#### Contents

Preface xiii
Acknowledgments xv

#### I

## Disease classification and possible diagnosis

- L Clinical features to consider in a patient with possible genetic disease
- Chrical genetics assessment: History and physical examination 3
- Family history information 4
- Resources of information relevant to developmental defects and genetic disorders 4
- Aspects of developmental delay 6
- Movement disorders and cerebral palsy 6
- WHO report on recommendations for community genetic services in low and middle income countries (2010) 11

References 22

- 2. Determining the presence of altered values in clinical laboratory studies
- Acutely ill patients in the newborn nursery or patients with possible metabolic disease 27
- Patients with dysmorphology 27
- Organic acidemias, organic acidurias 32
- Clinical utility of genome sequencing 33
- Exome sequencing and diagnostic value in inborn errors of metabolism 33
- Reanalysis of sequence data 35

References 38

3. Further laboratory-based investigations for possible gene- or genome-based disorders

Investigations in possible gene or genome-based disorders 41
References 71
Further reading 77

#### II

## Application of therapies and strategies for development of therapies

- 4. Review possible therapies to address clinical manifestations including symptoms and signs and abnormal results of metabolic, biochemical, gene-based studies
- Mitochondrial functions and dysfunctions in mitochondrial disorders 81
  Peroxisomes and genetic disorders involving peroxisomes 88
  Generation of stem cell including hematopoietic stem cells for therapy 92
  Glycogen storage diseases 102
  References 113
  - 5. Review of investigations and possible therapies to address underlying disease manifestations

Inherited disorders of vitamin metabolism 119 Biotin 122 X CONTENTS

Vitamin D hydroxylation deficient ricketts 123 Therapeutic development in specific germline genetic diseases 124 Range of therapeutic options in lysosomal storage diseases 125 Lysosomal diseases with abnormal storage of mucopolysaccharides and advances in therapy 127 Monoamine neurotransmitter disorders and approaches to therapy 143 Gene defects in monoamine neurotransmitter disorders 144 Dopamine Receptor Endocrine disorders 146 Congenital adrenal hyperplasia 148 References 153 Further reading 158

# 6. Functional impairments, known genetic disorders, and review reports of established and possible therapies for specific genetic diseases

Ciliopathies 159 Neuronal primary cilia and metabolism 162 Polycystic kidney disease 164 Monogenic kidney disease 166 Inborn errors of immunity 167 Specific immune disorders 167 Newborn screening for inborn errors of immunity 168 Severe combined immunodeficiency 169 Systemic lupus erythematosus 174 Alpha-1-antitrypsin deficiency 176 Achondroplasia 178 Hypophosphatasia 183 Hypophosphatasia and hypophosphatemic rickets 184 Cystic fibrosis 186 Cystic fibrosis gene mapping and gene product identification 186 Glycosylation 189 Biometals 191 Defects in DNA repair processes 193 Hearing and deafness 194 References 198

#### III

#### Discussion of specific diseases where gene therapy, gene-based therapies or small molecule-based therapies have been successful

## 7. Examples of diseases where appropriate therapies were discovered

Epilepsies: Genetic testing and relevance to
treatment 209
Systemic analysis and reanalysis of exome sequencing
data in epilepsy 211
Ion channel associated disorders 222
Therapeutic approaches to Duchenne Muscular
Dystrophy (DMD) 225
Hemoglobinopathies sickle cell disease, thalassemia
advances in treatment 229
Treatment of sickle cell disease and beta
thalassemia 231
Alpha thalassemia major 240
Spinal muscular atrophy 240
References 254

### 8. Therapies that address altered gene regulation

Examples of disorders due to altered transcription factor activity 263
Craniosynostosis 264
PCSK9 and hyperlipidemia 269
References 287

## 9. Defining disease mechanisms, designing therapies and roles of stem cells

Urea cycle disorders 293
Familial hypercholesterolemia and dyslipidemia 294
Stem cells and cell therapies 298
References 309
Further reading 312

CONTENTS Xi

#### IV

## Review research on therapeutic design

10. Review research designed to investigate gene function and possible impact of specific variants

Huntington disease 315

Treacher Collins syndrome (TCS) 321

Ribosome biogenesis and ribosomopathies 322

Vision and hearing: The visual cycle, retina and retinitis pigmentosa 323

Age related neurodegenerative conditions 337

APOE4 genetic variant and Alzheimer research 345

References 347

11. Designing therapies relevant in human genetic disorders

Section A: Designing therapies for specific diseases 355

Rare diseases, precision medicines, and orphan drug designations 358

Gene editing 369
Crispr CAS9 gene editing 369
Clinical trial designs for rare diseases 385
Section B: Pharmacogenetics
pharmacogenomics 390
References 399

#### V

## Clinical trials design and permissions

12. Clinical trial designs and permissions

Human subjects research 409
Bioinformatics and cheminformatics in discovery of new medications 414
CAR T-cell therapy in auto-immune diseases 421
Target discovery through genetic studies and development of therapies 423
References 425

Index 429