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Genetics and pharmacogenetics of mood disorders

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Summary

Genetic research in Psychiatry is viewed by clinicians with both hope and curiosity sometimes mixed with disillusionment. Indeed, in the last 30 years many results have not been confirmed and clinical applications are still missing. However, recent findings suggest that we are at the beginning of a new era. A set of variants within neuroplasticity and inflammation genes have been identified as a valid basis for both bipolar disorder and major depression. Similarly, a set of genes has been identified as a liability factor for response and tolerability to antidepressants and the first clinical applications are already in the market. However, some caution should be applied until definite findings are available.

Key words: genetics, pharmacogenetics, mood disorders

Genetics of mood disorders

These are indeed very interesting times for the field of genetics of mood disorders. We are at the dawn of a new era where genetics will enter in our everyday clinical activity. Psychiatrist will be offered a very powerful tool which will help them in the diagnoses and in the treatment of the patients. Further, the knowledge of the biologic mechanisms underlying mood disorders will lead to the development of new therapeutic compounds hopefully much more effective and tolerable compared to the ones that we have today.

Today we are receiving the fruit of more than thirty years of research in the field of genetics. Thirty years which were paved by enthusiasm and disappointment, enthusiasm when discoveries were performed and disappointment when the same discoveries could not be replicated in independent samples.

This is indeed what happened at the beginning of the mood disorders genetic studies. It was 1987, almost thirty years ago, when a breakthrough discovery was published in the high impact "Nature" journal. Janice Egeland published a paper reporting the discovery of a genetic marker located into the chromosome 11 linked to bipolar disorder [1]. This finding had a very wide resonance. Newspapers all over the world reported

that finally the genetic basis of mental illness was discovered. But the enthusiasm did not last long, after only two years, a re-evaluation of the same sample where two subjects did change clinical status from healthy to affected by bipolar disorder, changed the results that became completely insignificant [2].

This is only the first example of many which followed in the following decades where findings were reported but replication was not achieved. After 20 years, in 2008, we performed a thorough review of the issue and indeed concluded that no reliable signal was detected in the previous 20 years of studies despite the fact that many signals have been reported all over the genome, some of them also more than once, but none of them convincingly replicated [3].

The disappointment in the search for genetic determinants of mental disorders, and specifically of bipolar disorder, reached its maximum about 10 years ago, when the largest study so far on 3,000 subjects could not find any signal anywhere in the genome separating bipolar patients from healthy individuals [4]. In that period, many funding agencies reduced or stopped the funding for genetic research in psychiatry, and there was the general idea that the genetic determinants of mental disorders were so difficult to detect that proved to be an impossible target.

However, researchers did not lose the hope, and following the example of other complex diseases, such as hypertension of diabetes, hypothesized that much larger sample size was needed and therefore started collecting a huge cohort of subjects with the aim that at least 100,000 subjects were needed in order to detect liability gene variants which were supposed to confer small risks each in the range of 1.1–1.5 of odds ratio. This was a complete change compared to the previous aim, for many years in fact researchers believed that one or a few genes were responsible for the development of bipolar disorder. Now they realized that risk genes were in the range of 50–100 or more, each of them conferring a very mild and small risk. The Psychiatric GWAS Consortium was founded with the aim of collecting samples from all over the world in order to reach a sufficient sample size. Then the first findings came out when analyzing a sample of more than 7,000 bipolar subjects where it was possible to identify one of the first genes that now stand as definite risk factors for bipolar disorder, the CACNA1C gene variant [5]. In fact, in the following years this finding was replicated in a fairly consistent way. Similarly, for major depressive disorder, a sample of more than 70,000 subjects allowed to detect strong signals from 15 genes [6]. Therefore at present there is substantial evidence suggesting that the samples in the order of 100,000 are sufficient to detect all the genes that are responsible for developing mood disorders [7].

In fact heritability of both bipolar and depressive disorder is in the range of 50%, which means that genes alone are not sufficient to explain all the cases of mood disorders but they confer a substantial risk which is combined with environmental stressors to determine the final illness. But, which are those genes and why they confer the risk for more disorders? It is very interesting to see that many of those genes are linked with the issue of neuroplasticity and inflammation, two mechanisms that when

combined, decrease the possibility of the individual brain to react and be plastic to external stressors and influences.

This is why after 30 years of research the enthusiasm is now grounded: sufficiently large sample size allowed to identify the risk genes which are confirmed by the new replications. However, the clinical application of these findings is not yet available, but we can easily imagine that in the not-too-distant future we would be able to identify the risk of a subject to develop mood disorders by a simple DNA analysis that can be performed also from the saliva.

Pharmacogenetics of mood disorders

We have seen that in the field of genetics of mood disorders results are very interesting but clinical applications are not yet available. However, in the field of pharmacogenetics results are even more interesting and the first clinical applications are already available.

The knowledge of the genetic factors which underlie mood disorders is useful for an early diagnosis and for the discovery of new treatments. On the other hand the knowledge of genetic factors underlying the response and tolerability to treatments are useful for predicting response and also for the development of new treatments as well.

In fact, clinical factors alone are not sufficient to predict response to antidepressant. We all know that there are a series of clinical factors that can suggest that the patient can be more or less responsive to treatment, those factors are educational status, economic level, being married, having a long duration of the illness, having comorbid anxiety etc. [8, 9]. However, those findings cannot fully predict the outcome and still there is a variability that we cannot effectively detect from a clinical point of view because this variability is linked to genetic factors similarly to the genetics of mood disorders. Genetic factors are in fact responsible for about 50% of the variance in response to antidepressants [10].

One part of the genetic variance is due to pharmacodynamic variants, these are the CYP enzymes which metabolize drugs. About 10% of our patients are poor metabolizers and therefore they need lower dosage in order to avoid the appearance of side effects, another 10% of subjects are extensive metabolizers and therefore they need higher dosages of the drug [11]. The knowledge of their metabolizing status is now possible through a simple genetic analysis and this may give the clinician a substantial help in order to individualize the dosages needed by the single patient. Despite the fact that this information is already available in the label of many drugs, clinicians are not aware of this possibility and do not use it much in the clinical practice mainly because it is still quite expensive and not completely informative.

However, the largest part of pharmacogenetics of mood disorder is linked to pharmacodynamic factors, that is the interindividual variability in the target of the drugs such as transporters, receptors, enzymes etc. In fact, it is well known that the most

common antidepressant target and block the serotonin transporter, however, it is less known that the serotonin transporter is not the same in every individual, therefore we can easily hypothesize that subject with a reduced availability of serotonin transporters in their brain will benefit less from treatment with common serotonin reuptake inhibitors (SSRI). This was exactly the working hypothesis we had about 20 years ago, when the discovery of genetic factors linked to antidepressant efficacy started [12, 13]. We were thrilled to discover that genetic variants within the serotonin transporter were linked to SSRI efficacy, and in particular subjects with the short variant showed a markedly reduced response.

After this initial finding a number of studies replicated it, though not universally, and at present it is considered one of the most solid findings in the whole field of pharmacogenetics of mood disorders [14]. However, after 20 years reality proved to be much more complicated than initially believed. In fact, the short variant of the serotonin transporter not only reduces the number of transporter molecules in the brain, but it seems to confer also a reduced plasticity of the whole serotonin system. This reduced plasticity is present since the beginning of individual development and it brings a series of slight abnormalities in the brain which are characterized by a reduced hippocampal volume and activity (increasing the risk for depression), increased amygdala reactivity (increasing the risk for anxious behaviors), higher sensitivity to stressors, and finally to a reduced response to SSRIs given the reduced plasticity of the serotonin system – plasticity which is needed to achieve the antidepressant effect [15].

However, this variant alone cannot explain all the genetic variability, therefore other variants are involved as well. We recently observed that another variant (CHL1) can modulate the serotonin transporter function [16], that other factors modulating neuroplasticity are involved as well (e.g., BDNF) [17] and receptors variants which are target of the serotonin confer further modulation (e.g., 5HTR2A) [18].

A complete and detailed review of all factors known so far influencing antidepressant response can be found elsewhere for the interested reader [19].

In summary, we have seen how a number of variants within genes that are relevant for neurodevelopment and plasticity are influencing antidepressant response. The question therefore is: can we use this information in our everyday clinical practice? The answer is not straightforward, in fact, despite the fact that those genes are indeed important, a number of clinical factors that can modulate antidepressant response should be considered. We all know from our clinical activity that patients are characterized by a wide range of factors such as personality, temperament, defense mechanisms, self-esteem, intelligence and all the other demographic factors listed above which much modulate the genetic background [20]. Therefore, a complete prediction could be achieved probably only by combining the clinical and genetic predictors in a complex algorithm which takes into consideration the variability of each subject.

Nevertheless, in the recent years a number of companies are selling into the market prediction tools to be used in clinical practice. Those tools require the sampling of saliva from the patient, shipment to the company and in a few days the clinician receives

an output from the company which lists the drugs that are most likely to be effective in the specific subject and the drugs that should not be prescribed as a first-line (Figure 1). A number of papers suggest how this strategy is useful and it reduces costs by selecting the drugs that are most appropriate for each subject [21]. Unfortunately, not many independent replications have been performed, therefore at present we cannot suggest to use those tools with a complete confidence.

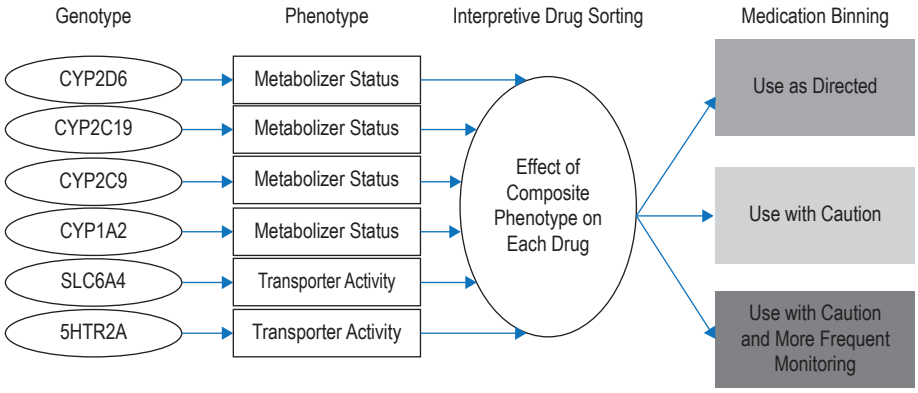

Figure 1. **An example of GeneSight commercial tool as a way of selecting the most appropriate drug**

Pharmacogenetics of mood stabilizers, on the other hand, is still at its beginning and therefore we cannot offer reliable findings so far.

In conclusion, after 30 years of researches genetics of mood disorder is starting to offer very interesting and reliable findings. A number of genes have been identified as liability factors for both bipolar disorder and major depression and the use of large sample sizes is likely to confirm in the future a definite genetic at risk profile. Regarding pharmacogenetics of antidepressants, findings are probably even stronger and in the recent years a number of companies started commercializing tools for use in everyday clinical practice to improve precision medicine. However, some caution should be considered until findings are unequivocally replicated.

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