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Genetic Predictors of Treatment Response for Pharmacological Agents and Brain Stimulation Devices in Mood Disorders

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Genetic predictors of treatment response and personalized medicine research are a very promising lines of research that has a great potential to inform and change the way we administer treatments in mood disorders (major depression and bipolar disorders), among other conditions. Treatment algorithms usually recommend a first line medication for a certain condition. If there is lack of response or unacceptable side effects, another medication is tried (sometimes from a different class of medications) or brain stimulation interventions are used such as Electroconvulsive Therapy (ECT) or Tran cranial Magnetic Stimulation (TMS). Brain stimulation interventions may have high efficacy even in patients who are medication-resistant. However, overall treatment algorithms usually involve a portion of the trial and error.

Lack of response might be due to either metabolism (i.e. pharmacokinetics, in case of medications) or lack of response at the brain receptor levels to brain stimulation therapeutics or medications (pharmacodynamics). Brain stimulation therapeutics transforms either magnetic or electric stimulus to an electric field in the brain that consequently results in action potential firings, neurotransmitters release, and receptor stimulation.

Metabolism of Medications (Pharmacokinetics)

Regarding pharmacokinetics, genetic polymorphism of enzymes like the Cytochrome P450 (CYP) metabolizing system of enzymes might provide important information. For instance, if a patient is an ultra-fast metabolizer of a certain medication, this will require a much higher medication dose than standard doses. While on standard doses, the patient may appear as a non-responder. On the other hand, slow metabolizers (due to genetic characteristics) might develop drug toxicity at standard or substandard doses, or experience high adverse effect profile [1]. Pharmacogentics may help determine if a specific patient's medication resistance is at the receptor level or at the level of metabolism.

Although there has been some progress in the genetic polymorphism of pharmacokinetics, there is still a lot to learn. For example, there has been some controversy in the actual degree of contribution of genetic polymorphism of pharmacokinetics. This controversy, at least in part, is likely due to the lack of knowledge of an important part of the equation: the receptor genetic polymorphism.

Receptor Genetic Polymorphism

The receptor genetic polymorphism predicting the efficacy of medications or potentially brain stimulation interventions at the level of brain receptor is a field that is still in its infancy. Of this kind of polymorphism, the most studied is the transcriptional control region of SLC6A4 of 5-serotonin transporter (5-HTT) gene or as commonly called the serotonin-transporter-linked polymorphic region (5-HTTLPR). The long allele of the 5-HTTLPR has been associated with more efficient transcription (thus greater serotonin uptake activity) compared to the short variant [2,3]. The seminal work by Smeraldi et al. [4] suggested that the homozygous long variant (l/l) and the heterozygotes (l/s) predict a better response to the SSRI fluvoxamine than the homozygous short variant (s/s). Most of the studies after that confirmed this finding of better response of SSRIs in association with the long arm of 5-HTTLPR, including a meta-analysis by Serretti et al. [5]. However, the STAR*D study that included a large clinical sample did not replicate this finding [6], among other studies [7]. Illi et al. [8] summarized the supporting and conflicting studies of the association of SSRIs with 5-HTTLPR in MDD [8]. The 5-HTTLPR has also been implicated in the development of MDD [9] and PTSD [10] after a traumatic event. It has also been to be associated with treatment response. Other receptor genotypes that received less attention in this regards are catechol-O-methyl transferase val158met polymorphism, and dopamine receptor polymorphism.

Receptor genotypes that have been implicated in treatment response in depressive episodes of mood disorders warrants further investigations to provide strong enough data of the likelihood of effectiveness of certain therapeutics in certain individuals. Moreover, further research is warranted on regions that have been demonstrated to be associated with these genetic polymorphisms (in imaging and genetic studies) including the amygdala, hippocampus, and dorsolateral prefrontal cortex.

This research will allow us to target therapeutics in a much more personalized approach, thus avoiding a lengthy trial and error process. This personalized medicine approach will be important to deliver targeted-treatment for each patient. This will allow the development of clear robust clinical indications and individualize treatments according to the patient's genetic pattern.

In conclusion, genetic predictors of treatment response could be examined with different treatment modalities used to treat mood disorders including medications, psychotherapy, and brain stimulation interventions.

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