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Guest Editorial / Misafir Editoryal

Update on Research into the Genetics and Pharmacogenetics of Bipolar Disorder

Thomas G. Schulze[1], Selen Ozkan[2]

[1]Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, München - Germany
[2]MSc in Bioinformatics for Health Sciences, Pompeu Fabra University, Barcelona - Spain

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Address reprint requests to / Yazışma adresi: Thomas G. Schulze, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, München - Germany

E-mail address / Elektronik posta adresi: thomas.schulze@med.uni-muenchen.de

Genetic Epidemiology of Bipolar Disorder

Bipolar disorder (BD) is a severe mental disorder that is characterized by recurrent episodes of mania, and depression. The phenotypic expression can be complemented by suicidal behavior, psychosis, comorbid anxiety, substance abuse, and rapid cycling (1). With a prevalence of ~1% and high risk of morbidity, it is a major health problem (2).

BD has been shown to be a highly heritable disease, with concordance rates being ~85% within twin studies (3). As in other psychiatric disorders, polygenic components have a role in the liability of the disorder. The combination of both genetic and environmental effects influence the risk of developing the disorder. Up to date, there have been several studies of BD including linkage analysis, candidate gene studies, and genome-wide association studies (GWAS). Moreover, it has been established that there is a genetic correlation between BD and schizophrenia conferred by common genetic variation, so called single nucleotide polymorphisms (SNPs), suggesting a shared genetic etiology between these diagnostic entities (4). Yet, our knowledge of the role of genetic factors in susceptibility of BD is still limited.

Given the fact that BD is a highly heterogeneous disorder, studies with more homogenized groups that gather samples with more specific properties, such as subphenotypes of BD or patients positively responsive to specific drug treatments, may help improve the efficiency of studies.

Main challenges in the treatment of BD, as in other disorders, are the differences of response to treatment within patients. Furthermore, adverse events and metabolic conditions caused by mood stabilizers and/or antipsychotic drugs can affect the treatment procedure of a patient (5).

Genetic Studies of the Bipolar Disorder Phenotype

Genetic studies of bipolar disorder initially focused on candidate gene studies. With the turn of the millennium, large-scale genome-wide association studies (GWAS) have increasingly replaced small and thus underpowered case-control candidate gene

association studies (4). Up to date, GWAS have robustly identified 18 significant loci (6). One of the most important and well-known GWAS findings were CACNA1C and ANK3 (7). CACNA1C encodes a plasma membrane L-type Ca^{2+} channel whereas ANK3 encodes ankyrin G that anchors sodium and potassium channels in neurons.

Pharmacogenetic Studies in Bipolar Disorder

Pharmacogenetics aims to identify how genetic variations affect the response to drugs and adverse events observed during the treatment. By doing so, the ultimate goal is to fulfill the promise of personalized treatment, also known as precision medicine. For pharmacogenetics studies to be successful, large sample sizes are required (as is true for any psychiatric genetic study). Furthermore, in pharmacogenetic studies, it is imperative to follow a strict research protocol and stringent phenotype characterization that can be reliably be performed across collaborating centers (5).

For more than 60 years, lithium has been used as first-line medication in treatment of BD as a mood stabilizer (8). Lithium is suggested to be involved in several signaling pathways and in the modulation processes of apoptosis, neuroprotection, neural plasticity, neurotransmission and circadian rhythms (9). The exact mechanism of action, however, has remained elusive thus far. One of the very first hypotheses for explaining how lithium acts is through inositol depletion (10). Lithium causes reduction of IMPase and phosphatases inositol-1,4 biphosphate 1-phosphatase; which are two crucial enzymes of inositol phosphate pathway. This results in an overall reduction of myoinositol levels in the system. Compared with other mood stabilizers, myoinositol levels have been reported to decrease only under lithium administration. Nevertheless, the relationship between this pathway and clinical responses of BD is still unclear (10).

Another well-studied target of lithium is glycogen synthase kinase 3 enzyme. When the enzyme is inhibited in the system, lithium affects several transcription factors and the Wnt signaling pathway, which are the downstream targets of this enzyme. Furthermore, lithium acts upon voltage-gated sodium channels and causes reduction of sodium influx, leading to decreased intracellular sodium levels, a property that has been observed for other mood stabilizers as well. Several other studies suggest that lithium has a role in neuroprotection and neural plasticity through reducing glutamergic activity, inhibiting pro-apoptotic factors, increasing antioxidant enzyme levels, and modulating mitochondrial activity (9).

Treatment response to lithium is quite heterogeneous, with roughly one third of patients showing excellent response and the remainder showing only partial response or no response at all. Patients may respond to lithium treatment in a short or long time, and there are varying adverse effects such as weight gain, tremor, chronic kidney disease, or hypothyroidism (9). Furthermore; response to lithium varies according to family history which underscores the important role of genetic factors; BD patients responding well to lithium typically show a high familial loading for BD (11). Other studies focusing on response to other treatments of BD, such as lamotrigine or divalproex, proposed that patients responding well to these drugs have a clinical phenotype and underlying biology that are completely different from those of lithium responders. Identification of heritable factors in relation to response to treatment is therefore important, and such information may eventually be used to guide the choice of medication choice (8).

Genome-wide Association Studies of Lithium Response

Pharmacogenomics studies of BD have so far focused mostly on lithium response. Most findings from candidate gene studies highlighted genes involved in inositol signaling pathway, circadian signaling system and several transmitter systems such as adrenergic, noradrenergic, dopaminergic etc (5). However, most of these findings were based on extremely small samples and failed to withstand correction for multiple testing or could not be replicated.

With regards to GWAS of lithium response, the first published study was based on 1,177 BD patients who received lithium, in which no SNP was found to reach genome-wide significance threshold (12). Subsequently, three other GWAS have been published on lithium response. One of them was a genome-wide study performed on 52 BD patients who were at the extreme ends of a 10-point treatment response scale of lithium. Among associated SNPs identified, selected ones were validated. The ACCN1 gene was found to play a possible role in lithium response, although the necessity of replication in a larger sample size was noted as well (13). The second GWAS in this list is from a Taiwanese group; they reported genome-wide significance for a SNP in the glutamate decarboxylase-like protein 1 gene (GADL1) that is only present in Asians. However, this finding could not be replicated in other independent samples from Asia (14). Finally, the largest GWAS of lithium response so far is the study of the Consortium on Lithium Genetics (ConLiGen; www.ConLiGen.org). ConLiGen was founded to conduct high quality, well-powered association studies of lithium treatment response (4). The ConLiGen study included over 2500 BD patients from more than 20 centers from 4 continents. Four SNPs in high linkage disequilibrium with each other reached genome-wide significance; they are located in a region coding for long, non-coding RNA (lncRNA) on chromosome 21 (15). While the specific role of this locus for lithium's mechanism of action has yet to be elucidated in subsequent studies, lncRNAs have been implicated in mechanisms of DNA regulation (16,17).

The Next Frontier: Next Generation Sequencing of Bipolar Disorder

The rapid advances in DNA sequencing technologies, followed by decrease in cost, have propelled large-scale sequencing studies. Whole exome sequencing (WES) and whole genome sequencing (WGS) technologies offer the prospect of major advances in the field, such as detecting the frequency and penetrance of variants, clarifying the relationship within the variants, further examining the importance of interaction between gene and environment. This kind of information is crucial for psychiatric genetics as it may help to further our understanding of etiology and to personalize therapies and potentially risk predictions (18). Many studies of WES and WGS are ongoing, and several informative preliminary data related with pathways involved in BD have already been published (19).

Whole Exome Sequencing

One of the first WES blended sequencing with pathway analyses in around 300 samples to analyze rare variants. The most significant pathway they found was MAPK signaling, in which genes coding for neuronal synapses were located, including CACNA1C (20).

Another study conducted WES on families with high incidence of BD and good response to lithium monotherapy. Samples from multigenerational family members with 36 total individuals per family were sampled and sequenced along with unaffected members who were used as controls (1). A missense mutation was identified in gene ZNF259, segregating in affected individuals only within the family, which further requires validation in a larger cohort (2).

The role of rare variants within BD was proposed by several studies, including a WGS study of 200 individuals from 41 bipolar families in which rare variants are shown to influence the neuronal excitability related genes such as calcium channel encoding ones (21). In addition, recent studies focused on the contribution of de novo mutations to the risk of BD, including de novo copy number variations (CNVs), which have been reported by many studies to have correlation with early onset of BD, compared to non-carriers (22,23). A WES study of BD, investigating the effect of de novo mutations upon disease etiology, identified 71 de novo point mutations and one de novo CNV in 79 BD probands, analyzing 237 exomes. Among these, loss-of-function and protein-altering mutations were located at genes that are highly intolerant to functional variations. While large-scale studies are required to truly understand their pathogenic role, considering the statistical significance

and similar WES results of de novo mutations in autism and schizophrenia, these observations are a promising first step (24,25).

Whole Genome Sequencing

Thus far, two studies have been reported on whole genome sequencing of BD patients (4). The first was performed in an isolated population, the Old Order Amish in North America. Applying a parent-child trio design, 50 individuals were selected for WGS from the pedigree. 30 non-synonymous, possibly deleterious variants were identified, which were rare according to the 1000 Genomes Project but found in 10-30% of patients and their first-degree relatives (26). Another study used BD whole genome sequence data to focus on variants in intronic and non-coding regions of CACNA1C and ANK3, two best-replicated susceptible genes of BD. The study was based on 99 individuals with an early age at onset and positive family history of BD. Based on the phenotypic observations of BD, in which there is full recovery between two states, it was suggested that the etiological base-pair changes could be affecting gene expression and mRNA translation rather than causing structural changes in proteins. Potential novel variants identified further need replication and validation in independent samples (27).

REFERENCES

1. Cruceanu C, Ambalavanan A, Spiegelman D, Gauthier J, Lafrenière RG, Dion PA, Alda M, Turecki G, Rouleau GA. Family-based exome-sequencing approach identifies rare susceptibility variants for lithium-responsive bipolar disorder. Genome 2013; 56:634-640. **[CrossRef]**

2. Kawakami N. Large scale epidemiology study of the prevalence of mental disorders: World Mental Health Japan Survey Second. A report of the Health Labour Sciences Research Grant from The Ministry of Health Labour and Welfare (H25-Seishin-Ippan-006), Tokyo, 2014.

3. McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch Gen Psychiatry 2003; 60:497-502. **[CrossRef]**

4. Shinozaki G, Potash JB. New developments in the genetics of bipolar disorder. Curr Psychiatry Rep 2014; 16:493. **[CrossRef]**

5. Budde M, Degner D, Brockmöller J, Schulze TG. Pharmacogenomic aspects of bipolar disorder: An update. Eur Neuropsychopharmacol 2017; 27:599-609. **[CrossRef]**

6. Budde M, Forstner AJ, Adorjan K, Schaupp SK, Nöthen MM, Schulze TG. Genetics of bipolar disorder. Nervenarzt 2017; 88:755-759. **[CrossRef]**

7. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007; 447:661-678. **[CrossRef]**

8. Cruceanu C, Alda M, Rouleau G, Turecki G. Response to treatment in bipolar disorder. Curr Opin Psychiatry 2011; 24:24-28. **[CrossRef]**

9. Pisanu C, Melis C, Squassina A. Lithium pharmacogenetics: where do we stand? Drug Dev Res 2016; 77:368-373. **[CrossRef]**

10. Atack JR. Inositol monophosphatase inhibitors–lithium mimetics? Med Res Rev 1997; 17:215-224. **[CrossRef]**

11. Cruceanu C, Alda M, Turecki G. Lithium: a key to the genetics of bipolar disorder. Genome Med 2009; 1:79. **[CrossRef]**

12. Perlis RH, Smoller JW, Ferreira MA, McQuillin A, Bass N, Lawrence J, Sachs GS, Nimgaonkar V, Scolnick EM, Gurling H, Sklar P, Purcell S. A genomewide association study of response to lithium for prevention of recurrence in bipolar disorder. Am J Psychiatry 2009; 166:718-725. **[CrossRef]**

13. Squassina A, Manchia M, Borg J, Congiu D, Costa M, Georgitsi M, Chillotti C, Ardau R, Mitropoulos K, Severino G, Del Zompo M, Patrinos GP. Evidence for association of an ACCN1 gene variant with response to lithium treatment in Sardinian patients with bipolar disorder. Pharmacogenomics 2011; 12:1559-1569. **[CrossRef]**

14. Chen CH, Lee CS, Lee MT, Ouyang WC, Chen CC, Chong MY, Wu JY, Tan HK, Lee YC, Chuo LJ, Chiu NY, Tsang HY, Chang TJ, Lung FW, Chiu CH, Chang CH, Chen YS, Hou YM, Chen CC, Lai TJ, Tung CL, Chen CY, Lane HY, Su TP, Feng J, Lin JJ, Chang CJ, Teng PR, Liu CY, Chen CK, Liu IC, Chen JJ, Lu T, Fan CC, Wu CK, Li CF, Wang KH, Wu LS, Peng HL, Chang CP, Lu LS, Chen YT, Cheng AT; Taiwan Bipolar Consortium. Variant GADL1 and response to lithium therapy in bipolar I disorder. N Engl J Med 2014; 370:119-128. **[CrossRef]**

15. Weng JTY, Chi YX, Wu LH, Lee CS, Cheng ATA. MicroRNA and gene expression profiling of response to lithium treatment for bipolar I disorder. Biomedical Engineering and Informatics (BMEI), 2015 8th International Conference on. IEEE, 2015. **[CrossRef]**

16. Hou L, Heilbronner U, Degenhardt F, Adli M, Akiyama K, Akula N, Ardau R, Arias B, Backlund L, Banzato CEM, Benabarre A, Bengesser S, Bhattacharjee AK, Biernacka JM, Birner A, Brichant-Petitjean C, Bui ET, Cervantes P, Chen GB, Chen HC, Chillotti C, Cichon S, Clark SR, Colom F, Cousins DA, Cruceanu C, Czerski PM, Dantas CR, Dayer A, Étain B, Falkai P, Forstner AJ, Frisén L, Fullerton JM, Gard S, Garnham JS, Goes FS, Grof P, Gruber O, Hashimoto R, Hauser J, Herms S, Hoffmann P, Hofmann A, Jamain S, Jiménez E, Kahn JP, Kassem L, Kittel-Schneider S, Kliwicki S, König B, Kusumi I, Lackner N, Laje G, Landén M, Lavebratt C, Leboyer M, Leckband SG, Jaramillo CAL, MacQueen G, Manchia M, Martinsson L, Mattheisen M, McCarthy MJ, McElroy SL, Mitjans M, Mondimore FM, Monteleone P, Nievergelt CM, Nöthen MM, Ösby U, Ozaki N, Perlis RH, Pfennig A, Reich-Erkelenz D, Rouleau GA, Schofield PR, Schubert KO, Schweizer BW, Seemüller F, Severino G, Shekhtman T, Shilling PD, Shimoda K, Simhandl C, Slaney CM, Smoller JW, Squassina A, Stamm T, Stopkova P, Tighe SK, Tortorella A, Turecki G, Volkert J, Witt S, Wright A, Young LT, Zandi PP, Potash JB, DePaulo JR, Bauer M, Reininghaus EZ, Novák T, Aubry JM, Maj M, Baune BT, Mitchell PB, Vieta E, Frye MA, Rybakowski JK, Kuo PH, Kato T, Grigoroiu-Serbanescu M, Reif A, Del Zompo M, Bellivier F, Schalling M, Wray NR, Kelsoe JR, Alda M, Rietschel M, McMahon FJ, Schulze TG. Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study. Lancet 2016; 387:1085-1093. **[CrossRef]**

17. Bauer M, Gitlin M. What Is Lithium and How Does It Work? The Essential Guide to Lithium Treatment. Springer International Publishing, 2016, p. 33-43. **[CrossRef]**

18. Biesecker BB, Peay HL. Genomic sequencing for psychiatric disorders: promise and challenge. Int J Neuropsychopharmacol 2013; 16:1667-1672. **[CrossRef]**

19. Kato T. Whole genome/exome sequencing in mood and psychotic disorders. Psychiatry Clin Neurosci 2015; 69:65-76. **[CrossRef]**

20. Chen YC, Carter H, Parla J, Kramer M, Goes FS, Pirooznia M, Zandi PP, McCombie WR, Potash JB, Karchin R. A hybrid likelihood model for sequence-based disease association studies. PLoS Genet 2013; 9:e1003224. **[CrossRef]**

21. Ament SA, Szelinger S, Glusman G, Ashworth J, Hou L, Akula N, Shekhtman T, Badner JA, Brunkow ME, Mauldin DE, Stittrich AB, Rouleau K, Detera-Wadleigh SD, Nurnberger JI Jr, Edenberg HJ, Gershon ES, Schork N; Bipolar Genome Study, Price ND, Gelinas R, Hood L, Craig D, McMahon FJ, Kelsoe JR, Roach JC. Rare variants in neuronal excitability genes influence risk for bipolar disorder. Proc Natl Acad Sci USA 2015; 112: 3576-3581. **[CrossRef]**

22. Malhotra D, McCarthy S, Michaelson JJ, Vacic V, Burdick KE, Yoon S, Cichon S, Corvin A, Gary S, Gershon ES, Gill M, Karayiorgou M, Kelsoe JR, Krastoshevsky O, Krause V, Leibenluft E, Levy DL, Makarov V, Bhandari A, Malhotra AK, McMahon FJ, Nöthen MM, Potash JB, Rietschel M, Schulze TG, Sebat J. High frequencies of de novo CNVs in bipolar disorder and schizophrenia. Neuron 2011; 72:951-963. **[CrossRef]**

23. Georgieva L, Rees E, Moran JL, Chambert KD, Milanova V, Craddock N, Purcell S, Sklar P, McCarroll S, Holmans P, O'Donovan MC, Owen MJ, Kirov G. De novo CNVs in bipolar affective disorder and schizophrenia. Hum Mol Genet 2014; 23:6677-6683. **[CrossRef]**

24. Neale BM, Kou Y, Liu L, Ma'ayan A, Samocha KE, Sabo A, Lin CF, Stevens C, Wang LS, Makarov V, Polak P, Yoon S, Maguire J, Crawford EL, Campbell NG, Geller ET, Valladares O, Schafer C, Liu H, Zhao T, Cai G, Lihm J, Dannenfelser R, Jabado O, Peralta Z, Nagaswamy U, Muzny D, Reid JG, Newsham I, Wu Y, Lewis L, Han Y, Voight BF, Lim E, Rossin E, Kirby A, Flannick J, Fromer M, Shakir K, Fennell T, Garimella K, Banks E, Poplin R, Gabriel S, DePristo M, Wimbish JR, Boone BE, Levy SE, Betancur C, Sunyaev S, Boerwinkle E, Buxbaum JD, Cook EH Jr, Devlin B, Gibbs RA, Roeder K, Schellenberg GD, Sutcliffe JS, Daly MJ. Patterns and rates of exonic de novo mutations in autism spectrum disorders. Nature 2012; 485:242-245. **[CrossRef]**

25. De Rubeis S, He X, Goldberg AP, Poultney CS, Samocha K, Cicek AE, Kou Y, Liu L, Fromer M, Walker S, Singh T, Klei L, Kosmicki J, Shih-Chen F, Aleksic B, Biscaldi M, Bolton PF, Brownfeld JM, Cai J, Campbell NG, Carracedo A, Chahrour MH, Chiocchetti AG, Coon H, Crawford EL, Curran SR, Dawson G, Duketis E, Fernandez BA, Gallagher L, Geller E, Guter SJ, Hill RS, Ionita-Laza J, Jimenz Gonzalez P, Kilpinen H, Klauck SM, Kolevzon A, Lee I, Lei I, Lei J, Lehtimäki T, Lin CF, Ma'ayan A, Marshall CR, McInnes AL, Neale B, Owen MJ, Ozaki N, Parellada M, Parr JR, Purcell S, Puura K, Rajagopalan D, Rehnström K, Reichenberg A, Sabo A, Sachse M, Sanders SJ, Schafer C, Schulte-Rüther M, Skuse D, Stevens C, Szatmari P, Tammimies K, Valladares O, Voran A, Li-San W, Weiss LA, Willsey AJ, Yu TW, Yuen RK; DDD Study; Homozygosity Mapping Collaborative for Autism; UK10K Consortium, Cook EH, Freitag CM, Gill M, Hultman CM, Lehner T, Palotie A, Schellenberg GD, Sklar P, State MW, Sutcliffe JS, Walsh CA, Scherer SW, Zwick ME, Barett JC, Cutler DJ, Roeder K, Devlin B, Daly MJ, Buxbaum JD. Synaptic, transcriptional and chromatin genes disrupted in autism. Nature 2014; 515:209-215. **[CrossRef]**

26. Georgi B, Craig D, Kember RL, Liu W, Lindquist I, Nasser S, Brown C, Egeland JA, Paul SM, Bućan M. Genomic view of bipolar disorder revealed by whole genome sequencing in a genetic isolate. PLoS Genet 2014; 10:e1004229. **[CrossRef]**

27. Fiorentino A, O'Brien NL, Locke DP, McQuillin A, Jarram A, Anjorin A, Kandaswamy R, Curtis D, Blizard RA, Gurling HM. Analysis of ANK3 and CACNA1C variants identified in bipolar disorder whole genome sequence data. Bipolar Disord 2014; 16:583-591. **[CrossRef]**