# CHAPTER 1

GENERAL INTRODUCTION & SCOPE OF THE THESIS

# 1.1 CLINICAL CHARACTERISTICS OF MIGRAINE

## Migraine with and without aura

Migraine is a common, disabling, episodic neurovascular headache disorder. The disease is characterized by recurrent attacks of headaches and associated autonomic and neurological symptoms. Migraine can be divided in two major subtypes: migraine without aura (MO) and migraine with aura (MA). MO attacks are typically characterized by recurrent, unilateral, pulsating headaches of moderate to severe intensity, lasting 4-72 hours that are aggravated by physical activity and often accompanied with nausea and/or vomiting, phonophobia and photophobia. Roughly one-third of migraine patients suffer from MA. MA is discriminated from MO by the presence of transient focal neurological symptoms that accompany the headache attacks. Aura symptoms usually last between 5 and 60 minutes and nearly always include visual symptoms (for an example see Figure 1). Less often sensory symptoms (i.e., paraesthesia) or dysphasic speech disturbances are experienced and, rarely motor symptoms.[1,2] Of all migraineurs, 33% have both types of migraine attacks.[3] Patients with MA suffer from less severe headache, some even may have attacks of migraine aura without headache. Prior to the aura and headache phase migraine patients may experience premonitory symptoms, such as mood disturbances, autonomic symptoms and concentration problems.[4] This premonitory phase can last up to 24 hours. Most frequently reported triggers for migraine attacks are too much or too little sleep, weather changes, missing a meal, certain food triggers (e.g., wine, chocolate, or cheese) and menstruation.[5] Some patients perceive higher mental stress levels before a migraine attack, however evidence suggests that this is more likely part of the premonitory phase of the migraine attack than a trigger.[6] Not the migraine attack itself, but the recurrence of attacks is clinically relevant and defines a migraine patient (according to ICHD-2 and 3 criteria: MO after 5 attacks without an aura and MA after 2 attacks with an aura).[7,8] As biomarkers for migraine are currently lacking, a diagnosis is based on a questionnaire and/or interview using diagnostic criteria that were provided by the International Headache Society in 1988; and in revised form in 2004 and 2013 (Table 1).[7,8]

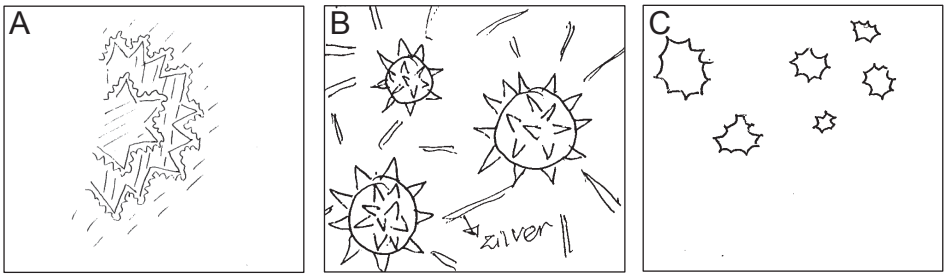


**Figure 1.** Drawings of visual aura symptoms by migraine patients from the Erasmus Rucphen Family (ERF) study. (**A**) Before the headache starts this patient experiences flashing star-shaped features that gradually increase and eventually cover one hemifield. These features last 10-30 minutes. (**B**) This patient describes the background to fade during minutes after which she sees dark-brown to black stars surrounded by silver colored rays lasting 10-15 minutes. After these visual disturbances the headache starts. (**C**) Before the headache this patient sees radar wheels which are present for 10-15 minutes.

**Table 1.** Diagnostic criteria for migraine with and without aura and familial hemiplegic migraine (ICHD-3 *beta*)[8]

| **Migraine without aura** |
|---|
| A. At least 5 attacks fulfilling criteria B-D |
| B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated) |
| C. Headache has at least two of the following four characteristics: |
| 1. unilateral location |
| 2. pulsating quality |
| 3. moderate or severe pain intensity |
| 4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) |
| D. During headache at least one of the following: |
| 1. nausea and/or vomiting |
| 2. photophobia and phonophobia |
| E. Not better accounted for by another ICHD-3 diagnosis. |
| **Migraine with aura** |
| A. At least 2 attacks fulfilling criteria B and C |
| B. One or more of the following fully reversible aura symptoms |
| 1. visual |
| 2. sensory |
| 3. speech and/or language |
| 4. motor |
| 5. brainstem |
| 6. retinal |
| C. At least two of the following four characteristics: |
| 1. at least one aura symptom spreads gradually over ≥ 5 minutes, and/or two or more symptoms occur in succession |
| 2. each individual aura symptom lasts 5-60 minutes |
| 3. at least one aura symptom is unilateral |
| 4. the aura is accompanied, or followed within 60 minutes, by headache |
| D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded. |
| **Hemiplegic migraine** |
| A. At least 2 attacks fulfilling criteria B and C |
| B. Aura consisting of both of the following: |
| 1. fully reversible motor weakness |
| 2. fully reversible visual, sensory and/or speech/language symptoms |
| C. At least two of the following four characteristics: |
| 1. at least one aura symptom spreads gradually over ≥ 5 minutes, and/or two or more symptoms occur in succession |
| 2. each individual non-motor aura symptom lasts 5–60 minutes, and motor symptoms last < 72 hours |
| 3. at least one aura symptom is unilateral |
| 4. the aura is accompanied, or followed within 60 minutes, by headache |
| D. Not better accounted for or by another ICHD-3 diagnosis, and transient ischaemic attack and stroke have been excluded. |

## Familial and Sporadic Hemiplegic Migraine

Hemiplegic migraine (HM) is a rare autosomal dominantly inherited subtype of migraine with aura that is characterized by transient hemiparesis during the attacks (Table 1).[8] Two types of hemiplegic migraine are recognized. In Familial Hemiplegic Migraine (FHM) there

is at least one first- or second-degree family member with attacks of hemiplegic migraine.[7,8] In Sporadic Hemiplegic Migraine (SHM), the family history is negative for patients with hemiplegic attacks. FHM and SHM attacks are clinically indistinguishable,[9] suggesting a common pathophysiological basis. An extensive epidemiological Danish population-based study investigated the prevalence of hemiplegic migraine, as well as the headache and aura characteristics, in comparison to those in MA.[10-12] The prevalence of both hemiplegic migraine types is 0.01%.[10] The mean age at onset is around 17 years (95% CI: 15-18; range 1-45 years), which is lower than for familial MA, which on average starts at 21 years.[11,12] Besides motor aura symptoms, FHM patients can have sensory (98%), visual (89%) and aphasic (72%) symptoms. Furthermore, 69% of FHM patients has co-occurrence with Basilar Migraine (BM).[11,13] Basilar-type migraine symptoms include dysarthria, vertigo, visual symptoms simultaneously in temporal and nasal fields of both eyes, ataxia, decreased level of consciousness and bilateral paraesthesias.[7,8] In three-quarter of FHM patients, the sequence of aura symptoms in FHM is the following: visual - sensory - motor - aphasic - basilar-type.[11] Apart from the motor aura symptoms, which are only experienced by FHM patients, the composition of symptoms and the order of appearance during an attack are very similar for FHM and MA.[11,12] However, FHM patients are more likely to experience two or more aura symptoms, the duration of symptoms is longer for FHM, the presence of BM symptoms only co-occurs with FHM, and the presence of headache more often accompanies FHM than MA.[11,12] Severe atypical FHM attacks may be prolonged (up to six weeks) and accompanied by confusion, decreased consciousness, fever, seizures, and even coma.[14] A minor head trauma is reported in 9% of FHM patients as the initiating event.[11,14] In addition, cerebral or coronary angiography can trigger attacks.[14]

## 1.2 THE MIGRAINE SPECTRUM

Clinical similarities indicate that a migraine spectrum exists ranging from MO to MA and FHM. Arguments for this spectrum are: i) apart from the hemiparesis, the aura and headache characteristics of FHM and MO/MA are similar; ii) within FHM families, family members can have attacks of MA and/or MO; iii) about two-third of FHM patients also has non-hemiplegic migraine attacks.[15] Thus, it can be hypothesized that FHM genes and their pathways also provide insight in the common forms of migraine.

## 1.3 WHAT HAPPENS DURING A MIGRAINE ATTACK?

Traditionally, two hypotheses exist regarding the etiology of migraine: the *neuronal* hypothesis and the *vascular* hypothesis.[16] In the classical, purely, vascular hypothesis the migraine aura is caused by intracerebral vasoconstriction, whereas the headache is attributed to (rebound) vasodilatation of cerebral and meningeal blood vessels.[17] This hypothesis has nowadays been abandoned.[18] Instead, migraine is now considered a primary brain disorder with neuronal events affecting blood vessels, i.e., a neurovascular disorder.

The aura is thought to be caused by a phenomenon termed Cortical Spreading Depression (CSD),[19] a brief wave (lasting seconds) of intense neuronal and glial depolarization that

slowly (2-5 mm/min) propagates across the cerebral cortex.[19,20] This would account for the spreading character and propagation rate of the aura symptoms. The wave is followed by a relatively long-lasting (≥ 20 min) neuronal suppression, which would explain the occurrence of positive and negative phenomena in aura symptoms.[21] Functional neuroimaging studies revealed similarities between blood flow changes in patients during visual aura's and CSD in experimental animals suggesting that CSD indeed occurs in humans.[22]

The origin of the headache is considered to be related to a dysfunction of certain brainstem nuclei.[23] Whether the first neurologic event in migraine is CSD or brainstem dysfunction is still a point of controversy and the two theories may not be mutually exclusive. However, in both scenarios, vasodilatation of cerebral and meningeal vessels, if present, is considered a secondary phenomenon occurring after activation of the trigeminovascular system (TGVS).[24] How does this system works? The TGVS consists of the cranial blood vessels, innervated by sensory afferent fibres of the ophthalmic division of the trigeminal nerve. Activation of these fibres leads to activation of second-order neurons in the trigeminal nucleus caudalis (TNC) and the two uppermost levels of the spinal cord dorsal horn, together termed the trigeminocervical complex. Impulses are relayed further forward to several thalamic nuclei, the ventrolateral area of the caudal periaquaductal grey region and the cerebral cortex, where the pain sensation is registered.

On a molecular level, activation of trigeminovascular efferents leads to the release of vasoactive neuropeptides (e.g., Calcitonin Gene Related Peptide (CGRP), Substance P, and Nitric Oxide (NO)), which are believed to cause neurogenic inflammation, central pain transmission, and headache. The role of neurogenic inflammation has never been demonstrated in patients, but in experimental animal models of migraine neurogenic inflammation of the dura and around the meningeal vessels has clearly been shown.[25] These experiments also provided evidence that CSD can activate the TGVS and induces vasodilatation of the middle meningeal artery.[25] A role for vasodilatation in migraine in humans is further supported by the fact that specific antimigraine drugs, the triptans and ergotamine, next to deactivation of the TGVS and inhibition of the release of vasoactive neuropeptides from perivascular nerve terminals, have a vasoconstrictive effect.[24] Recent studies have casted considerable doubt on whether our idea about the role of vasodilatation in migraine is correct. For instance, CGRP antagonists do not have a vasoconstrictive effect, but are effective in the treatment of migraine.[26] A study using a sensitive 3 Tesla MRA-technique, failed to show *in vivo* cerebral and meningeal vasodilatation in humans during migraine headache.[27] Nevertheless, although this study did not provide evidence for vasodilatation of *large* meningeal and cerebral vessels during migraine headache, it does not rule out a role for *small* cerebral vessels.

## 1.4 EPIDEMIOLOGY OF MIGRAINE

### Clinical epidemiology

The prevalence of migraine is more or less similar over Western countries, but varies for age and sex. The one-year prevalence of migraine varies between 17.1-25.0% in women and 5.6-7.5% in men.[28,29] Onset of migraine is in more than 90% of patients below the age of 50. Peak age of

onset is 10-12 years old for males and 14-16 years old for females, although attacks may start at any age.[28,30] The average female-to-male ratio is 3:1. The prevalence of migraine increases with age with a male preponderance in children under 12 and female preponderance at later ages. The one-year prevalence in women peaks at 35-40 years (33%) and then declines. In men, the one-year prevalence peaks between 50-55 years (15%).[28] Among active migraineurs the median attack frequency is 1-1.5 per month and the median attack duration is 24 hours.[28,30] Approximately 5% of the general population have at least 18 days of migraine per year and over 1% have at least 1 day of migraine per week.[24] Each year, approximately 2.5% of patients with episodic migraine develop new-onset chronic migraine (with more than half of the days per month headache).[31]

Migraine greatly affects the quality of life[32] and is rated by WHO among the most disabling disorders.[33] It is the most costly neurological disorder in the EU.[34] Current acute migraine therapies are far from optimal as not all patients respond to acute therapies and headache recurrence is a common problem. In general, the efficacy of migraine prophylactic drugs is limited. At most, 50% will have a 50% reduction in attack frequency.[35] In addition, currently available prophylactic drugs have a large risk of causing adverse effects. Therefore, better, especially preventative treatment options are clearly needed. In order to identify novel treatment targets it is important to unravel the molecular biological mechanisms involved in migraine. Identification of migraine genes may provide more insight into these mechanisms.

## Genetic epidemiology

Studies in families, twins and the general population showed that genetic factors play an important role in the pathogenesis of migraine, probably by lowering the threshold for migraine attacks.[36,37] First-degree relatives of probands with MO have an increased risk for MO of 1.9 and for MA of 1.4 compared with the general population. First-degree relatives of probands with MA had a 3.8-fold increased risk for MA, but no increased risk for MO.[36] Early age at onset and migraine severity and disability appear to be predictors for familial aggregation.[38]

In twins, families, or large (isolated) populations the proportion of genetic involvement in a disease can be calculated as heritability. Heritability estimates the proportion of variability in a trait (i.e., the phenotypic variance) that can be attributed to additive genetic factors and shared early environmental factors. Additive genetic effects are the sum of the independent effect of alleles. Thus, non-additive genetic effects caused by interaction between alleles at the same locus (dominance) or at two different loci (epistasis) are not measured. Heritability estimates in twin[39-44] and family-based[45] studies range from 0.33-0.53 for migraine in general, and 0.61-0.77 and 0.65-0.79 for MO and MA separately.[39-45]

Studies based on the Danish Twin Registry provided information on specific concordance rates for MO and MA. Concordance rates for monozygotic twins for both MO (28% *vs* 18%, p=0.04) and MA (34% *vs* 12%, p=0.04) are significantly higher than for dizygotic twins, indicating the importance of genetic factors.[46,47] In a study that includes almost 30,000 twin pairs affected by migraine from six countries, monozygotic correlations were at least twice the size of dizygotic correlations, also indicating a contribution of genes to the liability of migraine.[42] As neither the heritability estimates nor the concordance rates in monozygotic twins reach 100%, part of the migraine phenotype must be explained by environmental factors.

These family and twin data show that genetic factors play a role in migraine, however from these data no conclusion can be drawn about the pattern of inheritance. A large Danish population-based segregation analysis showed that MO and MA most likely have a multifactorial inheritance pattern, with a combination of genetic and environmental factors.[45]

## 1.5. GENETIC FINDINGS IN COMMON FORMS OF MIGRAINE

The most widely used strategies to map genes for migraine are linkage analysis and candidate gene association analysis.[48] These methods are aimed at identifying genetic variants with different effects sizes and allelic frequencies. The linkage approach generally yields genes with a large effect size and a low population allele frequency, whereas candidate gene association studies test potential migraine gene variants with a low effect size and relatively high allele frequencies in the population.

### Linkage studies

Linkage analysis requires DNA and clinical information of one or more (large) families containing multiple affected members, a genome wide scan (a narrow grid of polymorphic markers evenly spaced over the genome) and a statistical test (expressed as the Logarithm of the odds (LOD) score) to find out which markers are inherited along with the disease in the families. When a chromosomal region (locus) is transmitted with the disease phenotype within families, this region is likely to contain the gene of interest. Linkage analysis has been successful in FHM (where one gene with a large effect size is implicated in one family), where it lead to the identification of three genes.[49-51] For complex migraine (MO and MA) linkage analyses can also be performed, but the power is much more limited compared to monogenic disorders. The contribution of genes to the total disease risk is small or modest, making it hard to detect them. Linkage studies have identified migraine susceptibility loci on chromosomes Xq24-q28, 1q31, 4q21, 4q24, 6p12 -p21.1, 10q22-q23, 11q24, 14q21.2-q22.3, 15q11-q13 and 19p13.[52-64] With the exception of a few loci (4q21-q24 and 10q22-q23), none have been clearly replicated and for all migraine loci the causative gene still needs to be identified. Next to the small effect size of the variants involved, this is likely due to genetic heterogeneity but also clinical heterogeneity in the end-diagnosis of migraine.

### Association studies

Association studies are aimed at detecting genetic variants that are more common in people with migraine than in unaffected persons, ideally from the same population, i.e., allele frequencies are compared. Association studies may be targeted to a biological candidate gene or performed with a genome wide scan. The genetic variants examined are usually single nucleotide polymorphisms (SNPs), DNA variants that represent variation in a single base.[48] Genetic association studies have greater power than linkage studies to detect genes with a small effect and require collection of large numbers of cases and controls, instead of large families. A significantly increased frequency of an allele of a polymorphism would suggest either that it directly affects the risk of migraine or that the polymorphism is located very close to the locus involved in the disorder and is transmitted with this disease locus (i.e., linkage disequilibrium

(LD), the non-random association of alleles at two or more loci on a chromosome that is gradually lost over generations by recombination). Alternatively, the association is false positive and due to some underlying stratification or admixture (substructure) of the population.

Although a large number of candidate gene association studies were performed in migraine, many are of limited value because of important limitations (e.g., small sample size and consequent low power to detect association, no correction for multiple testing, and/or no clear description of migraine subtypes). Association studies have investigated the possible association between migraine and polymorphisms in genes with a hypothesized function in migraine pathways. Amongst others, genes with a neurotransmitter function (mainly serotonin, dopamine) or involvement in hormonal, inflammatory or vascular pathways have been investigated (for review see de Vries et al., 2009).[65] The only variant to date that was found to be associated with migraine with aura in several, but not all[66-68] studies is the C677T polymorphism of the *MTHFR* gene (methylenetetrahydrofolate reductase).[69] At the start of this thesis, Genome Wide Association studies for migraine had not been published yet.

### Genetic isolates

An alternative approach to study genetics of migraine is to make use of a genetically isolated population. Genetic isolates have several advantages compared to outbred populations. In an isolate genetic variability is reduced because a small number of founders, the occurrence of population "bottlenecks" (such as famine, wars, or infectious disease epidemics) and the absence of migration leading to more inbreeding and genetic drift.[70] This makes it more likely that patients in an isolate have a disease due to a similar underlying genetic defect that is inherited from a common ancestor. Isolates may vary in genetic diversity, depending on the extent of genetic drift and founder effects.[71] Another advantage of genetically isolated populations is that subjects generally have a more uniform lifestyle, culture and environment, which are therefore better controlled. This makes it more likely that a difference between healthy and diseased subjects reflects genetic effects instead of environmental effects. Extensive genealogical records allow reconstruction of extended pedigrees and the collection of unascertained phenotype data prevents selection bias for specific diseases. A disadvantage of isolates may be that some genetic variants are isolate-specific and findings cannot be extrapolated to the general population. However, a genome wide linkage study on depression in ERF showed that this does not account for all variants, as the results found in ERF could be replicated in an independent population.[72]

In this thesis, migraine is studied a Dutch genetic isolate (The Erasmus Rucphen Family (ERF) study). The advantage of the ERF isolate compared to the Finish and Icelandic isolates[73] is that it is a much younger isolate (i.e., 10-20 generations) with high levels of LD,[74] making it particularly useful in the mapping of complex diseases such as migraine.[75]

## 1.6 GENETIC FINDINGS IN MONOGENIC FORMS OF MIGRAINE

Two types of monogenic migraine forms exists. Monogenic FHM, a migraine subtype at the severe side of the migraine spectrum and monogenic migraine syndromes in which migraine is part of the clinical spectrum.

## Genetic and clinical spectrum of FHM and the relation with migraine relevant diseases

FHM is genetically heterogeneous: three genes have been identified. Clinically, hemiplegic migraine attacks of the three subtypes (FHM1, FHM2, and FHM3) cannot be distinguished. FHM may present as 'pure' FHM or be associated with various comorbid diseases. As FHM families exist without mutations in any of the three FHM genes, at least a fourth and probably more FHM genes exist. All three FHM gene products are intimately involved in the modulation of ion transport across neuronal and glial cell membranes, suggesting that FHM, and possibly also common types of migraine, at least in part, are cerebral 'ionopathies'.

FHM1 is caused by mutations in the *CACNA1A* gene located on chromosome 19p13.[51] *CACNA1A* encodes the pore-forming α1 subunit of voltage-gated neuronal $Ca_V2.1$ (P/Q-type) calcium channels and is involved in the modulation of release of neurotransmitters at peripheral and central synapses. To date, over 50 *CACNA1A* mutations have been associated with a wide variety of symptoms. Almost twenty FHM1 gene mutations are known that represent a broad clinical spectrum. More than half of them are associated with cerebellar signs (i.e., slowly progressive ataxia, dysartria and gaze-evoked nystagmus).[14] About 20% of FHM1 families have cerebellar signs.[14] Epilepsy can also be part of the clinical spectrum of FHM1 mutation carriers.[76] Several *CACNA1A* mutations are associated with a decreased level of consciousness during FHM attacks[77-79] or even coma,[14,80-83] sometimes in combination with seizures.[80,83] *CACNA1A* mutations can also cause Episodic Ataxia type 2 (EA2) and Spinocerebellar Ataxia type 6 (SCA6).[51,84] Whereas FHM1 is caused by missense mutations, EA2 mutations mostly are nonsense, frameshift, or splice site,[51] and rarely missense mutations.[85] SCA6 is a so-called polyglutamine disorder caused by small expansions of a CAG repeat located in the distal end of the *CACNA1A* gene.[84] In rare cases, epilepsy (i.e., absence and generalized tonic-clonic seizures) has also been reported in EA2 patients.[86,87]

FHM2 is caused by mutations in the *ATP1A2* gene that is located on chromosome 1q23. *ATP1A2* encodes the α2-subunit of Na+/K+ pumps.[49] Sodium potassium ATPases are responsible for translocating sodium ions out of the cell, while they import potassium ions. The release of sodium ions provides a steep sodium gradient essential for the import of glutamate through glutamate transporters. Thus, ATPases, directly or indirectly, modulate re-uptake of potassium and glutamate from the synaptic cleft into glia cells. Over 35 *ATP1A2* mutations have been identified. With the exception of a few, FHM2 mutations are mostly missense mutations located in the large intracellular loop, which harbors important regulatory domains for ion transport. Although most FHM2 mutations are associated with pure FHM,[49,88-91] additional clinical features have also been reported in *ATP1A2* mutation carriers. In clear contrast to FHM1, cerebellar signs are very rare in FHM2.[92-94] Other FHM2 associated clinical features include, epilepsy,[49,95,96] permanent mental retardation,[95] prolonged hemiplegia,[97] coma,[90] and alternating hemiplegia of childhood (AHC). Alternating hemiplegia of childhood is a rare neurological disorder, with unknown etiology, that resembles FHM and initially was regarded as a migraine variant.[98] A link between FHM and alternating hemiplegia of childhood (AHC) was shown by the identification of an *ATP1A2* mutation in a Greek family with atypical AHC.[99,100] In contrast, the screening of the FHM genes *CACNA1A* and *ATP1A2* gene in a set

of *typical* AHC patients did not reveal any causal mutations.[101,102] *ATP1A2* mutations were also found in basilar-type migraine[103] and the common forms of migraine.[104]

FHM3 is caused by specific missense mutations in the *SCN1A* gene that is located on chromosome 2q24.[50] *SCN1A* encodes the α1-subunit of neuronal $Na_V1.1$ voltage-gated sodium channels that play an important role in the generation and propagation of action potentials. The FHM3 gene was originally identified in three related German families with the Q1489K mutation.[50] An association of *SCN1A* with FHM is rather surprising because over 150 mutations in this gene are known to cause childhood epilepsy (i.e., severe myoclonic epilepsy of infancy (SMEI) or generalized epilepsy with febrile seizures (GEFS+)).[105,106] With the identification of a second *SCN1A* L1649 mutation in an FHM family of North American decent, the link between *SCN1A* and FHM was firmly established.

FHM gene mutations can also be found in SHM patients, although the chance of identifying a causal mutation is much lower compared to FHM. Whereas in a Dutch clinical-based SHM sample of 39 SHM patients the prevalence of ATP1A2 mutations was 15 %, only in 1 % *ATP1A2* mutations were identified in 100 patients from a Danish population-based sample.[107,108] The prevalence of *CACNA1A* gene mutations in SHM patients lies between 1 and 5 %.[107-109] The chance of identifying an *ATP1A2* or *CACNA1A* mutation is further increased by early age at onset and presence of additional symptoms (such as ataxia or epilepsy).[110] No *SCN1A* mutations have been identified in SHM patients.[107]

## Examples of monogenic syndromes associated with complex migraine

Migraine can also be part of the clinical spectrum of other monogenic syndromes. Hence, the identification of genes for these syndromes may further our understanding of the mechanisms involved in migraine. The monogenic syndromes CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) and HVR (Hereditary Vascular Retinopathy) (later renamed RVCL (Retinal Vasculopathy with Cerebral Leukodystrophy) and CHARIOT (Cerebral Hereditary Angiopathy with Vascular Retinopathy and Impaired Organ Function caused by *TREX1* mutations)) are described below.

### CADASIL

The clearest example of a monogenic syndrome in which migraine is prominent is Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL). CADASIL is an autosomal dominant late-onset arteriopathy that is clinically characterized by recurrent transient ischemic attacks (TIAs) and strokes and cognitive decline, psychiatric symptoms and dementia.[111] In about one-third of patients migraine with aura occurs, often as the presenting symptom several years before the onset of other symptoms.[112] CADASIL has distinct neuroradiological features that are usually manifest prior to the first stroke.[113,114] The most important features are white matter hyperintensities (WMH) and lacunar infarcts. WMHs are symmetrically distributed in the deep and periventricular white matter. Typical for CADASIL is the bilateral involvement of the anterior temporal lobes and external capsule. Histopathologically, CADASIL is characterized by the deposition of granular osmiophilic material (GOM) in the basement membrane and surrounding

extracellular matrix of vascular smooth muscle cells (VSMCs) as well as the degeneration and eventual disappearance of VSMCs. CADASIL is caused by mutations in the *NOTCH3* gene, located on chromosome 19q13.2-p13.1 encoding a cell surface receptor protein that, in human adult tissue, is solely expressed in vascular smooth muscle cells.[115,116] The pathophysiological mechanism that leads to increased aura prevalence in CADASIL is unknown, however increased CSD susceptibility, involvement of the migraine brainstem area or a direct shared genetic susceptibility have been suggested.[117]

### Hereditary Vascular Retinopathy (later renamed RVCL and CHARIOT)

A second monogenic cerebrovascular syndrome where migraine is part of the clinical spectrum is hereditary vascular retinopathy (HVR).[118,119] HVR was reported in a large Dutch family and is primary characterized by a vascular retinopathy. Besides, migraine and Raynaud's phenomenon segregates in this family. HVR was mapped to chromosome 3p21.1-p21.3.[120] Genetic testing revealed that two additional families with overlapping clinical features were also linked to this locus: cerebroretinal vasculopathy (CRV)[121] and hereditary endotheliopathy with retinopathy, nephropathy and stroke (HERNS).[122] Although many genes in the linked region were sequenced, the causal gene had not been identified at the start of this thesis. Despite being linked to the same locus, there seemed a considerable variation in clinical symptoms between families. For example, nephropathy appeared specific for HERNS. The occurrence of cerebral mass lesions was reported in both the HERNS and CRV family, but not in the HVR family, where only a minor degree of cerebral white matter change was observed in some patients. Migraine was most prominent in the HVR family. The presence of different 3p21 haplotypes suggested that the clinical variation might be caused by different mutations in the same gene, although the presence of different retinopathy genes in the same region could not be excluded.[120] Two other families with a similar phenotype were also reported in the literature.[123,124] In a German case report in addition to retinopathy and an intracerebral mass lesion, the elevation of liver enzymes and colonic teleangiectasias was striking.[123] An Australian family presented with a clinical picture that resembled that of HERNS.[124] As migraine and Raynaud's phenomenon were also present in branches of the Dutch HVR family without retinopathy, one can speculate whether the genetic defect underlying the retinopathy may also (at least in part) be responsible for the increased prevalence of migraine and Raynaud's phenomenon. A genetic, family-based, association study demonstrated that the chromosome 3 locus indeed seem to enhance the susceptibility for Raynaud's phenomenon and migraine in the HVR family.[125]

## 1.7 COMPLEX MIGRAINE AND USE OF COMORBID DISEASES TO IDENTIFY GENETIC FACTORS

Research into comorbidity of the common forms of migraine may provide insight in shared epidemiological risk factors or pathophysiological mechanisms involved in both diseases. The term comorbidity refers to the greater than coincidental association of two conditions in the same individual.[126] Comorbidity itself is no evidence for a shared etiological background between

two diseases.[127] First of all, the association may be spurious, for example as a consequence of biased ascertainment or diagnostic uncertainty. Second, a simple unidirectional causal relationship may underlie the association. Third, shared environmental risk factors may play a major role. It can also be that comorbidity may be caused by a common genetic predisposition. Identification of such shared genetic risk factors may define previously unexpected biological pathways that link diseases together.[128] The study of comorbidity of migraine with and without aura may provide useful endophenotypes for genetic studies. Endophenotypes may assure more robust and consistent phenotyping of patients, decreasing clinical heterogeneity. Furthermore, endophenotypes may be helpful in the identification of genetic risk factors by reducing genetic heterogeneity. Migraine has been associated with a wide range of neurological, psychiatric and cardiovascular conditions.[126] A clear example is epilepsy, which is found to be comorbid with common migraine in population based studies,[129,130] and often co-occurs with FHM. A possible shared genetically determined pathophysiological pathway is suggested by the finding that many epilepsy genes as well as the known FHM genes encode ion transporters.[76,131] Besides epilepsy, in this thesis, depression and the association with cardiovascular diseases are under discussion.

## Depression

Depression, like migraine, is a chronic episodic disorder. A depressive episode according to the DMS-IV criteria is characterized by a period of at least 14 days with depressed mood or loss of interest or pleasure combined with cognitive and vegetative symptoms leading to impairment in social, occupational or other important areas of functioning.[132] For clinical practice, various well validated screening instruments for depression have been developed that measure depressive symptoms, such as the Hospital Anxiety and Depression Scale (HADS) and the Centre for Epidemiological Studies Depression scale (CES-D).[133,134] These scales can be used for scientific purposes as well because they enable efficient assessment of depression in large populations.

Migraine and depression co-occur more frequently within subjects than to be expected by chance. Population-based studies range considerably with respect to the increased risk of depression in migraineurs, but in most studies odds ratios are at least doubled and consistently higher for patient with MA than for MO.

In migraineurs comorbid depression is often associated with chronification of migraine,[135,136] decreased quality of life[137] and the development of medication overuse headache.[135-137] The pathogenesis of both conditions, especially how episodes are being triggered and how symptoms may become chronified, is poorly understood. Interestingly, the comorbidity is bidirectional. Not only migraine patients have an increased risk to develop depression, but depressive patients also have an increased risk to develop migraine.[138] This bidirectional relationship suggests that migraine and depression share common etiological factors. This might be due to shared genetic factors, however this has never been investigated.

## Cardiovascular disease

Several observational studies have shown that migraine, specifically MA, is a risk factor for ischemic stroke. A meta-analysis from 2005 of eleven retrospective case-control and three prospective cohort studies showed pooled increased relative risks of 1.83 (95% Confidence

Interval (CI) 1.06-3.15) for MO, and 2.27 (95% CI 1.61-3.19) for MA.[139] This risk was higher in young female migraineurs below 45 years old and highest when using oral contraceptives. Additional support for an association between migraine and ischemic stroke comes from imaging studies. In the population-based CAMERA study evidence was presented that MA patients have a fourteen-fold increased risk of silent infarct-like lesions in the posterior circulation territory of the brain (i.e., the cerebellar region), a risk which increases with increasing attack frequency.[140] The specific MRI characteristics of these lesions suggest an infarct origin.[141] Also, from the CAMERA study it became clear that in women with migraine the risk for deep white matter lesions is increased compared to controls, with no difference between MO and MA patients. This risk also increases with higher attack frequency. Whether vascular changes in migraine are restricted to the cerebral vasculature or also systemically present is not yet clear. Systemic vascular dysfunction is suggested by the association of migraine with an unfavorable cardiovascular risk factor profile,[142] prothrombotic and vasoactive factors,[143,144] and the relation with systemic endothelial dysfunction.[145] The reported association of migraine with ischemic heart disease points to systemic vascular dysfunction, although at the start of this thesis no large follow-up studies were performed and cross-sectional studies reported conflicting results.[146-150]

## SCOPE OF THE THESIS

In this thesis clinical and genetic aspects of migraine and related syndromes are investigated. The studies described can be divided in three main parts.

The first part focuses on syndromes associated with FHM gene mutations. FHM may manifest in a 'pure' form or present as a more extensive syndrome with additional clinical features (**chapter 2**). The clinical spectrum of FHM1-3 and the relation with closely related migraine relevant diseases such as Alternating hemiplegia of Chilhood (AHC) (**chapter 3**), Early Seizures and Cerebral Edema after Trivial Head Trauma (ESCEATHT) (**chapter 4**), epilepsy (**chapter 5 and 6**) and episodic ataxia (**chapter 7**) is studied. The description of this clinical spectrum is important to learn more about the genotype-phenotype correlation and because of the implications for genetic testing. In addition, these studies may finally lead to more insight in the common forms of migraine, by providing pathofysiological clues.

In the second part a monogenic syndrome is studied where migraine is part of the clinical spectrum. **Chapter 8** describes the identification of *TREX1* as the causal gene for Retinal Vasculopathy with Cerebral Leukodystrophy (RVCL), formerly known as HVR, HERNS, CRV, and later (chapter 9) renamed CHARIOT. Next, in **chapter 9**, the clinical spectrum and the genotype-phenotype correlation is evaluated in eleven CHARIOT families with five different *TREX1* mutations**.** How the mutated *TREX1* gene causes disease is unknown. Therefore, in **Chapter 10** we explore the hypothesis whether endothelial dysfunction plays a role by using clinical tests assessing hemodynamic changes in *TREX1* mutation carriers compared to a control group and patients with CADASIL. The identification of the underlying gene and the study of the functional consequences and the clinical spectrum of CHARIOT may also improve our insight in (novel) pathways involved in migraine.

For the last part of this thesis migraine patients were identified in the Erasmus Rucphen Family (ERF) study, a genetically isolated population in the South-West of the Netherlands. The study of migraine and comorbid disorders can be used to define endophenotypes that are more robust and thought to have reduced genetic and clinical heterogeneity. Consequently, identification of genetic risk factors may be more successful. Comorbidity of migraine with depression (**chapter 11**) and atherosclerosis (**chapter 12**) was investigated. For depression it was also studied whether shared genetic factors underlie the comorbid relation with migraine.

A general discussion of the findings presented in this thesis and suggestions for future research are given in **Chapter 13**.

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