

Contents

Contributors	ix	14: Allergy: Basic mechanisms and tests	137
Foreword	xx	<i>Sai H.K. Mung</i>	
Preface	xxi	15: Evaluation of the immune system	149
A Tribute to Bill Scott-Brown	xxiii	<i>Maira Thomas, Elizabeth Drewe and Richard J. Powell</i>	
Acknowledgements	xxiv	16: Cancer immunology	157
Volume 2 – Table of Contents	xxv	<i>Osama Al Hamarneh and John Greenman</i>	
Volume 3 – Table of Contents	xxix	17: Human papillomavirus	167
Abbreviations	xxxiii	<i>Mustaffa Junaid and Hisham M. Mehanna</i>	
Section 1 Basic Sciences			
Cell biology			
1: Molecular biology	3	18: Connective tissue diseases: ENT complications	173
<i>Michael Kuo, Richard M. Irving and Eric K. Parkinson</i>		<i>Eileen Baildam</i>	
2: Genetics in otology and neurotology	15	Microbiology	
<i>Mohammed-Iqbal Syed</i>		19: Microorganisms	181
3: Gene therapy	29	<i>Ursula Altmeyer, Penelope Redding and Nitish Khanna</i>	
<i>Seiji B. Shibata and Scott M. Graham</i>		20: Viruses and antiviral agents	195
4: Mechanisms of anticancer drugs	39	<i>Richard B. Townsley, Camille A. Huser and Chris Hansell</i>	
<i>Sarah Payne and David Miles</i>		21: Fungal infections	205
5: Radiotherapy and radiosensitizers	51	<i>Emily Young, Yujay Ramakrishnan, Laura Jackson and Shabzada K. Ahmed</i>	
<i>Christopher D. Scrase, Stewart G. Martin and David A.L. Morgan</i>		22: Antimicrobial therapy	221
6: Apoptosis and cell death	59	<i>Ursula Altmeyer, Penelope Redding and Nitish Khanna</i>	
<i>Angela Hague</i>		23: Human immunodeficiency virus	229
7: Stem cells	69	<i>Neil Ritchie and Alasdair Robertson</i>	
<i>Navin Vig and Ian C. Mackenzie</i>		Haematology	
8: Aetiology and pathogenesis of goitre	75	24: Blood groups, blood components and alternatives to transfusion	239
<i>Neil Sharma and Kristien Boelaert</i>		<i>Samah Alinam, Kate Pendry and Michael F. Murphy</i>	
9: Genetics of endocrine tumours	83	25: Haemato-oncology	249
<i>Waseem Ahmed, Prata Upasna and Dae Kim</i>		<i>Robert F. Wynn and Mark Williams</i>	
Wound healing			
10: Soft and hard tissue repair	93	26: Haemostasis: Normal physiology, disorders of haemostasis and thrombosis	259
<i>Sarah Al-Himdani and Ardesbir Bayat</i>		<i>Elizabeth Jones and Russell David Keenan</i>	
11: Skin flap physiology	107	Pharmacotherapeutics	
<i>Colin MacIver and Stergios Doumas</i>		27: Drug therapy in otology	275
12: Biomaterials, tissue engineering and their application in the oral and maxillofacial region	119	<i>Wendy Smith</i>	
<i>Kurt Busuttill Naudi and Ashraf Ayoub</i>		28: Drug therapy in rhinology	283
Immunology			
13: Defence mechanisms	125	<i>Wendy Smith</i>	
<i>Ian Todd and Richard J. Powell</i>		29: Drug therapy in laryngology and head and neck surgery	293
		<i>Wendy Smith and Rogan Corbridge</i>	

Perioperative management

- 30: Preparation of the patient for surgery 301
Michael Murray and Urmila Ratnasabapathy
- 31: Recognition and management of the difficult airway 309
Valerie Cunningham and Alistair McNarry
- 32: Adult anaesthesia 333
Daphne A. Varveris and Neil G. Smart
- 33: Adult critical care 351
Robert I. Docking and Andrew Mackay
- 34: Paediatric intensive care 361
Louise Selby and Robert Ross Russell

Safe and effective practice

- 35: Training, accreditation and the maintenance of skills 369
B. Nirmal Kumar, Andrew Robson, Omar Mirza and Baskaran Ranganathan
- 36: Communication and the medical consultation 379
Uttam Shiralkar
- 37: Clinical governance and its role in patient safety and quality improvement 389
Samit Majumdar and S. Musheer Hussain
- 38: Medical ethics 395
Paul Baines
- 39a: Medical jurisprudence in otorhinolaryngology 409
Maurice Hawthorne
- 39b: Medical negligence in otorhinolaryngology 427
Maurice Hawthorne
- 40: Non-technical skills for ENT surgeons 453
Simon Paterson-Brown and Stephen R. Ell

Interpretation and management of data

- 41: Epidemiology 465
Jan H.P. van der Meulen, David A. Lowe and Jonathan M. Fishman
- 42: Outcomes research 483
Iain R.C. Swan and William Whitmer
- 43: Evidence-based medicine in medical education and clinical practice 495
Phillip Evans
- 44: Critical appraisal skills 503
Paul Nankivell and Christopher Coulson

Advances in technology

- 45: Electrophysiology and monitoring 525
Patrick R. Axon and Bruno M.R. Kemecy

- 46: Optical coherence tomography 533
Jameel Muzaffar and Jonathan M. Fishman
- 47: Recent advances in technology 541
Wai Lup Wong and Bal Sanghera
- 48: Image-guided surgery, 3D planning and reconstruction 559
Ghassan Alusi and Michael Gleeson
- 49: Interventional techniques 569
James V. Byrne
- 50: Laser principles in otolaryngology, head and neck surgery 581
Brian J.G. Bingham
- 51: Contact endoscopy of the upper aerodigestive tract 587
Mario Andrea and Oscar Dias

Section 2 Head and Neck Endocrine Surgery**Overview**

- 52: History of thyroid and parathyroid surgery 597
Waraporn Imruetaicharoenchoke, Ashok R. Shaha and Neil Sharma
- 53: Developmental anatomy of the thyroid and parathyroid glands 603
Julian A. McGlashan
- 54: Developmental anatomy of the pituitary fossa 611
John Hill and Sean Carrie
- 55: Physiology of the thyroid and parathyroid glands 619
Martin O. Weickert
- 56: Physiology of the pituitary gland 629
Mária Hérincs, Karen Young and Márta Korbonits
- 57: Imaging in head and neck endocrine disease 643
Steve Colley and Sabena Fareedi
- 58: Thyroid and parathyroid gland pathology 651
Ram Moorthy, Sonia Kumar and Adrian T. Warfield

Thyroid disease

- 59: Clinical evaluation of the thyroid patient 705
Andrew Coatesworth and Sebastian Wallis
- 60: Investigation of thyroid disease 709
Anthony P. Weetman
- 61: Benign thyroid disease 717
Christopher M. Jones and Kristien Boelaert
- 62: Management of differentiated thyroid cancer 751
Hisham M. Mehanna, Kristien Boelaert and Neil Sharma

63: Management of medullary thyroid cancer 757 <i>Barney Harrison</i>	80: Thyroid and parathyroid surgery: Audit and outcomes 893 <i>David Chadwick</i>
64: Management of anaplastic thyroid cancer/lymphoma 765 <i>James D. Brierley and Richard W. Tsang</i>	81: Medicolegal aspects of head and neck endocrine surgery 899 <i>Barney Harrison</i>
65: Management of locoregionally recurrent differentiated thyroid cancer 773 <i>Iain J. Nixon and Ashok R. Shaha</i>	
66: Non-surgical management of thyroid cancer 779 <i>Laura Moss</i>	
Thyroid surgery	Pituitary disease
67: Thyroidectomy 793 <i>Ricard Simo, Iain J. Nixon and Ralph P. Tufano</i>	82: Clinical evaluation of the pituitary patient 905 <i>Sean Carrie, John Hill and Andrew James</i>
68: Surgery for locally advanced and nodal disease 805 <i>Joel Anthony Smith and John C. Watkinson</i>	83: Investigation of pituitary disease 915 <i>Thozhukat Sathyapalan and Stephen L. Atkin</i>
69: Minimally invasive and robotic thyroid surgery 811 <i>Neil S. Tolley</i>	84: Primary pituitary disease 923 <i>Christopher M. Jones and John Ayuk</i>
70: Surgery for the enlarged thyroid 819 <i>Neeraj Sethi, Josh Lodhia and R. James A. England</i>	85: Surgical management of recurrent pituitary tumours 941 <i>Mihir R. Patel, Leo F.S. Ditzel Filho, Daniel M. Prevedello, Bradley A. Otto and Ricardo L. Carrau</i>
Parathyroid disease	86: Adjuvant treatment of pituitary disease 951 <i>Andy Levy</i>
71: Clinical evaluation of hypercalcaemia 827 <i>Mo Aye and Thozhukat Sathyapalan</i>	Section 3 Rhinology
72: Investigation of hyperparathyroidism 833 <i>M. Shahed Quraishi</i>	87: Anatomy of the nose and paranasal sinuses 961 <i>Dustin M. Dalgorf and Richard J. Harvey</i>
73: Management of hyperparathyroidism 843 <i>Neil J.L. Gittoes and John Ayuk</i>	88: Outpatient assessment 977 <i>Martyn L. Barnes and Paul S. White</i>
74: Management of persistent and recurrent hyperparathyroidism 851 <i>David M. Scott-Coombes</i>	89: Physiology of the nose and paranasal sinuses 983 <i>Tira Galm and Shabzada K. Ahmed</i>
75: Management of parathyroid cancer 857 <i>Pamela Howson and Mark Sywak</i>	90: Measurement of the nasal airway 991 <i>Ron Eccles</i>
Parathyroid surgery	91: Allergic rhinitis 999 <i>Quentin Gardiner</i>
76: Bilateral parathyroid exploration 865 <i>R. James A. England and Nick McIvor</i>	92: Non-allergic perennial rhinitis 1011 <i>Jameel Muzaffar and Shabzada K. Ahmed</i>
77: Minimally invasive parathyroidectomy 873 <i>Parameswaran Rajeev and Gregory P. Sadler</i>	93: Occupational rhinitis 1017 <i>Hesham Saleh</i>
78: Surgical failure and reoperative surgery 879 <i>Schelto Kruijff and Leigh Delbridge</i>	94: Rhinosinusitis: Definitions, classification and diagnosis 1025 <i>Carl Philpott</i>
Thyroid and parathyroid outcomes	95: Nasal polyposis 1037 <i>Louise Melia</i>
79: Complications of thyroid and parathyroid surgery and how to avoid them 887 <i>Erin A. Felger, Dipti Kamani and Gregory W. Randolph</i>	96: Fungal rhinosinusitis 1047 <i>Eng Cern Gan and Amin R. Javer</i>
	97: Medical management for rhinosinusitis 1059 <i>Claire Hopkins</i>

viii Contents

98: Surgical management of rhinosinusitis.....	1071	109: Granulomatous conditions of the nose	1211
<i>A. Simon Carney and Raymond Sacks</i>		<i>Joanne Rimmer and Valerie J. Lund</i>	
99: The frontal sinus	1081	110: Abnormalities of smell	1227
<i>Salil Nair</i>		<i>Richard L. Doty and Steven M. Bromley</i>	
100: Mucocoeles of the paranasal sinuses	1107	111: Disorders of the orbit.....	1243
<i>Darlene E. Lubbe</i>		<i>Nithin D. Adappa and James N. Palmer</i>	
101: Complications of rhinosinusitis	1113	112: Diagnosis and management of facial pain	1253
<i>Stephen Ball and Sean Carrie</i>		<i>Rajiv K. Bhalla and Timothy J. Woolford</i>	
102: The relationship between the upper and lower respiratory tract	1125	113: Juvenile angiofibroma	1265
<i>Nigel K.F. Koo Ng and Gerald W. McGarry</i>		<i>Bernhard Schick</i>	
103: Nasal septum and nasal valve.....	1135	114: Endoscopic management of sinonasal tumours....	1269
<i>Shabram Anari and Ravinder Singh Natt</i>		<i>Alkis J. Psaltis and David K. Morrissey</i>	
104: Nasal septal perforations	1149	115: Surgical management of pituitary and parasellar diseases	1281
<i>Charles East and Kevin Kulendra</i>		<i>Philip G. Chen and Peter-John Wormald</i>	
105: Management of enlarged turbinates	1157	116: Extended anterior skull base approaches.....	1289
<i>Andrew C. Swift and Samuel C. Leong</i>		<i>Carl H. Snyderman, Paul A. Gardner, Juan C. Fernandez-Miranda and Eric W. Wang</i>	
106: Epistaxis	1169	117: Imaging in rhinology	1305
<i>Gerald W. McGarry</i>		<i>Gregory O'Neill</i>	
107: Nasal and facial fractures.....	1183	Index	1319
<i>Dae Kim and Simon Holmes</i>			
108: CSF leaks	1203		
<i>Scott M. Graham</i>			

Volume 2 – Table of Contents

Section 1 Paediatrics

- 1: Introduction to paediatric otorhinolaryngology**
Raymond W. Clarke
- 2: The paediatric consultation**
Raymond W. Clarke
- 3: Recognition and management of the sick child**
Julian Gaskin, Raymond W. Clarke and Claire Westrope
- 4: Anaesthesia for paediatric otorhinolaryngology procedures**
Crispin Best
- 5: The child with special needs**
Kate Blackmore and Derek Bosman
- 6: The child with a syndrome**
Thushitha Kumanandam and Haytham Kubba
- 7: Management of the immunodeficient child**
Fiona Shackley
- 8: Hearing screening and surveillance**
Sally A. Wood
- 9: Hearing tests in children**
Glynis Parker
- 10: Management of the hearing impaired child**
Chris H. Raine, Sue Archbold, Tony Sirimanna and Soumit Dasgupta
- 11: Paediatric implantation otology**
James Ramsden and Piyal Mukherjee
- 12: Congenital middle ear abnormalities**
Jonathan P. Harcourt
- 13: Otitis media with effusion**
Peter J. Robb and Ian Williamson
- 14: Acute otitis media**
Peter A. Rea and Natalie Ronan
- 15: Chronic otitis media**
William P.L. Hellier
- 16: Microtia and external ear abnormalities**
Iain Bruce and Jaya Nichani
- 17: Disorders of speech and language**
Suzanne Harrigan and Andrew Marshall
- 18: Cleft lip and palate**
David M. Wynne and Louisa Ferguson
- 19: Craniofacial anomalies**
Benjamin Robertson, Sujata De, Astrid Webber and Ajay Sinha
- 20: Balance disorders in children**
Louisa Mordin and Gavin A.J. Morrison
- 21: Facial paralysis in children**
S. Musher Hussain
- 22: Epistaxis**
Mary-Louise Montague and Nicola E. Starritt
- 23: Neonatal nasal obstruction**
Michelle Wyatt
- 24: Rhinosinusitis and its complications**
Daniel J. Tweedie
- 25: Lacrimal disorders in children**
Caroline J. MacEwen and Paul S. White
- 26: The adenoid and adenoidectomy**
Peter J. Robb
- 27: Paediatric obstructive sleep apnoea**
Steven Powell
- 28: Stridor**
Kate Stephenson and David Albert
- 29: Acute laryngeal infections**
Lesley Cochrane
- 30: Congenital disorders of the larynx, trachea and bronchi**
Chris Jephson
- 31: Acquired laryngotracheal stenosis**
Michael J. Rutter, Alessandro de Alarcón and Catherine K. Hart
- 32: Juvenile-onset recurrent respiratory papillomatosis**
Rania Mehanna and Michael Kuo
- 33: Paediatric voice disorders**
Ben Hartley and David M. Wynne
- 34: Foreign bodies in the ear, nose and throat**
Adam J. Donne and Katharine Davies
- 35: Paediatric tracheostomy**
Mike Saunders

- 36: Perinatal airway management**
*Pensée Wu, May M.C. Yaneza, Haytham Kubba,
W. Andrew Clement and Alan D. Cameron*
- 37: Cervicofacial infections**
Nico Jonas and Ben Hartley
- 38: Diseases of tonsils, tonsillectomy and tonsillotomy**
Yogesh Bajaj and Ian Hore
- 39: Salivary glands**
Neil Bateman and Rachael Lawrence
- 40: Tumours of the head and neck**
Fiona McGregor and James Hayden
- 41: Cysts and sinuses of the head and neck**
Keith G. Trimble and Luke McCadden
- 42: Haemangiomas and vascular malformations**
Daniel J. Tweedie and Benjamin E.J. Hartley
- 43: Drooling and aspiration**
Haytham Kubba and Katherine Ong
- 44: Reflux and eosinophilic oesophagitis**
Ravi Thevasagayam
- 45: Oesophageal disorders**
Graham Haddock

Section 2 The ear

Audio-vestibular medicine

- 46: Anatomy and embryology of the external and middle ear**
Peter Valentine and Tony Wright
- 47: Anatomy of the cochlear and vestibular system: Relating ultrastructure to function**
Jonathan Gale and Andrew Forge
- 48: Physiology of hearing**
Soumit Dasgupta and Michael Maslin
- 49: Physiology of equilibrium**
Floris L. Wuyts, Leen K. Maes and An Boudewyns
- 50: Perception of sounds at the auditory cortex**
Frank E. Musiek and Jane A. Baran
- 51: Psychoacoustic audiometry**
Josephine E. Marriage and Marina Salorio-Corbetto
- 52: Evoked measurement of auditory sensitivity**
Jeffrey Weibing and Nicholas Leaby
- 53: Prevention of hearing loss**
Shankar Rangan and Veronica Kennedy
- 54: Hearing aids**
Harvey Dillon
- 55: Beyond hearing aids: An overview of audiological rehabilitation**
Lucy Handscombe
- 56: Age-related sensorineural hearing impairment**
Linnea Cheung, David M. Baguley and Andrew McCombe
- 57: Noise-induced hearing loss and related conditions**
Andrew McCombe and David M Baguley
- 58: Autosomal dominant non-syndromic SNHL**
Polona Le Quesne Stabej and Maria Bitner-Glindzicz
- 59: Ototoxicity**
Andy Forge
- 60: Idiopathic sudden sensorineural hearing loss**
Tony Narula and Catherine Rennie
- 61: Tinnitus and hyperacusis**
Don McFerran and John Phillips
- 62: Evaluation of balance**
Adolfo M. Bronstein
- 63: Ménière's disease**
Vincent W.F.M. van Rompaey
- 64: Benign paroxysmal positional vertigo**
Yogan Saman and Doris-Eva Bamion
- 65: Superior semicircular canal dehiscence**
Harry R.F. Powell and Shakeel R. Saeed
- 66: Vestibular neuritis**
Charlotte Agrup
- 67: Vestibular migraine**
Louisa Murdin and Lina Luxon
- 68: Vestibular rehabilitation**
Marousa Pavlou
- 69: Auditory neuropathy spectrum disorder and retrocochlear disorders in adults and children**
Rosalyn A. Davies and Raj Nandi
- 70: Understanding tinnitus: A psychological perspective**
Laurence McKenna, Elizabeth Marks and David Scott
- 71: Auditory processing disorders across the age span**
Doris-Eva Bamion and Cristina Ferraz B. Murphy
- 72: Neuropsychiatric aspects of vestibular disorders**
Julius Bourke, Georgia Jackson and Gerald Libby

Otology

- 73:** Clinical examination of the ears and hearing
George G. Browning and Peter-John Wormald
- 74:** Furunculosis
Malcolm P. Hilton
- 75:** Myringitis
Samuel A.C. MacKeith
- 76:** Keratosis obturans, primary auditory canal cholesteatoma and benign necrotizing otitis externa
Tristram H.J. Lesser
- 77:** Acquired atresia of the external ear
Jonathan P. Harcourt
- 78:** Otitis externa and otomycosis
Simon Carney
- 79:** Periochondritis of the external ear
James W. Loock
- 80:** Exostosis of the external auditory canal
Phillip J. Robinson and Sophie J. Hollis
- 81:** Osteoradionecrosis of the temporal bone
James W. Loock
- 82:** Acute otitis media and otitis media with effusion in adults
Anil Banerjee
- 83:** Chronic otitis media
George G. Browning, Justin Weir, Gerard Kelly and Iain R.C. Swan
- 84:** Myringoplasty
Charlie Huins and Jeremy Lavy
- 85:** Ossiculoplasty
Daniel Moualed, Alison Hunt and Christopher P. Aldren
- 86:** Eustachian tube dysfunction
Holger H. Sudhoff
- 87:** Otoendoscopy
David A. Bowdler, Annabelle C.K. Leong and David D. Pothier
- 88:** Tuberculosis of the temporal bone
Ameet Kishore
- 89:** Otosclerosis
Christopher P. Aldren, Thanos Bibas, Arnold J.N. Bittermann, George G. Browning, Wilko Grolman, Peter A. Rea, Rinze A. Tange and Inge Wegner
- 90:** Otological effects of Paget's disease
Ian D. Bottrill

- 91:** Ear trauma
Stephen C. Toynton

- 92:** Otalgia
Philip D. Yates

Implantation otology

- 93:** Bone-conduction hearing aids
James Ramsden and Chris H. Raine
- 94:** Cochlear implants
Andrew Marshall and Stephen Broomfield
- 95:** Middle ear implants
Maarten J.F. de Wolf and Richard M. Irving
- 96:** Auditory brainstem implants
Shakeel R. Saeed and Harry R.F. Powell

Section 3 Skull base

- 97:** Imaging of the temporal bone
Steve Colley
- 98:** Anatomy of the skull base and infratemporal fossa
Charlie Huins
- 99:** Evaluation of the skull base patient
Jeyanthi Kulasegarah and Richard M. Irving
- 100:** Vascular assessment and management
Joe J. Leyon, Kurdow Nader and Sivarup Singh Chavda
- 101:** Natural history of vestibular schwannomas
Mirko Tos, Sven-Eric Stangerup and Per Caye-Thomasen
- 102:** Surgical management of vestibular schwannomas
Shakeel R. Saeed and Christopher J. Skilbeck
- 103:** Stereotactic radiosurgery
Paul Sanghera, Geoffrey Heyes, Helen Howard, Rosemary Simmons and Helen Benghiat
- 104:** Neurofibromatosis 2
Gareth Evans
- 105:** Non-vestibular schwannoma tumours of the cerebellopontine angle
Simon K.W. Lloyd and Scott A. Rutherford
- 106:** Middle fossa surgery
Raghu N.S. Kumar, Sunil N. Dutt and Richard M. Irving
- 107:** Jugular foramen lesions and their management
Rupert Obholzer
- 108:** Petrous apex lesions
Michael Gleeson

109: Approaches to the nasopharynx and Eustachian tube
Gunesh P. Rajan

110: Tumours of the temporal bone
Marcus Atlas, Noweed Ahmad and Peter O'Sullivan

111: Clinical neuroanatomy
John J.P. Patten

112: The facial nerve and its non-neoplastic disorders
Michael Gleeson

113: Tumours of the facial nerve
Patrick R. Axon and Samuel A.C. MacKeith

114: Osteitis of the temporal bone
Cheka R. Spencer and Peter Monksfield

115: Squamous carcinoma of the temporal bone
Liam Masterton and Neil Donnelly

116: Complications of skull base surgery
Abdul Karim Nassimizadeh and Chris Coulson

Volume 3 – Table of Contents

Section 1 Head and Neck

- 1: History**
Patrick J. Bradley
- 2: Aetiology of head and neck cancer**
Pablo H. Montero, Snehal G. Patel and Ian Ganly
- 3: Epidemiology of head and neck cancer**
Kristen B. Pytynia, Kristina R. Dahlstrom and Erich M. Sturgis
- 4: Staging of head and neck cancer**
Nicholas J. Roland
- 5: The changing face of cancer information**
Richard Wight
- 6: Introducing molecular biology of head and neck cancer**
Nikolina Vlatković and Mark T. Boyd
- 7: Nasal cavity and paranasal sinus malignancy**
Cyrus Kerawala, Peter Clarke and Kate Newbold
- 8: Nasopharyngeal carcinoma**
Raymond King-Yin Tsang and Dora Lai-Wan Kwong
- 9: Benign salivary gland tumours**
Jarrod Homer and Andy Robson
- 10: Malignant tumours of the salivary glands**
Vincent Vander Poorten and Patrick J. Bradley
- 11: Tumours of the parapharyngeal space**
Suren Krishnan
- 12: Oral cavity tumours including lip reconstruction**
Tim Martin and Omar A. Ahmed
- 13: Oropharyngeal tumours**
Terry M. Jones with Mererid Evans
- 14: Tumours of the larynx**
Vinidh Paleri, Stuart Winter, Hannah Fox and Nachi Palaniappan
- 15: Rehabilitation after total laryngectomy**
Yvonne Edels and Peter Clarke
- 16: Management of hypopharyngeal cancer**
Prathamesh Pai, Deepa Nair, Sarbani Ghosh Laskar and Kumar Prabhaskar
- 17: Neck metastases from an unknown primary**
Ricard Simo, Jean-Pierre Jeannon and Maria Teresa Guerrero Urbano
- 18: Metastatic neck disease**
Vinidh Paleri and James O'Hara
- 19: Principles and practice of radiotherapy in head and neck cancer**
Sara Meade and Andrew Hartley
- 20: Quality of life and survivorship in head and neck cancer**
Simon Rogers and Steve Thomas
- 21: Palliative care for head and neck cancer**
Catriona R. Mayland and John E. Ellershaw
- 22: Transoral laser microsurgery**
Mark Sayles, Stephanie L. Koonce, Michael L. Hinmi and David G. Grant
- 23: Anatomy as applied to transoral surgery**
Mark Puvanendran and Andrew Harris
- 24: Chemotherapy**
Charles G. Kelly
- 25: Cysts and tumours of the bony facial skeleton**
Julia A. Woolgar and Gillian L. Hall
- 26: Head and neck pathology**
Ram Moorthy, Adrian T. Warfield and Max Robinson
- 27: Open conservation surgery for laryngeal cancer**
Volkert Wreesman, Jatin Shah and Ian Ganly
- 28: Measures of treatment outcomes**
Helen Cocks, Raghav C. Dwivedi and Aoife M. I. Waters
- 29: Applications of robotics in head and neck practice**
Chris Holsinger, Chafeek Tomeh and Eric M. Genden
- 30: Biologically targeted agents in head and neck cancers**
Kevin J. Harrington and Magnus T. Dillon
- 31: Prosthetic rehabilitation of head and neck defects**
Chris Butterworth
- 32: Multidisciplinary team working**
Andrew Davies, Nigel Beasley and David Hamilton
- 33: Nutritional considerations**
Rachael Donnelly, Susannah Penney, Sian Lewis, Lesley Freeman and Pippa Lowe

- 34:** Speech voice and swallow rehabilitation after chemoradiation
Justin W.G. Roe and Katherine A. Hutcheson
- 35:** Surgical anatomy of the neck
Laura Warner, Christopher Jennings and John C. Watkinson
- 36:** Clinical examination of the neck
James O'Hara
- 37:** Imaging of the neck
Ivan Zammit-Maempel
- 38:** Neck trauma
Andrew J. Nicol and Johannes J. Fagan
- 39:** Benign neck disease
Ricard Simo, Jean-Pierre Jeannon and Enyinnaya Ofo
- 40:** Neck space infections
James W. Moor
- 41:** Anatomy and embryology of the mouth and dentition
Barry K.B. Berkovitz
- 42:** Benign oral and dental disease
Konrad S. Staines and Alexander Crighton
- 43:** Salivary gland anatomy
Stuart Winter and Brian Fish
- 44:** Physiology of the salivary glands
Mrganke De and T. Singh
- 45:** Imaging of the salivary glands
Daren Gibson and Steve Colley
- 46:** Non-neoplastic salivary gland diseases
Stephen R. Porter, Stefano Fedele and Valeria Mercadante
- 47:** Anatomy of the pharynx and oesophagus
Joanna Matthan and Vinidh Paleri
- 48:** Physiology of swallowing
Joanne Patterson and Stephen McHanwell
- 49:** Causes and assessment of dysphagia and aspiration
Helen Cocks and Jemy Jose
- 50:** Functional investigations of the upper gastrointestinal tract
Joanne Patterson and Jason Powell
- 51:** Pharyngitis
Sharan Jayaram and Conor Marnane
- 52:** Cricopharyngeal dysphagia
Nimesh N. Patel and T. Singh
- 53:** Oesophageal diseases
Shajahan Wahed and S. Michael Griffin
- 54:** Neurological disease of the pharynx
Kim Ab-See and Miles Bannister
- 55:** Rehabilitation of swallowing disorders
Maggie-Lee Huckabee and Sebastian Doeltgen
- 56:** Chronic aspiration
Guri S. Sandhu and Khalid Ghufoor
- 57:** Temporomandibular joint disorders
Andrew Sidebottom
- 58:** Anatomy of the larynx and tracheobronchial tree
Nimesh N. Patel and Shane Lester
- 59:** Physiology of the larynx
Lesley Mathieson and Paul Carding
- 60:** Voice and speech production
Paul Carding and Lesley Mathieson
- 61:** Assessment and examination of the larynx
Jean-Pierre Jeannon and Enyinnaya Ofo
- 62:** Evaluation of the voice
Julian A. McGlashan
- 63:** Structural disorders of the vocal cords
Yakubu Gadzama Karagama and Julian A. McGlashan
- 64:** Functional disorders of the voice
Paul Carding
- 65:** The professional voice
Declan Costello and Meredydd Harries
- 66:** Speech and language therapy for voice disorders
Marianne E. Bos-Clark and Paul Carding
- 67:** Phonosurgery
Abie Mendelsohn and Marc Remacle
- 68:** Movement disorders of the larynx
Declan Costello and John S. Rubin
- 69:** Acute infections of the larynx
Sanjai Sood, Karan Kapoor and Richard Oakley
- 70:** Chronic laryngitis
Kenneth MacKenzie
- 71:** Contemporary management of laryngotracheal trauma
Carsten E. Palme, Malcolm A. Buchanan, Shruti Jyothi, Faruque Riffat, Ralph W. Gilbert and Patrick Gullane

72: Upper airway obstruction and tracheostomy
Paul Pracy and Peter Conboy

73: Physiology of sleep and sleep disorders
John O'Reilly

74: Obstructive sleep apnoea: Medical management
Dev Banerjee

75: The surgical management of snoring and obstructive sleep apnoea
Bhik Kotecha and Mohammed Reda Elbadauey

76: Laryngotracheal stenosis in adults
Guri S. Sandhu and S.A. Reza Nouraei

77: Reflux disease
Mark G. Watson and Kim Ab-See

78: Paralysis of the larynx
Lucian Sulica and Babak Sadoughi

79: Outpatient laryngeal procedures
Matthew Stephen Broadhurst

Section 2 Plastic Surgery

80: Rhinoplasty following nasal trauma
Charles East

81: Pre-operative assessment for rhinoplasty
Hesham Saleh and Catherine Rennie

82: External rhinoplasty
Santdeep Paun

83: Revision rhinoplasty
Claudia Rudack and Gerhard Rettinger

84: Aesthetic dorsal reduction rhinoplasty
Julian M. Rowe-Jones

85: Nasal reconstruction
Ullas Raghavan

86: Pinnaplasty
Victoria Harries and Simon Watts

87: Blepharoplasty
Brian Leatherbarrow

88: Surgical rejuvenation of the ageing face
Gregory S. Dibelius, John M. Hilinski and Dean M. Toriumi

89: Non-surgical rejuvenation of the ageing face
Lydia Badia, Peter Andrews and Sajjad Rajpar

90: History of reconstructive surgery
Ralph W. Gilbert and John C. Watkinson

91: Grafts and local flaps in head and neck cancer
Kenneth Kok and Nicholas White

92: Pedicled flaps in head and neck reconstruction
Ralph W. Gilbert and John C. Watkinson

93: Reconstructive microsurgery in head and neck surgery
John C. Watkinson and Ralph W. Gilbert

94: Benign and malignant conditions of the skin
Murtaza Khan and Agustin Martin-Clavijo

95: Facial reanimation surgery
Demetrius Evriviades and Nicholas White

96: Partial and total ear construction
Cher Bing Chuo

97: A combined prosthetic and surgical approach
Hitesh Koria, M. Stephen Dover and Steve Worrollo

GENETICS IN OTOTOLOGY AND NEUROTOLOGY

Mohammed-Iqbal Syed

Introduction	15	Genetics of neurofibromatosis type 2	21
Molecular genetics of hearing loss	15	Genetics of familial paragangliomas	22
Molecular genetics of non-syndromic hearing impairment (NSHI)	16	References	25

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using a variety of relevant generic keywords, including: DNA, genetics, hereditary hearing loss, connexin 26, neurofibromatosis 2 and familial paragangliomas.

INTRODUCTION

Advances in molecular genetics have helped to identify causative genes and proteins responsible for pathologies; this knowledge is pertinent to molecular target therapy and promises novel therapeutic interventions.

This chapter aims to review the mechanisms and principles of molecular genetics of hearing impairment, vestibular schwannoma, and glomus tumours, and will keep the reader abreast of new developments that may be relevant to identifying and treating these diseases in clinical practice.

MOLECULAR GENETICS OF HEARING LOSS

Hearing loss is the most frequent sensory impairment in humans, with significant social and psychological implications. Permanent childhood hearing impairment of a moderate or greater degree (i.e. detection thresholds 40 decibels hearing level averaged across 0.5, 1, 2 and 4 kHz) is present at birth in about 1.6 per 1000 live births, of which approximately 1.0 in 1000 are bilateral impairments and 0.6 in 1000 are unilateral impairments.^{1,2} However, studies have shown that the prevalence of permanent childhood hearing impairment continues to increase through infancy, and by the school entry hearing screen (4–5 years of age) possibly affects 3.5 per 1000 children.² It is estimated that at least

two thirds of cases of childhood-onset hearing loss have a genetic cause, with the remaining third caused by environmental factors (e.g. cytomegalovirus infection, meningitis, acquired conductive loss, and the impact of extracorporeal membrane oxygenation (ECMO)).³ Improved clinical knowledge, awareness, and advances in antibiotics and vaccines has led to a decline in hearing loss resulting from environmental factors. Likewise, significant progress in the genetics of hereditary hearing impairment (HHI) has improved our understanding of the causes and early detection of HHI.

Classification

The most useful distinction in hereditary hearing impairment (HHI) is syndromic versus non-syndromic. When SNHL occurs in isolation it is termed non-syndromic and when it is accompanied by other systemic disturbances it is termed syndromic. The majority of hearing impairments are non-syndromic (~70%), whereas a minority are syndromic (~30%).

Non-syndromic HHI is further classified by mode of inheritance:

- Autosomal recessive ~80%
- Autosomal dominant ~18%.⁴

Rare modes of transmission include X-linked and mitochondrial transmission, which account for the remaining 2% of hearing impairment.

MOLECULAR GENETICS OF NON-SYNDROMIC HEARING IMPAIRMENT (NSHI)

Thus far, more than 100 forms of non-syndromic hearing impairment (NSHI) have been discovered (see the Hereditary Hearing Loss website at <http://hereditary-hearingloss.org>). Most of these are still identified as loci: only the chromosomal location of the defective gene is known.

The different gene loci for non-syndromic deafness are designated DFN (for DeafNess). Loci are named based on mode of inheritance:

- DFNA: Autosomal dominant
- DFNB: Autosomal recessive
- DFNX: X-linked.

The number following the above designations reflects the order of gene mapping and/or discovery and this information is regularly updated on the Hereditary Hearing Loss website.

Genes for NSHI have been categorized by the function of the proteins each gene encodes. Several superfamilies are represented, including gap junctions, myosins, adhesion proteins and ion channels.

Unlike in some conditions where a common mutation in just one gene is responsible for the majority of cases (e.g. the $\Delta F508$ deletion of three nucleotides in the *CFTR* gene in cystic fibrosis), hearing loss is genetically very heterogeneous involving mutations in many genes.⁵ It is therefore not possible to predict the risk of developing hearing loss from assessing a single or even a selection of the genes that have currently been identified.⁶

The most frequent causative genes are discussed below.

Gap junction proteins

Thus far, three connexin genes have been implicated in NSHI: *CX26*, *CX30*, and *CX31*, corresponding to the proteins connexin 26, connexin 30, and connexin 31, which are designated by their molecular mass.

GJB2 (connexin 26) is by far the foremost prominent hearing impairment gene. The discovery that *GJB2*, located at the DFNB1 locus, is a causative gene for hearing impairment⁷ led to the unexpected revelation that more than half of the recessive NSHL and approximately 30% to 50% of innate hearing loss are due to *GJB2* mutations.^{7,8} Among the 300 mutations documented worldwide up to now (see The Human Gene Mutation Database at www.hgmd.org), one particular mutation, 35delG, is responsible for 70% of all the *GJB2* mutations.⁹ This finding made an enormous impact in the hearing loss field, as it facilitated diagnostic and genetic screening of NSHL patients. Another mutation imperative to note is 167delT, which is most frequent among Ashkenazi Jews and is also present in Palestinians.¹⁰

The connexion-deafness homepage (<http://davinci.crg.es/deafness/>) provides a database of all published mutations as well as common polymorphisms in *GJB2* and other connexin genes. More than 100 unique non-syndromic *GJB2* gene variants have already been described. The reported mutations mostly include mutation types that can be detected by sequencing analysis, such as nonsense, missense, splicing and frameshift mutations.

Myosins

Numerous types of unconventional myosins have been identified as NSHI causing genes: *MYO1A*, *MYO3A*, *MYO6*, *MYO7A* and *MYO15A* (encoding myosin I, myosin IIIA, myosin VI, myosin VIIA and myosin XVA proteins, respectively). The term 'unconventional' myosins refers to all non-muscle myosin subclasses (in contrast with the 'conventional' myosins that include only the myosin II subclass). Expression of these unconventional myosins is not limited to the cells and tissues of the inner ear, yet the expression of their dysfunction is largely restricted to hearing impairment.

The myosin VI protein was first implicated in the hearing mechanism when it was found to be mutated in the spontaneously deaf mouse Snell's *waltzer* (*sv*).¹¹ The role of myosin VI in human deafness remains to be determined.

Myosin VII has been linked to both rodent and human deafness. Mutations in the *MYO7A* human homologue were identified as the genetic cause for Usher syndrome type 1B¹² and Usher syndrome type 2A.¹³ Contiguous to this discovery, human *MYO7A* was also linked to NSHL in two distinctive loci: DFNB2¹⁴ and DFNA11.¹⁵

Myosin XV is the largest of all the myosin heavy chains and mutations in myosin XV have been pathogenically linked to DFNB3 in humans and shaker 2 phenotype in mice. Myosin XV is a critical factor in the evolvment of the hair bundle and in the staircase formation of the bundle¹⁶ and it binds another deafness molecule, whirling at the tip link zone, suggesting that the two molecules might control stereocilia elongation patterning during development and may be implicated in stabilizing connections between stereocilia.¹⁷

Pendrin

Mutations in the pendrin gene *SLC26A4* are the second most frequent cause of autosomal recessive NSHL, accounting for up to 3.5% of cases.¹⁸ *SLC26A4*, which codes for an anion transport protein, also underlies Pendred syndrome, which is one of the most common forms of syndromic hearing impairment.

Adhesion proteins

Adhesion proteins include a diverse group of distinct protein families including integrins, selectins, members of the immunoglobulin superclass family and cadherins.

Cadherin 23 is a vital member of a specific unit designated for maintaining stereocilia inter-cohesion.¹⁸

More than 20 mutations in the *CDH23* gene have been identified in people with non-syndromic hearing impairment and more than 30 mutations have been shown to cause the Usher syndrome type 1D. The *USH1D* locus was found to coincide with the recessive NSH1 locus *DFNB12*, which is associated with prelingual moderate to profound hearing loss. These data suggested that *DFNB12* and *USH1D* in fact are mutually derived from *CDH23* allelic mutations, both resulting in syndromic and non-syndromic forms of hearing loss.^{19, 20}

Autosomal dominant non-syndromic hearing impairment

Unlike autosomal recessive non-syndromic hearing loss, in autosomal dominant non-syndromic hearing loss there is not a single identifiable gene responsible for the majority of cases. The clinical manifestations and molecular genetics of known genes causing autosomal

dominant non-syndromic hearing impairment are outlined in [Table 2.1](#).

Autosomal recessive non-syndromic hearing impairment

Fifty per cent of people with autosomal recessive non-syndromic hearing impairment have mutations in *GJB2*.⁸ The other 50% of cases are attributed to mutations in numerous other genes. The clinical manifestations and molecular genetics of known genes causing autosomal recessive non-syndromic hearing impairment are outlined in [Table 2.2](#).

X-linked non-syndromic hearing impairment

DFNX3 is characterized by a mixed conductive-sensorineural hearing loss, the conductive component of

TABLE 2.1 Clinical manifestations and molecular genetics of known genes causing autosomal dominant non-syndromic hearing impairment

Locus name	Gene symbol	Onset/Decade	Audioprofile	Test availability
DFNA1	<i>DIAPH1</i>	Postlingual/1 st	Low frequency progressive	Clinical
DFNA2	<i>KCNQ4</i>	Postlingual/2 nd	High frequency progressive	Clinical
DFNA2B	<i>GJB3</i>	Postlingual/4 th	High frequency progressive	Clinical
DFNA3	<i>GJB2</i>	Prelingual	High frequency progressive	Clinical
	<i>GJB6</i>			Clinical
DFNA4	<i>MYH14</i>	Postlingual	Flat/gently downsloping	Clinical
DFNA5	<i>DFNA5</i>	Postlingual/1 st	High frequency progressive	Clinical
DFNA6/14/38	<i>WFS1</i>	Prelingual	Low frequency progressive	Clinical
DFNA8/12	<i>TECTA</i>		Mid-frequency loss	Clinical
DFNA9	<i>COCH</i>	Postlingual/2 nd	High frequency progressive	Clinical
DFNA10	<i>EYA4</i>	Postlingual/3 rd , 4 th	Flat/gently downsloping	Clinical
DFNA11	<i>MYO7A</i>	Postlingual/1 st		Clinical
DFNA13	<i>COL11A2</i>	Postlingual/2 nd	Mid-frequency loss	Clinical
DFNA15	<i>POU4F3</i>	Postlingual	High frequency progressive	Clinical
DFNA17	<i>MYH9</i>	Postlingual	High frequency progressive	Clinical
DFNA20/26	<i>ACTG1</i>	Postlingual	High frequency progressive	Clinical
DFNA22	<i>MYO6</i>	Postlingual	High frequency progressive	Clinical
DFNA23	<i>SIX1</i>	Prelingual	Downsloping	Clinical
DFNA25	<i>SLC17A8</i>	Postlingual/2 nd –6 th decades	High frequency progressive	Clinical
DFNA28	<i>TFCP2L3</i>	Postlingual	Flat/gently downsloping	Clinical
DFNA36	<i>TMC1</i>	Postlingual	Flat/gently downsloping	Clinical
DFNA39	<i>DSPP</i>	Postlingual	High frequency progressive	Research only
DFNA44	<i>CCDC50</i>	Postlingual	Low to mild frequencies progressive	Clinical
DFNA48	<i>MYO1A</i>	Postlingual	Progressive	Clinical
DFNA50	<i>MIR96</i>	Postlingual/2 nd	Flat progressive	Clinical
DFNA51	<i>TJP2</i> & <i>FAM189A2</i>	Postlingual/4 th	High frequency progressive	Research only

Source: Adapted from Van Camp & Smith [2010] Van Camp G, Smith RJH. The Hereditary Hearing Loss Homepage, 2010, with permission. Available from <http://hereditaryhearingloss.org/>.

TABLE 2.2 Clinical manifestations and molecular genetics of known genes causing autosomal recessive non-syndromic hearing impairment

Locus name	Gene symbol	Onset	Type	Test availability
DFNB1	GJB2	Prelingual	Usually stable	Clinical
	GJB6			Clinical
DFNB2	MYO7A	Prelingual, postlingual	Unspecified	Clinical
DFNB3	MYO15	Prelingual	Severe to profound; stable	Clinical
DFNB4	SLC26A4	Prelingual, postlingual	Stable, progressive	Clinical
DFNB6	TMIE	Prelingual	Severe to profound; stable	Clinical
DFNB7/11	TMC1			Clinical
DFNB8/10	TMPRSS3	Postlingual, prelingual	Progressive, stable	Clinical
DFNB9	OTOF	Prelingual	Usually severe to profound; stable	Clinical
DFNB12	CDH23	Prelingual	Severe to profound; stable	Clinical
DFNB16	STRC	Prelingual	Severe to profound; stable	Clinical
DFNB18	USH1C	Prelingual	Severe to profound; stable	Clinical
DFNB21	TECTA	Prelingual	Severe to profound; stable	Clinical
DFNB22	OTOA	Prelingual	Severe to profound; stable	Clinical
DFNB23	PCDH15	Prelingual	Severe to profound; stable	Clinical
DFNB24	RDX	Prelingual	Severe to profound; stable	Clinical
DFNB25	GRXCR1	Prelingual	Moderate to profound; progressive	Research only
DFNB28	TRIOBP	Prelingual	Severe to profound; stable	Clinical
DFNB29	CLDN14	Prelingual	Severe to profound; stable	Clinical
DFNB30	MYO3A	Prelingual	Severe to profound; stable	Clinical
DFNB31	DFNB31	Prelingual	—	Clinical
DFNB32/82	GPSM2	Prelingual	Severe to profound; stable	Research only
DFNB35	ESRRB	Unknown	Severe to profound	Clinical
DFNB36	ESPN	Prelingual	—	Clinical
DFNB37	MYO6	Prelingual	—	Clinical
DFNB39	HGF	Prelingual	Severe to profound; downsloping	Clinical
DFNB49	MARVELD2	Prelingual	Moderate to profound; stable	Clinical
DFNB53	COL11A2	Prelingual	Severe to profound; stable	Research only
DFNB59	PJVK	Prelingual	Severe to profound; stable	Clinical
DFNB61	SLC26A5	Prelingual	Severe to profound; stable	Clinical
DFNB63	LRTOMT	Prelingual	Severe to profound; stable	Clinical
DFNB67	LHFPL5	Prelingual	Severe to profound; stable	Clinical
DFNB73	BSND	Prelingual	Severe to profound; stable	Research only
DFNB77	LOXHD1	Postlingual	Moderate to profound; progressive	Clinical
DFNB79	TPRN	Prelingual	Severe to profound; stable	Clinical
DFNB84	PTPRQ	Prelingual	Moderate to profound; progressive	Research only

Source: Adapted from Van Camp & Smith [2010] Van Camp G, Smith RJH. The Hereditary Hearing Loss Homepage, 2010, with permission. Available from <http://hereditaryhearingloss.org/>.

which is caused by stapedial fixation. In contrast to other types of conductive hearing loss, surgical correction is precluded because an abnormal communication between the cerebrospinal fluid and perilymph results in leakage ('perilymphatic gusher') and complete loss of hearing when the oval window is fenestrated or removed.

Clinical manifestations and molecular genetics of known genes causing X-linked non-syndromic hearing impairment are summarized in Table 2.3.

Mitochondrial non-syndromic hearing impairment

The genes and mutations associated with mitochondrial non-syndromic hearing impairment are outlined in Table 2.4.

TABLE 2.3 Clinical manifestations and molecular genetics of X-linked non-syndromic hearing impairment

Locus name	Gene	Onset	Type and degree	Frequencies
DFNX1 (DFN2)	PRPS1	Postlingual	Progressive sensorineural; severe to profound	All
DFNX2 (DFN3)	POU3F4	Prelingual	Progressive, mixed; variable, but progresses to profound	All
DFNX4 (DFN6)	SMPX	Postlingual	Progressive sensorineural; mild to profound	All

Source: Adapted from Van Camp & Smith [2010] Van Camp G, Smith RJH. The Hereditary Hearing Loss Homepage, 2010, with permission. Available from <http://hereditaryhearingloss.org/>.

TABLE 2.4 Mitochondrial Non-syndromic Hearing Impairment

Gene symbol	Mutation	Severity	Penetrance	Test availability
MT-RNR1	961 different mutations	Variable	Highly variable, aminoglycoside induced	Clinical
	1494C>T			
	1555A>G			
MT-TS1	7445A>G	Severe to profound	Highly variable	Clinical
	7472insC			
	7510T>C			
	7511T			
MT-CO1	7444G>A	Severe to profound	Complete, aminoglycoside associated; associated with MT-RNR1 1555A>G	Clinical

Source: Adapted from Van Camp & Smith [2010] Van Camp G, Smith RJH. The Hereditary Hearing Loss Homepage, 2010, with permission. Available from <http://hereditaryhearingloss.org/>.

Molecular genetics of syndromic hearing impairment (SHI)

Hearing impairment is denoted as an integral clinical phenotype in more than 400 genetic syndromes.²¹ Syndromic forms of hearing impairment are estimated to be responsible for up to 30% of prelingual deafness, but its contribution to deafness is relatively small reflecting the occurrence and diagnosis of postlingual deafness.

Syndromic hearing loss is discussed further by modes of inheritance.

Autosomal dominant syndromic hearing impairment

WAARDENBURG SYNDROME (WS)

WS is mostly a genetic autosomal dominant disorder, considered to be the most frequent autosomal dominant form of syndromic hearing loss, constituting approximately 2% of all congenital hearing impairment.²²

The primary phenotypes observed in this syndrome may include variable degrees of sensorineural hearing loss, pigmentation abnormalities (skin, hair, eyes), dystopia canthorum (wide distance between the inner corners of the eyes). Gastrointestinal symptoms like constipation and Hirschsprung disease, neural tube and limb defects may also be observed. Four different types of WS (I to IV) have been described, grouped by distinct physical characteristics. WS I characteristically has the presence and WS II the absence of dystopia canthorum. In WS III there are

typically limb abnormalities and in WS IV Hirschsprung disease is present.

All of WS1 and some of WS3 cases are associated with mutations in the *PAX3* gene. WS2 is caused by mutations in the transcription factors *MITF* and *SNAI2*. WS4 is due to alterations in *EDNRB*, *EDN3* or *SOX10* genes.²³

BRANCHIOOTORENAL SYNDROME

Branchiootorenal (BOR) syndrome is the second most prevalent autosomal dominant syndromic type of hearing loss.²⁴ The major features of this syndrome are hearing loss (conductive, mixed or sensorineural) in association with branchial cleft cysts or fistulae, deformities of the external, middle or internal ear, and renal malformations.

In approximately 40% of families segregating a BOR phenotype, mutations in *EYA1* can be identified; in a few other families mutations have been found in *SIX1*²⁵ and *SIX5*.²⁶

STICKLER SYNDROME

Stickler syndrome comprises of progressive sensorineural hearing loss, cleft palate, abnormal development of the epiphysis, vertebral abnormalities and osteoarthritis. Three types are recognized, based on the molecular genetic defect: STL1 (*COL2A1*), STL2 (*COL11A1*) and STL3 (*COL11A2*). STL1 and STL2 are characterized by severe myopia, which predisposes to retinal detachment; this aspect of the phenotype is absent in STL3 because *COL11A2* is not expressed in the eye.