Lithium genetics

Drs Thomas G Schulze, **Marcella Rietschel**, **Francis J McMahon**, **Michael Bauer** and **Martin Alda** discuss their work on the role of genetics in determining response to lithium treatments, and how this research can benefit patients suffering from bipolar disorder and other psychiatric conditions





What first drew you to psychiatric genetics and what was the motivation for studying bipolar disorder?

TS: Around 40 per cent of people experience psychiatric disorders at some point, so there is a definite scientific and societal need to understand the causes and treatment of mental illness. Both hereditary and environmental factors play roles in psychiatric disorder and for many major psychiatric illnesses the genetic contribution is quite substantial; in the case of bipolar disorder the contribution of genes to overall risk is around 80 per cent. So, genetic research would appear a logical strategy if we are to alleviate the suffering of people with the illness. This must be complemented by other lines of research, but I believe it is a path worth taking.

Can you explain the reasons behind you co-founding the International Consortium on Lithium Genetics (ConLiGen)?

MR: Lithium is a mainstay in the therapy of bipolar disorder and is even successfully applied in treatment-refractory depression. Yet, we do not know much about its mechanism of action. Studies into the biology of lithium response have so far been limited by very small sample sizes. That is what we want to change through ConLiGen. For the last four years, we have been establishing the largest resource for genetic studies on lithium response, collaborating with partners from across the globe.

How has lithium, unlike many other psychiatric drugs, outlasted various pharmacotherapeutic 'fashions', remaining an indispensible element in contemporary psychopharmacology?

MB: Likely because it is a very effective treatment for a subgroup of patients. These lithium responders often recover fully from their illness and remain well as long as they continue taking lithium. I would also like to point out lithium's value to treat and prevent acute depressive episodes in unipolar depression. Adding lithium to a treatment regime with antidepressants is currently the best evidenced augmentation therapy in the treatment of depressed patients who do not respond to antidepressants. Lithium has also been known to reduce very substantially the risk of suicide in people with bipolar disorder and depression.

What are some of the new treatment regimens that have been developed to counteract resistance to primary treatment or prophylaxis?

MA: A number of alternative treatments exist such as the use of anticonvulsants or antipsychotics. Interestingly, these seem to work well in clinically different type of patients than those who respond to lithium. For instance, we know that bipolar patients who have frequent and rapid mood switching or

comorbid anxiety do better on anticonvulsants such as lamotrigine or valproate. Similarly, second-generation antipsychotics can be effective for certain patients, but clinical predictors of response have yet to be reliably established. Finally, patient education and certain types of psychotherapy are useful additions to medication treatment.

To what extent must treatment options be tailored to the needs of the individual to be successful?

FM: Whilst mental disorders are a leading cause of healthy life lost to illness in the developed world, they are also of increasing importance in developing countries. No available treatments act as cures, and treatments which effectively manage symptoms are hard to obtain for many patients. This is where personalised medicine can step in, helping to identify groups of patients who may benefit from a specific medication or combinations of treatments. Personalised medicine may also help restore to use effective medications that have been shunned in clinical practice out of concern for severe side-effects that occur in a few patients, by identifying those at risk.

And finally, how do you hope your research to advance over the next decade, and what do you expect the impact will be on the long-term outcomes of psychosis?

TS: Firstly, through our current genome-wide association study, we hope to learn more about the pharmacogenetics of lithium response in bipolar disorder. Beyond this, we are continuously extending our database to include information on clinical symptoms or adverse events. This will help show which patients are more likely to develop severe side-effects and thus will tremendously help guide treatment strategies. Ultimately, we may consider using the ConLiGen framework to reach beyond bipolar disorder and include studies on major depression or even neurodegenerative disorders, for which lithium is currently being explored as a treatment option. ConLiGen has already been a success, thanks to the amazing collaborative spirit, and we would like to carry that spirit forward.

An improved **response to treatment**

A new initiative is providing a solution to challenges facing lithium parmacogenetics, suggesting that lithium response differs according to genetic variations; knowledge that could aid in tailoring treatments for individual patients

THE MODERN PSYCHIATRIC diagnosis of bipolar disorder refers not to a single illness, but to an entire spectrum of conditions. These were first elucidated in the 19th Century by French physicians Jules Baillarger and Jean-Pierre Falret. Falret later became the first to identify the genetic underpinning of the illness with his observation of the elevated frequency of the disorder within sufferers' families. It is this role that genetics plays in both causing the condition and in the comparative effectiveness of different treatments, particularly lithium, which provided the inspiration for Drs Thomas G Schulze and Francis J McMahon to co-found the International Consortium of Lithium Genetics (ConLiGen).

Lithium – something of a workhorse in the battle against bipolar disorder – has been used to treat various ailments since its discovery over 200 years ago. Despite this awareness of its medicinal properties, it was much later in 1949 that Australian psychiatrist John Cade inadvertently discovered the powerful effect of lithium in tranquilising guinea pigs. Exploring the psychoactive effects of the ion further, Cade was later able to successfully treat patients' mania by applying lithium salts, making the metal the first effective medication to treat a mental illness. More than 60 years on from this breakthrough, modern research only serves to further substantiate lithium's position at the front-line in the treatment of bipolar disorder, as the drug continues to prove itself as an effective mood stabiliser. Research led by one of ConLiGen's members, Professor Michael Bauer, has served to establish lithium as not only an excellent treatment for bipolar disorder, but as a useful tool in the acute treatment of depression, where when used in conjunction with antidepressants lithium has helped to stabilise sufferers of unipolar depression and prevent dangerous relapses.

FRAGMENTARY UNDERSTANDING

Despite the successes that have been achieved through the application of lithium treatment, the drug remains an ineffective course of action for a large proportion of bipolar sufferers. Not all patients are so-called 'lithium responders' and it has become a task of great importance to be able to establish whether or not a given patient will benefit from lithium treatment. Unfortunately, the fragmentary state of our current understanding of both the pathophysiology of bipolar disorder and the mechanism of action of lithium means that current medical knowledge is unable to provide answers to these questions. The challenge of developing an accurate comprehension of bipolar disorder roots principally from its heterogeneity, which is the variation in the illnesses encompassed by the diagnosis, and the intrinsic complexity of the human brain and nervous system.

Attempts to gain insight into the significant role of genetics in bipolar disorder have also been frustrated. The community has come to realise that the illness is highly polygenic, with hundreds or even thousands of genes playing a role in giving

THE INTERNATIONAL CONSORTIUM ON LITHIUM GENETICS (CONLIGEN) – GENOME-WIDE ASSOCIATION STUDIES OF LITHIUM RESPONSE IN BIPOLAR DISORDER

OBJECTIVES

Bipolar disorder is a devastating psychiatric illness, characterised by frequent mood swings and a high risk of suicide. Lithium is a pharmacotherapeutic mainstay, yet the mechanisms of its action are unknown. The main aim is to disentangle the genetic underpinnings of response to lithium through a collaborative effort of unprecedented scope.

KEY PARTNERS

International Group for the Study of Lithium Treated Patients (IGSLI; www.igsli.org)

Pharmacogenomics of Bipolar Disorder (PGBD; www.lithium.ucsd.edu)

KEY COLLABORATORS

For a full list of collaborators, please visit **www.conligen.org/members.html**

FUNDING

National Institute of Mental Health (NIMH)

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CONTACT

Professor Thomas G Schulze, MD
Project Coordinator

Chief, Section on Psychiatric Genetics
Department of Psychiatry and Psychotherapy
University Medical Center
Georg-August-Universität
Von-Siebold-Str. 5
37075 Göttingen
Germany

T +49 551 39 67 30
F +49 551 39 227 98
E thomas.schulze@med.uni-goettingen.de

www.conligen.org

PROFESSOR THOMAS G SCHULZE graduated with an MD from the University of Erlangen-Nuremberg in 1997. After a residency in psychiatry at the University of Bonn, he held several positions in the US (Baltimore, Bethesda, Chicago) and Germany (Mannheim). In 2010, he was appointed Professor of Psychiatric Genetics at the University of Göttingen.

rise to the disorder. This makes using genetics to determine risk extremely challenging as each individual gene confers only a negligible risk, whilst a proper understanding of the likely course of a patient's progression can only be unlocked by fully disentangling the complicated web of interactions both between groups of genes and between genes and the environment. For this to be possible, a large and credible bank of information comprising patients' genetic makeup and their responses to lithium treatment must be compiled and analysed. However, despite this need, the pharmacogenetic datasets regarding lithium have a tendency to be circumstantial and inconclusive.

COLLABORATIVE EFFORT

Beyond the pharmacogenetics, lithium treatment outcomes also depend on external factors such as compliance, side-effects and patient education; factors that are not always considered by clinicians or researchers. This is what Schulze and McMahon sought to change when they, with the support of researchers from the International Group for the Study of Lithium-Treated Patients (IGSLI) and the National Institute of Mental Health (NIMH), founded ConLiGen in 2008.

ConLiGen is an international collaborative effort supported by researchers from across Europe, North and South America, Asia and Australia. The consortium is focused on compiling a large databank which will enable scientists to conduct high-quality analyses of data on patients' responses to lithium treatment. Now with information on several thousand cases at its disposal, ConLiGen has begun a genome-wide association study (GWAS). Cutting-edge genomic analysis screens the entire genome for common factors which may underlie the differences observed in responses to lithium treatment. This information is then used to model networks of genes which may parallel the manner in which lithium influences the central nervous system, offering insight into the mechanism of the drug. It is hoped that the analysis undertaken by ConLiGen will help to uncover genetic variations that define a patient's response to lithium.

ALTERNATIVE TREATMENTS

This research will make possible ConLiGen's primary goal: to illuminate the genetic makeup that defines lithium responders. The understanding permitted by this knowledge will allow treatment programmes to be tailored to each individual's responsiveness, only employing lithium where it will be effective. For patients who do not respond to lithium, there are other avenues of treatment available. These include: the prescription of anticonvulsants such lamotrigine or valproate, which have been more effective at treating patients who suffer from more frequent and rapid mood switching or comorbid anxiety; or the prescription of second-generation antipsychotics, which have been effective in certain cases, though the clinical predictors that allow doctors to identify suitable candidates have not yet been developed. Interestingly, both anticonvulsants and antipsychotics have been shown to be effective in a clinically different category of patients than lithium responders, again highlighting the importance of ascertaining to which category a patient belongs.

The ConLiGen initiative is now partnering with the Pharmacogenomics of Bipolar Disorder (PGBD) study, which parallels ConLiGen's ambitions in that its aim is to identify genetic variants that are associated with responses to mood stabiliser medications that might ultimately be useful as a predictive test. In the future, PGBD and ConLiGen will join forces and samples to provide a fuller picture of how patients with bipolar disorder respond to different treatment options.

REAL IMPACT

ConLiGen is a substantial undertaking but once its ambitious goals are achieved, the knowledge gained will have the power to make a real impact on the suffering of those with bipolar disorder. Using these findings, it will be possible for treatment programmes to be more effectively and accurately tailored to the needs of the individual. In addition, medical professionals will be able to more accurately determine which treatment path is most suitable for a patient, allowing them to readily identify cases where treatment is not working, and provide suitable alternative strategies for dealing with these cases. This will allow treatment programmes to be devised that are better aligned with the needs and unique situation of each patient. Ultimately, the work undertaken by ConLiGen may help to more readily alleviate the suffering of those with bipolar disorder.

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ConLi+Gen
The international Consortium on Lithium Genetics