Commentary

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Personalized medicine in psychiatric disorders: prevention and bioethical questions

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Abstract

La medicina personalizzata rappresenta un emergente approccio alla medicina, che mira ad applicare l'attuale conoscenza scientifica nello studio della suscettibilità individuale allo sviluppo di determinate patologie al fine di prevenirne l'insorgenza e identificare la risposta ad un trattamento farmacologico. Lo scopo del presente studio è quello di analizzare le implicazioni etiche dell'applicazione di tale approccio nella prevenzione delle malattie psichiatriche, attraverso lo studio di specifiche variazioni genetiche e modificazioni epigenetiche. Tuttavia, dallo studio del genoma umano attraverso specifiche tecnologie scientifiche originano numerose domande di natura bioetica.

Personalized medicine is an emerging approach to medicine that applies scientific knowledge to predict individual susceptibility to certain pathologies and to identify their response to pharmacological treatments. The aim of the study is to analyze the ethical implications of the use of personalized medicine in the prevention of psychiatric disorders, through the study of specific genetic variations and epigenetic modifications. However, the use of technologies aimed at studying the human genome, in order to prevent these pathologies, cause many bioethical questions. ***Clin Ter 2019; 170(6):e421-424. doi:10.7417/CT.2019.2169***

Key words: *bioethical, epigenetic modifications, genetic variations personalized medicine, prevention, psychiatric disorders*

Introduction

Personalized medicine is included in the so-called 4P Medicine, together with Predictive, Preventive and Participatory medicine (1). The term personalized medicine refers to an emerging approach to medicine that applies scientific knowledge, mainly genomics and proteomics, to predict individual susceptibility to certain pathologies and to identify their response to pharmacological treatments (2). This approach is based on the great interindividual biological variability between patients that, even when presenting similar symptoms or suffering from the same pathology, can react differently to the same drugs (3). The goal of this type of approach is to customize drug therapy on the bases of specific genetic characteristics of each individual in a given time period (4), in order to optimize the effectiveness-safety balance. This scientific approach arises from the acquisition of DNA nucleotide sequences, genetic variants and gene and protein expression through epigenetic processes. The medical application mainly concerns the therapeutic approach in oncology, psychiatry and neurology.

Objectives

The purpose of the following discussion is to analyze current issues about the application of personalized medicine in psychiatric pathology, with particular reference to the ethical aspects related at the use of pharmacolagical therapy with antipsycothics. More specifically, mental disorders are characterized by pathological alteration affecting cognitive functions (thinking, conception, concentration, attention, etc.), affective sphere (mood, feelings, anxiety), behavior and quality of interpersonal relationships. As for the causes of these pathologies, these are far from being understood. What is certain is that most of them derive from the interaction of several factors: biological vulnerability (predisposing genetic factors), environmental factors (psychological trauma, etc.), stressful events during life (traumatic separations, mourning, migration, disorders, etc.), drug abuse.

Discussion

One of the applications of personalized medicine in psychiatry consists in seeking susceptibility factors and protective factors for the development of psychiatric disorders through the analysis of genetic variations.

Although depending on the gene sequence, these determinants do not reflect a Mendelian inheritance model and correlate with an increased risk of developing certain pathologies. The main genetic variants analyzed in the field of psychiatric disorders include coding regions involved in the synthesis, transport and catabolism of neurotransmitters. The correlation between specific genetic profiles and the

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development of disorders has been demonstrated for major depressive disorder (5), bipolar disorder and schizophrenia. As far as depressive disorder is concerned, it shows a family aggregation in 40-70% of cases; the polymorphisms mainly involved include the serotonergic system and elements of the HPA axis. Furthermore, the risk of developing bipolar disorder in the presence of specific genetic variants of the HPA axis, or of molecules involved in the metabolism of monoamines ranges from 60 to 85%. The heritability of schizophrenia varies from 50 to 80% and genetic polymorphisms mainly concern genes involved in neurodevelopment. Table 1 lists the main polymorphisms involved in psychiatric disorders (6).

The susceptibility to psychiatric pathologies already described does not only derive from the presence of certain genetic polymorphisms but also from epigenetic variations (7). Epigenetics is the study of changes in gene expression not associated with a change in nucleotide sequence. As regards its role in psychiatry, epigenetic mechanisms influence the normal patterns of neurodevelopment and brain function and, consequently, the mechanisms involved in the "maldevelopment" implicated in some psychiatric disorders. It also plays a role in neurogenesis, neuronal differentiation, specification of cellular differentiation and development of dendrites.

Epigenetic changes occurring during uterine life remain stable throughout life, however epigenetic remodeling may occur during adult life under the influence of environmental factors, such as drugs, chemical substances, psychosocial factors, and psychotherapy. The dynamism of epigenetic processes and their susceptibility to environmental influences make them a potential target for therapeutic interventions, both psychopharmacological and psychotherapeutic. The epigenetic mechanisms that regulate gene expression in the nervous system include post-translational modifications of histones, DNA methylation, changes in non-coding RNA and chromatin remodeling mediated by the Polycomb protein group, mediators of plasticity during neurodevelopment (8). Specifically, on the basis of experimental studies an association between the development of psychiatric disorders and the chromatin remodeling of the BDNF promoter with gene underexperssion has been hypothesized, as far as variations in methylation patterns of COMT and RELN regulatory regions. The multifactorial model of psychiatric disorders etiology is shown in Figure 1.

Conclusion

In the psychiatric field most of the studies related to the personalized medicine focus on tailored therapy to enhance benefits and reduce complications (9,10). We want to investigate the potential application of personalized medicine in the field of psychiatric pathology prevention, based on individual risk profiling.

It is well known that preventive strategies are applicable and effective in some chronic disorders, such as the use of drugs (statins, antihypertensives, etc.) associated with lifestyle changes for cardiovascular disorders; we do not have similar examples for psychiatric disorders prevention yet with the use of pharmacological theraphy. In fact, it is known that, in the etiology of psychiatric disorders, a fundamental role is played by environmental stressors whose occurrence is nearly impossible to prevent. How can we

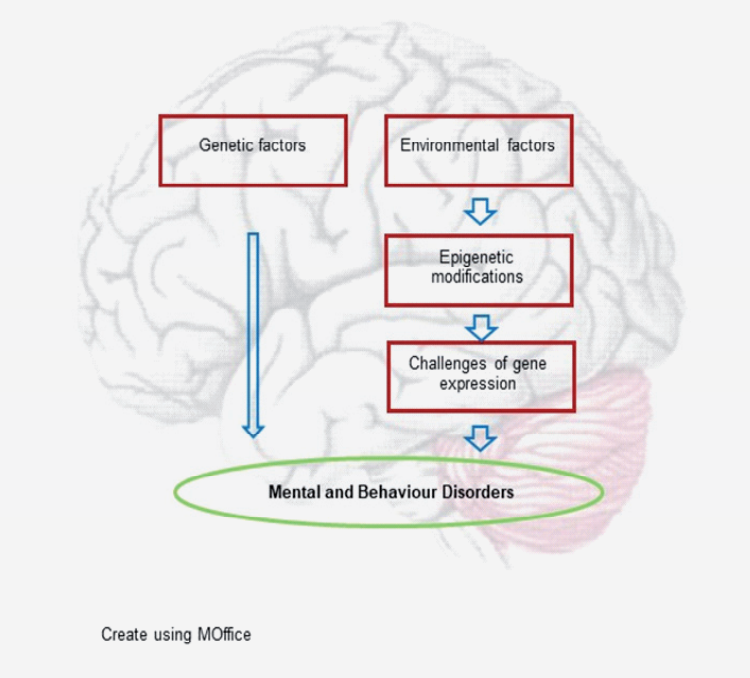

Fig. 1. Psychiatric Disorderss derive from interaction of genetic and environmental factors. Environmental factors determine epigenetic modifications on genes involved in synaptic plasticity and neurodevelopment, modifying their expression.

Table 1.this table represents the main genetic variations correlated with the development of Major Depressive Disorder, Bipolar Disorder and Schizophrenia. Full name of mentioned gene is also indicated.

Psychiatric Desease	Gene	
Major Depressive Disorder	5-HTT	[Serotonin Transporter]
	TPH1	[Tryptophan hydroxylase-1]
	TPH2	[Tryptophan hydroxylase-2]
	FKBP5	[FKBP prolyl isomerase-5]
	CRHR1	[Corticotropin relasing hormone receptor-1]
	CRHPB	[Corticotropin-releasing factor-binding protein]
	HTR3A	[5-hydroxytryptamine receptor-3A]
	SYNE1	[Spectrin repeat containing nuclear envelope protein-1]
	NR3C1	[Glucocorticoid receptor]
Bipolar Disorder	FKBP5	[FKBP prolyl isomerase-5]
	ARNTL	[Aryl idrocarbon receptor nuclear translocator-like protein-1]
	TIMELESS	[Timeless Circadian Receptor]
	CLOCK	[Clock Circadian Regulator]
	SYNE1	[Spectrin repeat containing nuclear envelope protein-1]
	COMT	[Catecol-O-Metiltrasferasi]
Schizophrenia	MHC region on chr6	[Major Histocompatibility Complex]
	COMT	[Catecol-O-Metiltrasferasi]
	DISC1	[Disrupted in Schizophrenia-1]
	DISC2	[Disrupted in Schizophrenia-2]
	ZNF804A	[Zinc finger protein-804A]
	TCF4	[Transcription factor-4]
	NRG1	[Neuregulin-1]
	RELN	[Reelin]
	HTR2A	[5-hydroxytryptamine receptor-2A]
	TPH2	[Tryptophan Hydroxylase-2]
	KCNH2	[Potassium voltage-gated channel subfamily H member-2]

prevent the occurrence of trauma, mourning or violence? Is clear how personalized prevention should derive from the identification of intrinsic risk factors that are genetic variants and constitutional epigenetic modifications or eventually induced by environmental stressors.

We suggest that specific genetic test of susceptibility should be administered to high or intermediate risk groups such as people from familial pathology clusters or with history of recent major psychological trauma, regardless actual clinical symptoms. At this point, a question naturally arises: is it ethically correct to give notice to a person who does not have a psychiatric condition who is at risk of developing it? In fact, these pathologies are still the object of social stigma and fear which ingenerates a feeling of discomfort towards those who are affected. Moreover, in light of this, one wonders whether such information could constitute a stress element that would itself increase the risk of developing such pathologies.

In addition, in the hypothesis of being able to apply new technologies with preventive aim in psychiatry, doctor-patient communication and informed consent plays an important role. The information must be clear, simple, understandable and concrete, in the presence of competent personnel. In fact, the choice to undergo the test must be voluntary and who decide to do this test need an exhaustive genetic and psychological counseling. Medical staff has to establish whether reccomend preventive treatments or not.

Preventive strategies could consist in the implementation of psychotherapy, and administration of drug therapy. In the latter case, however, given the possible manifestation of side effects, it would be essential to evaluate the risk/benefit ratio of the psychopharmaceutical, which is variable for everyone.

In fact, it seems relevant to evaluate the ethicality of administering a psychopharmacological treatment in a "healthy" subject. It would seem that, in these subjects, the risk/benefit ratio is inclined towards the first, due to the psychiatric drugs adverse effects. However, considering that part of the pharmacological action of these molecules is linked to epigenetic protective mechanisms (11), it cannot be excluded that these drugs can be applied in primary prevention.

Considering functional deficit in individuals at high risk for psychosis and the relevant damage resulting after the first psychotic episode, a pharmacological preventive intervention should be taken in great consideration.

Some studies analyzed the efficacy of psychological and pharmacological preventive approach on these individuals. Schmidt et al. in a randomized, placebo-controlled trial used a combination of psychological therapy with N-cetyl-l-cysteine (a safe molecule with glutamatergic, neuroprotective and anti-inflammatory properties) (12). A multicentric study used omega-3 fatty acids and cognitive-behavioural management for patients at ultra-high risk of schizophrenia and other psychotic disorders (13).

Although the innovative feature of these experiments, drugs used presented a good tolerability profile. Conversely, the application of antipsychotic drugs, molecules associated with side effects, requires a preliminary bioethical evaluation in subjects at risk of psychosis.

Obviously, the possible administration of this therapy requires adequate communication and informed consent.

However, given the current scientific knowledge, it appears very difficult to answer these questions, requiring further studies aimed at deepening the application of personalized medicine in the prevention of psychiatric disorders.

Moreover, a further integration concerning genetics, psychiatric and medico-legal issues, (with particular regard to bioethicsand hyspopatology), is recommended (14-20)..

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