or characteristics and those without them to identify SNP alleles that differ in the compared groups. These studies need to be very large, involving thousands of people, to help rule out chance as a reason for differences, given the very large number of statistical comparisons being made. Many loci have been identified through this approach. However, most of the evidence has come from populations of European origin. The relatively few studies of African American populations and studies of Asian women who did not smoke find both similarities and differences in the genetic regions involved.

As of this writing (2017), the contribution of genetic factors to TRHD, specifically tobacco-related cancers, cannot be estimated precisely because of the insufficient evidence available on this subject particularly about non-European-origin populations. Progress has been made in identifying and characterizing specific genetic variants that influence stages along the tobacco use continuum as well as in estimating the risk of developing tobacco-related cancers, as detailed in this section, but the inventory of genetic risk factors is far from complete for different population groups.[306] In addition, these genetic studies have been undertaken primarily to determine disease etiology rather than to address TRHD[307]; therefore, these studies have typically been performed within a restricted range of sociodemographic groups, which has limited the ability to translate findings to TRHD. Also, genetic investigations have favored methodological approaches that circumvent the heterogeneity of smoking behaviors and cancer risk in order to be able to detect genetic signals—an approach that minimizes the complexity of interactions between genes and environmental factors that lead to disease as opposed to investigating these interactions.[307]

As of 2017, genetic factors do not readily explain TRHD because genetic variants account for a modest proportion of the heritable variance in smoking behaviors, and because of the scarcity of genetic studies in relevant populations such as racial/ethnic and LGBT groups. Large, replicated studies conducted primarily with populations of European origin have clearly established genetic susceptibility loci as involved in tobacco dependence, quantity of use, cessation, and lung cancer risk, both tobacco-related and not tobacco-related. These genetic factors have a modest effect on risk of tobacco behaviors and cancer risk, yet help elucidate the biological mechanisms underlying tobacco behaviors and lung cancer risk and may have important implications for stratifying groups for interventions, such as cessation treatments, that may be most effective for them.

Some large-scale studies of African American populations and studies of Asian women who did not smoke find both similarities and differences compared to populations of European origin in the genetic regions involved in both smoking behaviors and lung cancer risk. Similarities include the importance of loci in *CYP2A6* involved in nicotine metabolism and the nicotinic cholinergic system, especially the *CHRNA5-CHRNA3-CHRNB4* gene cluster. The latter is related to tobacco quantity and dependence as well as cessation and may also be involved in lung cancer risk independent of its role in tobacco use behaviors. However, African Americans and Asians each have other distinct loci, both in those and other genetic regions. These genetic factors are only part of a complex web of behavioral, biological, environmental, social, and other characteristics that contribute to TRHD.

The state of knowledge about the genetic risk for smoking behaviors and lung cancer continues to be characterized by significant gaps and a need for further research. To more fully understand TRHD, more research is needed, as described below.

More Large Studies in a Wider Range of Populations

Data on the numerous genetic regions and genes that have been investigated as potential risk factors in the etiology of lung cancer come primarily from Asian, European, and European American populations; additional genetic association studies are needed for minority populations.[308]

Many of the studies of African Americans have achieved the large sample sizes needed by pooling data from multiple studies. The associations observed in a number of studies of nonsmoking women in Asia, specifically China,[293,294] may or may not apply to women in the United States. It would be very difficult to obtain an adequate sample size of Asian Americans for GWASs. There are very few studies in Hispanic populations or in populations defined by sexual orientation. It is important to conduct studies in other ethnic groups because they account for the majority of the human population (Asians) and genetic variation (Africans). There are also few studies in these populations that have examined in detail smoking phenotypes such as age of initiation and cessation. And most studies that break ground in new areas, such as the functional implications of these variants, are done in populations of European origin first because the large number of study participants needed are easier to assemble, and studies in other populations come much later.

Some ways to help achieve the large sample sizes needed for assessing genetic risks in these relevant populations include fostering pooling data whenever possible. Although pooling projects have been successfully conducted and are critical to research progress, racial and ethnic minority individuals are still significantly under-represented in existing human population studies. Large-scale cohorts and case-control studies with good representations by race/ethnicity and SES are necessary to further our understanding of racial/ethnic disparities in the risk for lung cancer. One such cohort, described in the Southern Community Cohort Study, offers the potential to assess genetic risk factors among African Americans and European Americans of similar socioeconomic backgrounds while incorporating biomarkers of cigarette exposure and accounting for environmental factors such as menthol smoking.[309]

Furthermore, to understand underlying risk differences among populations and the specific role of genetic factors, analyses should address interacting and interrelated environmental factors, such as SES, education level, diet, smoking behaviors, and other carcinogen exposures.[310] Most importantly, a concrete understanding of the prevalence, amount, and intensity of smoking within each high-risk group (e.g., race/ethnicity, SES, sexual orientation) is necessary because smoking is the predominant risk factor for lung cancer; thus all other risk factors (genetic or environmental) need to be understood in the context of smoking. However, it will be challenging to obtain the large sample sizes needed for such studies.

By furthering our understanding of the biological basis of smoking behaviors and by disaggregating high-risk populations by interindividual risk, genetic factors will help guide novel treatments and help tailor intervention strategies. Although there is a small body of research that suggests that having certain genotypes may influence smoking cessation success with different cessation treatment approaches, this has not been examined within different population groups.

Most of the effects of individual gene variants on lung cancer risk found to date have been modest. However, it is possible that risk models incorporating genetic variations across multiple genes could capture more of the variance in lung cancer susceptibility than is captured by any of these factors acting alone. For example, a greater proportion of lung cancer risk could be accounted for by the combined effect of: (1) two metabolic-activating enzymes, *CYP1A1* and *MPO*; or (2) a metabolic-activating

enzyme, *CYP1A1*, and a metabolic-inactivating enzyme, *GSTM1*; or (3) a metabolic-activating enzyme, *CYP2A6*, and nicotinic receptors, *CHRNA5-CHRNA3-CHRNB4*.[135,240,311]

Lung Cancer Heterogeneity

The heterogeneity of lung cancer might also confound investigations. Lung cancer is a disease with multiple histological subtypes, each having a different relationship with smoking behaviors.[253] For example, adenocarcinoma is currently the most prevalent lung cancer type among smokers,[215] but adenocarcinoma shows a more modest association with cigarettes smoked per day and with years of smoking relative to other subtypes.[253] As such, the smoking patterns of a population under study and the proportion of a given histological lung cancer subtype could influence a researcher's ability to detect genetic and nongenetic associations, and future research on TRHD would benefit from separate studies of cancer subtypes or from correcting for cancer subtypes by using procedures analogous to those employed to correct for population stratification.[312] Fortunately, investigators are increasingly publishing genetic data associations for specific lung cancer histologic types and finding that some susceptibility loci are specific for certain histologic types.[218]

Although lung cancer has been the focus of this chapter, a better understanding of genetic contributions to other cancers would be valuable. Studies on never-smokers could also shed light on understanding disparities in racial/ethnic, sex, and LGBT groups.

Gene–Environment Interactions

The importance of environmental factors is highlighted by migration studies, which find that the cancer risks of generations born after the original immigration resemble the risks found in the adopted country rather than the ancestral land.[310]

In addition to combined gene risk models, further progress in understanding the genetic factors associated with cancer risk requires a diligent assessment of gene–environment interactions. Such studies are challenging to conduct because they require large sample sizes. The degree of interaction between variations in metabolic genes and cigarette smoke exposure typically varies with the level of exposure.[200] For instance, at lower versus higher levels of cigarette exposure, variations in genes such as *CYP2A6*, *CYP2A13*, *CYP1A1*, *GSTM1*, and *MPO* are more prominently associated with lung cancer risk.[135,224,225,251,313,314] In contrast, the association of variations in the *CHRNA5-CHRNA3-CHRNB4* subunit genes with lung cancer changes little with the level of cigarette smoke exposure.[107,135] Future genetic association studies employing biomarkers of smoking dose and quantitative records of historical cigarette exposure will help characterize gene–environment interactions and their relationship to lung cancer risk.[197] In addition to smoking dose, environmental factors that are unique to high-risk groups such as LGBT and lower socioeconomic groups must be investigated.

In the future, as more genetic association studies employ analytical approaches that incorporate and evaluate gene–environment interactions, population heterogeneity, biomarkers, and more precise behavioral measures, more of the genetic variance in smoking behaviors will be explained.[315] Multigene models that assess the combined effect of multiple genetic variants on smoking characteristics may be more informative than studying genetic factors one at a time.

Biomarkers

Biomarkers of smoking dose could offer insight into the paradox of worse health outcomes among African American smokers despite their greater proportion of light smoking. Differences in lung cancer risk between African Americans, Native Hawaiians, and other racial/ethnic groups are greatest at lower levels of cigarette consumption (e.g., no more than 10 cigarettes per day).[2] However, there is emerging evidence that African Americans smoke more intensively at lower levels of daily cigarette consumption than other racial/ethnic groups.[96,316] The higher rates of lung cancer could be explained by greater carcinogen exposure despite consuming fewer cigarettes daily, coupled with the fact that a greater proportion of African Americans have slower carcinogen detoxification capabilities.

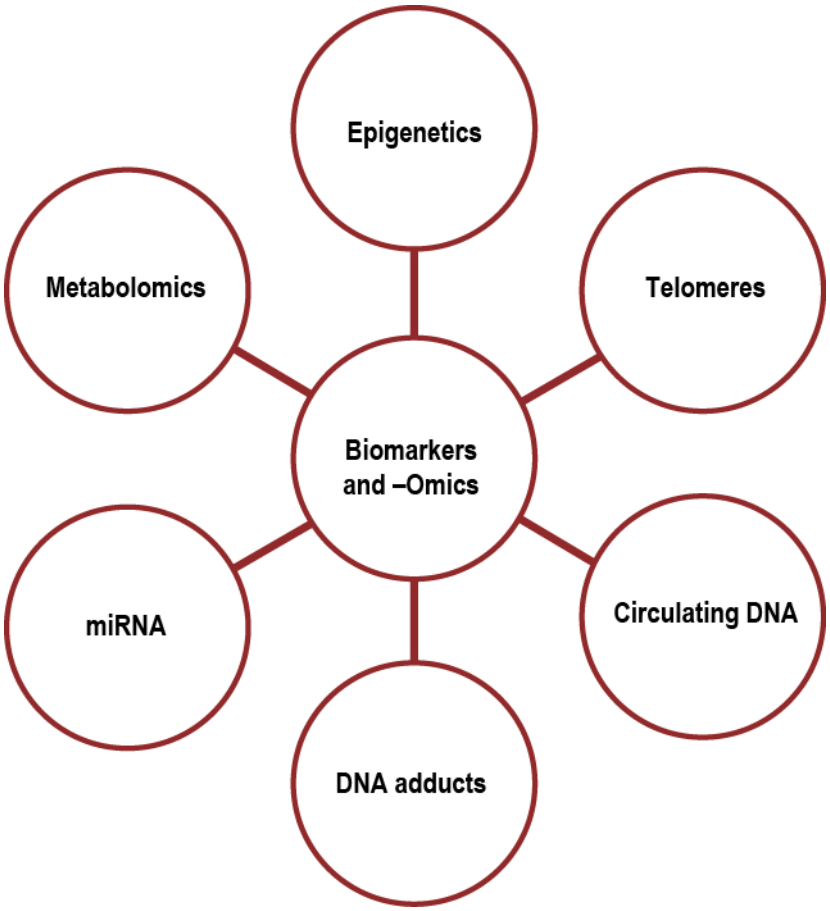
In addition to amassing genetic data on the relevant populations of interest, it is critical to incorporate better biomarkers and surrogates for cigarette smoke exposure. As smoking is the predominant risk factor for lung cancer, smoking biomarkers must be properly validated among different groups of interest and incorporated and/or controlled for to investigate the contribution of other risk factors, genetic or nongenetic, to TRHD. For example, African American smokers would be predicted to have lower cigarette exposure compared with European American smokers based on self-reported number of cigarettes smoked; however, using such biomarkers as total nicotine equivalents, it becomes apparent that African American smokers can achieve comparable levels of cigarette exposure despite smoking fewer cigarettes per day.[96,316] The fact that this amount of cigarette exposure can be achieved despite smoking fewer cigarettes suggests differences in smoking topography. Topography could also interact with genetic factors to influence disease risk, given that the depth of inhalation, an aspect of topography, is believed to contribute to disease risk.[317] Thus, without properly accounting for cigarette exposure, relevant genetic and nongenetic factors could be obscured by differing self-reported smoking behaviors among populations.

Expanded Genetic Characterization and Other High-Throughput Characterization Approaches ("-Omics")

Cigarette smoke exposure is causally associated with numerous cancers and is the leading risk factor for lung cancer.[188–191] Cigarette smoke contains more than 69 carcinogens, among which PAHs and nitrosamines have the strongest causal association with lung carcinogenesis.[207] Variations in the genes that influence smoking behaviors might indirectly influence lung cancer risk by altering carcinogen exposure (i.e., tobacco intake). Variations in genes such as DNA repair genes can also increase individuals' underlying susceptibility to the damage caused by carcinogens.

Increasingly, more sophisticated data is being generated: exome sequencing, gene expression, epigenetic data from shared online databases and consortia. It will be important to study the role of epigenetic changes and gene expression in addition to the genetic changes. Also, functional studies are helping unravel the basis for the effect of the genes involved. It will be very important that these studies are performed in multiple population groups to better understand TRHD. Epigenetics is another promising research avenue to better understand the environmental component of gene–environmental interactions influencing TRHD as both smoking and social environmental stressors appear to influence epigenetic patterns.[318–320] These and many other examples of -omics and biomarkers approaches are shown in Figure 3.6.

Figure 3.6 Types of Biomarkers and -Omics Technologies That Could Help Understanding of TRHD



Complex Interrelationships

It is important to understand the impact of all other environmental and host factors of smoking. Sexual orientation is important and understudied. Poverty and many associated exposures (diet, obesity, work/home environment, geographic location), pollution, health care access, education, and many other factors contribute as well. Comorbidities, such as chronic obstructive pulmonary disease and immune-related conditions such as HIV, and family history of cancers and other conditions are also important.

The challenges in applying genetic findings from one population to another, even when dealing with a causative variant as opposed to a tag SNP, are numerous. There is also the issue of the potential contribution of correlated and as yet poorly defined risk factors. For example, race/ethnicity, which genetic researchers typically use to represent geographic/ancestral origin and genomic variability, also encompasses correlated environmental, economic, and sociocultural factors that can influence disease risk.[321,322] Likewise, the effect of a gene variant on a particular outcome (e.g., smoking persistence) is likely influenced by multiple interacting genetic and environmental components that could differ across populations.[15] Similarly, other populations experiencing TRHD, such as lower SES groups and LGBT groups, may experience environmental risk factors that could interact with genetic risk factors. Thus, without a better understanding of genetic and nongenetic risk factors and their potential interactions in the manifestation of tobacco-related diseases, it is not straightforward to extrapolate genetic findings

from one population to another, even when the impact of a genetic variant on the function of a gene is known.

As our knowledge of genetic and nongenetic factors and their interactions with each other and with smoking behaviors increases, a clearer picture of TRHD will emerge. In addition, as key genetic and nongenetic risk factors become uncoupled from race/ethnicity, SES, and LGBT status, it should become feasible to predict whether a particular individual will suffer disproportionately from TRHD without having to rely on these demographic categories.

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