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"Clinical and Molecular Investigations on Migraine: Genetic Basis, Phenotypic Characteristics, Chronicity and Management"

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The two most common forms of migraine are migraine without aura and migraine with aura, the so called “common forms of migraine”. Familial aggregation is frequent and segregation analysis is compatible with the concept of migraine being a complex genetic disease. In contrast, familial hemiplegic migraine, a rare subtype of migraine, is inherited in an autosomal dominant fashion.

Investigating the genetic basis of migraine, disease causing mutations and genes responsible for the phenotpyes of FHM1 and FHM2 were extensively studied in common forms of migraine using different methods (linkage analysis, mutation analysis, association studies). FHM locus 1 and 2, as well as known mutations in these gene and other possibly relevant loci for migraine were not present in large samples of migraine families or individual cases. Headache is a prominent feature also in mitochondrial diseases; neither the mutation causing the MELAS Syndrome nor the mutation causing the MERFF phenotype were found in large sample of migraine patients. We concluded that variances in the mitochondrial genome do not play a significant role in migraine. Following up on published evidence of a X-chromosomal factor in migraine, we embarked, in an international collaborative project, on screening the entire x-chromosome for linkage in 61 families from Germany, Spain and the USA and described a new locus for migraine on Xp22 in common forms of migraine.

In a pathophysiological study, a discreet disturbance in smooth pursuit eye movements was documented and defined as a potential endophenotype, linking clinical presentation and possible anatomic origin, which might be of use in further genetic studies.

The mechanism of chronicity was investigated clinically by analysing pain coping strategies in migraineurs and at a molecular level by studying a possible influence of the serotonergic system on chronicity and depression. To optimize therapeutic management, we participated in a multicentre survey into usage of complementary alternative medicines in our migraine patients.

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List of abbreviations:

WHO: Word Health Organisation

BC: before Christ

IHS: International Headache Society

MO: Migraine without aura

MA: Migraine with aura

FHM: familial hemiplegic migraine

CM: chronic migraine

TM: transformed migraine

CSD: cortical spreading depression

PET: positron emission tomography

BOLD: blood oxygen level dependent

SPEM: smooth pursuit eye movements

ENG: electronystagmography

RR: relative risk

SNP: single nucleotide polymorphism

LOD: logarithm of the odds

KPI: Kiel Pain Inventory

HTTLPR: serotonin transporter linked polymorphic region

CAM: complementary alternative medicine

1 Introduction

The World Health Organisation (WHO) states on its web site, that headache disorders are among the most common disorders of the nervous system. 47% of the adult population have headache at least once within the last year and that headache disorders are associated with personal and societal burdens of pain, disability, damaged quality of life and financial costs. Only a minority of headache sufferers are diagnosed appropriately. The WHO summarizes, that headache is "underestimated, under-recognized and under-treated throughout the world" (www.who.int).

While tension type headache is the most frequent headache, migraine is the most common reason for seeking medical help. Care for patients with migraine is a challenge in our daily clinical practice, not only due to the number of affected patients, but also due to the immense suffering the disease imparts on the individual person affected. It ranks first between the most disabling diseases in neurology as shown in the 2010 version of the Global Burden of Disease report [1]. Almost 3% of worldwide disability attributable to a specific disease is due to migraine [2]. Not only direct health related costs are considerable, also cost in economy due to loss of productivity is relevant for societies. In the EU, the total annual cost of headache amongst adults aged 18-65 years was calculated at €173 billion, €111 billion apportioned to migraine (64%) alone. Of these 93% are indirect costs related to reduced productivity and absenteeism [3].

1.1 History, Epidemiology

Over time various models of migraineous headache and its cure have existed. Rapoport and Edmeads give a concise overview in [4], which is shortly summarized in the following: Trepanations found in skulls dating from the Neolithic period (8500 to 7000BC) have been probably performed to relieve the respective person from headache, possibly migraine. "Malevolent beings within the head" causing the headache should be able to leave the skull. This kind of operations have been performed over a long period of time up to the mid 17th century. Medical documents from Egypt describe migrainous headache on the "Ebers"-Papyrus dating back to about 1200BC. For treatment it was recommended "to bound a clay effigy of a sacred crocodile firmly round the head". About 800 years later the Greek physician Hippocrates thought that "vapours rising from the stomach to the head" were causing migraines, thereby leaving the attribution of the headache to external ghosts. From this time dates the first description of symptoms probably describing a migraine aura. Galen eventually described a half-sided headache in the second century AD. His "hemicrania" gradually transmuted to "migraine". This theory held on, until in 1664 Thomas Willis related the headache to the blood

vessels. 200 years on, in 1873 Edward Lieving proposed that migraine was due to “nerve storms evolving out of the optic thalamus”. End of the 18th century it was tried to converge both theories and Moebius stated “parenchyma is the master, circulation the servant”, formulating a “neurovascular” theory of migraine, which, albeit with much greater complexity, represents the current concept of the pathophysiology of migraine. Ergot, produced by the fungus Claeviceps purpurea, was introduced by W.H. Thompson as an effective therapy for migraine in the 1880s. The isolation of a pure ergot alkaloid ergotamine in 1920 was the beginning of modern migraine treatment, only recently abandoned in favour of the Triptans in the late eighties of the 20th century [4].

The prevalence is 4% in children, 6% to 13% in males, and 15% to 33% in female adults [5–9]. The “Deutsche Migräne und Kopfschmerzgesellschaft” conducted a comprehensive survey evaluating the prevalence of headache in Germany for adults as well as for children and adolescents in 2004: Migraine was present in 11% of Germans (6-months prevalence) and tension type headache in 31%. Cluster headache was present in 0.15%, chronic migraine in 0.2% [10].

Headache is not only a problem of the adult population. Nearly 70% of children between 12 and 15 years of age have headache (12-month prevalence), 4.4% have frequent headaches. 20% have migraine and 20% have tension type headache. Headache prevalence increases with age. Have 39% of children aged seven headache, this number goes up to 63% in adolescents aged 14. 6.5% of these children have headache once a week [10–13]. Overall, prevalence is highest from ages 25 to 55, the peak years of economic productivity. A gap between peak incidence in adolescence and peak prevalence in middle life indicates that migraine is a condition of long duration [14].

1.2 Headache Classification

Two main types of headache disorders are distinguished. The *“secondary”* headache disorders, where headache is the symptom of a long list of underlying diseases and the *“primary”* headache disorders, where the headache is the disorder itself.

The defining common denominator in the *primary headaches* is the absence of pathognomonic deviations in any diagnostic procedure available to date. By definition, results from radiology, laboratory medicine, electrophysiology, or clinical status have to be normal. Thus, for better diagnostic and lastly scientific reasons it has been tried to establish a valid list of diagnostic criteria solely based on clinical symptomatology. The breakthrough was achieved with the diagnostic criteria of the International Headache Society (IHS) first published in 1988 and now available in their third edition [15–17]. In ICHD-III, *migraine* is listed as the first out of four categories of primary headaches,

followed by *tension type headache*, *cluster headache and other trigeminal autonomous headaches* and a fourth group of *other primary headache disorders* (like primary cough headache, primary headache associated with sexual activity, primary stabbing headache or new daily persistent headache among many others).

Migraine is divided in six main disease presentations namely [1.1] migraine without aura (MO) and [1.2] migraine with aura (MA), [1.3] chronic migraine, [1.4] complications of migraine, [1.5] probable migraine and [1.6] episodic syndromes that may be associated with migraine. Migraine with aura is further classified in migraine with typical aura, migraine with brainstem aura, hemiplegic migraine and retinal migraine. Hemiplegic migraine comprises familial hemiplegic migraine type 1, 2, 3 and "other loci" as well as sporadic hemiplegic migraine (*Table 1*).

Table 1: Classification of Migraine according to ICHD-III

	Classification of Migraine(ICHD-III)
1.1	Migraine without Aura
1.2	Migraine with aura
	Migraine with typical aura
	Typical aura with headache
	Typical aura without headache
	Migraine with brainstem aura
1.2.3	Hemiplegic migraine
	Familial hemiplegic migraine (FHM)
	Familial hemiplegic migraine type 1 (FHM1)
	Familial hemiplegic migraine type 2 (FHM2)
	Familial hemiplegic migraine type 3 (FHM3)
	Familial hemiplegic migraine, other loci
	Sporadic hemiplegic migraine
1.2.4	Retinal migraine
1.3	Chronic migraine
1.4	Complications of migraine
1.5	Probable Migraine
1.6	Episodic syndromes that may be associated with migraine

The criteria for migraine with and without aura, as well as for familial hemiplegic migraine are found in *table 2 and 3.* Remarkably, the characteristics of the headache phase is the same for all subtypes of migraine. Classification in different subgroups is solely based on aura characteristics, inheritance pattern and the course of disease. The headache is characterized by half-sided, throbbing pain of moderate to severe intensity accompanied by hypersensitivity to light and sound and/or symptoms such as nausea and vomiting. Aura, present in up to 20-25% of migraineurs have spreading neurologic signs referred to cortex or brainstem dysfunction. It includes disturbances of vision, speech, sensibility, motor function (hemiparesis), and rarely coma as seen with uncommon severe migraine variants such as familial hemiplegic migraine (FHM)[18].

Table 2: Diagnostic criteria for migraine without aura and migraine with aura (ICHD-III: 1.1 and 1.2)

	Migraine without aura	Migraine with Aura
A	At least five attacks1 fulfilling criteria B–D	At least two attacks fulfilling criteria B and C
B	Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)	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	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)	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	During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia	Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded
E	Not better accounted for by another ICHD-3 diagnosis.	

Table 3: Diagnostic criteria for Hemiplegic migraine and familial hemiplegic migraine (ICHD-III: 1.2.3)

	Hemiplegic Migraine	Familial Hemiplegic Migraine
A	At least two attacks fulfilling criteria B and C	Fulfils criteria for 1.2.3 Hemiplegic Migraine
B	Aura consisting of both of the following: 1. fully reversible motor weakness 2. fully reversible visual, sensory and/or speech/language symptoms	At least one first- or second-degree relative has had attacks fulfilling criteria for 1.2.3 Hemiplegic migraine
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 by another ICHD-3 diagnosis, and transient ischaemic attack and stroke have been excluded	

1.3 Pathophysiology

Migraine symptoms arise from a combination of vascular and neuronal events. Respective hypotheses were already formulated in previous century by the late H.G. Wolff in his outstanding work done between 1939 and 1962 [19,20]. Recent advances, partly based on the availability of new technology, confirmed some of these early assumptions and shed some light on the basic pathological mechanisms occurring during a migraine attack.

Imaging studies demonstrate, that the brain stem is active during migraine. There are bidirectional connections with the trigeminovascular system as well as diencephalic structures involved in pain processing facilitating the pain to spread. For example, after stimulation of blood vessels and/or the dura mater trigeminovascular afferents can induce pain that is perceived as “headache”. (For review see [21]).

The role of cortical spreading depression in this context is heavily debated. There is substantial evidence that cortical spreading depression (CSD) is the electrophysiological correlate of the migraine aura and possibly acts as trigger for the headache [22]. CSD is a depolarization of neuronal and glial

membranes due to a sudden loss of membrane resistance and ionic gradients followed by long lasting suppression of neuronal activity. High K^+ in the tissue undergoing CSD is believed to depolarize adjacent brain tissue, and in this way the CSD wave propagates into contiguous gray matter at an average speed of 3mm/min. Evidence of CSD in humans was obtained only recently, using functional MRI during migraine and epidural and intracortical recordings in injured brain [23,24]. There is evidence that these changes of electrolytes cause activation of the caudal portion of the trigeminal nucleus in the brain stem by diffusion towards local blood vessels. Subsequently collateral axons of the activated neurons in the trigeminal ganglion release proinflammatory peptides in the meninges and their vessels leading to a local inflammatory reaction and subsequently pain [25].
A knock in mouse model carrying a human mutation that causes familial hemiplegic migraine showed, that this genetic variation produces a gain of function in neuronal Cac2.1 channels facilitating initiation and propagation of CSD induced by electrical stimulation in vivo by impaired neurotransmitter release, supporting the above described hypotheses [26,27].

For migraine without aura Positron Emission Tomography (PET) in a single patient with a spontaneous migraine attack showed a broadly propagated wave of oligaemia associated with the headache. Additionally, MRI blood oxygen level-dependent (BOLD) studies of patients with spontaneous migraines showed propagated suppression of visually evoked BOLD signal. These alterations in cortical function and blood flow show patterns of spread that suggest CSD to be present also in migraine without aura [28].

In summary, CSD appears to be one of the most plausible explanations for migraine with aura, the pathological 'trigger' for migraine without aura that leads to the sequence of cortical events remains, however, unclear.

1.4 Heritability

Speculations on heritability of migraine appear comparably late in historical documents. We have reviewed this in [31]: Some medieval sources occasionally relate to familial aggregation. For example in the Jewish scripture Midrash it is stated, that "in twin sisters, one finds headache often also in the other twin" [32]. In 1672 Thomas Willis stated in his work "De anima brutorum" that migraine might be inborn [33]. Samuel Auguste Tissot (1728-1797) published criteria for migraine, which included heritability in 1780 [34]. Since then, the heritability of migraine was established as a diagnostic criterion and finally found its way in the first comprehensive headache classification of the Ad-hoc-Committee in the 20th century [35]. The currently favoured classification published for the first time in 1988 by the International Headache Society, recently published in their 3rd version, abandoned that criterion

except for the subtype “familial hemiplegic migraine” [17,36]. In summary, heritability of migraine has been an essential diagnostic criterion for centuries. However, before the introduction of the IHS classification in 1988, all studies into migraine were seriously hampered due to methodological issues regarding inaccurate diagnosis.

Studies on twins can give a fairly accurate notion on influence of genes on the heritability of a disease or syndrome. Comparison studies on monozygotic and dizygotic twins in migraine estimate the genetic component or heritability at 40-65% [37,38]. If one analyses family structures carefully using segregation analyses, there is no evidence for autosomal dominant or recessive or x-chromosomal inheritance. However, the risk of a first degree relative of a person with migraine also to have migraine is significantly increased (RR=1.88) [39]. While a genetic component in common migraine is evident, phenocopies, variable age- and sex-related penetrance, genetic heterogeneity, and a strong contribution from environmental factors obscure the identification of the genetic basis of common forms of migraine up to this day. Summarizing all results from segregation analyses, migraine is thought to be a so called complex genetic disorder [40].

2 Genetics of Migraine

With advances in technology and methodology, it is now possible to investigate large samples for possible genetic associations with migraine. Results from the latest International Headache Genetics Consortium genome-wide association meta-analysis of 23.285 migraine cases and 95.425 controls of European ancestry identified 142 single-nucleotide polymorphisms (SNP) at 12 loci significantly associated with migraine susceptibility, besides 1.168 SNPs in 134 loci which were suggestive of linkage. These loci were not confined to any specific pathway or tissue. Twelve loci may be associated with genes with known function in synaptic or neuronal regulation in support of current concepts of migraine pathophysiology [41].

In contrast, familial hemiplegic migraine (FHM) is inherited in an autosomal dominant fashion. In 1994, FHM was linked to chromosome 19p13 [42] and, subsequently, the first gene for FHM was discovered. Mutations in the voltage dependent calcium channel gene, CACNA1A, were found to cause familial hemiplegic migraine in about 50% of all families investigated [43]. Some years later mutations in two other genes, ATP1A2 and SCN1A have been identified in families and patients with pure hemiplegic migraine [44,45].

The three genes identified with FHM encode proteins that regulate glutamate availability in the synapse. FHM1 (CACNA1A) encodes the pore-forming 1 subunit of the P/Q type calcium channel [18,43]; FHM2 (ATP1A2) encodes the alpha-2 subunit of the Na/K-ATPase pump [44]; and the FHM3 (SCN1A) encodes the alpha-1 subunit of the neuronal voltage-gated Nav1.1 channel [45]. Collectively, these genes regulate transmitter release, glial ability to clear (reuptake) glutamate from the synapse, and the generation of action potentials [40]. These findings provide the most plausible explanation for the "generalized" neuronal hyperexcitability of the migraine brain.

In some families, migraine is part of a complex phenotype with other symptoms along the headache. In these families disease causing mutations have been found in two further genes, namely PRRT2 and ATP1A3 respectively [46,47].

2.1 Own Research

2.1.1 CACNA1A, ATP1A2, Serotonin Receptor Gene 1Db

After the first disease causing mutations in CACNA1A gene on chromosome 19 were identified for FHM the question arose, whether mutations in this gene also are involved in the much more

frequent types of migraine like migraine without aura and migraine with aura (so called “common forms of migraine”). There was convincing evidence for this assumption:

- Variation of migraine symptomatology is variant as well in migraine families and as in individual patients. Common migraine is also present in families, where some members have hemiplegic auras in connection with their headache, indicating variation of symptoms in FHM families.
- Migraine with hemiplegic migraine, migraine with “typical” aura or migraine headache without aura have been described to occur in one and the same patient [48].
- Transmission in some families with common forms of migraine clearly indicates autosomal dominant inheritance.
- Common migraine had already been linked to the FHM locus on chromosome 19 in a French pedigree [49]
- Sib-pair analysis provided evidence for an involvement of the FHM1 locus in common forms of migraine [50].

All this evidence led to the hypothesis, already formulated in the first publications reporting linkage to chromosome 19p, that this same gene might also be involved in the aetiology of common forms of migraine (MO and MA). To test this hypothesis, we selected four large migraine pedigrees with common forms of migraine. Migraine was diagnosed according to IHS criteria. We focussed on pedigrees with different types of migraine where migraine semiology was highly uniform in affected members throughout a pedigree. Two pedigrees were diagnosed with migraine without aura and in two pedigrees all affected members suffered from migraine attacks with aura. Out of 35 family members tested 16 were classified as affected. There was no evidence of X-linked or maternal transmission by segregation analysis. Linkage analysis was performed using eight polymorphic markers, including the intragenic marker D19S1150, spanning the entire interval comprising the CACNL1A4 gene for linkage. Multiple recombination events between the migraine phenotype and the complete marker haplotype excluded this gene in all pedigrees to be involved in the pathogenesis of the disease. The strength of the study was, that we used large pedigrees each with sufficient power to detect or exclude linkage on its own. We carefully selected only pedigrees where the disease was found in uniform expression in each affected member.

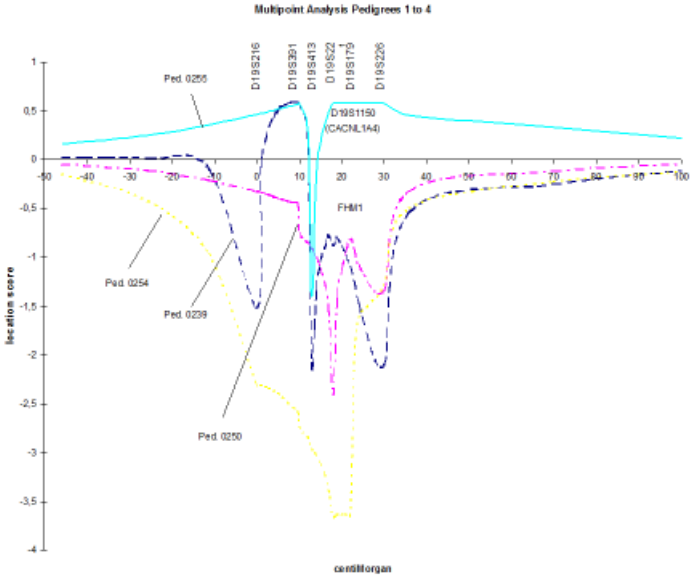

Fig. 1: LOD scores of the four families tested excluding linkage to the CACNA1A gene

*(**Wieser T**, Gräber S, Günther M, Leal S, Evers S, Zierz S, et al. Exclusion of Common Forms of Migraine in Four German Pedigrees from the FHM Region and the CACNL1A4 Gene on Chromosome 19p13. In: Olesen J, Bousser M-G, editors. Genetics of Headache Disorders. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 151-155).*

In this same set of families, we also excluded the FHM 2 locus on chromosome one as well as one pharmacologically interesting locus in the region of the serotonin receptor gene 1Db *(Published as poster: **Wieser T**, Gräber S, Evers S, Zierz S and Deufel T: Autosomal Dominant Migraine With and Without Aura: Exclusion of the FHM1, FHM2 and SHT 1db Locus In Four Multiplex Families. 9th Congress of the International Headache Society, June 1999, Barcelona, Spain).*

In summary, four migraine families with suspected high genetic load could not be linked to genes relevant for familial hemiplegic migraine using linkage analysis.

Linkage analysis is a statistical method and false negative as well as false positive findings cannot be ruled out, even when highest standards of study design are applied. Therefore, to further investigate the role of the CACNA1A gene in the common forms of migraine, we decided to perform mutation analysis in a large sample of migraine patients. The advantage of that approach is, that more robust results are obtained (mutation “yes” or “no”) and larger samples can be investigated. CACNA1A is a very large gene with 47 exons and a coding sequence of 6783 base pairs. Thus, mutation analyses by

direct sequencing of the entire gene was at that time not a feasible approach. We decided to screen for the six to date identified mutations, known to result in the FHM phenotype [43,51,52]. Further we screened the four exons (4,16,17 and 36) using single strand confirmation polymorphism technology for variations in their coding sequence. The respective exons were selected, because they had been known to harbor these disease causing mutations in FHM patients.

143 patients were diagnosed according to IHS criteria. 118 had migraine without aura, 21 had migraine with aura, 4 had migrainous headache not completely fulfilling all IHS diagnostic criteria (probable migraine according to later formulated classification criteria). The disease was transmitted most likely in an autosomal dominant fashion in the families of 29 patients, 55 had at least one first degree relative with migraine. All other had no other known family member with migraine headaches. The mutations R192Q, R583Q, T666M, V714A, V1457L and I1811L were not found in our patient sample; no other hitherto unknown mutation was found by screening the entire exons listed above known to contain most of the mutations known to date. Bearing in mind that the T666M mutation in particular is quite frequent in chromosome 19 linked families, we assumed that common forms of migraine are unlikely to share the same molecular pathology; yet, the possibility that they might be allelic disorders with mutations located in other regions of the CACNA1A gene could not entirely be ruled out.

*(**Wieser T**, Mueller C, Evers S, Zierz S, Deufel T. Absence of FHM mutations in common forms of migraine. Clinical Chemistry and Laboratory Medicine 2003;41(3):272-5)*.

2.1.2 Mitochondrial Mutations in Migraine

Dysfunction of the mitochondrial system is thought to play an important role in several neurodegenerative diseases, whereby mitochondrial dysfunction is closely associated with mechanisms of neuro-inflammation and the production of reactive oxygen species. Especially brain and muscle are highly dependent on oxidative metabolism and are therefore the most severely affected tissues in disorders, where mitochondrial dysfunction plays a pivotal role. A variety of morphological, biochemical, imaging and genetic studies have provided evidence that mitochondrial dysfunction may also play a role in migraine susceptibility [53]. Biochemical assays of platelets and muscle biopsies performed in migraine sufferers have shown a decreased activity of the respiratory chain enzymes. Reduced phosphocreatine levels, increased inorganic phosphate, and other abnormalities suggesting altered brain and skeletal muscle energy metabolism, have been demonstrated in migraine patients using phosphorus magnetic resonance spectroscopy (31P-MRS) of brain and skeletal muscle, implicating mitochondrial dysfunction [54,55]. Further evidence provides the

fact that in some classical disorders caused by mitochondrial dysfunction migraine like headaches are found as a typical feature. In MELAS Syndrome (**m**itochondrial **e**ncephalomyopathy, **l**actic **a**cidosis and **s**troke like episodes) and in MERRF (**m**yoclonus **e**pilepsy with **r**agged **r**ed **f**ibers) halfsided headaches are part of the clinical picture.

To address the question, whether migraine is possibly a mitochondrial disorder, we analysed the mitochondrial mutations 3243A->G, the so called "MELAS-mutation" and 8344A->G (to be found in up to 80% in MERRF patients) in 50 migraine patients. DNA was prepared from 10 ml blood by standard procedures. After DNA amplification with PCR and restriction analysis with the respective enzymes was performed to investigate the mitochondrial mutations. Neither mutation was found in our patient sample, giving no evidence for a substantial role of these two mutations in migraine pathophysiology.

However, this does not rule out a mitochondrial contribution to this complex phenotype. It is well known that the brain needs a continuous and sufficient supply of energy in the form of ATP in order to function efficiently. It is therefore highly feasible that any interruption in energy production could result in neuronal dysfunction and lower the threshold for initiation of a migraine attack. Since the fact that the mitochondrial genome encodes just a few proteins, thousands of proteins are still found within the mitochondria. The majority of the proteins are encoded by the nuclear genome and are transported into the mitochondria via membrane receptor proteins. Investigating just two mutations covered an important, but, alas, certainly only small aspect of mitochondrial dysfunction in migraine. *(Deschauer M, **Wieser T**, Zierz S. Investigation of Mitochondrial Mutations in Migraine. In: Olesen J, Bousser M-G, editors. Genetics of Headache Disorders. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 161-164, ISBN-13: 978-0781726481).*

2.1.3 Linkage Study X Chromosome

To analyze complex traits and to detect variation with only a small effect contributed by a single factor, a large sample size is a prerequisite. Bearing this in mind, we embarked on a collaborative project to study as many as 61 migraine families from Germany, Spain and the United States with the aim to identify a genetic locus for the common forms of migraine. Epidemiological studies have consistently revealed a post-pubertal and age-related female to male preponderance of 1: 2-3 for all forms of migraine [39,56,57]. This exceeds the possible influence of female hormones on disease [58] and remains largely unexplained. Observation of migraine families reveals a possible bias for transmission and MO probands of the less affected sex (males) have a higher proportion of affected first degree relatives [59,60]. These findings suggest the involvement of an X dominant genetic factor. This was

supported by evidence for linkage and allele sharing to Xq24-28 found in two Australian migraine pedigrees [61].

Based on these findings we designed our study to identify a X-chromosomal factor in common types of migraine, screening the entire X chromosome for linkage. Thirteen families were collected in Germany, nineteen in Spain and twenty nine in the United States of America. Families with male to male transmission were not investigated. The study comprised 454 members, the mean family size was 7,4 with mean 3,6 members per family affected. Twenty six were pure MO families with all affected members suffering from MO only, seven were pure MA families with all affected having MA; four families were diagnosed as FHM. The remaining twenty four families were "mixed" families with more than one type of migraine running in the pedigree. At first eighteen fluorescent labelled markers spaced on average 10 cM apart spanning the entire X-chromosome were screened using the Linkage Mapping Panel 28 by Applied Biosystems. A positive LOD score at Xp22 and allele sharing at Xq24-28 then prompted further evaluation of additional markers in both regions. A LOD score of 2.86 (at theta = 0.1) was obtained for marker DXS8051. Allowing for heterogeneity resulted in a HLOD of 2.80 with alpha being 0.29. DXS1223 (telomeric) and DXS987 (centromeric) were identified as the flanking markers defining the region of interests (LOD supported interval of 1.0) spanning approximately 7.5 cM according to the Sanger Center Chrom X Map. On the physical map this region of approximately 7 MB spans the interval from bp 7 365 655 to bp 14 154 191 according to the Sanger Center database. Non parametric single point lod score was 2.85 for DXS8051, indicating a new locus for common forms of migraine on Xp22.

The identified region contains a number of genes, of which some have been associated with human disease already like KAL1 (Kalmann-Syndrome, or Oral-Facial-Digital-Syndrome Type I). Also the voltage gated chloride channel CLCN4 is located in this region, which certainly is an intriguing finding, bearing in mind that all migraine genes identified so far have been ion channel genes.

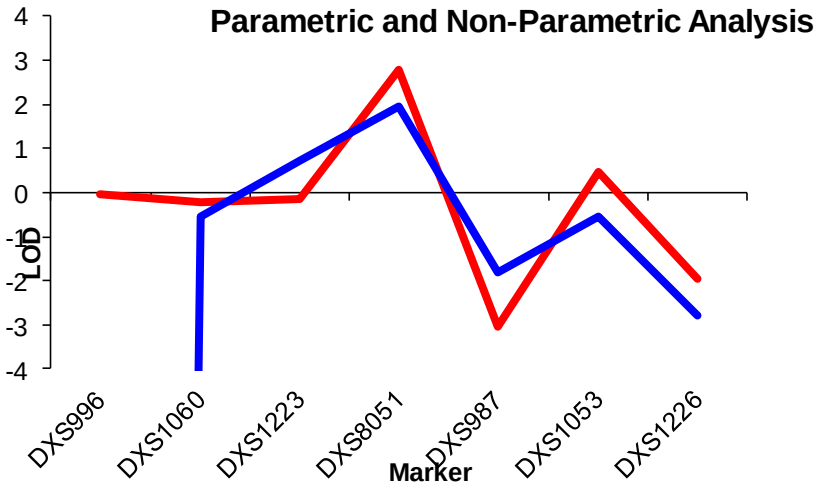

Fig.2: Lod scores for 61 families combined indicating linkage to Xp22

*(**Wieser T,** Pacual J, Oterino A, Soso M, Barmada M, Gardner KL A novel locus for familial migraine on Xp22. Headache 2010;50(6):955-962)*

2.1.4 Linkage Study Chromosome 4

Using the same set of families expanded by families with male to male transmission, we investigated a locus for migraine with aura on chromosome 4q24 which was described in 2002 in 50 Finnish migraine families [62]. Exclusion of this locus among 78 families of European and US-American descent suggested, that the finding may be restricted to the Finnish population and would be compatible with the expected genetic heterogeneity of migraine *(Published as poster: **Wieser T**, Pascual J, Barmada M, Soso M, Oterino A, Gardner K: Absence of linkage to the chromosome 4q24 Finnish migraine locus among 78 migraine families of European descent. Am J Hum Genet, 2001. Supp. 71 (4): 480)*.

2.1.5 Association Studies Using MTHFR and ACE Polymorphisms

Bearing in mind the concept of complex genetic diseases that one or possibly several genetic polymorphisms act in combination with environmental factors to produce a certain phenotype, it seems promising to investigate the possible interactions of gene variations deriving from one pathophysiologically important pathway. It can be expected that the interplay of multiple genetic variants could contribute to a much greater extent on disease susceptibility than any single variant on its own [63].

With the interaction between cranial blood vessels and the brain´s neural circuitry in mind, there is a rationale for investigating the potential role of genes affecting the vasculature, and their contribution

to the pathophysiology of migraine. The two most intensively investigated polymorphisms are the C66T polymorphism in the MTHFR gene and the I/E polymorphism in the ACE gene. Both enzymes are known to affect the vasculature and to change cerebral blood flow. MTHFR regulates circulatory homocysteine levels, which interact with endothelial cells. Experiments in animal models suggested that hyperhomocysteinemia might enhance the susceptibility to migraine by increasing the sensitivity of cerebral arteries. Angiotensin I converting enzyme involved in blood pressure regulation and electrolyte balance. It is further able to inactivate bradykinin, a potent vasodilator. A meta-analysis focusing on the C667T polymorphism in MTHFR established indeed an association of migraine with aura and the TT genotype, but this was not significant if only Caucasians were analysed [64]. Similar results were obtained for the ACE I/E polymorphism. It has been reported to be associated with migraine, however significant results could only be demonstrated in certain populations; when all studies were combined, results were no longer significant in Caucasians. Positive results in MA were being driven by a study in Asians and in MO by a study investigating a turkish population [64].

We conducted a study with the aim to confirm previous reports which showed, that functional variants of these two genes increase migraine susceptibility in combination [65]. We investigated the prevalence of the functionally relevant polymorphisms C667T in the MTHFR gene and I/D polymorphism in the ACE gene in 401 patients with migraine and compared the prevalence with that in 258 migraine-free controls using a chi square statistic and binary logistic regression.

Susceptibility to migraine was neither increased by each polymorphism on its own, nor in combination. In summary, we could not replicate a previous study that showed significant increase is migraine susceptibility for two polymorphisms in two genes affecting relevant pathways.

*(Essmeister R, Kress HG, Zierz S, Griffith L, Lea R, **Wieser T**. MTHFR and ACE Polymorphisms Do Not Increase Susceptibility to Migraine Neither Alone Nor in Combination. Headache 2016; 56(8):1267-73)*

3 Pathophysiology and Phenotypes

The concept of a paroxysmal neuro-vascular inflammation causing the migrainous headache is outlined above. Much of the recent progress in elucidating the molecular basis of migraine by molecular genetic studies is compatible with the concept of CSD. However, very little is known as to how and why these attacks are generated.

It was in a letter to Lancet as early as in 1932 that Phillips described pathological spontaneous nystagmus in a migraine patient and connected this clinical sign to cerebellar pathology [29]. Recent detailed clinical description of patients with familial hemiplegic migraine showed, that cerebellar signs can be found in 50 % of the pedigrees.

3.1 Own Research

3.1.1 Elektronystagmography

Careful clinical examination to exclude an underlying pathologic condition which is the cause of the headache is indispensable in the work up of headache patients. While investigating bulbar movement and checking for end-position gaze evoked nystagmus and convergence, we observed that patients with migraine displayed somewhat “nervous” eyes with frequent correction saccades and perturbed smooth pursuit eye movements (SPEM).

Following up on this clinical observation, we have investigated these patients by electronystagmography (ENG) with the aim to obtain specific findings between attacks that may provide a clinical sign reflecting continuous dysfunction of cerebellar or brain-stem structures involved in generating SPEM and possibly migraine attacks. We selected 25 patients with a mean age of 40 years suffering from migraine without aura. Interictal ENG was done with a mean interval of nine days since the last migraine attack along with two control groups matched by age and sex (one containing patients with chronic tension-type headache and the other comprising healthy probands). ENG recordings of saccades, spontaneous nystagmus, smooth pursuit eye movements, and optokinetic nystagmus were taken following standard procedures [30].

Velocity gain in smooth pursuit eye movements had a tendency to be delayed in migraine patients as compared to healthy controls as well as patients with chronic tension-type headache; yet, this parameter failed to reach statistical significance. Determining, the phase of eye movement, which represents the delay of eye position in relation to the target, however, resulted in a significant alteration unique to migraine patients.

Our observation of ENG alterations indicates a persistent brain-stem dysfunction. The importance of the brain stem for the genesis of migraine attacks has been outlined above. Despite the limited spatial resolution of PET it was shown that the foci of maximum increase of regional cerebral blood flow coincided with the anatomical structures of the dorsal raphe nucleus and the locus coeruleus, adjacent to the parapontine formatio reticularis, nucleus reticularis tegmenti pontis and pontine nucleus. These structures contain a high number of Purkinje cells discharging during pursuit at rates proportional to eye velocity and are important premotor centers responsible for the generation of saccades and smooth pursuit eye movements.

We concluded that persistent, interictal alterations of smooth pursuit eye movement are an electrophysiological expression of the suspected brain stem dysfunction in migraine patients. Intriguingly, such eye movement abnormalities are part of the clinical spectrum of inherited ataxias. Episodic ataxia type 2 and spinocerebellar ataxia type 6 are allelic conditions to hemiplegic migraine with mutations in CACNA1A. This links migraine with brain stem dysfunction, ataxia and possibly CACNA1A mutations.

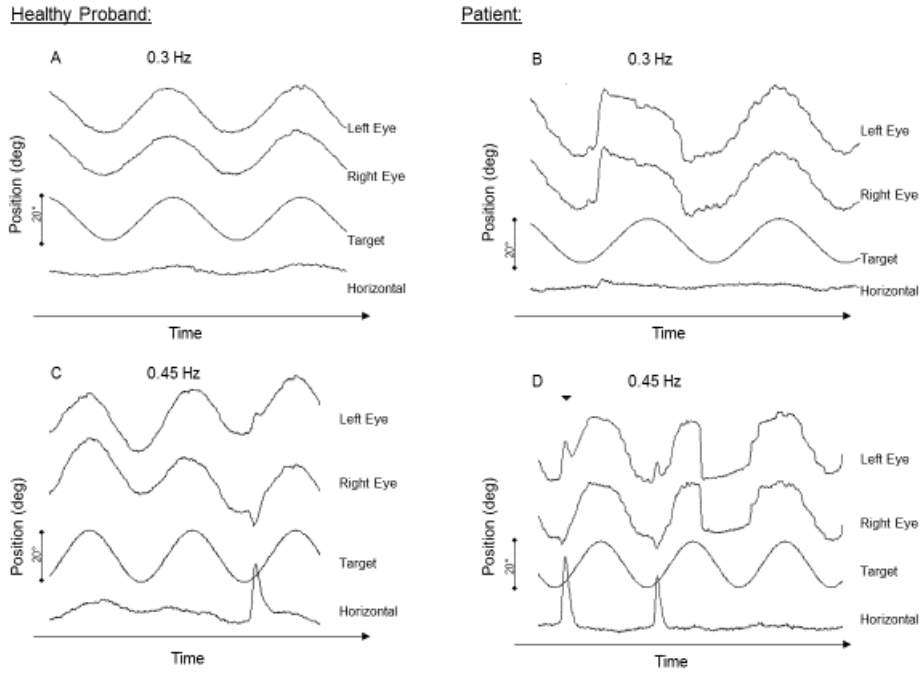

Fig.3: Recording of a patient compared to a healthy control, which clearly shows impaired smooth pursuit as suspected by our clinical observation.

*(**Wieser T**, Wolff R, Hoffman KP, Schulte-Mattler W, Zierz S. Persistent Oculomotor Disturbance in Migraine Without Aura. Neurological Sciences 2004; 25:8-12)*

4 Chronicity and Therapeutic Management

In a time dependent manner, pain is categorized as acute, sub-acute and chronic pain, with some variation in each category. Acute pain is defined as pain shorter than 30 days up to six weeks, sub-acute pain from one to six months and chronic pain from three to 12 months. While duration alone is certainly an important factor, other aspects of ongoing pain play an even greater role in patient care. So other definitions have been formulated like “pain that extends beyond the expected period of healing” [66] or “problematic pain” [67]. Chronic pain is significantly associated with other conditions (“co-morbidity”) like depression and anxiety. The longer the pain persists the more increases the burden and disability for the respective patient.

4.1 Somatic and Psychological Risk Factors

The processes behind chronicity of pain in general and in migraine are not well understood. Some risk factors for chronicity have been identified such as obesity, hypertension and stressful life events; psychological factors like chronic distress in daily life, depression, pain related cognition and coping behavior seem also to play an important role [68–70]. It is quite likely that genetic factors are also involved in pain chronicity. Altered sensitivity to drugs, comorbidity and behavioral peculiarities regarding drug intake, drug dependence, and possibly pain coping besides heightened pain sensitivity due to altered pain related neurotransmission pathways can be genetically modified. The latter are summarized under the terms “facilitation” and “sensitisation”, processes which can occur in the central nervous system but also locally in the peripheral nervous system, that is in the nerve endings, respectively. The molecular details of peripheral and central sensitization become more and more unveiled. Enhancing synaptic efficacy by altered transmitter release and response, leading to increased excitability of neurons and finally resulting in anatomic reorganization following nerve injury is the basic concept [71]. Genetic research to date has focused on genes involved in serotonergic neurotransmission like *SLC6A4*, *COMT*, *MAO A* and serotonin receptors, and also on dopamine, inflammatory mediators and opioid receptors, and deals largely with generalized pain syndromes like chronic widespread pain and fibromyalgia. Although results in some studies were significant, it could often not be confirmed and no single gene gave convincing evidence for a significant role in pain chronicity [72–74].

Besides these physiologic mechanisms, substantial evidence has been generated for the importance of psychological mechanism in pain chronicity in a number of excellent prospective studies, especially in low back pain research. These studies supported and expanded the concept of the bio-psycho-

social model of chronic pain, which acknowledges the importance of psychological as well as social/environmental factors in the propagation of pain and is to date the best construct for research in chronic pain [75,76,77].

In headache, there is much less evidence for the above described mechanisms for pain chronicity. Sensitisation has also been suspected [78,79], however experimental data are lacking. Studies showed that female sex, high frequency of headaches before transformation to chronic pain, obesity, stressful life events, hypertension and alcohol overuse, among others, are known risk factors for chronic headache [80]. 80% of chronic headache patients overuse analgesics. Although a risk factor, analgesic overuse on its own is neither necessary nor sufficient to induce chronicity.

In contrast to almost all other pain conditions, chronicity in migraine and tension type headache is defined by *frequency* additionally to duration with at least 15 days of headache per month for at least three months.

The classification criteria for "chronic migraine" (CM) have changed over time, which is relevant to the studies discussed below. While CM was not listed in the first classification of 1988 at all as a separate entity, it has been incorporated in the 2006 edition as a migraine complication. Diagnostic criteria required the presence of migraine without aura on 15 or more days per month during the last 3 months in the absence of medication overuse [36]. A revision in 2006 required migrainous headache only in 8 out of at least 15 days/month. In the latest version the absence of medication overuse is no longer a prerequisite. This allows the diagnosis of CM much more often; however the distinction of medication overuse headache and chronic migraine became somewhat blurred.

In parallel, starting already in the nineteen eighties an entity called "transformed migraine" (TM) was described to characterize a type of migraine that clinically changed, worsened, or become more complicated over time. Medication overuse is seen as part of the process in TM [81–83]. Debate about the relationship of chronic migraine and transformed migraine is still ongoing. For studies into chronicity the distinction is relevant, since TM takes a developmental factor into account. We therefore used for our investigations into risk factors of chronicity the definition of transformed migraine. Diagnostic criteria for CM and TM are shown in *Table 4*.

Table 4: Diagnostic criteria for transformed migraine and chronic migraine

	Transformed Migraine (according to [82])	Chronic Migraine (ICHD-III)
A	Daily or almost daily (>15d/month) head pain for > 1 month	Headache (tension-type-like and/or migraine-like) on >15 days per month for >3 months and fulfilling criteria B and C
B	Average headache duration >4 h (if untreated)	Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura
C	At least one of the following: 1. History of episodic migraine meeting any HIS criteria 1.1-1.6 2. History of increasing headache frequency with decreasing severity of migrainous features over at least 3 months 3. Headache at some time meets HIS migraine criteria 1.1–1.6 other than duration	On >8 days per month for >3 months, fulfilling any of the following: 1. criteria C and D for 1.1 Migraine without aura 2. criteria B and C for 1.2 Migraine with aura 3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D	Does not meet criteria for new daily persistent headache or hemicrania continua	Not better accounted for by another ICHD-3 Diagnosis
E	At least 1 of the following 1. There is no suggestion of one of the disorders listed in groups 5–11 2. Such a disorder is suggested, but it is ruled out by appropriate investigations 3. Such a disorder is present, but first migraine attacks do not occur in close temporal relation to the disorder	

4.2 Therapeutic Options

Regarding therapy, the implementation of an efficient regiment based on fast acting and effective acute relief medication is an important issue in the management of migraine patients; the treatment of the single migraine attacks should be accompanied by a long-term prophylactic pharmacotherapy, when certain prerequisites are fulfilled. Evidence based recommendations are formulated by national headache societies giving a choice of first and second line options. Almost as important as

the medication based treatment is the education of the patient regarding all aspects of the disease he or she is suffering from. This includes knowledge about the assumed pathophysiology, prognosis, therapeutic options and mechanisms of actions and possible side effects of medication. The better the patient is informed the better is adherence and compliance of the recommended therapies. Education and pharmacotherapy should be accompanied by measures of relaxation, stress reduction, certain changes of life style and the knowledge about non-medication based alternative therapies like acupuncture and sports among others. For some patients even invasive therapies (e.g. stimulation of the greater occipital nerve) can be an option, but careful selection of the patients is mandatory. Co-morbidities have to be acknowledged and respected in the therapeutic regimen, especially depression, which has been shown to be associated with migraine. For patients with exceptionally high burden of disease multidisciplinary-integrative programs should be offered [92].

4.3 Own Research

4.3.1 Psychological Risk Factors of Chronicity

To elucidate the influence of pain coping strategies on the course of headache we investigated patients with different kinds of headaches regarding pain coping behaviour, depression and somatic factors like use of acute relief medication. The concept of the study was to analyse the coping behaviour of headache patients according to the avoidance-endurance model formulated by Hasenbring et al. [84] and test for association with chronicity.

211 patients were included in the study. Headache diagnoses were based on ICHD-II, transformed migraine was diagnosed according the criteria published by Silberstein et al [82] (*see Table 4*).

Questionnaires were used to investigate coping strategies and depression. Patients completed the "Allgemeine Depressions-Skala", the German version of the Center for Epidemiologic Studies Depression Scale, a validated screening tool for depressive symptoms [85,86]. Pain coping behaviour, pain related cognitions and emotional reactions were assessed with the Kiel Pain Inventory (KPI). This is a validated tool to group pain patients with respect to their pain-related cognitions and coping behaviour evaluating both the fear-avoidance as well as the endurance pattern. Patients indicate on a seven point Likert scale (0 = never, 6 = always) the extent to which they experienced the respective feeling/ thought/behaviour. Several items of the KPI are grouped according to their respective aspect regarding pain coping and summed up scores composed. The *Avoidance of Social and Physical Activities Scale* is a 19 item scale assessing the tendency of patients to avoid physical activity and withdraw from their social context during pain. The *Catastrophizing Thoughts Scale* is a five item

scale describing the threatening aspects of pain. The *Thought Suppression Scale* consists of four items describing the appeal of not to think about the pain and to keep up. The *Behavioural Endurance Scale* comprises 11 items focusing on efforts to continue current activities despite pain. The *Minimization Scale*, consisting of four items, describes pain-related thoughts of minimizing the meaning of the pain during current activities. Only regarding behaviour patients are asked to differentiate between "strong" and "light" pain, so one can analyze whether they behave differently when suffering a milder headache attack (migraine) or episode (tension type headache) or stronger headache attack or episode. According to the "Avoidance–Endurance" model, subject to the level of occurrence (cut-off point is 3) of these differentiated reactions to pain on the cognitive, emotional and behavioural level, patients can be categorized into four coping styles: "depressive– avoidant", "depressive–suppressive", "elevated mood– suppressive" and "flexible coping with pain". The KPI does not require patients to experience pain at the time of administration. Concurrent and prospective validity have been studied in several longitudinal studies. It has also been shown that the KPI is a reliable instrument in headache patients [84,87].

Depression was high in the overall sample, with significant differences between patients with episodic and chronic migraine, as expected. Two thirds of all patients used dysfunctional coping strategies with high prevalence of "endurance" behaviour with differences between chronic and episodic headache types. Only a third of all patients (33%) used positive coping strategies with flexible reactions to pain (21% of patients with CTTH and 30% of patients with TM). There was neither a difference for pain intensity (Wilcoxon test: p=0.5) nor for pain frequency (ordinal logistic regression: p=0.4) in the entire sample when patients with functional and dysfunctional coping were compared. Further, against all theoretical assumptions, avoiding, endurance, minimization or thought suppression were not associated with higher pain frequency or pain intensity.

Against our hypothesis, differences in coping style between episodic and chronic forms of headache were not as different as expected. With these results at hand, we suggest that "disadvantageous" coping styles should be weighted differently in migraine compared to low back pain, where the use of active coping is certainly beneficial to avoid passivity and immobilization. In contrast, avoiding of activity showed a trend to lower frequency of pain in the patients of our study, but the statistical significance was lost when computing a multivariate logistic regression. As such, avoidance was not a pain reducing strategy.

Although avoiding and endurance are important risk factors for chronic low back pain, in headache, the avoidane-endurane model is not a suitable model to study the influence of psychological risk factors for chronicity in migraine or other types of headache.

*(**Wieser T,** Walliser U, Womastek I, Kress HG Dysfunctional Coping in Headache: Avoidance and Endurance are not Associated with Chronic Forms of Headache. Eur J Pain. 2012 Feb;16(2):268-77)*.

4.3.2 Genetic Risk factors for Chronicity/SLC6A4

Another factor in migraine chronicity might be altered pain processing, as for example mediated through the serotonergic system. Serotonin synaptic turn over (transcriptional activity and, in consequence, reuptake capacity) is genetically modified by several positive and negative regulatory elements within the *SLC6A4* promoter region [88]. Humans carry a common 44-base pair insertion/deletion polymorphism in the promoter region of the *SLC6A4* gene (serotonin transporter linked polymorphic region; 5-HTTLPR) that is found in two forms, long (l) and short (s). Individuals with either one or two copies of the s allele (40-70% of a given population) appear to have fewer serotonin transporters than individuals with an l/l genotype. Furthermore, the l/l genotype is associated with a 1.4 to 1.7 times increase in mRNA and an about two fold increase in uptake capacity [89]. The s-allele modulated the effects of stressful life events in the development of depression [90]. Interestingly, it had also been associated with a higher attack frequency in migraine patients [91]. We hypothesized that by influencing attack frequency the s-allele is a risk allele for migraine chronicity. Further, since it was shown before that high attack frequency is associated with depression, and the s-allele, independently, was also associated with depression, this genotype is also a risk factor for depression.

292 patients were included in the study. 253 patients (86%) were female; 58 had MA (20%) and 235 MO; the mean age of participants was 43.3 years. Mean attack frequency per month was 3.7, with 75% having 1 attack per week or less and 17% having between 4 and 10 attacks per month; 7 patients (2%) fulfilled the criteria for CM (more than 15 headache days/month). Depression was absent in 185 patients (63%), and mild depression was found in 60 (20%); 51(17%) patients had clinically relevant depression. No association of genotype was found with migraine subtypes MA ($c2 = 2.28$, d.f. = 2, $P = .32$) or MO ($c2 = 1.24$, d.f. = 2, $P = .54$). Multinomial logistic regression analysis did not produce evidence for association of the *5*-HTTLPR polymorphism with either *depression risk* or *migraine attack frequency* in 293 migraine patients, with all tests producing p-values >0.05. There was no significant difference in *migraine attack frequency* score between group L (2.05±0.05) and

group S (1.94±0.12). The mean score for l/l individuals (2.12±0.08) also did not differ from s/s, s/l individuals (1.98±0.06).

The present study, using a large cohort of German and Austrian headache patients, failed to confirm the hypothesis that was derived from results from earlier reports that a specific genetic background regarding the serotonergic system is an influencing factor on disease phenotype of either migraine or depression. The functionally relevant serotonin transporter gene polymorphism was not associated significantly with either migraine attack frequency or with presence or absence of depression in our patients and as such with chronicity.

*(**Wieser T**, Dressler K, Evers S, Gaul C, König D, Hölzl D, Berger K, Nyholt D, Deufel T No Influence of 5-HTTLPR Gene Polymorphism on Migraine Symptomatology, Comorbid Depression and Chronification. Headache 2010; 50(3): 420-430).*

4.3.3 Survey on Usage of Complementary Alternative Medicines

Frequently, patients rely on additional alternative medicines, to enhance their well being or to reduce the intake of medications. Not much is known how frequently, and what exactly our patients take additionally to our recommendations. So we took part in a survey to investigate the extend of complemental alternative medicines (CAM) in migraine and headache patients. 432 patients were investigated by a questionnaire regarding their usage of CAM. Use of CAM was reported by the majority of patients (81,7%). Most frequently used were acupuncture (58,3%), massage (46,1%) and relaxation technics (42,4%). “To leave nothing undone” and “to be active against the disease” were given as the most frequent motivations. As compared to non-users, CAM-users were of higher age, showed a longer duration of disease, a less intensity of headache, were more satisfied with conventional prophylaxis, and showed higher willingness to gather information about headaches. It is crucial to explore this behaviour in our patients, that we are able to encourage the patients in some things they try (like relaxation technics) and on the other hand prevent damage or unnecessary costs for possibly harmful medicines they are willing to try.
*(Gaul C, Eismann R, Schmidt T, May A, Leinisch E, **Wieser T**, Evers S, Henkel K, Franz G, Zierz S. 2009, Use of complementary and alternative medicine in patients suffering from primary headache. Cephalalgia 2009;29(10):1069-78)*

5 Summary

The studies summarised here were performed with the aims 1) to better understand the genetic basis of migraine, 2) to better define its clinical and pathophysiological spectrum, and 3) to identify factors that determine the course and severity of the disease. Investigations were done at a molecular level, using the methods of mutation and genetic linkage analysis in single patients and pedigrees and association studies in large, multi-centre study cohorts; clinical endo-phenotypes were defined to test neurophysiologic concepts. Finally, the problem of disease chronification is addressed studying psychological factors and, again, in molecular association studies of suspected genetic risk factors in the serotonin pathway.

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Liste der 10 relevanten Originalarbeiten der kumulativen Habilitationsschrift:

1. Evers S, **Wieser T**, Ringelstein EB. Genetik der Migräne. Nervenarzt 1996; 67(10):837-45

2. **Wieser T**, Wolff R, Hoffman KP, Schulte-Mattler W, Zierz S. Persistent Oculomotor Disturbance in Migraine Without Aura. Neurological Sciences 2004; 25:8-12

3. **Wieser T**, Gräber S, Günther M, Leal S, Evers S, Zierz S, et al. Exclusion of Common Forms of Migraine in Four German Pedigrees from the FHM Region and the CACNL1A4 Gene on Chromsome 19p13. In: Olesen J, Bousser M-G, editors. Genetics of Headache Disorders. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 151-155, ISBN-13: 978-0781726481

4. **Wieser T**, Mueller C, Evers S, Zierz S, Deufel T. Absence of FHM mutations in common forms of migraine. Clinical Chemistry and Laboratory Medicine 2003 ;41(3):272-5

5. Deschauer M, **Wieser T**, Zierz S. Investigation of Mitochondrial Mutations in Migraine. In: Olesen J, Bousser M-G, editors. Genetics of Headache Disorders. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 161-164, ISBN-13: 978-0781726481

6. **Wieser T,** Pacual J, Oterino A, Soso M, Barmada M, Gardner KL. A novel locus for familial migraine on Xp22. Headache 2010; 50(6):955-962

7. Essmeister R, Kress HG, Zierz S, Griffith L, Lea R, **Wieser T**. MTHFR and ACE Polymorphisms Do Not Increase Susceptibility to Migraine Neither Alone Nor in Combination. Headache 2016; 56(8):1267-73

8. **Wieser T**, Dressler K, Evers S, Gaul C, König D, Hölzl D, Berger K, Nyholt D, Deufel T. No Influence of 5-HTTLPR Gene Polymorphism on Migraine Symptomatology, Comorbid Depression and Chronification. Headache 2010; 50(3): 420-430

9. **Wieser T,** Walliser U, Womastek I, Kress HG. Dysfunctional Coping in Headache: Avoidance and Endurance are not Associated with Chronic Forms of Headache. Eur J Pain 2012;16(2):268-77

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Thesen

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Thesen zur Habilitationsschrift

"Clinical and Molecular Investigations on Migraine: Genetic Basis, Phenotypic Characteristics, Chronicity and Management"

Zur Erlangung des akademischen Grades
eines habilitierten Doktors der Medizin (Dr. med. habil)
für das Fachgebiet

Neurologie

Vorgelegt
der Medizinischen Fakultät
der Martin-Luther-Universität Halle-Wittenberg

von Thomas Alexander Wieser

geboren am 12. August 1964 in München

1.) Migräne ist eine komplexe genetische Erkrankung. Aus Zwillingsstudien wird angenommen, dass der genetische Anteil an der Erkrankung zwischen 45% und 60% liegt. Nur die sehr seltene Unterform der hemiplegischen Migräne (die sog. Familiäre Hemiplegische Migräne) wird autosomal dominant vererbt. Insgesamt wird von großer genetischer Heterogenität bei Migräne ausgegangen. Es finden sich allein für die familiäre hemiplegische Migräne bereits drei verschiedene Gene, in denen Mutationen zum Ausbruch der Erkrankung führen; und auch dies auch nur in 50% der untersuchten Familien. Bei ca. 50% der Familien mit dieser Diagnose bleibt die Ursache noch unbekannt. Für die überaus häufige Migräne ohne Aura und Migräne mit Aura konnte bislang noch kein krankheitsauslösender Gendefekt nachgewiesen werden. In großen genomweiten Assoziationsstudien konnten eine Vielzahl von Genloci identifiziert werden, deren weitere Erforschung noch ansteht. Somit muss zunächst die Frage gestellt werden, ob es sich bei den verschiedenen Unterformen der Migräne um allelische Krankheiten oder um genetisch distinkte Entitäten handelt (genetische Heterogenität).

2.) Zur Erforschung der genetischen Ursachen von Migräne können verschiedene Methoden und Ansätze gewählt werden. Mittels Linkage Analysen können Gen-Orte (Loci) identifiziert werden, die für die Erkrankung relevante genetische Veränderungen (Mutationen, Deletionen, Duplikationen, etc.) enthalten. Mit dieser Methode ist es auch möglich, die Rolle bereits bekannter Gene oder Gen-Orte in neuen Familien oder auch größeren Studienpopulationen zu untersuchen. In Assoziationsstudien können bekannte genetische Polymorphismen mit der Erkrankung oder mit lediglich gewissen Merkmalen (Häufigkeit, Typ, Begleiterkrankungen) assoziiert werden und dadurch Aufschluss zur Pathophysiologie liefern. Mittels Mutationsanalysen können direkt krankheitsauslösende Veränderungen in bekannten Genen identifiziert werden.

3.) Wir haben zunächst vier Familien mit den häufigen Migräneformen Migräne ohne Aura (n=2) und Migräne mit Aura (n=2) identifiziert und exakt analysiert. In allen vier Stammbäumen zeigten sich von der Krankheit Betroffene in jeder Generation. Somit war der Vererbungsmodus in diesen Stammbäumen mit einem autosomal dominanten Erbgang vereinbar. Die Familien unterschieden sich von familiärer hemiplegischer Migräne zum einen dadurch, dass keine Aura vor den Kopfschmerzen auftrat (n=2) oder nur typische Auren vor den Kopfschmerzen zu verzeichnen waren (n=2). Somit stellte sich die Frage, ob autosomal dominant erbliche Migräne ohne hemiplegische Auren genetisch mit klassischer familiärer hemiplegischer Migräne verwandt ist. Mittels Linkage-Analyse wurde untersucht, ob die

bekannten Genveränderungen für FHM 1 (CACNA1A-Gen) und FHM 2 (ATP1A2) in unseren Familien eine Rolle spielen. Dies konnte ausgeschlossen werden, und ergab somit einen ersten Hinweis darauf, dass sich familiäre hemiplegische Migräne von den häufigen Migräneformen genetisch unterscheidet, insbesondere auch dann, wenn die Krankheit dominant vererbt wird.

4.) Etwa bei der Hälfte aller Familien mit familiärer hemiplegischer Migräne, deren genetische Ursache eruierbar ist, finden sich Mutationen im CACNA1A Gen und die Erkrankung ist somit als FHM 1 zu klassifizieren. Bei 40% davon findet man die Mutation Thr666Met. Die klinische Präsentation von Migräne-Attacken in FHM Familien ist hoch variabel. So finden sich bei betroffenen Patienten ebenso Migräne-Kopfschmerzen, die ohne Aura auftreten. Um eine genetische Überlappung von FHM mit sogenannter gewöhnlicher Migräne (damit werden die häufigen Formen Migräne ohne Aura und Migräne mit Aura zusammengefasst) auszuschließen wurden 143 Patienten mit gewöhnlicher Migräne auf die Mutation Thr666Met und drei weitere häufige Mutationen untersucht und die entsprechenden Exone auf genetische Varianten gescreent. Weder bekannte noch bislang nicht beschriebene Mutationen konnten in diesem großen Kollektiv gut charakterisierter Patienten mit Migräne gefunden werden. Somit konnte gezeigt werden, dass familiäre hemiplegische Migräne und „gewöhnliche“ Migräne genetisch distinkte Entitäten sind.

5.) Einige Aspekte der Migräne deuten auf eine mitochondriale Dysfunktion hin. Zwei „klassische“ mitochondriale Erkrankungen, das MELAS Syndrom und das MERFF Syndrom, haben Kopfschmerzen als signifikantes klinisches Merkmal. Bei unserer Untersuchung in 50 Patienten mit Migräne fand sich weder die MELAS Mutation 3243A->G noch die Mutation 8344A->G, die in 80% der MERFF Fällen nachzuweisen ist. So können wir mit hoher Wahrscheinlichkeit ausschließen, dass Migräne-Kopfschmerzen Ausdruck dieser beiden definierten mitochondrialen Erkrankungen sind.

6.) Bei Migräne sind Frauen häufiger betroffen als Männer. Dieser Unterschied lässt sich nicht alleine auf hormonelle Faktoren zurückführen. Eine genaue Analyse des Vererbungsmodus in Familien mit Migräne zeigt Vereinbarkeit mit einem X-dominanten Erbgang. Somit ist ein auf dem X-Chromosom lokalisierter genetischer Faktor eine mögliche Erklärung für diese Ungleichheit in der Betroffenheit der beiden Geschlechter. Um diese Hypothese zu bestätigten, untersuchten wir in einer internationalen Kollaboration 61 Familien mit Migräne (teils ohne Aura, teils mit typischen Auren, teils mit hemiplegischen Auren) auf einen X-

chromosomalen Faktor. Mit einem LOD Score von 2,86 für den Marker DXS8051 konnten wir einen neuen Locus auf Xp22 identifizieren und damit unsere Hypothese bestätigen.

7.) Chronifizierung ist bei Kopfschmerzerkrankungen nicht allein über die Dauer der Erkrankung definiert, da viele primäre Kopfschmerzen per se über einen langen Zeitraum bestehen. In die Definition der Chronifizierung geht deshalb zusätzlich die Kopfschmerzfrequenz ein. Die Ursachen von Chronifizierung sind weitgehend unbekannt. Genetische Faktoren könnten bei diesem Prozess eine Rolle spielen. Chronische Schmerzen, insbesondere auch die Migräne, sind in hohem Ausmaß von einer depressiven Verstimmung begleitet (Co-Morbidität). Ein funktional relevanter Polymorphismus im Serotonintransporter Gen (SERT) konnte mit der Frequenz von Migräneattacken in einer japanischen Patientengruppe korreliert werden. In davon unabhängigen Untersuchungen konnte gezeigt werden, dass derselbe Polymorphismus auch für die Ausprägung der Erkrankung Depression eine Rolle spielt. Wir prüften daher die Hypothese, dass eine genetische Variante, die zum einen Einfluss auf die Migräneattacken-Frequenz hat und zum anderen die Ausprägung einer Depression begünstigt, ein relevanter Faktor in dem Prozess der Chronifizierung von Migräne darstellt, die ja durch eine hohe Attackenfrequenz definiert ist und in der Regel von einen Depression begleitet ist. Im Ergebnis unserer Studie konnten wir einen solchen Zusammenhang nicht feststellen. Das Risiko - S - Allel war nicht signifikant mit chronischer Migräne assoziiert.

8.) Neben möglichen genetischen Faktoren ist die Rolle psychologischer Faktoren im Prozess der Schmerz-Chronifizierung mehrfach belegt. So konnte für psychologische Faktoren wie Angst, charakteristisches Verhalten (Vermeiden) oder dysfunktionale Schmerzbewältigung nachgewiesen werden, dass sie beim Prozess der Chronifizierung von Schmerzerkrankungen eine Rolle spielen. Derartige Zusammenhänge sind besonders gut für den Rückenschmerz untersucht. Das Avoidance-Endurance Modell von Hasenbring hat eine hohe Aussagekraft dahingehend, ob Patienten mit bestimmten Mustern in ihrer Schmerzbewältigung einen chronischen Rückenschmerz entwickeln. Für uns stellte sich nun die Frage, ob dieses Modell auf den Chronifizierungsprozess von Kopfschmerzen übertragen werden kann. Wir konnten zeigen, dass Kopfschmerz-Patienten zum großen Teil (60%) dysfunktionale Schmerzbewältigungsstrategien verwenden. Somit sollten in der Behandlung von Patienten mit Migräne oder Kopfschmerz vom Spannungstyp frühzeitig auf entsprechende psychologische Risikofaktoren geachtet werden.

9.) Für den Rückenschmerz konnte herausgearbeitet werden, dass insbesondere Vermeidungs- und Durchhaltestrategien (Avoidance/Endurance) negative Auswirkungen haben und einen Risikofaktor der Chronifizierung darstellen. Für den Rückenschmerz wird vermutet, dass in Folge von „Vermeidung“ eine Dekonditionierung einhergehend mit Muskelabbau auftritt. In Konsequenz kommt es zu Überbelastung entsprechender Strukturen und zu mehr Schmerz. Dieses Konstrukt kann für Kopfschmerzen, insbesondere Migräne keine Bedeutung haben, da muskuläre Vorgänge in der Pathophysiologie keine Rolle spielen. Vermeiden findet sich zwar häufig, ist aber z.B. dadurch zu erklären, dass, wie schon in den klinischen Kriterien festgehalten, Aktivität zu Schmerzverstärkung führt. Dass dadurch mittelfristig eine Attackenhäufung induziert wird, ist nicht anzunehmen. Analog soll „Durchhalten“ über muskuläre Überbelastung zu Schmerzverstärkung führen. Auch dieser Mechanismus kann für Migräne keine Bedeutung haben. „Durchhalten“ fand sich in unserer Untersuchung ebenfalls häufig, und häufiger bei chronischen Patienten. Am ehesten ist der Zusammenhang jedoch in dem dadurch erheblich erhöhten Stress-Niveau des Patienten zu sehen. Stress ist ein bekannter Auslösefaktor für Kopfschmerz und Migräneattacken. Ein erhöhtes Stress-Niveau kann über diesen Weg zu häufigeren Attacken führen und dadurch zu Chronifizierung. Zusammengefasst muss festgestellt werden, dass aufgrund krankheitsspezifischer Eigenschaften das Avoidance-Endurance Model von Hasenbring zur Rolle von psychologischen Risikofaktoren der Chronifizierung von Rückenschmerzen auf Kopfschmerzerkrankungen nur teilweise übertragbar ist.

10.) Funktionelle Bildgebung lokalisiert einen Ausgangspunkt für Migräne in bestimmten Arealen des Hirnstammes. Topographisch finden sich dort neuronale Strukturen unter anderem zur Koordination langsamer Augenfolgebewegungen (Smooth Pursuit). In der klinischen Untersuchung von Patienten mit Kopfschmerzen war auffallend, dass ausschließlich Patienten mit der Diagnose Migräne bei Untersuchung der Bulbusmotilität und der Blickfolge Auffälligkeiten zeigten. Dieses Phänomen wurde mittels Elektronystagmographie untersucht. In der Tat ließen sich signifikante Abweichungen bei Untersuchung der langsamen Aufgenfolgebewegungen bei Patienten mit Migräne im schmerzfreien Intervall nachweisen. Wir interpretierten diese als Ausdruck einer anhaltenden Pathologie im Hirnstamm im Bereich des Migräne-Generators.

Tabellarischer Lebenslauf

Geboren am 12.8.1964	in München
	Eltern Jutta und Ernst Wieser, Dipl.-Ing.,
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1980 – 1988	Mitglied der Nationalmannschaft Eiskunstlauf
1981; 1987	5. Platz Juniorenweltmeisterschaft; Deutscher Vizemeister
1984	Hochschulreife (Abitur), Pestalozzi-Gymnasium München
1984 – 1986	Zeitsoldat d. Bundeswehr, Sportfördergruppe
1987 – 1994	Studium Humanmedizin, Ludwigs-Maximilians-Universität, München
1996	Promotion „magna cum laude“ zum Dr. med., LMU München

Beruflicher Werdegang

1.7.1994 bis 31.12.1995	Arzt im Praktikum und Beginn der Weiterbildung im Fach Neurologie, Klinik und Poliklinik für Neurologie, Westfälische-Wilhelms-Universität Münster (Dir.: Prof. Dr. med. B. Ringelstein)
15.1.1996 bis 31.3.2004	Wiss. Mitarbeiter und Assistenzarzt in Weiterbildung, Klinik und Poliklinik für Neurologie, Martin-Luther-Universität Halle/Wittenberg (Dir.: Prof. Dr. med. S. Zierz), Aufbau und Leitung der Kopfschmerzambulanz; Strahlenschutzbeauftragter
30.6.2003	Anerkennung zum Facharzt für Neurologie
1.4.2004 bis 31.7.2006	Klinik für Neurologie, Medizinische Universität Wien, mit Tätigkeit in der Schmerzambulanz der Abteilung für Anästhesie und Allgemeine Intensivmedizin B zur Ausbildung zum Schmerztherapeut (Leiter Prof. Dr. HG Kress); Fortbildungsbeauftragter der Abteilung
1.8.2006 bis 31.1.2014	Oberarzt an der Klinik für Neurologie, Krankenhaus Göttlicher Heiland Lektor an der Medizinischen Universität Wien im Fach Neurologie Leiter des klinischen Schwerpunktes Schmerz (Etablierung einer Schmerzambulanz und Einrichtung einer stationären multimodalen

	Schmerztherapie für chronische Schmerzpatienten) Leitung der Stroke-Unit (4 Betten) Mitglied im Arbeitskreis Qualitätssicherung
28.3.2007	Zusatzbezeichnung „Spezielle Schmerztherapie“
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Wissenschaftlicher Werdegang

1990 – 1996	Dissertation „Analyse der Mutationen in Exon 11 des CFTR-Gens in der süddeutschen Patientenpopulation“, Betreuer: Prof. Dr. A.A. Roscher, Universitätskinderklinik München
1994 – 1995	als Arzt im Praktikum, Neurologische Universitätsklinik Münster: - Mitarbeit an einer großen Studie zur Sekundärprophylaxe des Schlaganfalls (Acetylsalicylsäure versus Piracetam) (Prof. Grotemeyer) - Mitarbeit in der dortigen Kofpschmerzspezialsprechstunde (Prof. Evers) - Teilnahme an wissenschaftlichen Studien bei primären Kopfschmerzsyndromen - Beginn der genetischen Arbeiten über familiäre Formen der Migräne (Prof. Dr. Evers, Prof. Dr. Deufel)
15.1.1996 – 1.4.2004	als wiss. Mitarbeiter, Neurologische Universitätsklinik Halle: - Aufbau einer Kopfschmerzambulanz und einer regelmäßigen interdisziplinären Schmerzkonferenz - Aufbau des Molekularbiologischen Labors der Klinik und einer Arbeitsgruppe zu Genetik und Pathophysiologie des Kopfschmerzes; Fortführung der Arbeiten über familiäre Migräne; - Botulinumtoxin bei chronischem Spannungskopfschmerz; - Psychosoziale Risikofaktoren der Schmerzchronifizierung (mit Dr. U. Walliser, Psychosomatik MLU Halle); Augenbewegungsstörungen bei Migräne; - Wissenschaftliche Arbeiten zur Molekulargenetik von metabolischen Myopathien (Carnitin Plamityltransferase Mangel, mitochondrialen Myopathien, autosomal dominanter Ataxie (ADCA III) und PROMM (mit Prof. Dr. T. Deufel, Univ. Jena)
Sept. 2000 – Mai 2001 und Sept. 2001 – Feb. 2002	Forschungsaufenthalt (Post Doc) Arbeitsgruppe Prof. K. Gardner, Department of Neurology, University of Pittsburgh: Betreuung einer internationalen, multizentrischen Studie zur Genom-weiten Suche nach neuen Migräne-Loci; Familiengenetische Untersuchungen zur Kartierung neuer Migräne-Loci an eigenen und amerikanischen Stammbäumen

- Charakterisierung eines neuen Lokus für familiäre Migräne auf dem X-Chromosom
- Identifizierung eines neuen Lokus für ein Dystonie/Kopfschmerz-Syndrom auf Chromosom Xq28

April 2004 – Juli 2006

Als Facharzt für Neurologie an der Klinik für Neurologie, MUW/AKH Wien, Tätig in der Schmerzambulanz des AKH Wien, Abteilung für Spezielle Anästhesie und Schmerztherapie:

- Weiterführung der molekulargenetischen Arbeiten zur Migräne (Migräne und Depression) und metabolischen Myopathien (CPT und Maligne Hyperthermie)
- Förderung der wissenschaftlichen Tätigkeit durch Österreichischen Nationalbankfond Jubiläumsfond (ONB12107) und Stiftung für Pathobiochemie und Molekulare Diagnostik
- In Zusammenarbeit mit der Kopfschmerzambulanz der Universität Halle Untersuchung zum Gebrauch alternativer Behandlungsformen bei Kopfschmerzen (mit Dr. C. Gaul, Univ. Essen)

August 2006 – Januar 2014

Als Oberarzt Neurologie im Krankenaus Göttlicher Heiland/Wien:

- Leitung der Stroke Unit, Leitung des Abteilungsschwerpunktes Schmerz
- Weiterführung der molekulargenetischen Arbeiten zur Migräne (Assoziationsstudien MTHFR und ACE Gen mit Prof. HG Kress und Prof. L Griffith)
- Rekrutierung von Patienten mit ischämischen Schlaganfall für IST-3 (The third international stroke trial (IST-3) of thrombolysis for acute ischäemic stroke)
- Rekrutierung von Patienten mit ischämischen Schlaganfall für die Studie „Endovascular treatment of acute ischemic stroke in Vienna“

Seit Februar 2014

Chefarzt der Abteilung für Neurologie 2 am AWO-Fachkrankenhaus Jerichow

- Aufbau einer stationären Abteilung für Schmerztherapie für zur Behandlung schwerst chronifizierter Schmerzpatienten gemäß OPS
- Aufbau einer interdisziplinären Schmerzkonferenz im Jerichower Land
- Verantwortlich für die Fortbildung der im Hause tätigen Assistenzärzte

Mitgliedschaft in Fachgesellschaften

- Deutsche Gesellschaft für Neurologie
- Deutsche Migräne und Kopfschmerzgesellschaft (Von 2000 bis 2004 Regionalbeauftragter für Sachsen-Anhalt)
- Verein für Neurologie und Psychiatrie, Wien
- Deutsche Schmerzgesellschaft

Wissenschaftliche Kooperationen

- Prof. Dr. T. Deufel, Institut für klinische Chemie und Laboratoriums-diagnostik, FSU, Jena (PROMM, familiäre Migräne, ADCA III)
- Prof. R. Krahe, Anderson Cancer Center, University of Texas, Houston, USA

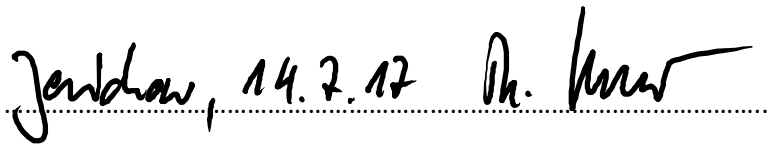
(PROMM)
- Dr. U. Walliser, Klinik für Psychosomatik und Psychotherapie, MLU Halle (Psychosoziale Risikofaktoren der Schmerzchronifizierung)
- Prof. K. Gardner, Department of Neurology, University of Pittsburgh USA (Genetik familiärer Migräne)
- Prof. HG Kress, Universität Wien, Österreich (Genetik der Migräne, Maligne Hyperthermie)
- Prof. D. Nyholt (Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Brisbane, Queensland 4029, Australia)
- Prof. L. Griffith und L. Rod (Genomics Research Centre, Institute of Health and Biomedical Innovation, QUT, Brisbane, Australia)

Berlin, 14.7.17 .....

(Ort/Datum/Unterschrift)

Selbstständigkeitserklärung:

Hiermit wird versichert, dass ich diese Habilitationsleistung selbstständig verfasst habe und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt habe.



(Ort/Datum/Unterschrift)

Erklärung über frühere Habilitationsversuche

2009 habe ich um die Erteilung der Venia Docendi für das Fach Neurologie an der Medizinischen Universität Wien ersucht.

Mit Beendigung meines Aufenthaltes in Wien habe ich um Einstellung des bis dahin noch nicht abgeschlossenen Verfahrens gebeten. Der entsprechende Nachweis der Einstellung des Verfahrens liegt vor.

Andere frühere oder abgelehnte Verfahren bestehen nicht.

An keiner anderen Fakultät oder Universität ist aktuell ein Habilitationsverfahren anhängig.

Innsbruck, 14.7.17 .....

(Ort/Datum/Unterschrift)

Danksagung

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