Orofacial Pain
From Basic Science to Clinical Management
The Transfer of Knowledge in Pain Research to Education
Second Edition

Edited by
Barry J. Sessle, MDS, PhD, DSc(hc), FRSC, FCAHS
Gilles J. Lavigne, DMD, FRCD(C), PhD
James P. Lund, BDS, PhD, FCAHS
Ronald Dubner, DDS, PhD

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Preface to the Second Edition

Some of the most common pains occur in the orofacial region. Because this region of the body has special importance in eating, drinking, speech, and the expression of our feelings, pain occurring in this region has particular significance to the orofacial pain patient. The effect of chronic orofacial pain on a patient is particularly serious because it can be associated with emotional, psychologic, and social disturbances that compromise the patient’s quality of life and well-being. Furthermore, changing population demographics will likely increase their bearing on dental practice in most countries over the coming decades as more people become middle-aged or elderly—the age range when chronic orofacial pain conditions are most prevalent.

Thus, there is a rapidly growing interest in the field of orofacial pain. In the 8 years since the first edition of this book was published, new approaches have been developed in the diagnosis and management of orofacial pain conditions, and our knowledge of the neurobiologic, molecular, and genetic processes involved in orofacial pain has advanced. However, the decision to publish a second edition was based on a need not only to update the basic science and clinical information, but also to expand the book’s reach by including new topics related to pain genetics, pain and motor control and dysfunction, and management of headaches and pain-related movement disorders. We accomplished these goals by providing updated information in the relevant chapters and by adding four new chapters. New cases have also been added to illustrate how orofacial pain conditions may be differentially diagnosed and managed (see chapter 27).

The philosophy of this second edition remains true to that of its predecessor, namely to provide a comprehensive, integrated, concise, and evidence-based synthesis of the topic of orofacial pain through a translational bridging from molecules and cellular mechanisms to diagnostic and management approaches. The main target audience of the book is still dental students and clinicians; in addition, it will undoubtedly prove a valuable source of information for neuroscience graduate students and medical residents who want to learn more about orofacial pain processes and their clinical correlates, and for those scientists and clinicians interested in translational research using pain models.

We are grateful to Fong Yuen (University of Toronto Faculty of Dentistry) for her excellent work as editorial assistant for this second edition of the book and to the staff at Quintessence Publishing for their dedication and help in bringing it to fruition. We also thank the authors of the chapters, who have worked with the editors to ensure that each chapter provides an up-to-date and evidence-based overview of its topic.
The model for this book is the *Studies in Physiology Series* published by the British Physiological Society (Cody FW [ed]; Portland Press, London, 1995). The purpose of these publications is to present a summary of current knowledge in a particular field to teachers of physiology. Contributing authors are asked to keep their papers short and simple, so that they are readily accessible to undergraduate students. They are also told to use summary figures and diagrams rather than complex reports of data, to keep the number of references small, and to cite reviews rather than research reports whenever possible.

Drs James Lund and Gilles Lavigne saw that this approach would be useful for teachers of oral biology, oral medicine, and facial pain; for students in faculties of dentistry and medicine; and for clinicians who want to be better informed. While scientists and graduate students use original reports and sophisticated literature reviews of the type published in *Critical Reviews in Oral Biology and Medicine* for their research and coursework, there is a paucity of material on dental and orofacial research suitable for the nonexpert. This problem is of growing importance because, as many dental faculties heed the call to improve the teaching of basic and applied science and in particular to integrate emerging scientific evidence into patient care, appropriate materials are not available to their students. Drs Lund and Lavigne recognized that there was a particular need for concise summaries of knowledge about orofacial pain and asked two of the pre-eminent experts in the field to join them as coeditors: Dr Ronald Dubner, chief editor of the journal *Pain*, and Dr Barry Sessle, editor-in-chief of the *Journal of Orofacial Pain* and president of the International Association for the Study of Pain.

Some of you may ask, why another volume on orofacial pain? Aren’t there enough published reviews and textbooks on the subject already? It is true that much has been written, particularly about temporomandibular disorders (TMDs), but the best of the newer publications are written for the researcher and graduate student. Most of those books that are written for the dental student and clinician are heavy on opinion but light on evidence. In preparing this book, we have tried to include the major topics that would be found in an undergraduate curriculum. In particular, we made sure that acute pain and chronic pain states other than TMDs are covered. We asked each of the authors, who were chosen for their expertise in the field, to distinguish between data and anecdote; if they could find no good evidence for or against current practice, they were asked to state so. Each of us took responsibility for one of the four sections (Section I, The Clinical Problem and Epidemiology; Section II, Neurobiology of Pain; Section III, Pain and Behavior; and Section IV, Management of Orofacial Pain) and worked with the contributing authors to ensure a uniformity of expression and continuity of content within and between the sections. We have tried to make sure that the book provides a comprehensive, integrated synthesis of the topic and that it is not just a series of loosely connected chapters.

Most of the chapters in this book were first presented as papers at a symposium for teachers of orofacial pain held in Vancouver on March 10, 1999, in conjunction with the American and Canadian Associations of Dental Schools and the International Association for Dental Research. We wish to thank Dean Edward Yen of the Faculty of Dentistry of the University of British Columbia for facilitating the organization of the conference and Mmes Christiane Manzini and Francine Guitard for their assistance in Vancouver. Mme Lucille Gendron was our editorial assistant and coordinated the arrangements for the conference.

We also acknowledge the financial support of the Canadian Medical Research Council, Block Drug Company Inc, the Quebec Oral Health Network of the Fonds de Recherche en Santé du Québec, the Association of Canadian Faculties of Dentistry, the International Association for Dental Research—Neuroscience Group, the Canadian Association for Dental Research, the American Academy of Orofacial Pain, the Association of University Teachers of Orofacial Pain Programs, and the Oral Physiology Commission of the International Union of Physiological Sciences.

We owe special thanks to the authors, who had to put up with more interference than usual from the editors, and finally to Quintessence for their help with the production of the book, which we hope is only the first in a series. We have already begun to plan the next on normal and abnormal movements of the orofacial region and upper aerodigestive tract.
Contributors

Pierre Blanchet, MD, FRCP(C), PhD
Associate Professor
Department of Stomatology
Faculty of Dental Medicine
Université de Montréal
Neurologist
Université de Montréal Hospital Centre
Montreal, Quebec, Canada

M. Catherine Bushnell, PhD
Harold Griffith Professor of Anesthesia
Director, Alan Edwards Centre for Research on Pain
Department of Anesthesia and Faculty of Dentistry
McGill University
Montreal, Quebec, Canada

Thuan T.T. Dao, DMD, MSc, PhD, FRCD(C)
Associate Professor
Faculty of Dentistry
University of Toronto
Toronto, Ontario, Canada

Antoon De Laat, LDS, GHO
Professor
Department of Oral and Maxillofacial Surgery
School of Dentistry
Catholic University of Leuven
Leuven, Belgium

Raymond A. Dionne, DDS, PhD
Scientific Director
National Institute of Nursing Research
National Institutes of Health
Bethesda, Maryland, USA

Mark Drangsholt, DDS, PhD
Assistant Professor
Departments of Oral Medicine and Dental Public Health Science
School of Dentistry
University of Washington
Seattle, Washington, USA

Ronald Dubner, DDS, PhD
Professor and Chair
Department of Biomedical Sciences
University of Maryland Dental School
Baltimore, Maryland, USA

Samuel F. Dworkin, DDS, PhD
(Hon: DSci, DrOdont)
Professor Emeritus
Department of Oral Medicine
School of Dentistry
Department of Psychiatry and Behavioral Sciences
School of Medicine
University of Washington
Seattle, Washington, USA

Eli Eliav, DMD, PhD
Professor and Director of the Division of Orofacial Pain
Robert and Susan Carmel Endowed Chair in Algesiology
Department of Diagnostic Sciences
New Jersey Dental School
The University of Medicine and Dentistry of New Jersey
Newark, New Jersey, USA

Jocelyne S. Feine, DDS, HDR
Professor and Director of Graduate Studies in Oral Health Sciences
Faculty of Dentistry
Department of Epidemiology and Biostatistics
Department of Oncology
Faculty of Medicine
McGill University
Montreal, Quebec, Canada

James R. Fricton, DDS, MS
Professor
Department of Diagnostic and Biological Sciences
School of Dentistry
University of Minnesota
Minneapolis, Minnesota, USA
Sharon M. Gordon, DDS, MPH, PhD
Associate Professor
Biomedical Sciences Director of Curriculum
University of Maryland Dental School
Baltimore, Maryland, USA

Jean-Paul Goulet, DDS, MSD, FRCD(C)
Professor
Department of Stomatology
Faculty of Dental Medicine
Université Laval
Quebec, Quebec, Canada

Charles S. Greene, BS, DDS
Clinical Professor and Director of Orofacial Pain Studies
Department of Oral Medicine and Diagnostic Sciences
College of Dentistry
University of Illinois at Chicago
Chicago, Illinois, USA

Kenneth M. Hargreaves, DDS, PhD
Professor and Chair
Department of Endodontics
University of Texas Health Science Center at San Antonio
San Antonio, Texas, USA

G. Rex Holland, BSc, BDS, PhD
Professor
Department of Cariology, Restorative Sciences, and Endodontics
School of Dentistry
University of Michigan
Ann Arbor, Michigan, USA

Yoshiki Imamura, DDS, PhD
Professor
Department of Oral Diagnosis
School of Dentistry
Nihon University
Tokyo, Japan

Koichi Iwata, DDS, PhD
Professor and Chairman
Department of Physiology
School of Dentistry
Nihon University
Tokyo, Japan

Takafumi Kato, DDS, PhD
Associate Professor
Division of Oral and Maxillofacial Biology
Institute for Oral Science
Matsumoto Dental University
Shiojiri, Japan

Asma A. Khan, BDS, PhD
Assistant Professor
Department of Endodontics
University of Texas Health Science Center at San Antonio
San Antonio, Texas, USA

Gilles J. Lavigne, DMD, FRCD(C), PhD
Professor and Canada Research Chair in Pain, Sleep and Trauma
Department of Oral Health
Faculty of Dental Medicine
Université de Montréal
Montreal, Quebec, Canada

Linda LeResche, ScD
Professor
Department of Oral Medicine
School of Dentistry
University of Washington
Seattle, Washington, USA

Frank Lobbezoo, DDS, PhD
Professor
Department of Oral Function
Academic Centre for Dentistry Amsterdam
University of Amsterdam
Amsterdam, The Netherlands
Marco L. Loggia  
McGill Centre for Research on Pain  
Department of Neurology and Neurosurgery  
McGill University  
Montreal, Quebec, Canada

James P. Lund, BDS, PhD, FCAHS  
Professor  
Alan Edwards Centre for Research on Pain  
Faculty of Dentistry  
McGill University  
Montreal, Quebec, Canada

William Maixner, DDS, PhD  
Professor and Director  
Center for Neurosensory Disorders  
Departments of Endodontics and Pharmacology  
School of Dentistry  
University of North Carolina  
Chapel Hill, North Carolina, USA

Bruce Matthews, BDS, PhD  
Professor  
Department of Physiology and Pharmacology  
School of Medical Sciences  
University of Bristol  
Bristol, United Kingdom

Mitchell B. Max, MD  
Visiting Professor of Anesthesiology and Medicine  
Director of Molecular Epidemiology of Pain Program  
Center for Pain Research  
University of Pittsburgh  
Pittsburgh, Pennsylvania, USA

Pierre Mayer, MD, FRCPC  
Associate Professor  
Faculty of Medicine  
Director, Sleep Laboratory  
Centre Hospitalier de l'Université de Montréal  
Montreal, Quebec, Canada

Charles McNeill, DDS  
Professor Emeritus and Director  
UCSF Center for Orofacial Pain  
University of California, San Francisco  
San Francisco, California, USA

Jeffrey S. Mogil, PhD  
E.P. Taylor Professor of Pain Studies  
Canada Research Chair in the Genetics of Pain  
Department of Psychology and Alan Edwards Centre for Research on Pain  
McGill University  
Montreal, Quebec, Canada

Greg Murray, BDS, MDS, PhD, FRACDS  
Professor of Dentistry  
Jaw Function and Orofacial Pain Research Unit  
Faculty of Dentistry  
University of Sydney  
Sydney, New South Wales, Australia

Jeffrey P. Okeson, DMD  
Professor and Chair  
Department of Oral Health Science  
Director of Orofacial Pain Program  
College of Dentistry  
University of Kentucky  
Lexington, Kentucky, USA

Sandro Palla, Dr Med Dent  
Professor and Chair  
Department of Masticatory Disorders, Removable Prosthodontics and Special Care Dentistry  
Center for Dental and Oral Medicine and Cranio-Maxillofacial Surgery  
University of Zurich  
Zurich, Switzerland

Pierre Rainville, PhD  
Associate Professor  
Department of Stomatología  
Faculty of Dental Medicine  
Université de Montréal  
Montreal, Quebec, Canada

Ke Ren, MD, PhD  
Professor  
Department of Biomedical Sciences  
University of Maryland Dental School  
Baltimore, Maryland, USA
Michael W. Salter, MD, PhD, FRSC
Professor and Canada Research Chair in Neuroplasticity and Pain
Faculties of Dentistry and Medicine
Director of University of Toronto Centre for the Study of Pain
University of Toronto
Senior Scientist and Head
Program in Neurosciences & Mental Health
Hospital for Sick Children
Toronto, Ontario, Canada

Eric L. Schiffman, DDS, MS
Associate Professor
Department of Diagnostic and Biological Sciences
University of Minnesota
School of Dentistry
Minneapolis, Minnesota, USA

Petra Schweinhardt, MD, PhD
Assistant Professor
Alan Edwards Centre for Research on Pain
Faculty of Dentistry
McGill University
Montreal, Quebec, Canada

Ze’ev Seltzer, BMS, Dr Med Dent
Professor and Canada Research Chair in Comparative Pain Genetics
Faculties of Dentistry and Medicine
University of Toronto
Toronto, Ontario, Canada

Barry J. Sessle, MDS, PhD, DSc(hc), FRSC, FCAHS
Professor and Canada Research Chair in Craniofacial Pain and Sensorimotor Function
Faculties of Dentistry and Medicine
University of Toronto
Toronto, Ontario, Canada

José Tadeu Tesseroli de Siqueira, DDS, PhD
Orofacial Pain Clinic
Dentistry Division and Neurology Department
Hospital das Clínicas
School of Medicine
University of Sao Paulo
Sao Paulo, Brazil

Christian S. Stohler, DDS, Dr Med Dent
Professor and Dean
Baltimore College of Dental Surgery
University of Maryland Dental School
Baltimore, Maryland, USA

Peter Svensson, DDS, PhD, Dr Odont
Professor and Chair
Department of Clinical Oral Physiology
School of Dentistry
Faculty of Health Sciences
University of Aarhus
Aarhus, Denmark

Edmond Truelove, DDS, MSD
Professor and Chair
Department of Oral Medicine
University of Washington
Seattle, Washington, USA

Chantal Villemure, PhD
Research Associate
Alan Edwards Centre for Research on Pain
McGill University
Montreal, Quebec, Canada

Charles G. Widmer, DDS, MS
Associate Professor
Department of Orthodontics
University of Florida
Gainesville, Florida, USA

Alain Woda, DDS, PhD
Professor
Laboratory DIDO
Faculty of Dentistry
Université d’Auvergne
Clermont-Ferrand, France
As shown throughout this book, chronic pain syndromes affecting the craniofacial region constitute an unsolved clinical problem because they are common, cause incalculable suffering and incapacitation, and are difficult to treat by existing therapies. Available painkillers currently provide only partial pain relief that is compromised by side effects. A clinically driven subfield in pain genetics is the focus of this chapter since it seeks genetic factors that explain interindividual differences in the susceptibility to develop chronic orofacial pain in order to account for the variance and also to identify new drug targets. On this basis, this chapter introduces the reader to pain genetics, describes the rationale and some methodological considerations that underlie studies in pain genetics, and explains the background for the forecast that genetics may discover new treatment targets. For a broader perspective with greater detail, see Mogil.¹

**Why Is the Variance in Chronic Orofacial Pain Important?**

Any number of outcomes may emerge when an anatomically complex region responds to injury, disease, or exposure to toxins. Therefore, it should come as no surprise that there are large interindividual differences in chronic orofacial pain. Each patient presents with a unique combination of spontaneous pain, stimulus-evoked pain, and pain aggravated by movement. Individuals with the same pathology may present highly variable pain intensity, the location where pain is felt, duration and frequency of pain episodes, and affective-emotional impact of chronic orofacial pain on quality of life and daily activities; even the description of what the pain feels like (e.g., burning, crushing) may be different, as well as the analgesic efficacy derived from painkillers (for examples, see Aubrun et al²).

Figure 9-1 provides an example of the variability in chronic pain intensity presented by 228 traumatic leg amputees. After controlling for confounding variables such as height of the amputation, years since amputation, and ethnicity, enormous differences in phantom leg pain levels are apparent. While about 25% of the amputees never suffered from pain in the missing leg, approximately 75% reported having pain episodes occurring at relatively regular times, with the same episode duration and typical intensity within individuals. A few amputees only had very faint pain, a few others
Fig 9-1  The typical intensity of phantom leg pain as reported by 228 leg amputees using a visual analog scale (VAS), where 0 represents “No pain” and 10 represents “The most intense pain imaginable.” (Seltzer, unpublished data).

Fig 9-2  Percentage of individuals experiencing the traumas or pathologies listed on the right who developed the chronic pain syndromes on the left. CRPS-I = complex regional pain syndrome, type I.
suffered from maximal pain, and the rest presented with pain ranging between these extremes. Note that in this example, the majority of amputees reported phantom pain. This is an exception; in most cases the percentage of individuals developing chronic pain after some insult is lower, as Fig 9-2 suggests.

**Is Chronic Orofacial Pain a Heritable Trait?**

The enormous variance in attributes describing chronic pain and the excess of females presenting with chronic orofacial pain (see chapters 1 and 13) suggest that the susceptibility to develop such pain may be heritable, that is, passed on from one generation to the next via genetic mechanisms. The following equation shows that, like any biologic trait, the phenotypic variance of chronic orofacial pain (VARp) is produced by genetic (VARG) and environmental or nongenetic sources (VARE), and their interaction (VARi):

\[ \text{VAR}_P = \text{VAR}_G + \text{VAR}_E + \text{VAR}_I \]

A phenotype is any measurable or categorizable trait that describes some feature of an organism (eg, height), whereas a genotype refers to the genetic constitution of an individual within its species. Studies on the incidence of trigeminal neuralgia and familial migraine in twin pairs and pedigrees demonstrate the involvement of genetic factors.11 A few reports have already identified chromosomal regions, and even a small number of specific genes and single mutations affecting migraines, headaches, and chronic orofacial pain,12,13 as well as chronic pain in body parts other than the head.14-16 Studies in animal models of painful neuropathies have established that levels of chronic pain are considerably heritable.17-20 Furthermore, manipulations of individual genes by overexpression, deletion (in transgenic “knock-out” experiments), or inhibition of expression using small interfering ribonucleic acid (siRNA) or antisense oligodeoxynucleotide injections have identified more than 240 rodent genes that have some demonstrated role in pain.21-23

**What Is the Size of the Heritable Component in Chronic Orofacial Pain?**

Estimating heritability in chronic orofacial pain is not simple because the only measurable variance is that of the pain (VARp). However, the use of sophisticated statistics to analyze data from the incidence of chronic pain in closely related individuals has enabled researchers to measure the genetic and environmental variance in several chronic pain syndromes, thereby estimating the broad-sense heritability (H2), a value that reflects all genetic contributions to a population’s phenotypic variance. This is depicted in the following equation:

\[ H^2 = \frac{\text{VAR}_G}{\text{VAR}_P} \]

The importance of estimating heritability in chronic orofacial pain is in the ability to forecast the extent to which pain could be treated if pharmacologically addressing the genetic component. Figure 9-3 shows data from studies that estimated the size of H2 in various chronic pain syndromes. On average, genetic factors account for approximately 40% of the variance in chronic pain levels, similar to the average value in animal models of painful neuropathies.24 This calculation carries an optimistic message for pain patients, because it suggests that drugs developed on the basis of genetic knowledge could provide meaningful pain relief.
How Can We Find Orofacial Pain Genes?

Phenomics of chronic orofacial pain

The overall goal in discovering pain genes is to provide evidence of a statistically significant "association" between a pain trait and some genetic marker (usually single nucleotide polymorphisms [SNPs]) in or near these genes. Thus, "genes for pain" are nothing more than genes associated with variability in the phenotypes collected from participants in a given cohort. Each pain syndrome is a unique and complex experience characterized by multiple sensory-discriminative, affective-emotional and cognitive-evaluative variables; therefore, to faithfully represent the pain, a clinician should characterize it in as much detail as is practical. It is not enough to determine whether a patient does or does not have pain and limit the description to pain intensity. Pain phenomics is the research field that constructs questionnaires for quantifying phenotypic pain data for genetic studies. Phenomic questionnaires for chronic orofacial pain are currently unavailable.

Collecting DNA samples

Since there are no available national or international repositories of deoxyribonucleic acid (DNA) samples that would enable interested researchers
to get samples for a genetic study, they must collect their own cohorts, a process that generally takes years. For several reasons related to statistical power, a researcher needs to recruit several hundreds of genetically unrelated pain patients with the same syndrome and hundreds of controls matched for age, ethnicity, sex, etc, who have had the same surgery, disease, or trauma but did not develop chronic pain. Such cohorts are sufficient to discover genes that have major effects on pain levels. Identifying smaller-effect “modifier” genes necessitates a larger study group measured in thousands rather than hundreds of participants.

Following approval by Institutional Ethics Review Boards to conduct genetic experiments in humans, potential participants are recruited. Every recruited participant signs an informed consent form and undergoes an interview to fill out a structured and validated pain phenotyping questionnaire. DNA for genetic studies is usually extracted from white blood cells. DNA from a venipunctured blood sample of 10 to 20 mL is enough for many hundreds of genotypings. But even this quantity of genotypings is limited. Because collecting a cohort of pain patients and their matched controls is so laborious and expensive, some investigators invest in whole genome amplification, a process that provides as many copies of the whole genome as is affordable or needed. Other investigators “immortalize” the DNA by introducing it into a cell line of lymphoblasts that continuously produce donor DNA. The lymphoblasts may also be used for messenger ribonucleic acid (mRNA) expression analyses as a substitute for the patient’s tissues. It is also advisable to keep the plasma of the blood sample and store it for future analyses of proteins, peptides, and cytokines whose levels are possibly affected by the genes studied and can therefore be used as indicators of changes occurring in the trigeminal system during chronic orofacial pain. When venipuncturing for a blood sample is not possible, a clinician could use commercially available kits to extract high quantities of good-quality DNA from saliva.25

Genotyping DNA in search of chronic orofacial pain genes

Two types of polymorphic genetic markers (marker loci) are currently used for genotyping individuals in a cohort: short tandem repeats (STRs)—also called microsatellites—and SNPs. Each individual carries two identical (ie, homozygous) or different (ie, heterozygous) alleles at each marker locus (eg, aa, ab, and bb genotypes). The level of significance of the statistical association between the frequency of carriers of these three genotypes and levels of the trait that characterize chronic orofacial pain is interpreted as a preliminary indication that a causative gene or its part (in the case of microsatellite markers), or causative SNP (when using SNP markers), is nearby. An additional step of positional refinement is then needed to identify the point mutation(s) responsible for the pain trait. This is done by comparing sequences of the relevant DNA interval, seeking mismatches that segregate with pain levels.

SNPs that control chronic orofacial pain may be identified in one ethnic group but not in others. Therefore, meeting treatment needs of peoples of various ethnic origins necessitates studying many ethnic groups. Failure to control for ethnicity can also confound genetic association studies via “population stratification.”26

It should be noted that much genomic variation is not produced by SNPs at all but by copy number variants and other more complex polymorphisms.27 If no sequence mismatches in a gene under study are found to segregate with chronic pain levels, it is possible that the gene is still implicated in the variance of the pain trait by other genetic mechanisms, (eg, by controlling gene expression levels). In one such scenario, another gene could affect splice variation and editing of the mRNA transcript of the pain gene, which determines how many copies of the mRNA of this gene are to be produced and what type of protein is to be produced. Identification of such mechanisms necessitates quantification of mRNA expression levels in situ (ie,
in neural structures where the gene is expressed). Since human material is usually unavailable for research, animal models may serve as surrogates, complemented if needed by comparing mRNA expression levels of lymphoblasts with immortalized DNA of patients with chronic orofacial pain and controls.

Two genotyping approaches can be used to identify chronic orofacial pain genes: (1) studying candidate genes implicated in chronic pain by prior information, and (2) an unbiased scan of all genes in the genome, screened at once in a single run (called genome-wide association study [GWAS]), followed by studying identified candidates.

**Candidate gene approach**

This approach tests the hypothesis that SNPs on one or more genes of known identity segregate in the tested cohort with traits related to chronic orofacial pain. The candidacy of such genes is inferred from the literature as having a known or potential role in pain mechanisms\(^{18}\) (for example, see Diatchenko et al\(^{16}\)).

**Genome-wide association study**

Screening candidate genes by looking “under the streetlight” at known pain-relevant genes carries the risk of missing many other genes for which no knowledge exists to date. This disadvantage is avoided when using the unbiased GWAS approach, which genotypes polymorphisms on approximately 500,000 to 1,000,000 SNPs preselected as capable of detecting nearby mutation(s) affecting a trait under investigation in all genes on the genome. The markers are arranged as microarrays on “chips” that can identify all the chronic orofacial pain genes an individual carries. The chips are commercially available from several producers but are still not economically feasible.

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**How Can Pain Medicine Advance in the Postgenomic Era?**

When all major genetic variations that affect chronic orofacial pain are discovered, novel diagnostic kits will be developed to identify the risk an individual carries for developing chronic orofacial pain; this type of knowledge will be useful in planning treatment choices if, for example, that individual will undergo maxillofacial surgery. The same knowledge is expected to result in the development of prognostic kits that could identify which treatment is genetically most beneficial for an individual. Similar kits could select better subjects for clinical trials, thereby minimizing costs and shortening drug development times. Novel preventive treatments could provide effective “preemptive analgesia” and better postoperative care. New chronic orofacial pain mechanisms could be discovered by studying neurons or glial cells expressing the identified pain genes, and better animal models could be developed based on their relevance to human orofacial pain genes. Finally, applying gene therapy could “patch” the genome of individuals born with “bad” gene variants that carry the risk for chronic orofacial pain. The rapid advancements made in the Human Genome Project raise the hope that this futuristic scenario may become a reality in our lifetime.

**Summary**

This chapter has emphasized the importance of clinically observable interindividual variability in chronic orofacial pain conditions as a clue suggesting that these syndromes are complex heritable traits. This means that these conditions are controlled by genetic determinants that interact with the environment. The chapter also provided estimates that the size of the heritable component in
chronic pain is approximately 40%, indicating that drugs based on genomic knowledge could be effective painkillers. Next, the primary molecular approaches currently used to discover genes for chronic pain were introduced. Finally, several practical outcomes that are likely to result from the Human Genome Project were described, thereby highlighting the clinical relevance of pain genetics to orofacial pain conditions.

References

"I feel your pain": Empathy can increase pain

There is now evidence that witnessing the distress of others can alter pain perception, independent of imitative behavior. Langford and colleagues\(^{16}\) showed that if a mouse is exposed to another mouse in pain, it displays increased pain sensitivity, but only if the two mice have had previous social contact with each other. The authors showed evidence that this social modulation of pain cannot be explained by imitation. They instead proposed that empathy, or a precursory form of it, can induce an increase in pain perception.

A similar phenomenon has now been shown in humans. In one study,\(^{17}\) participants' sensitivity to nonpainful and painful heat stimuli applied to the hand was measured during exposure to a neutral cityscape video to establish their baseline response. Then subjects were divided into two groups. A state of high empathy was induced by having one group of subjects watch a video of an actor telling a sad personal story, whereas a state of low empathy was induced in the other group of subjects with a video of the same actor describing how he managed to dupe somebody out of money. Thermal sensitivity was measured again while participants watched the video of the actor receiving painful or innocuous heat stimuli. Subjects in the high empathy group rated painful heat stimuli as more intense and unpleasant than did subjects in the low empathy group, but ratings of nonpainful heat did not differ between groups (Fig 11-2). As in the mice, the increased pain could not be explained by imitative behavior.

**Fig 11-2** Effects of empathy on pain perception. Increased empathy resulted in increased perceived (a) intensity and (b) unpleasantness of painful stimuli but not for nonpainful stimuli. The high empathy group reported the 48°C stimulus as significantly more intense and unpleasant than the low empathy group. Graphs show the average rating for each temperature while the participants watched the testing video minus the baseline rating recorded while the participants watched the neutral cityscape video. Bars represent mean ± SEM. \(P = .06; *P < .05; **P < .01\). Adapted with permission from Loggia et al.\(^{17}\)
Why does empathizing with others affect our own pain perception?

A number of studies using functional magnetic resonance imaging (fMRI) of the brain have shown that watching somebody in pain leads to the activation of brain areas involved in first-person perception of pain, such as the anterior cingulate cortex and rostral insula.\(^\text{18}\) It appears that empathy can sensitize pain pathways of the brain.

Placebo and Orofacial Pain

Placebo analgesia refers to the reduction of pain sensations after administration of an inert agent, i.e., one that does not possess any specific activity for the condition being treated. As discussed above, psychosocial factors, such as faith in the therapeutic procedure or desire for pain relief, play a role in the effectiveness of any medical or dental treatment. The administration of a placebo reveals the effects of these factors that are normally entangled with the specific effects of the active treatment. Brain imaging has been extremely useful in establishing that placebo analgesia is indeed real by showing that placebo-induced pain relief is associated with a concomitant decrease of brain activity in pain-processing areas such as the thalamus and the insular cortex\(^\text{19}\) (Fig 11-3). This means that reported pain reductions following placebos are real effects rather than being merely due to changes in pain reporting or compliance with experimental instructions.

How do placebos exert their analgesic effects?

About 30 years ago, Levine and colleagues\(^\text{20}\) showed that pain relief induced by administration of a placebo after dental surgery could be blocked by the opioid-receptor antagonist naloxone. Since then, numerous reports have supported the idea that endogenous opioids are important for placebo analgesia. Endogenous opioids are essential for the descending inhibitory control of pain. The brain stem PAG and rostroventral medulla are two key areas for descending pain control,\(^1\) and as noted above and in chapter 8, this circuitry is probably involved in the emotional modulation of pain.