

Contents

<i>Introduction</i>	vii
<i>Preface</i>	ix
<i>Contributors</i>	xi
1. Respiratory control disorders: from genes to patients and back	1
<i>David GOZAL</i>	
1.1 Introduction	1
1.2 Effect of sleep on breathing.....	2
1.3 Diagnostic approaches to the patient with suspected abnormalities in respiratory control	3
1.4 Potential consequences of delayed diagnosis and treatment	4
1.5 Where do we go from here?	4
1.6 Conclusion.....	5
References	6
2. Hereditary aspects of respiratory control in health and disease in humans.....	9
<i>John V. WEIL</i>	
2.1 Introduction	9
2.2 Inter-individual variation in human ventilatory control	9
2.3 Population and species differences.....	11
2.4 Familial clusters	12
2.5 Genetics <i>vs.</i> environment	16
2.6 Locus of hereditary effects	16
2.7 Conclusion.....	20
References	20
3. Phox2b and the homeostatic brain.....	25
<i>Jean-François BRUNET and Christo GORIDIS</i>	
3.1 Introduction	25
3.2 Expression pattern of <i>Phox2</i> genes.....	25
3.3 Gross phenotype of mouse mutants for <i>Phox2</i> genes.....	30
3.4 Cellular functions of <i>Phox2</i> genes.....	33
3.5 Ancestry of the homeostatic brain	38
3.6 Conclusion.....	38
References	38

4. Congenital central hypoventilation syndrome: from patients to gene discovery	45
<i>Ha TRANG</i>	
4.1 Introduction	45
4.2 Clinical presentation of CCHS	46
4.3 Genetic mutations in CCHS	50
4.4 Phenotype-genotype correlations	51
4.5 Conclusion.....	52
References	52
5. Structural and functional brain abnormalities in congenital central hypoventilation syndrome	57
<i>Ronald M. HARPER, Mary A. WOO, Paul M. MACEY and Rajesh KUMAR</i>	
5.1 Introduction	57
5.2 Structural injury and functional deficits in CCHS.....	58
5.3 Imaging findings.....	59
5.4 Cardiovascular control deficits	64
5.5 Potential mechanisms in injury.....	65
5.6 Conclusion.....	66
References	67
6. <i>In vitro</i> study of <i>PHOX2B</i> gene mutations in congenital central hypoventilation syndrome.....	71
<i>Tiziana BACCHETTI and Isabella CECCHERINI</i>	
6.1 Introduction	71
6.2 <i>PHOX2B</i> polyalanine expansions.....	73
6.3 <i>PHOX2B</i> frameshift mutations	77
6.4 Conclusion.....	79
References	81
7. Sudden infant death syndrome: study of genes pertinent to cardiorespiratory and autonomic regulation	85
<i>Debra E. WEESE-MAYER, Michael J. ACKERMAN, Mary L. MARAZITA, and Elizabeth M. BERRY-KRAVIS</i>	
7.1 Introduction	85
7.2 Cardiac channelopathy genes in SIDS.....	86
7.3 Serotonergic system genes in SIDS	88
7.4 Autonomic Nervous System (ANS) genes in SIDS.....	91
7.5 Nicotine metabolizing genes in SIDS.....	95
7.6 Clinical significance	97
7.7 Conclusion and directions for future research on genetic factors in SIDS	101
References	101

8. The genetic basis for obstructive sleep apnea: what role for variation in respiratory control?.....	111
<i>Susan REDLINE, Sanjay R. PATEL</i>	
8.1 Introduction	111
8.2 OSA: Definition and health impact	111
8.3 OSA: Evidence for a familial basis	113
8.4 Genetic etiology-risk factors and their use as intermediate phenotypes.....	115
8.5 Ventilatory control as an intermediate OSA risk factor	116
8.6 Evidence for genetically determined ventilatory control abnormalities in familial OSA.....	122
8.7 Candidate genes for OSA that may operate through ventilatory control	123
8.8 Inferences from other conditions which involve ventilatory control deficits.....	125
8.9 Studies from animals	126
8.10 Pleiotropy	126
8.11 Conclusion.....	126
8. References	127
9. Apnea and irregular breathing in animal models: a physiogenomic approach.....	137
<i>Motoo YAMAUCHI, Fang HAN, Kingman P. STROHL</i>	
9.1 Introduction	137
9.2 Measuring ventilatory behavior.....	138
9.3 Defining apnea and ventilatory irregularity.....	140
9.4 Models of apnea	145
9.5 Model of recurrent apneas	146
9.6 Conclusion.....	148
9. References	148
10. Genetic determinants of respiratory phenotypes in mice	153
<i>Clarke G. TANKERSLEY</i>	
10.1 Introduction	153
10.2 Experimental methods and design.....	156
10.3 Observations and results.....	158
10.4 Significance of genetic determinants.....	163
10.5 Conclusion.....	164
10. References	165
11. Genes and development of respiratory rhythm generation	169
<i>Jean CHAMPAGNAT, Gilles FORTIN, Muriel THOBY-BRISSON</i>	
11.1 Introduction	169

11.2	Primordial embryonic rhythm in the neural tube.....	171
11.3	Parafacial rhythm generators: induction requires <i>Krox20</i> in r3 and <i>Hoxa1</i> in r4.....	173
11.4	Onset of the respiratory rhythm generation	175
11.5	Neurotrophic control of breathing	178
11.6	Brainstem modulatory controls of breathing	180
11.7	Conclusion.....	181
	References	182
12.	Transcription factor control of central respiratory neuron development	191
	<i>Bruno C. BLANCHI and Michael H. SIEWEKE</i>	
12.1	Introduction	191
12.2	Brainstem populations of neurons participating in central breathing control.....	192
12.3	Mouse mutants of transcription factors governing development of respiratory neurons and breathing control.....	195
12.4	Conclusion.....	212
	References	213
13.	Lessons from mutant newborn mice with respiratory control deficits.....	223
	<i>Claude GAULTIER</i>	
13.1	Introduction	223
13.2	Developmental respiratory control disorders.....	224
13.3	The newborn mouse	225
13.4	Mutant newborn mice as models of abnormal respiratory rhythm	226
13.5	Mutant newborn mice with abnormal chemosensitivity	229
13.6	Clinical relevance of mutant newborn mice models.....	233
13.7	Conclusion.....	234
	References	235
14.	Tentative mouse model for the congenital central hypo- ventilation syndrome: heterozygous <i>Phox2b</i> mutant newborn mice	243
	<i>Jorge GALLEGO, Nélina RAMANANTSOA, Vanessa VAUBOURG</i>	
14.1	Introduction	243
14.2	Neonatal phenotype determination	244
14.3	Non-invasive ventilatory phenotyping in newborn mice.....	244
14.4	Sleep-disordered breathing in <i>Phox2b</i> ^{+/-} newborn mice	246
14.5	Sensitivity to CO ₂	246
14.6	Sensitivity to hypoxia.....	248
14.7	Arousal response to hypoxia.....	249
14.8	Sensitivity to hyperoxia.....	250

14.9 Effects of ambient temperature	250
14.10 Cognitive evaluation of Phox2b ^{+/−} mutant mice	251
14.11 Comparison between Phox2b ^{+/−} and CCHS phenotypes	251
14.12 Conclusion.....	253
References	254
15. Respiratory control abnormalities in necdin-null mice: implications for the pathogenesis of Prader-Willi Syndrome	259
<i>John J. GREER and Rachel WEVRICK</i>	
15.1 Introduction	259
15.2 Transgenic mouse models	259
15.3 Central respiratory deficit.....	260
15.4 General anatomical abnormalities within the CNS	264
15.5 Respiratory dysfunction in PWS	265
15.6 Conclusion.....	266
References	267
16. Possible role of bioaminergic systems in the respiratory disorders of Rett syndrome	271
<i>John BISSONNETTE and Gerard HILAIRE</i>	
16.1 Introduction	271
16.2 Clinical manifestations of respiratory disorders in RTT	272
16.3 Mouse models of RTT	273
16.4 Respiratory studies in mouse models of RTT	275
16.5 Bioaminergic systems, RTT and Mecp2 ^{−/y} mice	278
16.6 Possible link between bioaminergic and respiratory alterations in mice and RTT patients	280
16.7 Conclusions: bioamines, respiration and RTT	282
References	283
17. Respiratory plasticity following intermittent hypoxia: a guide for novel therapeutic approaches to ventilatory control disorders?	291
<i>Gordon S. MITCHELL</i>	
17.1 Introduction	291
17.2 Deficiencies in respiratory motor neuron activity underlie some ventilatory control disorders	292
17.3 Intermittent hypoxia induced respiratory plasticity and metaplasticity.....	294
17.4 Compensatory plasticity during ventilatory control disorders.....	298
17.5 Possible therapeutic approaches for ventilatory control disorders: lessons from LTF?	301
17.6 Conclusion.....	305
References	306
Index.....	313