



Vol 14, N° 2
<https://revistas.usb.edu.co/index.php/IJPR>
ISSN 2011-2084
E-ISSN 2011-7922

Phenomics: A Way to Increase and Refine Treatment Options in Psychopathology

Fenómica: una forma de aumentar y perfeccionar las opciones de tratamiento en psicopatología

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Declaration of data availability: All relevant data are within the article, as well as the information support files.

Conflict of interests: The author has declared that there is no conflict of interest.

How to Cite:
Cuartas-Arias, M. (2021). Phenomics: A Way to Increase and Refine Treatment Options in Psychopathology. *International Journal of Psychological Research*, 14(2), 6–8.
<https://doi.org/10.21500/20112084.5659>



From the findings of the human genome sequence in June 2000, when approximately 90% of the sequence of the three billion base pairs was already known, it was possible to formulate a central objective: to identify the genetic bases of complex traits. A complex trait in humans refers to characteristics that are exhibited in a person and are controlled by multiple genes, each contributing to the final expression of the phenotype or its observable characteristics (Houle et al., 2010).

At first, identifying a region of the genome with functional interest and proceeding to sequence it, establishes a fundamental strategy that aligns and refines the purpose of identifying therapeutic targets for different diseases. From this perspective, I refer to phenomics, and for the purposes of this communication, I will orient the concept to human phenomics, to human behavior, since the phenome concept is enabled within phenotype characteristics for many species with different systematic approaches, according to the genetics and the environmental and molecular interactions of a particular phenotype.

Human behavior has a complex inheritance, since genes participate in it and the environment contributes in the manifestation of traits. From this premise, and with the abundance of association genetics studies, it had been considered that the inheritance of traits is best studied from genomics, since it analyzes which genetic variants or polymorphisms influence the phenotype, rather than analyzing the phenotype in detail. However, with the numerous genome-wide studies (GWAs), it has been considered that deepening phenotype studies could improve and refine genetic causality. For example, obesity has an important genetic basis, since so far there are 2091 genes involved in this phenotype (Centers for Disease Control and Prevention, n.d.). Nevertheless, a factor that reshapes the onset, evolution, and treatment of obesity could potentially weigh more heavily on the environment than on genes. These limitations of genetic studies to explain the phenotype are observed even from GWAs, in which genetics for complex traits only account for modest phenotypic variance (Baes & Schenkel, 2020; Poldrack et al., 2016).



Now, we all recognize that one of the central objectives of modern biology is to analyze how a set of genetic instructions (genotype) interact in different ways with the environment of an individual, producing certain characteristics (phenotype). However, when the purpose is to analyze human behavior, why we develop a psychopathology or mental illness, trying to predict the phenotype from the genotype is a difficult problem to solve, since a large number of genes and gene products contribute to many of the phenotypes of interest, in addition to complex and changing environmental influences.

Let us illustrate this situation with an example: Serotonin (5-hydroxytryptamine) is a widely distributed neurotransmitter in the brain, involved in the regulation of several biological functions, including synaptogenesis and the organization and differentiation of cortical structures in morphogenesis. In addition, it comprises an extensive range of biological functions that regulate human behavior, from emotions and aggression to pleasure and sexuality. For this molecule, genetics has discovered one of the genes involved in the regulation of serotonergic neurotransmission, the SLC17A4 gene (Solute Carrier Family 6 Member 4), located on the long arm of chromosome 17 (17q11.1-q12), which codes for serotonin transport. It presents several genetic polymorphisms that could influence efficiency, transport, bioavailability, duration of response, and synapse. Additionally, it is known that some of its polymorphisms or genetic variants could be associated with the expression of neurodevelopmental disorders, mood, anxiety, eating disorders, personality disorders, psychotic disorders, and addictions. This situation illustrates, in behavioral genetics, how a gene contributes differently to phenotypes, which implies a greater complexity in the genetic architecture of a disease, since each genotype is analyzed for a large number of traits (Ospina-Duque et al., 2000).

In this context, when technological advances in molecular genetics allow rapid sequencing of entire genomes at increasingly lower cost, phenotypic studies are progressing in a different way. A phenotype is dynamic and incorporates different levels, from molecular expression and metabolism to the impact of the environment on the regulation of behavior. From this premise, human phenomics is linked as one of the disciplines within omics that seeks to determine and classify a phenotype, according to a series of parameters that allow identifying how the individual responds to different psychological and environmental situations. Phenomics is formulated from the phenotype, understood as that expression of a set of morphological, biochemical, physiological or behavioral traits, which may suggest a particular cluster or condition that is distinctive with respect to other individuals, and which may be modulated by particular environmental influences or events.

However, advances in behavioral genetics lie in the scenario of identifying the genotypic basis and the phe-

nomena of epistasis and pleiotropism, which affect phenotypic variation (Cuartas Arias et al., 2011; Morrison, 2015; Wagner et al., 2008). Undoubtedly, an even more complex scenario is if the search is done on mental illness or psychopathology, which corresponds to a complex mode of inheritance and where the weights or expression assumed for each of the behavioral characteristics are different and may be present in varying degree, frequency, and magnitude. Furthermore, it becomes necessary to evaluate the presence of phenocopies that constitute traits unrelated to genotypes, but with similar phenotype.

Therefore, refining the trait for the development of a study in phenomics, from a behavioral and personalized medicine perspective, requires the analysis of phenotypes at different levels and, of course, of their interaction, in order to estimate the degree of correlation between each of those characteristics that we consider traits, and that seek to exhibit the uniqueness of a phenotype. For this, the diagnosis and evolution of a particular clinical condition turn out to be fundamental in the phenotypic characterization. Here, we observe the first stumbling block in phenome studies to understand abnormal human behavior. I refer to clinical diagnosis. In this regard, there are diagnostic manuals such as the DSM-5 and now the ICD 11, which facilitate the specialist the systematization of clinical signs and symptoms in the phenotyping processes of mental illnesses, which nowadays have a high impact on public health. However, in the manuals there are still many challenges for the clinical diagnosis of a particular condition. For psychopathological, psychiatric analysis, response to medication, type of medication, sociocultural, sociodemographic conditions, gender, schooling, and occupation, they present some drawback in circumscribing and modeling the impact that environmental conditions and context have on the expression of the phenotype (Bach & First, 2018; Morrison, 2015).

Currently, different studies have sought to refine strict and relatively stable phenotypes in the most prevalent mental disorders. Nevertheless, sensitizing the assessment of clinical characteristics of interest, grouping variables that contribute different weights in the measurement of phenotype, socioeconomic level, nutrition and dietary supplements, sleep habits, physical activity, social and digital relationships, healthy leisure, sex life, and stable emotional ties, in sum, with neurocognitive performance, social inclusion and context, reformulate the risk, treatment, and prognosis in psychopathology studies from the phenomics (Wendt et al., 2020).

An additional challenge is with biologists, chemists, statisticians and mathematicians in the development of effective and robust computational and bioinformatics methods to reduce large and diverse phenomena data sets into representations that can be interpreted in a biological context to help explain an individual behavior and reasonably predict behavior in the face of a stressor.

Achieving the goal of predicting or making responsible inferences about how a clinical condition or habitus evolves will require the development of data standards and metadata descriptions of pre and post experiments in platforms to help computational approaches to data analysis (Velez, 2021).

The future of personalized behavioral medicine lies in this direction. From this perspective, approaches in phenomics are making progress in obtaining particular phenotypic and environmental information on individuals, not necessarily sick or with an underlying disease, but making a rigorous selection of data that could contribute to the explanatory matrix of phenotypic evolution and the current state of the individual.

Finally, David Houle's 2010 question about genomics—why not measure everything?—, it is also a necessary question when we ask about the phenotype associated with mental and psychopathological disorders (Houle et al., 2010; Wendt et al., 2020).

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