MIGRAINE EPIDEMIOLOGY AND PATHOPHYSIOLOGY
Introduction

What constitutes migraine, is not a trivial question. The characteristics of migraine vary greatly, both between patients and between attacks. A diagnosis of migraine used to be based on clinical experts' opinions. No precise criteria existed as to which number and combination of symptoms were required for a diagnosis. This made it difficult to compare one case to another. For this reason, it was decided that operational diagnostic criteria were necessary to improve and advance headache research. This was achieved in 1988 with the publication of the first edition of the International Classification of Headache Disorders (ICHD) by the International Headache Society (IHS; Headache Classification Committee of the International Headache Society, 1988). In 2004, a revised edition (ICHD-II) was published (Headache Classification Committee of the International Headache Society, 2004). The ICHD classification distinguishes primary and secondary headaches: primary headaches are headaches with no cause other than the headache disorder itself, whereas secondary headaches are headaches resulting from another disorder. The most common primary headaches are migraine and tension type headache. Other primary headaches are cluster headache and various other, less prevalent headache subtypes. This thesis will focus entirely on migraine. Migraine has various subtypes, the most common being migraine with aura (MA; ICHD-II 1.2) and migraine without aura (MO; ICHD-II 1.1). This distinction will be discussed in more detail in Chapter 5. Table 1.1 shows the diagnostic criteria for these subtypes, according to the second edition of the IHS classification. About one third of migraineurs have attacks of migraine with aura, but most MA patients have a relatively low aura frequency (Kelman, 2004).

The phases of a migraine attack

Typically, a migraine attack has several phases. The headache phase is often preceded by a prodrome (sometimes called pre-headache or premonitory phase), during which patients experience premonitory ('warning') symptoms, such as changes in mood or behavior (Bigal et al., 2009). Specific symptoms often reported are fatigue, yawning, and phonophobia (Schoonman et al., 2006). Craving certain foods can also be part of the prodrome (Blau, 1992). In a subgroup of patients, the headache phase is preceded by aura symptoms. Auras can occur in different modalities; by far the most common is the visual aura, which is reported by almost all patients who experience some form of aura, (Eriksen et al., 2004), but sensory and aphasic auras are also
INTRODUCTION

What constitutes migraine, is not a trivial question. The characteristics of migraine vary greatly, both between patients and between attacks. A diagnosis of migraine used to be based on clinical experts’ opinions. No precise criteria existed as to which number and combination of symptoms were required for a diagnosis. This made it difficult to compare one case to another. For this reason, it was decided that operational diagnostic criteria were necessary to improve and advance headache research. This was achieved in 1988 with the publication of the first edition of the International Classification of Headache Disorders (ICHD) by the International Headache Society (IHS; Headache Classification Committee of the International Headache Society, 1988). In 2004, a revised edition (ICHD-II) was published (Headache Classification Committee of the International Headache Society, 2004). The ICHD classification distinguishes primary and secondary headaches: primary headaches are headaches with no cause other than the headache disorder itself, whereas secondary headaches are headaches resulting from another disorder. The most common primary headaches are migraine and tension type headache. Other primary headaches are cluster headache and various other, less prevalent headache subtypes. This thesis will focus entirely on migraine. Migraine has various subtypes, the most common being migraine with aura (MA; ICHD-II 1.2) and migraine without aura (MO; ICHD-II 1.1). This distinction will be discussed in more detail in Chapter 5. Table 1.1 shows the diagnostic criteria for these subtypes, according to the second edition of the IHS classification. About one third of migraineurs have attacks of migraine with aura, but most MA patients have a relatively low aura frequency (Kelman, 2004).

THE PHASES OF A MIGRAINE ATTACK

Typically, a migraine attack has several phases. The headache phase is often preceded by a prodrome (sometimes called pre-headache or premonitory phase), during which patients experience premonitory (‘warning’) symptoms, such as changes in mood or behavior (Bigal et al., 2009). Specific symptoms often reported are fatigue, yawning, and phonophobia (Schoonman et al., 2006). Craving certain foods can also be part of the prodrome (Blau, 1992).

In a subgroup of patients, the headache phase is preceded by aura symptoms. Auras can occur in different modalities; by far the most common is the visual aura, which is reported by almost all patients who experience some form of aura, (Eriksen et al., 2004), but sensory and aphasic auras are also
reported. Visual aura symptoms are often described as ‘flickering lights’, ‘zigzag patterns’, ‘blind spots’ (also called scotomas), or other visual disturbances, that slowly move through the visual field. Sensory aura symptoms are commonly characterized as ‘tingling sensations in the limbs’ or ‘numbness’. Some patients experience aphasic speech disturbances (e.g. having trouble finding the right words). While visual aura symptoms frequently occur alone, sensory and aphasic aura usually occur in combination with at least one other type of aura. Usually, the different types of aura occur in succession (Eriksen et al., 2004), with the visual aura occurring first, followed by the sensory aura, and then by the aphasic aura (Cutrer & Huerter, 2007).

During or after the aura, the headache phase sets in. This phase can last several hours to several days. Migraine headaches are typically characterized by pounding, pulsating headache, which is often unilateral, moderate or severe in pain intensity and aggravated by routine physical activities such as walking stairs. Migraine headaches are commonly accompanied by nausea and/or vomiting, photophobia (hypersensitivity to light) and phonophobia (hypersensitivity to sound). The headache phase is followed by a resolution phase and often a postdromal ‘hangover’ (Blau, 1992).

<table>
<thead>
<tr>
<th>Table 1.1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The diagnostic criteria for migraine with and without aura, as defined by the International Headache Society (2004)</strong></td>
</tr>
<tr>
<td><strong>Migraine without aura (1.1)</strong></td>
</tr>
<tr>
<td>A.</td>
</tr>
<tr>
<td>B.</td>
</tr>
<tr>
<td>C.</td>
</tr>
<tr>
<td>1.</td>
</tr>
<tr>
<td>2.</td>
</tr>
<tr>
<td>3.</td>
</tr>
<tr>
<td>4.</td>
</tr>
<tr>
<td>D.</td>
</tr>
<tr>
<td>1.</td>
</tr>
<tr>
<td>2.</td>
</tr>
<tr>
<td>E.</td>
</tr>
</tbody>
</table>
Phase and often a postdromal (hypersensitivity to sound). The headache, vomiting, photophobia (hypersensitivity to light) and phonophobia (hypersensitivity to sound) are commonly characterized as 'tingling sensations in the limbs' or 'numbness'.

Some patients experience aphasic speech disturbances, that slowly move through the visual field. Sensory aura symptoms are reported. Visual aura symptoms are of different characteristics. Usually, the different types of aura occur in succession over >= 5 minutes. At least two of the following:

1. Homonymous visual symptoms and/or unilateral sensory symptoms
2. At least one aura symptom develops gradually over >= 5 minutes and/or different aura symptoms occur in succession over >= 5 minutes
3. Each symptom lasts >= 5 and <= 60 minutes

Headache fulfilling criteria B-D for 1.1 Migraine without aura begins during the aura or follows aura within 60 minutes

Not attributed to another disorder

**Migraine with aura (1.2)**

| A. | At least 2 attacks fulfilling criterion B |
| B. | Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1-1.2.6* |
| C. | Not attributed to another disorder |

**Typical aura with migraine headache (1.2.1)**

| A. | At least 2 attacks fulfilling criteria B-D |
| B. | Aura consisting of at least one of the following, but no motor weakness: |
| | 1. Fully reversible visual symptoms including positive features (e.g., flickering lights, spots or lines) and/or negative features (i.e., loss of vision) |
| | 2. Fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness) |
| C. | At least two of the following: |
| | 1. Homonymous visual symptoms and/or unilateral sensory symptoms |
| | 2. At least one aura symptom develops gradually over >= 5 minutes and/or different aura symptoms occur in succession over >= 5 minutes |
| | 3. Each symptom lasts >= 5 and <= 60 minutes |
| D. | Headache fulfilling criteria B-D for 1.1 Migraine without aura begins during the aura or follows aura within 60 minutes |
| E. | Not attributed to another disorder |

* 1.2.1 Typical aura with migraine headache; 1.2.2 Typical aura with non-migraine headache; 1.2.3 Typical aura without headache; 1.2.4 Familial hemiplegic migraine (FHM); 1.2.5 Sporadic hemiplegic migraine; 1.2.6 Basilar-type migraine. 1.2.1 is the subtype referred to as 'migraine with aura' throughout this thesis.

**Impact and costs to society**

Migraine is a disabling condition with a big impact on patients’ lives. During a migraine attack, patients are usually unable to continue their normal activities and will typically stay in bed for the duration of the attack. Therefore, especially when the attack frequency is high, the disorder can badly interfere with the patient’s work and social life.

Migraine headaches are undertreated and underdiagnosed; many patients never consult a physician, although estimates differ across studies and populations. For instance, in a French study (Lantéri-Minet et al., 2005), it was
reported that around 40% of migraineurs had never consulted a physician for their migraine, whereas a study in a US population reported almost 80% for headaches in general (Linet et al., 1989).

Due to the fact that many patients do not seek medical attention, the direct costs of migraine are comparatively low, but still quite substantial due to the high prevalence of the disorder. The indirect costs due to lost or reduced productivity are enormous. In a 2004 study the total annual costs of migraine were estimated at around 2 billion euros per year in the Netherlands only, and around 27 billion euros for all European countries together; 1.5 billion due to direct (healthcare) costs and 25.5 billion due to indirect costs (Andlin-Sobocki et al., 2005).

**Prevalence and Risk Factors**

One of the reasons for the high costs of migraine is its high prevalence. In a large US population-based study (N = 20,468) a 1-year prevalence of 18% in females and 6% in males was observed (Stewart et al., 1992). A study in a Dutch population sample (N = 6491) reported a lifetime prevalence of 33% in women and 13.3% in men. The 1-year prevalence was 25% and 7.5%, respectively (Launer et al., 1999). These are only the individuals who meet full IHS criteria for migraine with or without aura. Including individuals with probable migraine (i.e. migraine fulfilling all but one of the A-D criteria) results in a prevalence almost twice as high. A French study reported a prevalence of strict migraine of 16% in females and 6% in males; another 12% and 8% fulfilled criteria for probable migraine, respectively (Lantéri-Minet et al., 2005).

The onset of the disorder is usually in early adolescence, with a peak incidence between 10 and 15 years of age (Stewart et al., 1991). The prevalence is highest between 30 and 40 and then gradually decreases (Stewart et al., 1992). This pattern is most distinctive in females, with high prevalences between adolescence and menopause. In addition, many women have migraine attacks related to the menstrual cycle, which is referred to as menstrual migraine (Lay & Broner, 2009). Together with the 2-3 times higher prevalence of migraine in women, these observations strongly suggest a key role for hormones in the pathogenesis of migraine. Migraine attacks appear to be triggered particularly by sudden drops or increases in estrogen levels, which may explain the often reported decrease in migraine frequency during pregnancy, followed by a return of the migraine after delivery (Brandes, 2006).

The role of precipitating factors in causing migraine attacks remains somewhat controversial. In a study of migraine precipitants in clinical migraine
patients in the US, about three-quarters of all migraineurs reported that their migraines were at least occasionally caused by triggers. The most reported precipitating factors in this study were stress, hormones, not eating, weather and sleep disturbances (Kelman, 2007). Although patient reports of triggers are numerous, it is often unclear whether reported triggers are indeed causally involved. For instance, Schoonman et al. (2007) investigated the relationship between migraine and stress. They studied both perceived stress and objectively measured biological stress reactions. Although patients reported an increase in perceived stress in the days before an attack, they found no evidence for a biological stress response before or during migraine. This might be due to study limitations; however, one alternative explanation the authors suggest is that prior to the attack patients may perceive situations as more stressful, as a consequence of prodromal brain changes. The latter might also be the case for some other reported triggers. For instance, craving for sweet food is known to be a prodromal symptom; thus eating chocolate may be a symptom rather than a cause (Blau, 1992). Clearly however, this does not exclude the possibility that some reported trigger factors are truly causally involved in migraine attacks.

PATHOPHYSIOLOGY

It used to be thought that migraine was primarily a vascular disorder. Vascular changes were viewed as the primary cause of migraine attacks. However, this view became untenable when experiments showed that vasodilation can be induced without necessarily causing a migraine attack (Kruuse et al., 2003), while other studies showed that migraine can be induced without being accompanied by any vascular changes (e.g. Schoonman et al., 2008). These findings indicate that vascular changes are neither necessary nor sufficient for a migraine attack to occur, suggesting they are merely an epiphenomenon (Goadsby, 2009).

These days the dominating view is that migraine is a typical neurological condition. Although it remains speculative how exactly they relate to each other, three processes are important in migraine: 1) cortical spreading depression, 2) the activation of the trigeminovascular system (TGVS) and 3) the sensitisation of peripheral and central brain areas.

CORTICAL SPREADING DEPRESSION AND THE MIGRAINE AURA

Through the years, evidence has accumulated that the migraine aura is most likely caused by a brain event called cortical spreading depression (CSD). This phenomenon was first observed in a rabbit (Leao, 1944), and can also be
triggered in other laboratory animals. During CSD, a wave of intense depolarization, starting in the occipital lobe, propagates through the brain at a speed of approximately 2-5 mm/min., and is followed by a period of suppressed activity. This corresponds well with the progression of aura symptoms and explains both the positive (scintillations, tingling sensations) and the negative symptoms (scotomas and numbness) of the migraine aura. It may also explain why the different types of aura occur in succession, starting with a visual aura; this is consistent with the progression of the CSD wave through the different cortical areas, starting in the occipital lobe (Lauritzen, 2001).

Further evidence for the involvement of CSD in the migraine aura comes from animal studies. Hadjikhani et al. (2001) showed that CSD in experimental animals is associated with certain changes in cerebral blood flow (CBF), which are very similar to those observed in humans during a migraine aura.

The trigeminovascular system
Within the skull, pain sensitivity is primarily restricted to the meningeal blood vessels (Pietrobon & Striessnig, 2003), and this is where the headache in migraine is thought to originate. Most likely, the headache phase starts with some neural disturbance that activates the trigeminovascular system [TGVS] (Goadsby et al., 2002). The TGVS consists of the meningeal vessels, which are innervated by the first (ophthalmic) division of the trigeminal nerve. The trigeminal nerve projects to nuclei in the brain stem, such as the trigeminal nucleus caudalis (TNC), which in turn project to higher brain centers, including thalamus, hypothalamus and cortex. Activation of the TGVS causes the release of neuropeptides (including calcitonin gene-related peptide [CGRP] and substance P) from the peripheral trigeminal nerve endings (Goadsby et al., 1988). These neuropeptides are thought to play a role in causing and maintaining the headache (Bigal et al., 2009). The trigeminal afferents carry the pain signal via the brain stem to higher brain centers involved in the perception of pain (Pietrobon & Striessnig, 2003).

Peripheral and central sensitization
It is thought that the throbbing, pulsating nature of migraine headache, and the aggravation of the headache by activities that increase cranial pressure (e.g. walking stairs or coughing), are caused by a process of peripheral sensitization (Silberstein, 2004). Another important symptom often observed in migraine patients is cutaneous allodynia [i.e. a sensation of pain caused by stimuli that are not normally painful (see Burstein et al., 2000)]. This is thought to result
from central sensitization of neurons in the TNC, which receive input from dura and skin (Silberstein, 2004). Central sensitization is thought to play an important role in the later stages of the migraine attack (Bigal et al., 2009).

**THE CONNECTION BETWEEN AURA AND HEADACHE**

The view that the aura is caused by CSD has become generally accepted, and the same is true for the view that activation of the TGVS underlies migraine headache. However, the relationship between the aura and the activation of the TGVS and the start of the headache remains elusive. It has been hypothesized that CSD might activate the TGVS, and in a study with rats it was demonstrated that this is indeed possible (Bolay et al., 2002). The aura might thus be the cause of the migraine attack. This theory has been criticized, however, because it does not explain what happens in the majority of migraineurs who do not experience aura symptoms (Goadsby, 2001). It has been suggested that in these patients a ‘silent aura’ might occur, but there is limited evidence supporting this theory (see Sanchez-Del-Rio et al., 2006). Others argue that aura cannot be the trigger of migraine headache, due to the existence of aura without headache (ICHD-II 1.2.3; typical aura without headache) in some patients (Goadsby, 2009). Interestingly, however, Hauge et al. (2009), who recently investigated the effect of the newly developed CSD-inhibiting drug tonabersat reported that this drug prevents attacks with, but not attacks without aura in MA patients. If tonabersat indeed prevents migraine headache by preventing the aura, this would strongly point towards a causal role of aura in the subset of migraine attacks that are preceded by aura symptoms. However, the results of this relatively small study require replication at a larger scale to assess the potential implications of these findings.

**COMORBIDITY**

A fascinating feature of migraine is its higher than expected co-occurrence (comorbidity) with many other disorders. A wide range of conditions have been reported to be comorbid with migraine, including psychiatric disorders such as bipolar disorder, panic disorder and phobias, but also non-psychiatric conditions such as other chronic pain conditions, epilepsy, stroke, certain congenital heart defects and endometriosis (e.g. P. Anttila et al., 2001; Breslau et al., 1991; Hagen et al., 2002; Lamy et al., 2002; Merikangas et al., 1990; Merikangas et al., 1997; Nyholt et al., 2009; Von Korff et al., 2005). The reasons for these comorbidities remain largely unknown. The disorders could be
causally related, or share genetic and/or environmental risk factors, but in general, little is known about the mechanisms of comorbidity. The disorder most studied in the context of migraine comorbidity is undoubtedly depression. It has been suggested that for instance the serotonin or dopamine systems might be involved in both migraine and depression and hence explain the association between them (Breslau et al., 1991; Frediani & Villani, 2007). In a longitudinal study it was found that migraine and depression were bidirectionally related; migraineurs had an increased risk of developing depression, and vice versa (Breslau et al., 2000). Furthermore, it was recently shown in a bivariate genetic study of migraine and depression that the two traits were in part explained by shared genetic and non-shared environmental risk factors (Schur et al., 2009). The comorbidity of migraine and depression is investigated in more detail in Chapters 6 and 7 of this thesis.

**Genetics**

The heritability of migraine is undisputed. It was observed long ago that the disorder runs in families, and early twin studies noticed a higher concordance rate for migraine in monozygotic than in dizygotic twins, pointing towards a heritable component (Russell & Olesen, 1993). In a large analysis of twins in six European countries, including a total of 29,717 participants it was estimated that the heritability of migraine is approximately 40-50%. There was some indication that non-additive genetic effects may play a role but most individual studies lacked the power to detect this. Shared environmental factors do not seem to be important in migraine (Mulder et al., 2003). The common migraines (i.e. MO and MA) are most likely polygenic disorders. They do not show a distinctive pattern of inheritance such as observed in a classical Mendelian trait, influenced by a single gene. This is most likely the reason it has proven very difficult to find causative genes for common migraine.

**Familial Hemiplegic Migraine**

Unlike common migraine, Familial Hemiplegic Migraine (FHM) follows a Mendelian pattern of inheritance. This is the reason why most of our knowledge of migraine genetics comes from FHM studies. FHM is a rare and severe type of MA, characterized by temporary hemiplegia (i.e. motor weakness or loss of motor function on one side of the body) during the aura phase. Several mutations in 3 different genes have been identified that can cause FHM.

The first FHM gene was originally mapped to chromosome 1p13 in a parametric linkage study on two large FHM pedigrees (Joutel et al., 1993).
Several years later it was determined that the causative gene was the calcium channel, voltage-dependent, P/Q type, alpha 1A subunit (CACNA1A; Ophoff et al., 1996). Mutations in this gene are responsible for the disorder in a substantial percentage of FHM families, although estimates differ between studies (Joutel et al., 1994; Ophoff et al., 1994; Thomsen et al., 2007). The second FHM gene is the ATPase, Na+/K+ transporting, alpha 2 polypeptide (ATP1A2). This gene was identified in 2003 by De Fusco et al., after several linkage studies had already reported linkage to chromosome 1q23 (Ducros et al., 1997; Marconi et al., 2003). The ATP1A2 gene codes for the alpha-2 subunit of a Na+/K+ pump. Finally, in a genome-wide linkage analysis, Dichgans et al. (2005) mapped a third FHM locus to chromosome 2q24. They determined that the causal mutation was located in the sodium channel, voltage-gated, type I, alpha subunit (SCN1A) on chromosome 2q24. This gene codes for the alpha-1 subunit of a voltage-gated sodium channel. Interestingly, SCN1A has previously been implicated in epilepsy, which is fascinating given the reported comorbidity between migraine and epilepsy.

A possible mechanism by which these mutations affect FHM is by increasing the glutamate and potassium levels in the synaptic cleft, thus facilitating CSD (van den Maagdenberg et al., 2007). What the FHM mutations have in common is that they are all related to the functioning of ion channels. This has led to the hypothesis that not only FHM, but perhaps also common migraine could be viewed as a channelopathy. Whether ion channels play an important role in common migraine is still under investigation, however a recent association study of 155 ion channel genes did not find convincing evidence for their involvement in MO or MA (Nyholt et al., 2008).

**COMMON MIGRAINE: GENE-FINDING STUDIES**

The search for genes underlying common migraine has not been as successful as for FHM. As mentioned earlier, this is most likely due to the fact that common migraine is a complex disorder, influenced by many genes of small effect. In addition, the disorder may be genetically heterogeneous, i.e. different genes may underlie the phenotype in different individuals. Gene-finding studies for migraine commonly apply several different methods such as linkage analysis and candidate-gene association studies. These methods are described in more detail in Chapter 2.
Chapter 1

LINKAGE
Through the years, many linkage studies of migraine have been conducted in an attempt to localize genes for common migraine. Unfortunately, many results to date have remained unreplicated. However, with the increasing number of studies, several consistently replicated loci are beginning to emerge, for instance on chromosome 4q24 (V. Anttila et al., 2006; Wessman et al., 2002) and chromosome 10q22 (V. Anttila et al., 2006; V. Anttila et al., 2008; Nyholt et al., 2005). Thus, evidence is increasing that these regions indeed harbour one or more genes involved in common migraine. For a recent overview of migraine linkage results, see Oedegaard et al. (2009). A disadvantage of linkage studies is that they can often only provide a global indication of where a causative gene might be located. To date, the actual genes causing the reported linkage signals remain unidentified.

CANDIDATE GENE ASSOCIATION STUDIES
Association studies of migraine generally focus on several types of candidate genes. Genes coding for ion channels are of interest due to the findings in FHM, which all implicate ion channels. Genes involved in vascular function are studied because of the vascular changes observed in migraine and the association of migraine and stroke. Genes related to hormone function (e.g. estrogen and progesterone receptors) are candidates because of the sex differences in migraine prevalence and the observed changes related to ‘hormonal milestones’, and genes involved in neurotransmitter function (e.g. dopamine and serotonin receptors), could be candidates due to the suspected involvement of neurotransmitter pathways in migraine pathophysiology. One of the more consistent findings is the association of migraine (particularly migraine with aura) with the 5,10-methylenetetrahydrofolate reductase (NADPH) \( \textit{MTHFR} \) gene (e.g. Kowa et al., 2000; Rubino et al., 2009; Scher et al., 2006). However, in general, many initially positive association results for migraine failed to replicate consistently in follow-up studies (for a review, see Colson et al., 2007; de Vries et al., 2009). A likely explanation for the lack of success of the candidate gene method in migraine research is that our knowledge of migraine etiology is too limited to allow the identification of good candidates and/or the use of small samples with insufficient power.
Genome-wide association
A recent promising development in genetics research has been the introduction of genome-wide association (GWA) studies, the first of which started to be published in 2005. Since then, hundreds have followed and many disease-associated genes have been identified (Manolio & Collins, 2009). Due to the increased resolution compared to linkage studies, and the fact that prior hypotheses on the genes involved are not necessary, GWA studies hold some promise to detect common variants associated with migraine. However, to detect loci with a small effect, very large samples are needed (Visscher, 2008). This has recently led to the formation of large GWA consortia, to bring together the sample sizes necessary to identify significant disease associations.

Overview of the chapters in this thesis
In this thesis, I will first provide a short overview of the genetic epidemiological methods used in the different chapters (Chapter 2). Chapter 3 summarizes the ascertainment procedures for the data this thesis is based on, including details on the headache questionnaire that was used to assess migraine status. In Chapter 4, it is investigated whether and how a potential non-response bias might influence the collected data.

In the second section, the migraine phenotype and its relationship with depression is explored in more detail. Chapter 5 describes how the questionnaire data were analysed with latent class analysis (LCA) to investigate whether subtypes of migraine could be identified, and how the resulting classification was used as the phenotype in an analysis of the genetic architecture of migraine. In Chapter 6 migraine characteristics are compared between depressed and non-depressed individuals, while Chapter 7 explores whether migraine and anxious depression are genetically correlated, and how this association might be explained.

The third section addresses the issue of gene finding for migraine. A linkage study and a meta-analysis of genome-wide association studies are described (Chapters 8 and 9, respectively). Finally, in Chapter 10, an attempt is made to summarize the results of these studies into a coherent conclusion about the outcomes of this thesis and suggest future directions of research aimed at identifying genetic factors underlying an individual’s susceptibility to common migraine.
REFERENCES


References


Chapter 1


Chapter 1


