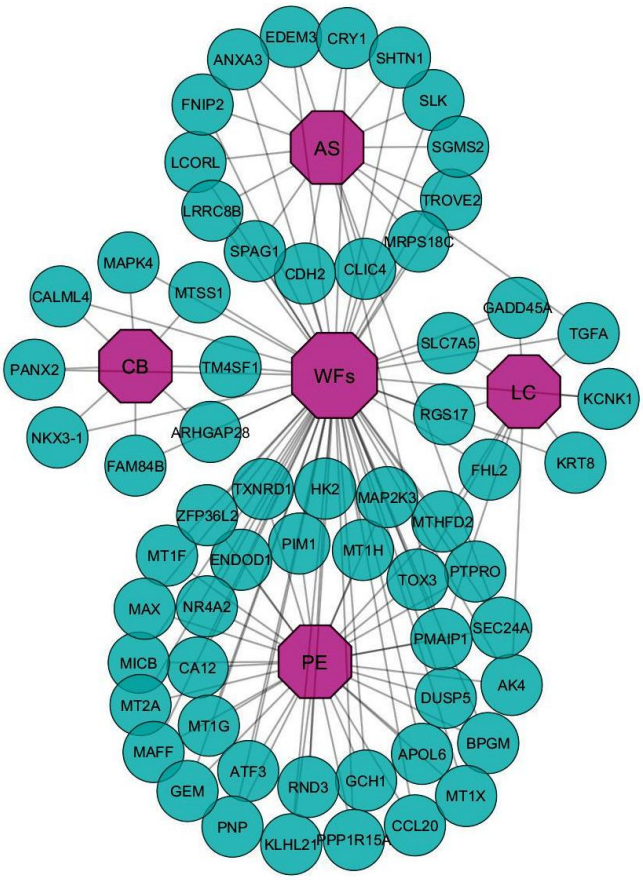


Figure 3: Gene-disease association network of Welding fumes (WFs) with Chronic Bronchitis (CB), Asthma (AS), Pulmonary Edema (PE) and Lung Cancer (LC). Octagon-shaped violet colored nodes represent different RSDs, and dark-cyan colored round-shaped nodes represent commonly down-regulated genes for WFs with the other respiratory system diseases. A link is placed between a disease and a gene if mutations in that gene lead to the specific disease.

3.2. Pathway and Functional Association Analysis

Pathways are the important key to understand the reactions of an organism for its internal changes. The pathway-based analysis is a modern technique to understand how different complex diseases are related to each other by underlying molecular or biological mechanisms [25]. We analyzed pathways of the commonly dysregulated genes of WFs and each RSDs using Enrichr, a comprehensive web-based tool for analyzing gene set enrichment [26]. Signaling pathways of the commonly differentially expressed genes in between WFs and each RSD were analyzed using four global databases includes KEGG, WikiPathways, Reactome and BioCarta. We collected and combined pathways from the mentioned four databases and selected the most significant pathways of each RSD after several steps of statistical analysis.

We found four significant pathways associated with CB as shown in figure 4(a). Among these pathways, 'Integrated Pancreatic Cancer Pathway' contains some important proteins

that are responsible to develop breast cancer in the human body [27]. The pathway 'Assembly of the motile cilium' is responsible to the formation of motile cilium such as respiratory cilium [28]. Methionine salvage is a pathway that performs six reactions in the human body and is responsible for the recycling of sulfur in the respiratory system [29]. The pathway 'Glyoxylate metabolism and glycine degradation' is responsible for overproduction of oxalate in human liver and lung. [30].

We found five significant pathways associated with AS as shown in figure 4(b). Among these pathways, 'Non-small cell lung cancer' consists of adeno, squamous cell and large-cell carcinoma that are responsible for approximately 75% of all lung cancer [31]. 'IL-1 Signaling Pathway' is responsible to control pro-inflammatory reactions in the injured tissue [32]. 'Glycogen synthesis' is responsible for several reactions to make glycogen in liver, muscle, lung and other tissues that serves as a major stored fuel [33]. 'Constitutive Signaling by EGFRvIII' is responsible for the development of tumors in the cell. 'Signaling by EGFRvIII in Cancer' is responsible for cancer in several cells of the respiratory system.

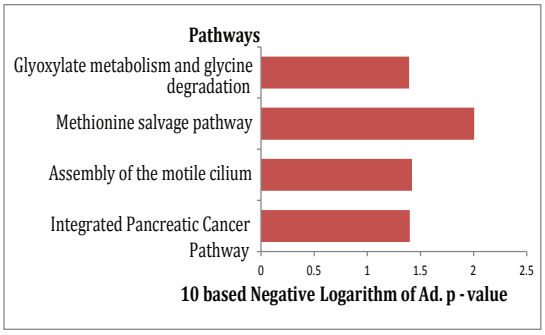
We found five significant pathways associated with PE as shown in figure 4(c). Among these pathways, 'Central carbon metabolism in cancer' is responsible for three transcription factors HIF-1, c-MYC and p53 that influence the regulation of tumor and cancer in cell [34]. 'Small cell lung cancer' is a highly aggressive neoplasm that is responsible for approximately 25% of all lung cancer [35]. 'TNF signaling pathway' is responsible for inflammation, immunity and cell survival. 'One carbon pool by folate' is responsible for progressing several forms of cancer [36]. 'Response to metal ions' is responsible for metallic effect in cell includes zinc, copper, and iron [37].

We found five significant pathways associated with LC as shown in figure 4(d). Among these pathways, 'Central carbon metabolism in cancer' is responsible for three transcription factors HIF-1, c-MYC and p53 that can coordinate regulation of tumor and cancer in cell [34]. 'Bladder Cancer' is responsible for developing several carcinomas in urinary tract, renal pelvis, ureter and bladder [38]. 'Signaling by activated point mutants of FGFR3' is responsible for several cancer including breast, prostate, bladder, cervical, neck and head [39]. 'Signaling by FGFR3 fusions in cancer' is specifically responsible for lung and bladder cancer [40]. 'TGF-beta receptor signaling in EMT' is responsible for the development of tumors in the early stage that can bring cancer in cells [41].

3.3. Gene Ontological Analysis

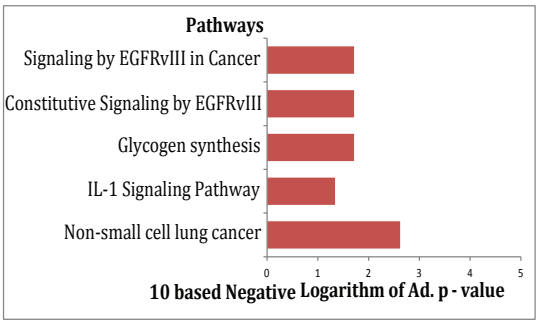
The Gene Ontology (GO) refers to a universal conceptual model for representing gene functions and their relationship in the domain of gene regulation. It is constantly expanded by accumulating the biological knowledge to cover regulation of gene functions and the relationship of these functions in terms of ontology classes and semantic relations between classes [42]. GO of the commonly dysregulated genes for each RSD and WFs were analyzed using two databases including GO Biological Process and Human Phenotype Ontology. We collected and concatenated gene ontologies from mentioned two databases, and performed several statistical analyses to identify the most significant ontologies of each respiratory system diseases. Notably, we found 15, 15, 24 and 17 gene ontology terms are associated with the CB, AS, PE and LC respectively as shown in table 1.

Pathway	Genes in the pathway	Adjusted p-value
Integrated Pancreatic Cancer Pathway	CHEK2, MAPK4	3.98E-02
Assembly of the motile cilium	BBS2, DYNC2LI1	3.80E-02
Methionine salvage pathway	APIP	9.86E-03
Glyoxylate metabolism and glycine degradation	BCKDHB	4.05E-02



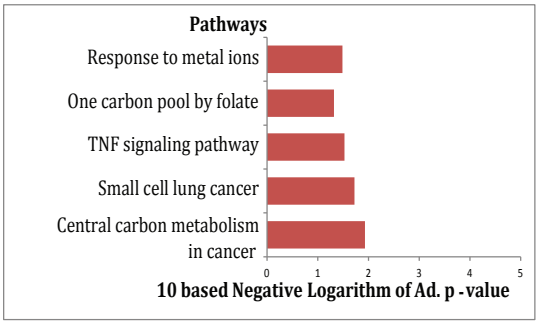
(a) Pathways associated with significantly commonly differentially expressed genes of the CB with WFs.

Pathway	Genes in the pathway	Adjusted p-value
Non-small cell lung cancer	TGFA, PLCG1	2.40E-03
IL-1 Signaling Pathway	PLCG1	4.58E-02
Glycogen synthesis	GYG2	1.93E-02
Constitutive Signaling by EGFRvIII	PLCG1	1.93E-02
Signaling by EGFRvIII in Cancer	PLCG1	1.93E-02



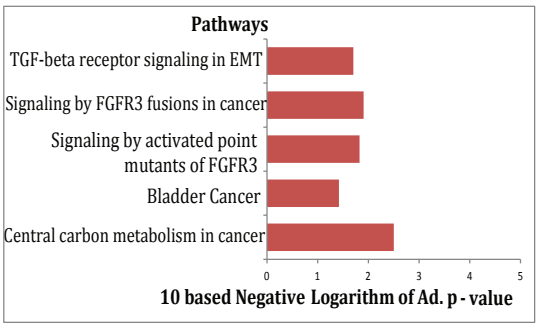
(b) Pathways associated with significantly commonly differentially expressed genes of the AS with WFs.

Pathway	Genes in the pathway	Adjusted p-value
Central carbon metabolism in cancer	FGFR3, HK2	1.17E-02
Small cell lung cancer	MAX, COL4A5	1.89E-02
TNF signaling pathway	MAP2K3, CCL20	2.98E-02
One carbon pool by folate	MTHFD2	4.79E-02
Response to metal ions	MT2A, MT1F, MT1G	3.27E-02



(c) Pathways associated with significantly commonly differentially expressed genes of the PE with WFs.

Pathway	Genes in the pathway	Adjusted p-value
Central carbon metabolism in cancer	SLC7A5, FGFR3	3.16E-03
Bladder Cancer	FGFR3	3.81E-02
Signaling by activated point mutants of FGFR3	FGFR3	1.49E-02
Signaling by FGFR3 fusions in cancer	FGFR3	1.24E-02
TGF-beta receptor signaling in EMT	PRKCZ	1.98E-02



(d) Pathways associated with significantly commonly differentially expressed genes of the LC with WFs.

Figure 4: Pathway analyses to identify significant pathways common to the WFs and the RSDs revealed by the commonly expressed genes.

Table 1: Gene ontology analyses to identify significant ontological pathways common to the WFs and the RSDs revealed by the commonly expressed genes.

GO Term	Pathway	Genes in the Pathway	Adjusted p-value
GO:2001233	Regulation of apoptotic signaling pathway	TPD52L1, NKX3-1	8.37E-04
GO:0060562	Epithelial tube morphogenesis	MTSS1, NKX3-1	1.52E-03
GO:0050678	Regulation of epithelial cell proliferation	MTSS1, NKX3-1	6.45E-03
GO:0046467	Membrane lipid biosynthetic process	ALDH3A2, SCCPDH	4.55E-03
GO:0051225	Spindle assembly	GOLGA8B, CHEK2	7.89E-03
GO:2001235	Positive regulation of apoptotic signaling pathway	TPD52L1, NKX3-1	7.15E-03
HP:0100631	Neoplasm of the adrenal gland	CHEK2	2.61E-02
HP:0002858	Meningioma	CHEK2	2.77E-02
HP:0007707	Congenital primary aphakia	BBS2	2.93E-02
HP:0100641	Neoplasm of the adrenal cortex	CHEK2	1.64E-02
HP:0002476	Primitive reflexes	ST3GAL3	1.48E-02
HP:0012126	Stomach cancer	CHEK2	1.48E-02

(a) Gene ontologies associated with the significantly commonly dysregulated genes of the CB with WFs.

GO Term	Pathway	Genes in the Pathway	Adjusted p-value
GO:2000323	Negative regulation of glucocorticoid receptor signaling pathway	CRY1	9.07E-03
GO:0031334	Positive regulation of protein complex assembly	PMAIP1, FNIP2	5.94E-03
GO:1904018	Positive regulation of vasculature development	ANXA3, PLCG1	8.17E-03
GO:0010634	Positive regulation of epithelial cell migration	ANXA3, PLCG1	4.25E-03
GO:0032147	Activation of protein kinase activity	SLK, TGFA, PLCG1	3.37E-03
GO:0043067	Regulation of programmed cell death	SLK, PMAIP1, DIP2A	4.98E-03
HP:0002492	Abnormality of the corticospinal tract	SPG7	1.29E-02
HP:0004469	Chronic bronchitis	SPAG1	1.55E-02
HP:0012261	Abnormal respiratory motile cilium physiology	SPAG1	2.44E-02
HP:0200073	Respiratory insufficiency due to defective ciliary clearance	SPAG1	1.16E-02
HP:0012384	Rhinitis	SPAG1	2.44E-02
HP:0000458	Anosmia	WDR11	2.82E-02
HP:0012387	Bronchitis	SPAG1	3.58E-02

(b) Gene ontologies associated with the significantly commonly dysregulated genes of the CB with WFs.

GO Term	Pathway	Genes in the Pathway	Adjusted p-value
GO:0071294	Cellular response to zinc ion	MT2A, MT1F, MT1G	1.08E-09
GO:0071276	Cellular response to cadmium ion	MT1G, MT1H, MT1X	9.74E-09
GO:0006882	Cellular zinc ion homeostasis	MT1F, MT1H, MT1X	1.37E-08
GO:0071280	Cellular response to copper ion	MT1X, MT1G, MT2A	1.83E-09
GO:0045926	Negative regulation of growth	MT2A, MT1F, MT1G	4.89E-07
GO:0046916	Cellular transition metal ion homeostasis	MT2A, MT1F, MT1G, MT1H, MT1X	3.34E-06
GO:1905898	Positive regulation of response to endoplasmic reticulum stress	PPP1R15A, PMAIP1	7.81E-04
GO:0071248	Cellular response to metal ion	MT2A, MT1F, MT1G	4.75E-06
HP:0002970	Genu varum	HPGD, FGFR3	2.61E-03
HP:0006297	Hypoplasia of dental enamel	ALDH3A2, FGFR3	3.32E-03

(c) Gene ontologies associated with the significantly commonly dysregulated genes of the PE with WFs.

GO Term	Pathway	Genes in the Pathway	Adjusted p-value
GO:1903708	positive regulation of hemopoiesis	N4BP2L2, HOXA5	4.18E-05
GO:0009132	nucleoside diphosphate metabolic process	AK4	9.96E-03
GO:0045647	negative regulation of erythrocyte differentiation	HOXA5	8.72E-03
GO:2000665	regulation of interleukin-13 secretion	PRKCZ	8.72E-03
GO:0044320	cellular response to leptin stimulus	LEPR	9.96E-03
GO:0045837	negative regulation of membrane potential	PMAIP1	8.72E-03
GO:2000394	positive regulation of lamellipodium morphogenesis	ENPP2	9.96E-03
GO:0050730	regulation of peptidyl-tyrosine phosphorylation	ENPP2, PRKCZ	5.14E-03
GO:0032754	positive regulation of interleukin-5 production	PRKCZ	9.96E-03
GO:0043065	positive regulation of apoptotic process	GADD45A, PMAIP1	6.47E-03
HP:0000975	Hyperhidrosis	SLCO2A1, FGFR3	5.38E-03
HP:0000522	Alacrima	FGFR3	1.24E-02
HP:0010662	Abnormality of the diencephalon	LEPR	1.86E-02
HP:0000495	Recurrent corneal erosions	FGFR3	1.49E-02
HP:0001413	Micronodular cirrhosis	KRT8	1.86E-02

(d) Gene ontologies associated with the significantly commonly dysregulated genes of the LC with WFs.

3.4. Protein-Protein Interaction Analysis

Protein-protein interaction network (PPIN) is the graphical representation of the physical connection of proteins in the cell. Protein-protein interactions (PPIs) are essential to every molecular and biological process in a cell, so PPIs is crucial to understand cell physiology in disease and healthy states [43]. We have used STRING database to analyze and construct protein-protein interaction subnetworks of the significantly commonly dysregulated genes of each RSD. We have clustered into four different groups of protein-protein interactions of four RSDs as shown in figure 5.

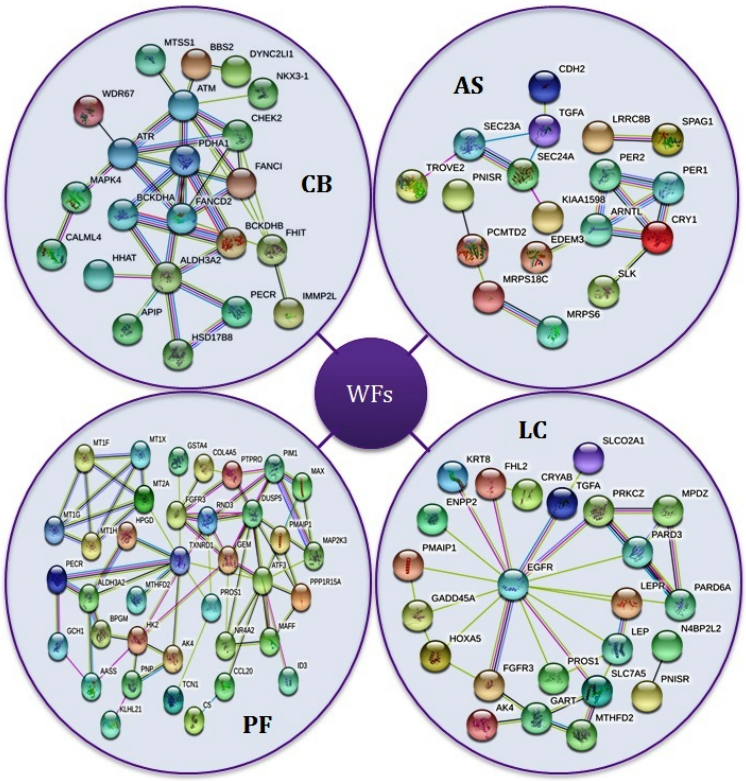


Figure 5: Protein-Protein Interaction Network of RSDs using STRING.

4. Discussion

We investigated the genetic effects of Welding fumes (WFs) to the development of respiratory system diseases (RSDs) based on the gene regulation analysis, gene-disease association networks, signaling pathways, gene expression ontologies and protein-protein interaction sub-networks. For the purpose of our study, we analyzed gene expression microarray data from WFs, Chronic Bronchitis (CB), Asthma (AS), Pulmonary Edema (PE), Lung Cancer (LC) and control datasets. We identified a massive number of significantly commonly differentially expressed genes in between WFs and RSDs by gene expression analysis. As there have a massive number of significantly commonly differentially expressed genes of WFs and

RSDs that indicates that WFs should have genetic effects on the development of RSDs. Our constructed two separate gene-disease association networks for up and down-regulated genes showed a strong evidence that WFs are highly responsible for the development of RSDs as shown in Figure 2 and 3. The pathway-based analysis is useful to understand how different complex diseases are related to each other by underlying molecular or biological mechanisms. We identified significant pathways of the commonly dysregulated genes of each RSD with the WFs. These identified pathways showed that WFs have a strong association with RSDs. Similarly, gene expression ontologies and protein-protein interaction sub-networks of the commonly differentially expressed genes determine that WFs is a major causative reason for the progression of the several RSDs on unsafe welder's health.

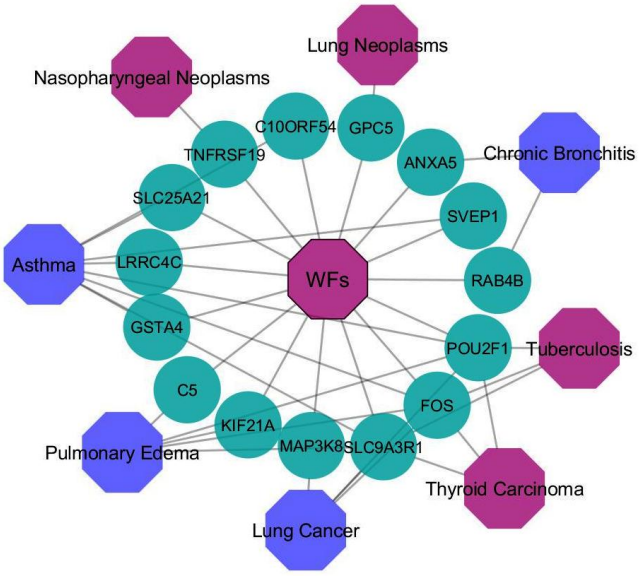


Figure 6: Gene-disease association network of Welding fumes (WFs) with several RSDs. Violet colored octagon-shaped nodes represent different RSDs, blue colored octagon-shaped nodes represent our selected four RSDs and round-shaped dark-cyan colored nodes represent differentially expressed genes for WFs. A link is placed between a disease and a gene if mutations in that gene lead to the specific disease.

We have used the gold benchmark databases (dbGAP and OMIM) to verify the outcome of our study and observed that there are a number of shared genes between the WFs and RSDs as shown in figure 6. For cross checking the validity of our study, we collected disease and genes names from OMIM Disease, OMIM Expanded and dbGap databases using significantly dysregulated genes of WFs. We concatenated the list of diseases as well as genes from the mentioned three databases and selected only respiratory system diseases (RSDs) after several steps of statistical analysis. Interestingly, we found our selected four RSDs among the list of collected RSDs from the mentioned databases as shown in figure 6. Therefore, it proved that WFs have a strong association for the development of CB, AS, PE and LC respiratory system diseases.

5. Conclusions

In this study, we have considered gene expression microarray data from welding fumes (WFs), Chronic Bronchitis (CB), Asthma (AS), Pulmonary Edema (PE), Lung Cancer (LC) and control datasets to analyze and investigate the genetic effects of WFs on respiratory system diseases (RSDs). We analyzed genes regulation, built gene-disease association networks, identified signaling pathways, identified gene expression ontologies and protein-protein interaction sub-networks of WFs and each RSDs. Our findings showed that WFs have a strong association on the development of RSDs. This kind of study will be useful for making genomic evidence based recommendations about accurate disease prediction, identification and therapeutic treatments. This study will also be useful for making society aware of the dangerous effect of welding on the human body.

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