

Susanne Bengesser / Eva Reininghaus

Genetics of Bipolar Disorder



Table of Contents

Preface	5
Abstract.....	7
Acknowledgements.....	9
1. Introduction.....	17
1.1 Bipolar Affective Disorder.....	17
1.1.1 History and Symptomatology of Bipolar Disorder	17
1.1.2 Pharmacotherapy	18
Mood Stabilization.....	19
Lithium.....	19
Antiepileptics	21
Atypical Antipsychotics	22
Antidepressant Therapy	23
Selective Serotonin Reuptake Inhibitors (SSRI).....	24
NASSA (Noradrenaline and Serotonin Specific	
Antidepressant)	24
SNRI (Serotonin and Noradrenaline Reuptake	
Inhibitor)	25
NARI (Noradrenaline Reuptake Inhibitor)	25
SRE (Serotonin Reuptake Enhancer).....	25
NDRI (Noradrenaline and Dopamine Reuptake	
Inhibitor)	25
Tricyclic Antidepressants.....	26
Tetracyclic Antidepressants	26
MAO Inhibitors.....	26
DSA (Dual Serotonergic Antidepressant).....	26
Bright Light Therapy	27
1.1.3 Epidemiology of Bipolar Disorder.....	27
1.2 Basic Principles of Genetics.....	27
1.2.1 Structure of DNA.....	27

1.2.2	Gene Expression- from DNA to Proteins	28
	Transcription.....	29
	Initiation of Transcription	30
	Elongation of Transcription	31
	Termination of Transcription	31
	Proteinbiosynthesis (Translation):	32
	Initiation of Protein Biosynthesis in Eukaryotes	33
	Elongation.....	34
	Termination.....	35
1.2.3	Replication.....	35
	Initiation of Replication	35
1.2.4	Epigenetics.....	36
1.2.5	Mutations	36
	Gene mutations	36
	Point mutations	36
	Insertions, Deletions, Duplications and Repeat	
	Polymorphisms	37
	Chromosomal mutations	37
	Structural Chromosomal Mutations	37
	Chromosome Number Aberrations	37
1.2.6	Methods of Molecular Bipolar Disorder Research	38
	Association Studies.....	38
	Genome Wide Association Studies (GWAS).....	38
	Linkage studies	39
2.	Methods.....	41
3.	Genetics of Bipolar Disorder	43
3.1	Heritability of Bipolar Disorder	43
3.2	Candidate Genes at One View	43
3.3	Genes of the Serotonergic System	60
3.3.1	Serotonin Receptor Genes	60
	5-HT1 Receptor Genes	60
	HTR1A.....	60
	HTR1B and HTR1D	62
	5-HT2 Receptor Genes	62
	HTR2A.....	62
	HTR2C Gene	65
	5-HT3 Receptor Genes	66
	5-HT4 Receptor Genes	67

	5-HT5 Receptor Genes	67
	5-HT6 Receptor Genes	67
	5-HT7 Receptor Genes	68
3.3.2	Serotonin Transporter Gene (= SLC6A4, SERT, 5HTT)	68
	Polymorphism of the 5-HTTLPR and the Untranslated Region.....	69
	The Variable-Number-Tandem-Repeat (VNTR) within Intron 2.....	69
	Insertion/deletion in the Promoter Region of the Serotonin Transporter	70
3.4	Genes Involved in Biogenic Amine Modulation.....	72
3.4.1	MAOA	72
	Animal Studies.....	73
	Antidepressants.....	73
	Association Studies.....	73
	CA-Repeat Microsatellite in Intron 2.....	74
	Fnu4H1 RFLP (Fnu4H1 Restriction Fragment Length Polymorphism).....	74
	EcoRV Polymorphism (T-to-C Substitution at Position-1460)	75
	T-to-A Substitution at Position 1077 (Promoter VNTR)	75
	Variable Number of Tandem Repeats (VNTR) Polymorphism in Intron 1	75
	Linkage studies	76
3.4.2	MAOB	76
3.4.3	COMT.....	76
3.4.4	TPH.....	78
3.4.5	TH.....	79
3.5	Clock Genes	80
3.5.1	The Circadian Oscillator in the Suprachiasmatic Nucleus.....	80
3.5.2	Role of clock genes in bipolar disorder	82
	ARNTL (BMAL1 or MOP3).....	82
	NPAS2	83
	NR1D1	83
	Period Genes (PER1, PER2, PER3).....	84
	CRY	84
	CLOCK.....	85
	DBP	85
	CSNKD.....	86

	CSNKE	86
	TIMELESS	86
	PPARGC1B	86
	Summary of clock genes	87
3.6	Growth Hormones	88
3.6.1	BDNF	88
	Functions of BDNF	88
	BDNF Signal Transduction	88
	BDNF Polymorphisms	89
	Dinucleotide repeat (GT) _n (BDNF-LCPR)	89
	Val66Met Polymorphism	89
	Association of BDNF Variants with Bipolar Disorder	89
	Antidepressants, Mood Stabilizers and Animal Studies ...	89
	Serum Levels of BDNF	90
	Linkage studies for chromosome 11	90
	GWAS- Genome wide association studies	90
	Genetic association studies and family based genetic studies	91
	Reasons for controversies	91
	BDNF and subtypes of bipolar disorder or related disease	92
	Summary of Association Studies for BDNF and Bipolar Disorder (BD)	93
3.6.2	NRG1	94
3.6.3	NCAM1	94
3.6.4	RELN	94
3.7	Genes of the Lithium signal transduction pathways	95
3.7.1	DGKH	95
3.8	Ion channels and associated proteins	95
3.8.1	ANK3	95
3.8.2	CACNA1C	96
3.8.3	NTNG1 and NTNG2	97
3.8.4	KCNC2	97
3.8.5	P2RX7/4	97
3.8.6	ATP2A2	98
3.8.7	SLC24A3	98
3.8.8	SLC39A3	98
3.9	HPA axis, cortisol and stress	98
3.10	Genes of the dopaminergic system	99
3.10.1	DAT1	100

3.10.2	DRD1	101
3.10.3	DRD2	102
3.10.4	DRD3	104
3.10.5	DRD4	105
3.10.6	DRD5	107
3.11	Genes of the noradrenergic system	108
3.11.1	NET (SLC6A2)	108
3.12	Genes of the GABAergic system	108
3.12.1	GABRB1	108
3.12.2	GABRB2	109
3.12.3	GABRB3	109
3.12.4	GABRA5	109
3.13	Genes of the Glutamatergic system	109
3.13.1	GRIN genes	109
3.13.2	GRIA1	110
3.13.3	GRM3	110
3.13.4	GRM4	110
3.13.5	GRM7	111
3.13.6	GRIK genes	111
3.14	Copy number variations (CNVs)	111
3.15	Others	112
3.15.1	GCHI	112
3.15.2	CHMP1.5	112
4.	Genetic overlaps between psychiatric diseases	115
4.1	Overlaps between mood disorders and schizophrenia	115
4.1.1	Schizophrenia	115
4.2	Overlaps between mood disorders and schizophrenia	116
4.2.1	Symptomatic overlaps between psychiatric diseases	116
4.2.2	Genetic overlaps between mood disorders and schizophrenia .	117
	COMT	117
	Serotonin transporter polymorphisms	118
	SERT (=5HTT = serotonin transporter gene)	118
	VNTR in intron 2 of the serotonin transporter gene	118
	Deletion/insertion in the promoter region of SERT	119
	G72/G30 gene (DAOA)	120
	DAO	120
	CACNA1C	120
	DTNBP1	120
	Neuregulin1	121

DISC 1	121
BDNF	122
MAOA	122
Dopamine receptor genes.....	123
DRD1	123
DRD2	123
DRD3	123
DRD4	124
DRD5	124
4.3 Summary of the overlaps between mental diseases	125
5. Gene-environment-interactions and prevention	131
5.1 Epigenetics	131
5.2 Sleep deprivation.....	132
5.3 Nutrition and famines.....	132
5.4 Infections and risk of bipolar disorder	133
5.5 Season of birth	133
5.6 Urban/rural residency and genotype	133
5.7 Antidepressant induced mania and genotypes.....	133
5.8 Stress, gene expression and bipolar disorder.....	134
5.9 Mood changes after delivery	135
5.10 Maltreatment and negative life events.....	135
5.10.1 MAOA polymorphism.....	135
5.10.2 Hypothalamic-pituitary-adrenal axis	136
5.10.3 FKBP5	136
5.10.4 Serotonin transporter 5-HTTLPR polymorphism	136
5.10.5 BDNF	137
5.10.6 COMT.....	137
5.11 Implications for clinical practice.....	138
5.11.1 Treatment and genotype.....	138
Antidepressant treatment and genotype	138
Antimanic treatment and genotype	138
5.11.2 Psychotherapy.....	138
5.11.3 Lifestyle changes	139
6. Conclusion	141
7. References.....	143