

# 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<br>Region.....                | 69 |
|       | The Variable-Number-Tandem-Repeat (VNTR)<br>within Intron 2.....                | 69 |
|       | Insertion/deletion in the Promoter Region of the<br>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<br>Polymorphism).....           | 74 |
|       | EcoRV Polymorphism (T-to-C Substitution at<br>Position-1460).....               | 75 |
|       | T-to-A Substitution at Position 1077 (Promoter<br>VNTR).....                    | 75 |
|       | Variable Number of Tandem Repeats (VNTR)<br>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<br>studies .....      | 91  |
|        | Reasons for controversies .....  | 91  |
|        | BDNF and subtypes of bipolar disorder or related<br>disease.....           | 92  |
|        | Summary of Association Studies for BDNF and<br>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 |