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Review article

A step forward into respiratory genetics: overview contribution of genetics in respiratory diseases

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Background: In developing countries, especially in Southeast Asia, there is a misconception that genetics is only relevant to dysmorphology and prenatal obstetrics. Respiratory diseases, which are the most prevalent, range from simple Mendelian (single gene) diseases to complex (polygenic) disorders, surely have genetic determinants. Now, even in this "post-genomic era" many clinicians are not aware of advances in genetics available for prevention, diagnosis, and therapy of respiratory diseases.
Objective: The aim of this study is not to serve as a comprehensive review of genetics or genomics but to highlight genetic information relevant to clinical practice. Here, we describe genetic information pertaining to some of the most frequently encountered respiratory diseases.
Methods: The present review was prepared by reviewing the current literature using PubMed and Web of Science searches.
Results: Knowledge of the basic principles and genetic terms is important in clinical practice. Based on that knowledge, we can now recognize much progress in the respiratory field. The single gene and complex diseases have been identified. Translating genetic information into prevention, diagnosis, or therapy of such diseases can have great potential benefit for patients.
Conclusion: Genomics and molecular genetics could be integrated in the clinical setting. Ultimately, genomic knowledge and approaches will become increasingly important in the clinical setting for many respiratory diseases.

Keywords: Genetics, genomics, lung diseases, medical sciences, respiratory

In the era after the completion of the Human Genome Project, an international research effort to determine the complete sequence of the human genome, knowledge of molecular medicine and genetics are progressing rapidly. There has been an explosion in the amount of genetic information available across many areas of medicine, including the respiratory field [1]. Many lung diseases clearly have a genetic component, and this provides an early clue to the disease mechanism [2]. Translating this information into routinely applied diagnostics will be a challenge, but it will also create a new approach to clinical practice with many benefits for the patient. However, for most clinicians, especially in developing countries, the genome era has not yet arrived.

The aim of this review is not to be a comprehensive study but is intended to overview some of the explosion of genetic data and its potential value for management and research in respiratory diseases. Finally we hope to stimulate pulmonologists and others clinicians to redefine their ideas regarding the conceptual basis for understanding disease. The present review related to genetics and respiratory medicine was prepared by reviewing the current literature using PubMed and Web of Science searches with the following terms: "genetic AND respiratory medicine", "respiratory genetic", and "lung AND genetic" as well as specific terms such as "asthma AND genetic" and "COPD AND genetic".

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Genetics of a single gene disorder

Single gene defects can be responsible for disease and may segregate with Mendelian inheritance (recessive, dominant, or X-linked). In fact, most single gene disorders affect a limited population. The most common single gene disorders involving the lung are α1-anti-trypsin deficiency and cystic fibrosis (CF) [3]. The genetic defect in cystic fibrosis impairs mucociliary clearance and shows autosomal recessive inheritance. Consequently, two unaffected carriers, each carrying one mutant copy of the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene, have a 25% probability of having a child with cystic fibrosis. The *CFTR* gene consists of 180,000 base pairs on the long arm of chromosome 7. The protein contains 1,480 amino acids, and more than 1,700 mutations are listed in the CFTR mutation database [4]. Deletion of three base pairs at position 508 (known as "508), which results in the loss of a phenylalanine, is the most common CF mutation. Others include missense mutations, such as G551D, nonsense mutations such as G542X, and frame shift mutations, such as c.3908dupA and Asn1303LysfsX6 [5, 6]. These *CFTR* mutations result in expression of a non-functional chloride channel. Mutations leading to CF have been classified as mild or severe depending upon the degree of function of the defective CFTR protein. Understanding of the genetic basis of the disease may help physicians to implement screening programs and classify phenotypic subtypes.

Genetics of complex diseases

Conditions resulting from the combination of environmental and polygenic factors are called complex or multi-factorial disorders. Complex disorders are difficult to study and treat because the specific etiologies of these disorders have not yet been identified. Some alleles might predispose to disease (susceptibility alleles), whereas others might be protective, or might be involved in severity and progression (modifying genes) [7].

Asthma

Asthma is one of the complex diseases with strong genetic and environmental components. Many researchers have reported that genetic factors play an important role in the development of asthma. Two general approaches have been widely used to study the genetics of asthma, candidate gene association studies, and a newer approach involving genome-wide association studies (GWAS) [9]. More than 100 candidate genes have been identified using candidate gene association studies, initially selected because their function is implicated in the pathophysiology of asthma. **Table 1** shows selected candidate genes based on candidate gene association studies. Candidate gene studies may focus on a single gene or on a few genes in combination. This study approach is relatively quick to perform, there is no need to collect pedigree information, and the statistical power may be high. However, results vary enormously and are often not replicated in follow-up studies since asthma is a complex disease that may be influenced by multiple genes or environmental effects. The latest technique to identify asthma genes is the genome-wide association study. This technique identifies chromosomal regions containing possible asthma susceptibility genes by genotyping hundreds of thousands of loci in different individuals without regard to their assumed biological function [8]. The first GWAS in asthma found that genetic variants in ORM1-like 3 (located on chromosome 17q21), regulating the *ORMDL3* gene, were strongly associated with asthma, and results were replicated in two cohorts [9]. Subsequently, other studies also confirmed this result in Asian population [10, 11].

Recently, Himes et al identified *PDE4D* as a novel candidate gene in asthma. This GWA study of 359 cases and 846 genetically matched controls was also replicated in 10 independent populations [12]. The phospodiesterase 4D, cAMP-spesific gene (phosphodiesterase E3 dunce homolog, Drosophila, PDE4D) likely has functions as a regulator of smooth muscle contractility in the airway, and PDE4 inhibitors have been developed as medications for asthma [12]. Many more GWA studies are currently underway, but early studies have reported different main loci and candidate genes associated with asthma. This evidence supports the common perception that asthma is extremely heterogeneous, in which multiple genes interact with each other, as well as with many unknown environmental factors [13, 14]. However, we can expect that some variants may have a critical effect on asthma in some high-risk populations in high-risk environments. The essential goal of genetic studies of asthma is to apply such information to clinical management such as risk stratification, prevention, and targeted therapy.

Table 1. Several candidate genes in non-cancer respiratory diseases

Gene	Chromosome	Study	Molecular Function	Possible mechanism
ASTHMA				
ORMDL3	17q12	Cantero-Recasens et al. [82]	Transmembrane protein	altered endoplasmic reticulum (ER)-mediated Ca2+ then increase unfolded-protein response (UPR)
PDE4D	5q11.2-q12.1	Himes et al. [12]	cAMP specific	a regulator of airway smooth-muscle contractility
ADAM33	20p13	Van Eerdewergh et al. [83]	Metalloprotease	Airway remodeling, Bronchial hyperresponsiveness
DPP10	2q14	Allen et al. [84]	Select regulatory molecule	Regulating activities of chemokine and cytokines
GPR154	7p15	Laitinen et al. [85]	G-protein coupled receptor	Bronchial epithelial and smooth muscle surface receptor
PHF11	13q14	Zhang et al. [86]	Double stranded DNA-binding protein	Serum total IgE regulation and altered Th1/Th2 cytokine release
HLA-G	6p21	Nicolae et al. [87]	Major histocompatibility complex antigen	Airway remodeling by inhibiting angiogenesis
COPD				
GSTP1	11q13	Putra, AC et al. [88], Smolonska J et al. [89]	Detoxify enzymes	catalyzing the conjugation of hydrophobic and compounds with reduced glutathione
*CHRNA**	15q25.1	Pillai et al. [34], Young et al. [44]	ligand-gated ion channels	Stimulation of nicotinic receptors by acetylcholine or tobacco-associated agonists
TNF	6p21.3	Sapey E et al. [90]	a multifunctional proinflammatory cytokine	Downstream inflammation of the lung
EPHX1	1q42.1	Putra, AC et al. [88], Smolonska J et al. [89]	Biotransformation enzymes	activation and detoxification of epoxides
*HHIP**	4q31	Pillai et al. [34] Young et al. [44]	an inhibitory protein for sonic hedgehog	signaling molecules in regulating morphogenesis
IPF				
SFTPC	8p21	Van Moorsel et al. [91], Garcia CK et al. [54]	pulmonary-associated surfactant protein C	increased endoplasmic reticulum stress in type II alveolar epithelial cells
IL6	7p21	Pantelidis P et al. [92]	Proinflammatory cytokine	Promote fibrogenesis
ACE	17q23.3	Morrison et al. [93], Grutters J.C et al. [94]	Catalyzing enzyme in conversion angiotensin I to angiotensin II	ACE increase angiotensin II and have been shown to promote lung fibrosis
TERT	5p15.33	Diaz de Leon et al. [60]	Ribonucleoprotein enzyme	Telomerase dysfunction evidenced by the progressive shortening of telomere length with age

*Based on GWAS, these genes are common to both COPD and lung cancer [44]

Chronic obstructive pulmonary disease

Similar to asthma, chronic obstructive pulmonary disease (COPD) is a complex disease with genetic and environmental components. COPD is characterized by irreversible airway obstruction resulting from oxidant-antioxidant [15], proteolysis-antiproteolysis [16], inflammation [17], xenobiotic metabolism, mucus homeostasis-host defense mechanisms, and airway hyper-responsiveness [18, 19]. Many genes implicated in the pathogenesis of COPD have been reported. The most prominent genetic factor related to the mechanism of COPD is alpha1-antitrypsin (AAT) deficiency. Patients with defective AAT secretion, usually associated with Z variant homozygosity, have only 10% of the normal plasma AAT level. Consequently, lung tissue is not properly defended against proteolytic attack from neutrophil elastase [20, 21]. However, only 1 to 2% of COPD patients have AAT deficiency, therefore other genes are believed to contribute in most COPD cases [22].

In our laboratory, we have performed case control studies for several candidate genes in COPD. We clarify that the frequency of *GSTP1* Ile105Val homozygotes was higher in COPD cases than in controls, especially in controls aged >51 years ($p = 0.031$) [23]. GSTP1 is an antioxidative enzyme that protects lung tissue from oxidative stress. This gene is a member of the glutathione-S-transferase family, which is known to be polymorphic with allele variants showing differences in enzyme activity. Substitution of isoleucine (Ile) by valine (Val) at amino acid position 105 inhibits the detoxification reaction and increases susceptibility to development of COPD [24, 25]. Furthermore, other antioxidative enzymes, such as epoxide hydrolase (EPHX1) and GSTM1, have been reported to be associated with severe COPD cases [23, 26].

COPD has been described as an organ pathology involving acute and chronic inflammation. Numerous mediators and cells have been implicated in the pathogenesis of COPD in response to the inflammation process. One of the important mediators is tumor necrosis factor-alpha (TNF-α). In animal models, overexpression of TNF-α has been shown to be associated with pathological features of COPD and pulmonary fibrosis [27]. One -308 TNF-α SNP is associated with increased promoter activity. Therefore, TNF-α polymorphism might contribute to COPD susceptibility and may influence pulmonary functional parameters [28-30]. Furthermore, since hypoxia is a common feature of COPD, we also examined polymorphisms in a key regulator of hypoxia, HIF-1α., and found a possible involvement of this gene in COPD [23]. Similarly with asthma, Several GWAS on COPD have been conducted and identified some candidate loci possibly associated with COPD such as *HHIP*, *CHRNA5*, *FAM13A* and *ADYC2* [31-35]. Indeed, COPD is a heterogeneous disease, and numerous studies have been published in an attempt to gain a clearer understanding of COPD pathogenesis. In the future, the combination of several approaches will likely lead to new insight into the genetics of COPD.

Lung cancer

Lung cancer is well known as a genetic disease, and many genetic events occur throughout the carcinogenesis process. In the genetic basis of lung cancer, there are two important areas that remain hot issues: genetic susceptibility to lung cancer and genetic changes accompanying lung carcinogenesis. Extensive evidences shows that tobacco smoking may cause lung cancer. Exposure to other environmental factors, such as radon and asbestos as well as occupational hazards, have been identified to contribute to the development of lung cancer. However, not all smokers or persons exposed to carcinogenic substances will develop lung cancer. This implies that genetic factors may influence susceptibility to lung cancer. Many investigators have reported genetic variants and abnormalities in lung carcinogenesis in genes responsible for metabolic enzymes [36], DNA repair [37, 38], cell cycle regulators [39], and many tissue-specific factors [40-44]. **Tables 2 and 3** show the summary of studies involving genetic polymorphism and abnormalities in lung cancer. In this review, we discuss the relationship between genetic polymorphism and lung cancer, with special emphasis on genes that regulate hypoxia, which is a hallmark of cancer microenvironment.

Hypoxia is defined as inadequate supply of oxygen. It is well known that many human tissues are exposed to low oxygen levels. Under hypoxic conditions, our cells initiate a variety of responses to maintain oxygen homeostasis. Hypoxia-inducible transcription is a central facet of the cellular response to a hypoxic environment. Hypoxia-inducible factor-1 (HIF-1) is a master regulator of hypoxia and is reported to induce more than 100 target genes,

including genes involved in hematopoesis (e.g. *EPO*), iron metabolism (e.g. transferin, transferin-receptor), angiogenesis and vascular tone (e.g. *VEGF*, heme oxygenease-1), energy metabolism (e.g. glucose transporter 1 and 3, lactate dehydrogenase A), cell proliferation and differentiation (e.g. IGF binding protein 1 and 3, TGF-β), pH regulation (e.g. carbonic anhydrase 9), and matrix metabolism/barrier function (e.g. collagen prolyl-4-hydroxylase-α1) [45]. Many investigators have studied polymorphisms in *HIF1A* since this gene is overexpressed in human cancers, whereas it is normally not expressed in mature normal tissues [46]. Two common *HIF1A* polymorphisms are *C1772T* and *G1790A*, which are located within or near the N-TAD region, which is critical for transactivation activity. Significant associations have been reported between HIF-1α polymorphisms and lung cancer [41, 47], breast cancer [48], head and neck cancer, renal cancer [49], colorectal [50], cervical and endometrial cancer [51].

In relation to lung cancer, Koukourakis et al. reported HIF-1α polymorphisms associated with protein expression in cancer cells and suggested that HIF-1α variants may increase tumor susceptibility or cause aggressive biological behavior [47]. In addition, the authors speculated that HIF-1α variants enhance down-regulation of DNA repair, resulting in defective DNA repair and hypermutation states. This may result in genetic instability and mutation in tumor suppressor genes such as p53 [41]. However, the role of HIF-1α polymorphisms in the susceptibility to lung cancer remains to be elucidated. Indeed, progress in genome analysis allows us to explore the molecular mechanisms of growth, invasion, and metastasis as a means to develop new therapeutics by targeting abnormal molecules.

Table 2. Frequent genetic polymorphisms and genetic abnormalities in lung cancer

Polymorphism	Gene	Molecular change	Possible functional change	Reference
Metabolizing enzymes	*CYP1A1*	*T→C* (*Msp*I site), intron 6	Increase enzyme activity and results increase level of genotoxic metabolites	[95, 96]
		A→G, exon 7, Ile462Val	Increase enzyme activity and thus production of reactive genotoxic metabolites	[95, 96]
	CYP2A6	*T→A*, Leu160His	Inactive enzyme	[97]
	CYP2E1	*G→C*, RsaI/PstI, 5'Flanking region	Less induction enzyme activity	[36]
		T→A, *Dra*I, intron 6	Less induction enzyme activity	[36]
	EPHX1	*T→C*, exon 3, Tyr113His	Reduce enzyme activity	[98]
		A→G, exon 4, His139Arg	Increase enzyme activity	[98]
	MPO	*G→A*, promoter region	Decrease enzyme level	[99]
	NQO1	*C→T*, exon 6, Pro187Ser	Decrease enzyme activity	[100, 101]
	GSTM1	Homozygous null genotype	None enzyme activity	[95, 102]
	GSTT1	Homozygous null genotype	None enzyme activity	[103, 104]
	GSTP1	*313A→313G*, Ile105Val	Reduce enzyme activity	[105, 106]
DNA repair	*ERCC2/XPD*	*A→C*, exon 23, Lys751Gln	Defect in nucleotide excision repair (NER)	[107]
	XRCC1	*G→A*, exon 11 Arg399Gln	Defect in base excision repair (BER)	[108]
	XRCC1	Exon 7, Arg194Trp	Defect in base excision repair (BER)	[109, 110]
	OGG1	C→G, Ser326Cys	Lower ability to prevent mutagenesis	
Cell cycle regulator	*TP53*	*G→C*, Exon 4, Arg72Pro	Less efficient growth suppression and apoptosis function	[111, 112]
		16 bp duplication Ins, Intron 3	Influence alternative splicing of p53 protein	[113]

Table 3. Common genetic abnormalities in lung carcinogenesis*

Genetic abnormalities	Non small cell lung cancer (NSCLC)	Small cell lung cancer (SCLC)
Frequency	80-85%	20-25%
Chromosome structural abnormality		
3p Loss	50-80%	>90%
Karyotype analysis	3p, 9p, 17p-loss	3p, 5q, 13q, 17p-loss
Telomerase activity	80-85%	90-100%
Tumor suppressor gene		
TP53 mutation	~50%	>75%
TP53 LOH	65%	90%
p53 (IHC)	40-60%	40-70%
RB1 LOH	~30%	~70%
Rb abnormalities (IHC)	15-30%	90%
P16 LOH	~70%	~50%
P16 Mutation	10-40%	<1%
p16 (IHC)	30-70%	0-10%
Oncogene		
EGFR mutation	10-40% (adenocarcinoma)	No
EGFR overexpression	40-80%	Rare
Ras mutation	15-20%	<1%
MYC amplification	5-10%	15-30%
Bcl2 expression	10-35%	75-95%

*Combined and modified from [114-118]

Idiopathic pulmonary fibrosis (IPF)

Idiopathic pulmonary fibrosis (IPF) represents a subgroup of diffuse parenchymal lung diseases and is defined as a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the histological appearance of usual interstitial pneumonia (UIP) on surgical (thoracoscopic or open) lung biopsy [52]. Over the wide spectrum of diffuse parenchymal diseases, the most frequently encountered is IPF/usual interstitial pneumonia. The etiology is not clearly defined yet, but the evidence suggests that genetic and environmental factors as well as increasing age could affect the pathogenesis of lung fibrosis. Multiple investigators have demonstrated positive associations between IPF and *SFTPC*, *TNF-α*, *IL-1RN*, *CR1*, *ACE*, *TGF-β1*, telomere length, and *TERT* in case-control studies, but identification and understanding of the functional roles of these genes is in its infancy [53, 54]. This review focuses on issues in genetic research in IPF, in particular the relationship with telomere length and telomerase gene mutations in familial pulmonary fibrosis and sporadic IPF.

Telomerase is a ribonucleoprotein enzyme consisting of two essential components: a catalytic component, telomerase reverse transcriptase (TERT); and an RNA template, telomerase RNA component (TERC or hTR). Telomerase can prevent shortening of telomeres, specialized structures that protect chromosome ends. Telomere shortening is a natural event in human life since telomere repeats (TTAGGG) at the end of chromosomes are characteristically lost during DNA replication due to the inability of DNA polymerase to replicate DNA in the 3' to 5' direction. The progressive loss of telomere repeats is thought to have implications in age-related diseases such as IPF [55, 56]. Disruption of telomere length homeostasis leads to premature aging in cells and chromosomal abnormalities. Recently, the findings of the short telomere length in cells with or without *TERT*/*TERC* mutations in families and individual with IPF suggest that telomerase dysfunction is important for the molecular pathogenesis of this disease [57, 58]. Telomere length received critical attention in the pathogenesis of IPF when Armanios et al [59] revealed that 6 out of 73 probands from the Vanderbilt Familial Pulmonary Fibrosis registry had heterozygous mutations in *TERT* or *TERC*, resulting in short telomeres. Furthermore, de Leon et al [60] also found shortening of telomere length in familial pulmonary

fibrosis (FPF) patients who have wild type for both *TERT* alleles in comparison to two control groups. Previously, other studies had already shown that 25% of subjects with sporadic IPF have short telomere length (<10th percentile) in the absence of telomerase mutations [58]. With regard to *TERT*/*TERC* mutations, most individuals who carry a heterozygous mutation have short telomeres, and 40% of 134 *TERT* mutation carriers with a mean age of 51 have a diagnosis of pulmonary fibrosis [60]. Finally, this evidence supports the idea that telomerase mutations increase susceptibility to IPF and suggests that pulmonary fibrosis is related to older age and short telomeres.

Pathogen genetics in respiratory infection

Tuberculosis

More than 125 years after Robert Koch found *Mycobacterium tuberculosis* as a causative agent in 1882, tuberculosis is still the most important problem in respiratory health care. Approximately one third of the world's population is considered to be latently infected with *Mycobacterium tuberculosis*, and 10% of these persons will develop active disease at some point in their lifetimes [61]. Moreover, the World Health Organization (WHO) estimates that around 489,000 cases of multidrug-resistant tuberculosis (MDR-TB) occur every year. MDR-TB is TB with resistance to at least two of the first line antimycobacterial drugs-isoniazid (INH) and rifampicin (RIF). Recently, appearance of extensively drug-resistant TB (XDR-TB), which are resistant to almost all first line and second line drugs, has further complicated efforts to eliminate this disease [62].

In the modern era, two of the many major problems that remain in tuberculosis include the need to obtain early diagnosis using faster and more accurate tools and concern of the emergence of drug-resistant tuberculosis. Advances in genome research and the completion of the *Mycobacterium tuberculosis* sequence in 1998 have stimulated research to solve such problems. Recently, technological developments have introduced DNA and RNA diagnostic tests to identify *Mycobacterium tuberculosis* with possible use in rapid detection of multidrug-resistant tuberculosis. Molecular tests to detect drug resistance in tuberculosis by screening for gene mutations are commercially available. This method is also known as the line probe assay and is based on amplifying target sequences from the organism under evaluation and then binding them to specific probes. Hybridization is revealed through a color reaction [63]. The first such method was the Line Probe Assay (LiPA) (INNO-LiPA Rif TB Assay, Innogenetics NV, Gent, Belgium) for detecting resistance to rifampicin. More recently is the Genotype MTBDR*plus* assay (Hain Lifesciences GmbH, Nehren, Germany) for detection of resistance to rifampicin and isoniazid. Meta-analysis of the accuracy of this rapid molecular method shows great promise [64, 65]. The Genotype MTBDR*plus* assay is able to detect rifampicin resistance with specificity and sensitivity nearly 100% and to detect INH resistance with specificity around 100% and sensitivity ranging between 70 and 90% [64]. Based on this evidence and expert opinion, WHO encourages many countries, especially those with a high MDR-TB burden, to adopt this line probe assay [62]. However, lack of money for investment in new diagnostic tools is still an obstacle, and the number of genes that can be analyzed remains limited, posing a special challenge for diagnosis of XDR-TB.

Streptococcus pneumonia

Pneumonia is defined as inflammation of the pulmonary parenchyma caused by infectious agents. The infectious agent can be bacterial, viral, fungal, and parasitic. Among them, *Streptococcus pneumonia* (the pneumococcus) is one of the major pathogens in children and adults worldwide [66]. Genome variation has been found to be important in understanding the virulence of pneumococcus and its interaction with the host. The genome of the pneumococcus consists of 2 to 2.2 million base pairs, and contains upwards of 2,000 genes, depending on the strain [67]. Investigators have identified pneumococcus virulence factors, including the polysaccharide capsule, surface protein, enzymes, toxin pneumolysin, and pilus [68, 69].

Clinical studies in humans have shown that genetic factors are also related to susceptibility to respiratory infections caused by *Streptococcus pneumoniae*. For example, polymorphisms in the *MBL2* gene are reported to be associated with pneumococcus pneumonia. The *MBL2* gene encodes a mannose-binding lectin (MBL), or protein (MBP), that is secreted by the liver as part of the acute-phase response and is involved in innate immune defense [70]. A recent meta-analysis shows that MBL concentration is related to common respiratory infection. Significant inter-individual variation in *MBL2*-related MBL levels with respiratory tract

infection in young men have been reported by Rantala etc. [71], specifically in community acquired pneumonia (CAP), in which *Streptococcus pneumoniae* was the most common causative agent [72]. However, the role of MBL deficiency in susceptibility to respiratory infection remains controversial since others studies have reported lack of association with infection [73].

Influenza

Unusual influenza virus subtypes for humans have been recognized recently, in particular, widespread outbreaks of H1N1 and H5N1 across Asia. Host-viral interaction is critical in the pathogenesis of virus infection. Keynan et al. [74] and Dawson et al. [75] highlighted unique perspectives on host–viral interactions by focusing on the effect of chemokine receptor 5 (*CCR5*) on the response to influenza viruses. The *CCR5* deficiency resulted in a sharp increase in mortality early in the course of influenza A virus infection [75]. Furthermore, Keynan et al. suggested that *CCR5* Δ32, a condition in which a 32-bp deletion in the *CCR5* gene, is one of the factors associated with increased severity of the illness among white patients with pandemic (H1N1) 2009 [74]. Current study shows that in response to human seasonal virus H1N1, the CCR5 had higher expression level and mediated migration of immune cells to the site of influenza virus infection, suggesting that these higher production levels of chemokines may account for the severity of influenza [76].

Pharmacogenomics in the respiratory field

An essential goal of research in genomic medicine is to translate such knowledge into viable treatment for human diseases. Increasing knowledge to identify novel genetic associations using molecular approaches with potential application to therapeutic agents is covered by the broad term pharmacogenomics [77]. Similarly, pharmacogenetics is the study of variability in drug response due to genetic inheritance [78]. Currently, numerous genetic findings have been carried into clinical practice. For example, mutations in epidermal growth factor receptor (EGFR) alter the response to gefitinib, an EGFR tyrosine kinase inhibitor. In addition, reduced bronchodilator drug dosages in asthma treatment related involving *ADBR2* polymorphisms have been demonstrated in clinical trials [79]. Many clinical studies have now been performed that examine the potential effect of these attractive targets for therapeutics.

On a more advanced level, many lung diseases have been examined as potential candidates for gene therapy. Cystic fibrosis and α1-antitrypsin (AAT) deficiency, both of which result from single gene mutations, have received a great deal of attention with regard to gene therapy. For single gene disorders, inserting a functional copy of the defective gene into airway epithelial cells by gene transfer is promising approach. Extending this concept to treat complex diseases such as lung cancer, pleura mesothelioma, and pulmonary fibrosis has been proposed. Many clinical trials using viral and non-viral vector strategies have been conducted [80, 81]. Unfortunately, the results of multiple clinical trials have varied and have revealed many limitations. However, many aspects of gene therapy, including efficiency, immune response, delivery methods, and target cells remain to be refined.

Conclusion

Genomics and molecular genetics have undergone a rapid transformation over the past decade, providing increasingly advanced data for clinicians and health practitioners. Unfortunately, the medical systems of most developing countries face a double burden. Overloaded healthcare systems result in increasing infection and chronic disease, while at the same time, lack of investment in science creates a big gap in genome research compared to advanced countries. With regard to respiratory genetics, we provide examples of available genomic data that could be integrated in the clinical setting. Ultimately, genomic knowledge and approaches will become increasingly important in the clinical setting for many diseases.

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