

PSYCHO-GENETICS AND GENETIC INFLUENCES ON BEHAVIOR

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Summary

The genetic basis of human behavior is being advanced through the development of techniques in genetic research; progress in molecular biology; and increasing collaborations between geneticists and psychiatrists.

Geneticists are describing genetically determined syndromes that constitute the behavioral phenotype. In contrast, other researchers are beginning with the behavioral features of psychiatric disorders and then are attempting to identify both the genetic bases of these disorders and their interrelationships with environmental factors. A major point in this article is differentiating the classic “physical” phenotype from the new “behavioral” phenotype. Issues of how different types of phenotypes are defined and measured are discussed. Particularly, the concept of behavioral phenotype is elucidated in a manner that makes the term more useful to mental health clinicians. The article then takes up the description of Down's syndrome, Williams syndrome, and fragile X

syndrome. In describing the genetic and clinical features of these syndromes, a major point is that a specific phenotypic feature of a clinical syndrome implies an integration of very complex functions that pertain to the expression of different phenotypic features. The article then describes issues pertaining to the genotype–environment relationship. It is noted that the study of behavioral phenotypes illustrates the role that single genes have in normal and pathological processes, whereas the current study of behavioral phenotypes does not provide quantitative data on the genetic proportion of the phenotypic variance of a feature. Three different types of correlations between genotype and environment are then described and the point is made that the genetic contribution to any clinical syndrome, even if significant, is never sufficient to explain the total phenotypic variance. Finally a synopsis is given of the role of genetic factors in the psychiatric disorders of autism, schizophrenia, and alcohol dependence.

1. Introduction

Since the early 1980s, the interest of several researchers has converged again on the genetic basis of human behavior. This new stimulus in studying these fields is mainly linked to the spectacular development of techniques in genetic research, and particularly in molecular biology, and to the growing collaboration between geneticists and psychiatrists. Experimental research in developmental genetics, psychiatry, and psychology is increasingly focusing on the importance of the influence that genes exert on normal and pathological human behavior.

On one side, geneticists have begun to describe, with ever-increasing frequency, those recurrent aspects of behavior, peculiar to genetically determined syndromes, that constitute what is known as the behavioral phenotype. Following the inverse path (i.e. starting from the behavioral features of psychiatric disorders), a different line of research has attempted to identify the genetic causes of these disorders and their relationships with environmental factors. The following dissertation will illustrate this double yet converging path, addressing a first part on genetics and behavior and a second part on genetics and psychiatric disorders. For each of the two lines of research, we have chosen to concentrate the discussion on some particularly significant syndromes.

2. Genetics and Behavior

2.1. Behavioral Phenotypes

The term phenotype is commonly used in genetics to define the set of features observable in each individual. The word, coined by Johannsen, comes from the combination of the two Greek words *phainein* (to show) and *typos* (feature) and is in contrast to the term genotype, which instead denotes people's hereditary genetic constitution, encapsulated in their DNA.

In the most common and classic usage, the term phenotype refers to the physical features of the individual, anatomical, or functional characteristics such as height, complexion, or arterial blood pressure. A phenotype can be described objectively. Thus, it can be broken down in constitutive elements that are usually measurable. This is

applicable both for macroscopic elements, previously illustrated and traditionally studied in anthropometry, and for microscopic or biochemical elements such as the cellular and extracellular components of tissues in the human body or the primary structure of globin molecules synthesized by blood cells. Complex physical features, such as the shape of the face, can be broken down themselves into simpler elements, easily interpreted in subjective and measurable terms. However, it is common knowledge that however a human face is broken down into simpler elements and measured in every detail, the resulting sum total will never have the same descriptive strength as the overall vision of the same face (the syndromologists' Gestalt). Until recently the phenotype was used merely to describe the "organic" features of an individual. Variations between the natures of two phenotypical features were ascribed to the resolution level of the observation and description of the features, yet the various features were categorized according to their "physicality." Dysmorphology developed almost exclusively through the delineation of physical phenotypes and their underlying pathogenic mechanisms.

Nowadays, however, due to recent efforts to extend syndrome characterization into the realm of cognition and behavior, the field of "behavioral phenotypes" has come into its own. As a consequence, the Society for the Study of Behavioral Phenotypes has been established. The object of phenotypical studies has thus officially gained a theoretical nature, yet the method of analysis has remained unchanged. Also in this case, in order to be applicable to complex phenomena such as cognition or behavior, the study necessitates breaking down the phenomenon into simpler elements that are more easily measurable. And it is also true that the degree of resolution of the cognitive or behavioral phenomenon (i.e. the degree of breakdown in simpler phenotypical elements to which the phenomenon under study needs to be subjected) does not always correlate with a more "accurate" descriptive ability of the phenomenon itself in its totality.

Both the classic "physical" phenotype and the new "behavioral" phenotype seem to have the same methodological difficulties in addressing the current necessity of measuring and objectifying in accurate descriptions the object of study in its essence. This fact, although it may seem strange, can be correlated to what is occurring in the study of complex features within the biological-molecular analysis: the molecular phenomena underlying the genesis, pathological or not, of a complex feature are not easily broken down into single discrete units interacting in only an additive modality.

The term behavioral phenotype was first suggested by William Nyhan to introduce the concept that behavior could be chemically determined (or genetically determined, as we would say today). According to a more restrictive definition, the behavioral phenotype, paraphrasing Nyhan, can be considered as a behavior that includes cognitive processes and social interaction style and that is associated in a consistent degree with a chromosomal or a genetically etiologic syndrome. In other words, the behavioral phenotype, according to this definition, exclusively pertains to pathology and not, as in the classic physical phenotype, to the normal variability of the features. As Flint reports, behavioral phenotype implies a causal relationship between organic lesion (genetic lesion) and behavior; it is not simply "syndrome-specific behavior." Most behavioral phenotypes are associated with chromosomal and microdeletions aneuploidies rather than to point mutations of single genes (microdeletions are deletions that can not be

measured through standard chromosome analysis but only with those cytogenetic techniques that employ molecular probes). This usually denotes that these phenotypes are imputable on an etiopathogenic ground to relevant imbalances in individual genotypes. For it is known that even in microdeletions the number of deleted genes can be high.

To the question whether the term behavioral phenotype should be restricted to those conditions of a genetic nature, one can answer that an ever-increasing number of usually sporadic syndromes with an unknown etiology are proving to be determined by genetic mutations: Rett syndrome is a recent example. However, as a general rule, it seems advisable to restrict the term to those conditions of proven genetic nature in order to avoid describing as part of a wider and more variable behavioral phenotype conditions associated with elevated heritability, but certainly very heterogeneous, as, for example, autism. A genetic mutation is a highly specific and sensitive marker of the corresponding illness and constitutes an absolute diagnostic tool as it is its presence that enables us to make a diagnosis, even for those subjects who do not express a classic phenotype, or its absence that rules one out, even when faced with a suspect phenotype. On the whole, the classification of illnesses on a clinical basis is currently undergoing profound reassessment induced by possible underlying genetic mutations: genetic heterogeneity breaks down phenotypes that are superimposable in differing causal conditions (*splitting*) whereas phenotypic heterogeneity traces back to the same cause different phenotypes, apparently not related (*lumping*).

According to the more restrictive definition of behavioral phenotype, a behavioral characteristic needs to be consistently associated with a condition or it has to be so common as to constitute a rule for that particular condition. A wider definition contemplates that the behavioral characteristic simply needs to show a greater preference or probability of being associated with a particular condition. However, for those rare syndromes with a small number of cases, it may prove especially difficult to demonstrate with sufficient evidence that a particular behavior is part of a behavioral phenotype. The aim that researchers have set themselves in the delineation of behavioral phenotypes is both clinical and learning the standard mechanisms that determine the expression of the features. In fact, the identification of a syndrome, which is usually rare, is facilitated by the inclusion among the diagnostic criteria of phenotypical elements, too, that are not physical. A higher diagnostic specificity gives greater possibilities of predicting and therefore of preventing and treating the syndrome. Furthermore, once a causal association between the genetic anomaly and a phenotypical feature has been established, our knowledge of the biological basis of behavior will increase. Consequently, what is called the behavioral “genetic dissection” will allow us to appreciate the single genetic determinant factors responsible for the genetic component of the total phenotypical variance.

Before going on to describe a few examples of behavioral phenotypes, and in reference to the preceding definitions, it would be apt to list some precautions in defining a behavioral phenotype. Also one must comply with the minimum requirements in diagnosing a phenotypical feature and the accuracy and pertinence of the measuring methods. As a general rule, the more restrictive the defining criterion of a feature, the

greater the level of homogeneity of the population, selected according to the feature and the accuracy of the conclusions.

Ascertainment bias can occur if patients with a condition associated with a characteristic behavioral phenotype are more likely diagnosed if that feature is present. This situation arises when, for example, patients are selected only from a population of people that show that behavioral feature, and not from a general population; or, in another version, if we select the patients only if they show that feature. The ascertainment bias distorts the strength of association between the behavioral phenotype and the underlying genetic anomaly and therefore leads to erroneous conclusions on the causal relationship (for example, giving a lower significance to other genetic or non-genetic factors). Besides, if we decide that the phenotype of a syndrome has to comprise constant and inalienable behavioral elements, we would exclude from our diagnosis those subjects who do not express the feature, even if they show the syndrome. However, it is realistic to consider that very few or no cognitive or behavioral features are specific to a given syndrome or that all subjects with the same syndrome would show a given feature.

Another possible source of bias is given by the association of a given phenotypical feature with other non-specific factors, such as intelligence quotient (I.Q.) or with physical anomalies that generically predispose the development of a given behavioral feature. Skuse, for example, urges the verification of how many other non-specific factors, such as low I.Q., can be associated with self-injurious behavior, common in several genetic syndromes. He points out the potential non-specific relationship between short stature and impairment in social communication in those subjects with syndromes characterized by, among other things, short stature. In these circumstances, statistical studies that compare a population of subjects with a given syndrome and the general population can allow us to evaluate how unequivocal is the association between a genetic anomaly and the phenotypical feature. Also, these statistical studies may reveal how elements of the phenotype caused by the genetic anomaly, but also present in the general population for other reasons, predispose in a non-specific way to the development of the behavioral feature under study. It is relevant, therefore, to be aware of the prevalence of that feature in the general population in order to carry out a comorbidity analysis.

Moreover, it is advisable in the delineation of a behavioral phenotype to exclude those features that are insufficiently specific, such as hyperactivity, impulsiveness, or generic personality elements such as anxiety. The same is applicable to I.Q. on a cognitive basis. The ideal clinical marker of a syndrome should be hardly alterable by the experience of a subject who is disturbed and be etiologically linked in a straightforward way to the genetic anomaly.

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Biographical Sketches

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