An Integrative Analysis of Genetic Risk Factors for Long-Term Functional Outcome in Bipolar Disorder

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Introduction

Despite large case-control genome-wide association studies during the last years - as in other complex disorders - the anticipated major breakthroughs in explaining the high heritability of bipolar disorder (BD) have remained elusive. Hence an alternative strategy is exploring quantitative rather than binary phenotypes. We studied the genetic basis of global functioning measured by the Global Assessment of Functioning (GAF) score. The GAF accounts for the social, occupational, and psychological functioning of a psychiatric patient and can be used as a comprehensive indicator for long-term functional outcome / course of illness. Hence this study fills a gap in the mainly cross-sectional research in psychiatric genetics.

Sample 1: GAIN BD	Sample 2: BOMA BD
N = 1,081 BD patients	*N* = 511 BD patients
DSM-IV diagnosis	DSM-IV diagnosis
European American	German
Affymetrix 6.0	Illumina HumanHap550v3 Illumina Human610 Illumina Human 660w
~2 541,685 SNPs	536,497 SNPs

410,943 SNPs*

*passed quality control in both samples (HWE ≥ 10-5, MAF ≥ 5%, call rate ≥ 95%)

Phenotype: Global Level of Functioning

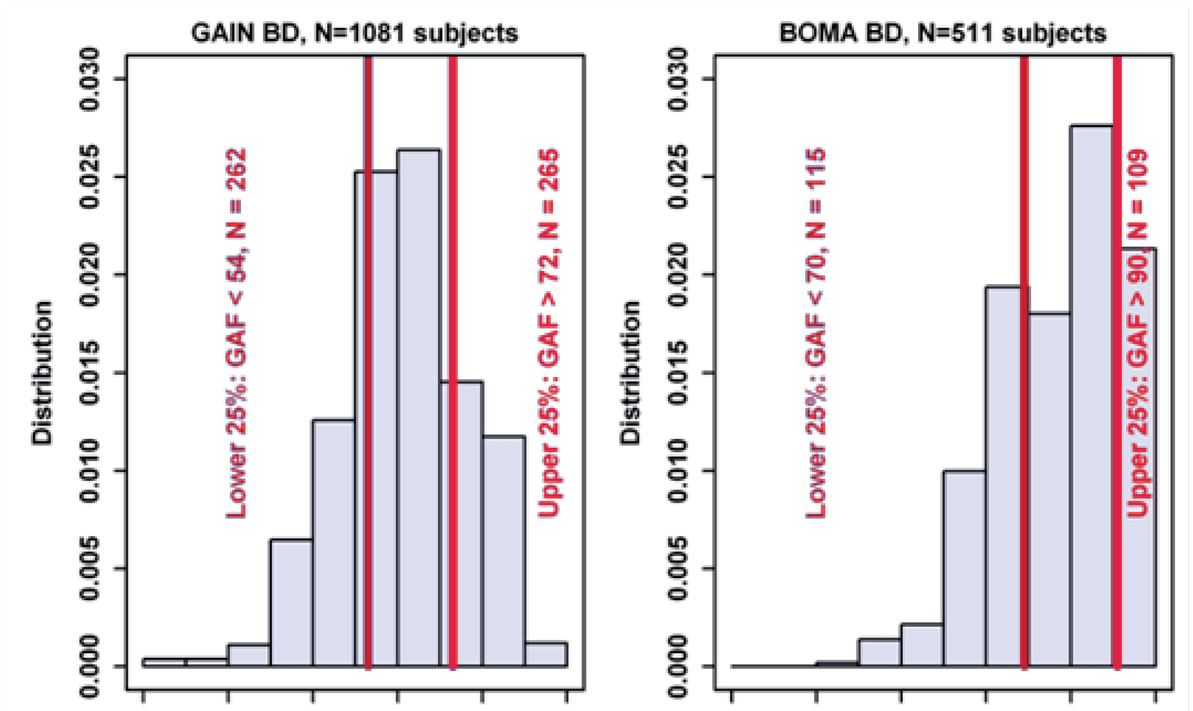
- measured by GAF score

The GAF score - described in DSM-IV-TR - is a numeric scale (0-100) that is used for rating the psychological, social and occupational functioning of adults.

	GAF	Advantage	Disadvantage
I	**Metric GAF** (quantitative)	full sample size	less contrast
II	**Contrast of GAF extremes** (case-case scenario on subjects with GAF values in the upper & lower sample quartiles)	higher contrast	reduced sample size

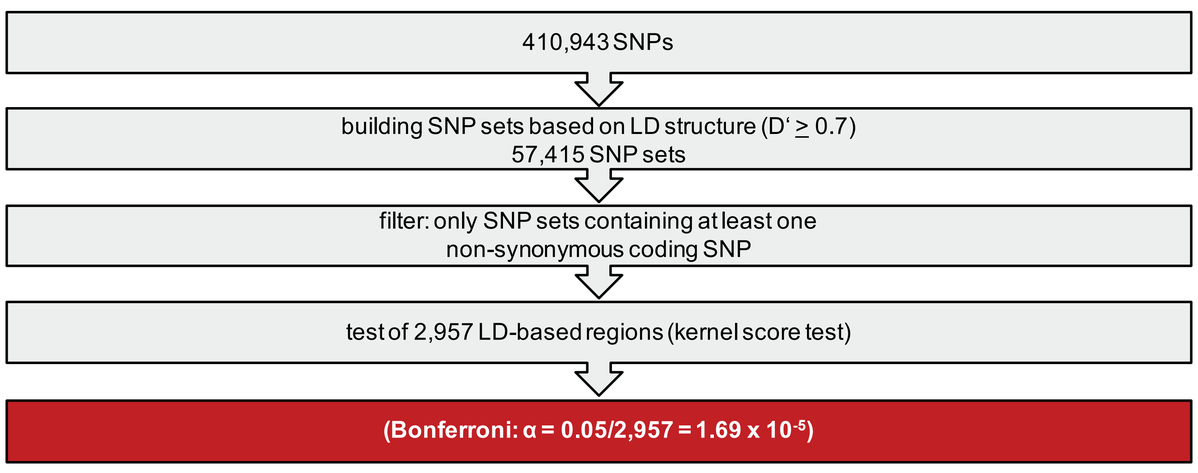
Phenotype: Interepisode GAF

Fig. 1: Distributions of GAF score in our samples



Analyses

Fig. 2: Filtering steps



Kernel score test

(SKAT, review Schaid 2010 Hum Hered; Friedrichs et al., 2016 BMC Genet)

- test for overall association of a set of markers
- Do the overall scores of the SNP sets explain the variance in the GAF score?
- higher power in moderate samples compared to SNP-wise analyses
- significance only if direction of effect consistent across both samples

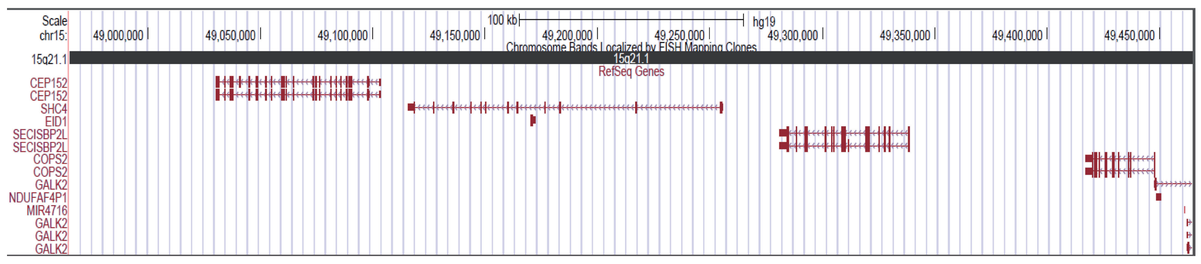
- *tested for both phenotype definitions*
- *adjusted for sex, duration of illness and sample*

Results

Kernel score test

One LD block, located on chr15q21.1, was significantly associated with the GAF score (kernel score test: $p=1.29 \cdot 10^{-5}$ metric GAF; $p=5.64 \cdot 10^{-6}$ GAF-extremes).

Genes in LD block on chr15q21.1



Meta-analyses of two BD patient samples adjusted for sex and duration of illness

SNP	MAF	Effect on metric GAF Beta[a]	Meta-analysis p-value	Effect on GAF Extremes Odds Ratio[b]	Meta-Analysis p-value	Gene
rs4474633	GAIN: 0.33 BOMA: 0.32	GAIN: -1.60 BOMA: -3.72	4.39×10^{-5}	GAIN: 1.48 BOMA: 2.21	1.33×10^{-5}	*intergenic SHC4 – SECISBP2L*
rs2413930	GAIN: 0.29 BOMA: 0.23	GAIN: -1.99 BOMA: -4.13	1.46×10^{-5}	GAIN: 1.63 BOMA: 2.62	5.80×10^{-6}	*intergenic SECISBP2L-COPS2*
rs586758	GAIN: 0.30 BOMA: 0.29	GAIN: -1.84 BOMA: -3.81	2.49×10^{-5}	GAIN: 1.63 BOMA: 2.31	2.01×10^{-6}	*GALK2*
rs2086256	GAIN: 0.35 BOMA: 0.35	GAIN: -2.28 BOMA: -3.23	1.14×10^{-5}	GAIN: 1.62 BOMA: 2.06	4.64×10^{-6}	*GALK2*
rs1904317	GAIN: 0.30 BOMA: 0.29	GAIN: -1.84 BOMA: -3.79	2.49×10^{-5}	GAIN: 1.63 BOMA: 2.28	2.21×10^{-6}	*GALK2*
rs11854184[c]	GAIN: 0.19 BOMA: 0.20	GAIN: 1.30 BOMA: 2.80	0.0132	GAIN: 0.75 BOMA: 0.56	0.0128	*SECISBP2L*

[a] The effect on metric GAF is a regression coefficient beta. Positive values indicate a protective effect of the minor allele.
[b] The contrast between upper and lower GAF quartile is an odds ratio. Values <1 indicate a protective effect.
[c] non-synonymous coding SNP

Discussion

Advantages	Disadvantages
Novel phenotype GAF	
proxy for course of illness	heterogeneous phenotype (time intervals; domains)
easy to assess	difficulty in finding comparable samples
clinically useful	
Methodological issues	
applicable also to moderate sample sizes	refinement of filter criteria needed
consistency check-up already included	further replication studies necessary

Conclusion

Our analysis of the GAF score in two BD samples found a consistently associated LD block on chromosome 15. This region will be examined more closely; including haplotype analysis and its relevance as potentially shared genetic factor in schizophrenia.

References

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Disclosure

The authors declare no conflict of interest.