Introduction

In the early days of studying human genetics, researchers focused on simple traits that were controlled by a single gene. These traits and diseases, such as albinism and phenylktonuria, were easy to study, since they followed straight-forward inheritance patterns.

However, researchers soon found that most human traits and hereditary conditions do not follow a simple pattern of inheritance that can be attributed to a defect in a single gene. Instead, most traits result from an intricate interplay between one or more genes and the environment. These include traits such as height, eye colour, skin colour, and intelligence. Similarly, many human diseases are controlled by the complex interaction of multiple genes with each other and with the environment. These diseases are called multifactorial diseases, implying that many factors are involved in causing the disease to occur.

Multifactorial (or complex) disorders are characterized by being controlled by several genes; each of these genes contributes to some extent to the collective genetic effect. Thus, the specific genetic component (genotype) interacts with the environment to produce a final phenotype.

Multifactorial diseases are usually difficult to study, because many genes can be involved in the condition with the exact number being unclear. Moreover, in most of the cases, there is a relatively large number of contributing genes, each of which have a small and difficult-to-detect role in the causality of the disorder. To complicate matters further, the environmental effectors can be very hard to identify and measure. Therefore, it is often quite challenging to dissect the interacting factors that work together in order for an individual to develop a multifactorial condition. The most important point to remember when dealing with complex diseases is that although having certain gene variants (mutations) can cause a person to be predisposed to a particular condition, it does not necessarily cause the disease to develop. Other factors are needed to trigger the condition. In the absence of such environmental triggers, the disease may never develop after all.

Heritability (H) is a measure of the contribution of genetic factors towards the development of a condition. A heritability value that is close to 1.00 indicates a predominantly genetic condition, while lower H values mean that the environmental contribution to the condition is high. Most data on heritability are derived from twin studies, where sets of identical and fraternal twins are studied to assess disease patterns. Importantly, genetic and environmental components are hardly mutually exclusive, and scientists usually allude to a “third component” in the causality of complex disorders. The latter component is the dynamic interaction between genes and environment, which is elucidated by epigenetic changes that occur ubiquitously throughout the body. It is hardly surprising; therefore, to find that in multifactorial diseases such as obesity, diabetes, asthma, arthritis, and some birth defects e.g. cleft palate/lip and several cancers, it is very difficult to tease apart the contributions from these different components.

Alarmingly, there has been a massive increase in incidence rates of many of these multifactorial conditions in the past few decades. This upward trend points towards a pronounced role of the environment in the development of these ‘lifestyle disorders’. On the other hand, a positive family history still remains the most important risk factor for the development of these diseases. In fact, a detailed study of the family history gives a good indicator of a person’s susceptibility to develop such dis-

orders. Having one or more family members with a certain multifactorial disorder, especially if they developed it a young age, is simply a risk factor for the condition, and the closer these relatives are, the greater the risk.

For some diseases, mutations and variants in genes have been identified that confer a clear susceptibility to certain conditions. Upon identifying the presence of a genetic risk factor (or more) in an individual through molecular analysis, the best strategy to prevent a full-blown disease is to avoid the triggering environmental factors. For instance, people with a high risk for developing cardiovascular conditions need to avoid calorie dense food. Similarly, fetal developmental abnormalities like spina bifida arise from defective genes in conjunction with low folate levels in the fetal environment. This condition can be avoided by adding folate to the maternal diet early on in pregnancy. However, this preventive strategy of avoiding the trigger/s only works if these have been identified.

A lot of research has gone into studying multi-factorial disorders, especially obesity, diabetes, cardiovascular diseases, and several cancers. In such cases, research is directed both at finding genes and variations in genes that predispose to these conditions as well as identifying the environmental factors that contribute to disease development. Generally, researchers now have a better understanding of the relationship between genetic and environmental triggers at the molecular level, and the focus is currently on studying these two components together. Obviously, research in this arena has a long way to go but elucidating the deep cellular mechanisms of these highly important conditions endows healthcare with better tools to combat and prevent these diseases efficiently and decisively.

Interplay between genes and environment in multifactorial diseases

Disease condition	Gene	Environmental trigger	Heritibility
Coronary Artery Disease	APOE	Smoking	0.65
Obesity	Leptin, Leptin receptor	Calorie rich diet	0.70
Neural tube defect	MTHFR	Low folate level in fetal environment	0.60
Schizophrenia	COMT	Marijuana exposure	0.85
Asthma	ORMDL3	Allergens	0.80
Cleft lip/palate	GSTT1	Maternal smoking	0.76
Diabetes Mellitus Type 1	HLA Class II genes	Early viral exposures	0.88