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GENOMICS RESEARCH CENTRE

Neurogenomics for Personalised Treatment of Migraine, Stroke and Epilepsy

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IHBI Research Themes

Health Determinants and Health Systems

Injury Prevention and Trauma Management

Chronic Disease and Ageing

Prevention Intervention Translation

>1200 researchers

Research Focus

- **Cancer research**

  - Prostate, breast, ovarian, skin and lymphoma

- **Cardiovascular disease and diabetes**

- **Mental health and neurological research**

- **Dementia and Ageing research**

- **Vision research**

Migraine

- Migraine is a frequent, debilitating and painful disorder that affects a large proportion of the population
- No laboratory based diagnostics and current treatments exhibit variable efficacy
- Migraine affects
  - 4% of children,
  - 6% of men, and
  - 18% of women

Stewart WF, et al (1992) Prevalence of migraine headache in the United States. JAMA 267: 64-69

Migraine Classification

- Recurrent attacks of headpain widely variable in intensity, frequency and duration
- nausea, vomiting, photophobia & phonophobia

Migraine without Aura

- recurrent headaches , 4-72 hours duration
- usually unilateral and pulsating

Migraine with Aura

- recurrent headaches, 4 - 72 hours duration
- preceded or associated with neurological symptoms such as visual disorders, unilateral numbness , weakness, speech defects

Migraine Genes

- shows strong familial aggregation
- RR (1.5-3.8), Twin heritability 40-65%
- complex disorder, environmental triggers
- MA and MO within same families and same individual
- Co-morbidity with several disorders eg epilepsy, CVD and depression – indicating potential shared genetic factors
- Number of genes unknown at present

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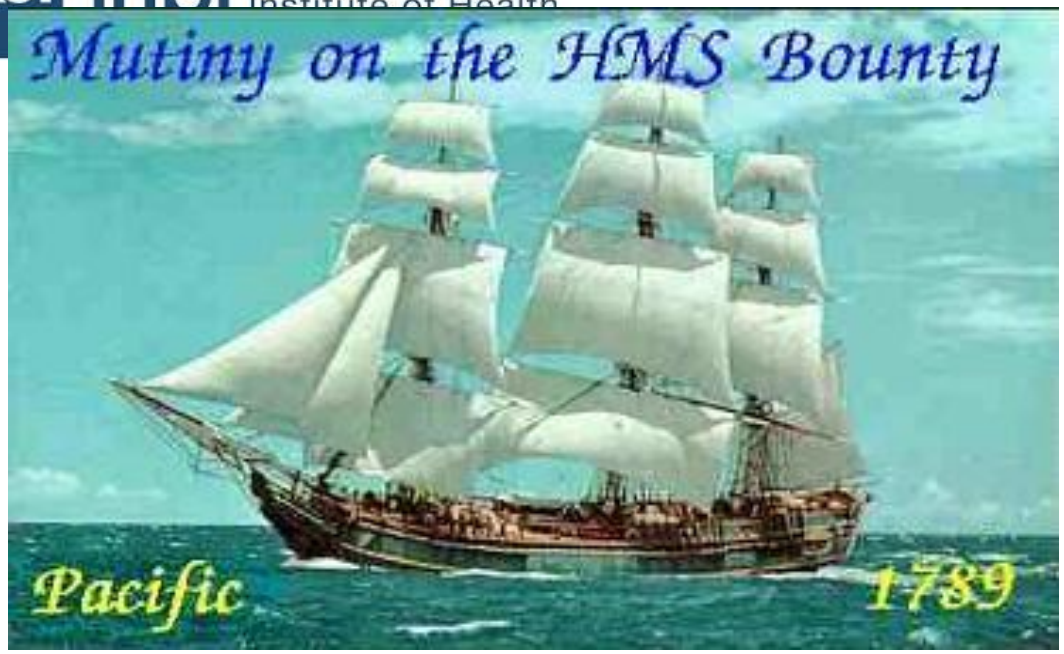
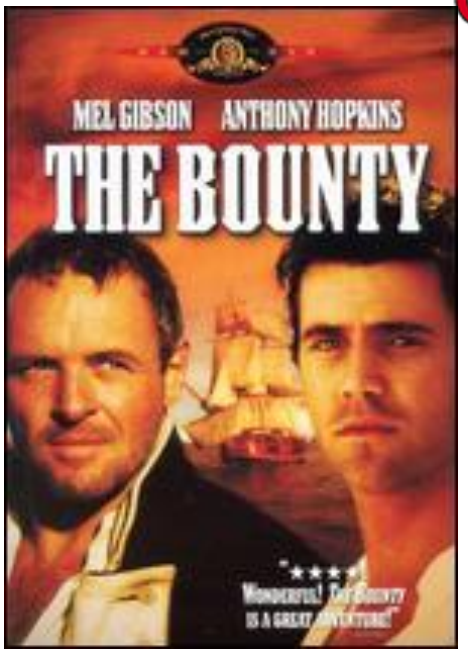
Study Populations

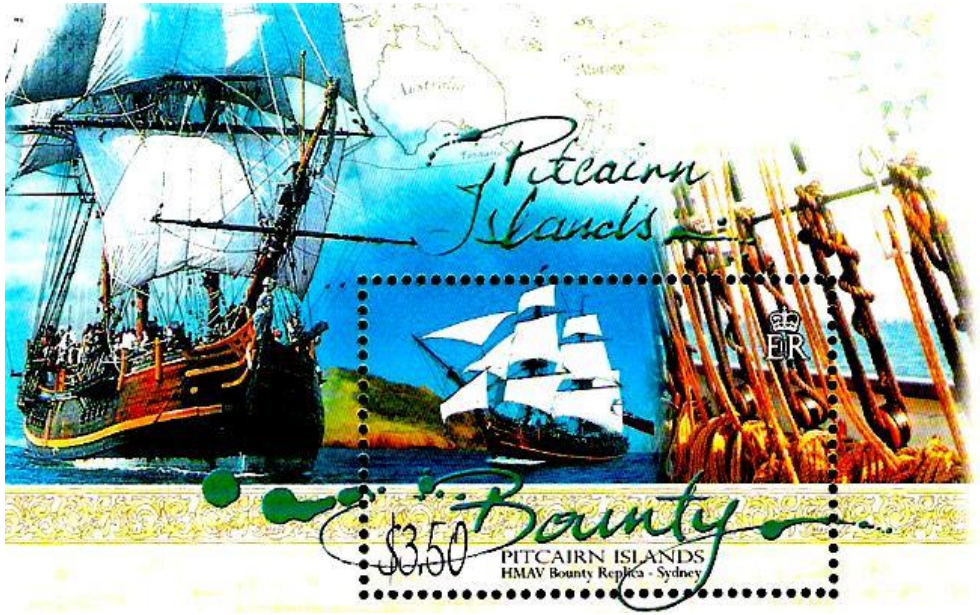
- **Cross-Sectional - case versus control**
  - **Affected 275 - Unaffected 275: ii) 300-300 iii) 500+/-**
  - **Age, sex and ethnicity matched**
  - **History, at least one affected relative**
  - **68% female, 63% MA**
- **Pedigrees - family linkage approach**
  - **>100 pedigrees, 15 with > 8 affected ascertained**
  - **av 12 affected, range 8-21; 12-55 total individuals**
  - **67% female, 68%MA**

Diagnosis using IHS Criteria


Mutiny on the HMS Bounty
Pacific
1789


MEL GIBSON
ANTHONY HOPKINS
THE BOUNTY


CLARK GABLE AS THE DARING MUTINEER IN THE SCREEN'S MOST EXCITING ADVENTURE STORY!
MUTINY ON THE BOUNTY
CHARLES LAUGHTON
CLARK GABLE
FRANCHOT TONE
HERBERT MUNDIN


Pitcairn Islands
Bounty
$3.50
PITCAIRN ISLANDS
HMAV Bounty Replica - Sydney

Norfolk Island Project

- Geographically remote, isolated population with known founder effect and well-defined family groupings
- Strong family groupings and well documented family histories
- 12 generational pedigree involving ~6300 Individuals- going back to 1780's
- Many of the current population can trace ancestry back to Pitcairn Island
- Limited number of original founders
  - 12 Maternal (Tahitian)
  - 9 Paternal (*Bounty* mutineers)

Migraine Molecular Genetics

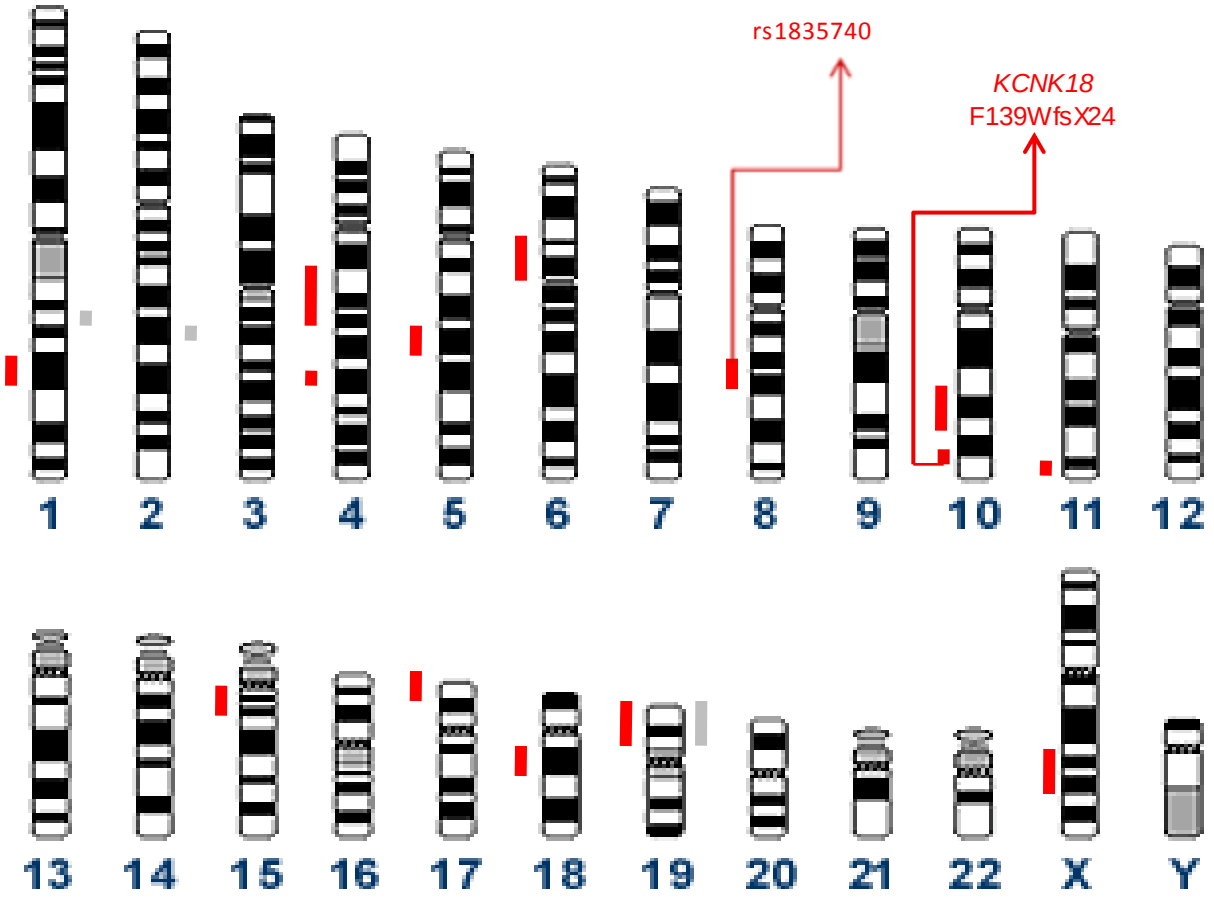


Figure. Genomic regions reporting significant evidence of linkage to migraine phenotypes (red) and FHM (blue). Migraine FHM

FHM Implicated Loci

- **FHM- severe, rare autosomal dominant form of migraine**
- **FHM1 mapped to C19 with mutations in a PQ calcium channel gene implicated - *Ophoff et al 1996, Cell***
- **FHM2 mapped to 1q23 with mutations in an ATPase gene implicated - *De Fusco et al 2003, Nature Genetics***
- **FHM3 mapped to 2q24 ,voltage gated sodium channel gene, SCN1A - *Dichigans et al 2005, Lancet***
- **NATA accredited diagnostic testing since 1999**

FHM Types 1, 2 and 3

- Familial Hemiplegic Migraine Types 1, 2 and 3
- FHM is considered a subtype of migraine with aura
- In addition to aura (sensory disturbances) FHM manifests with several more severe symptoms
- These include hemiparesis (one sided paralysis), deafness, nystagmus (involuntary eye movement), retinal degeneration and coma.
- Linked to mutations in CACNA1A, ATP1A2 and SCN1A

CACNA1A
Episodic Ataxia Type 2 (EA2)

- Genetic disease primarily characterized by episodes of poor balance and coordination.
- Episodes can be precipitated by trauma, stress or chemical triggers (e.g. caffeine)
- Additional symptoms include partial paralysis, migraine, altered vision, slurred speaking, tinnitus, nausea.
- Has an effective treatment in the form of acetazolamide.
- Caused by mutations in CACNA1A

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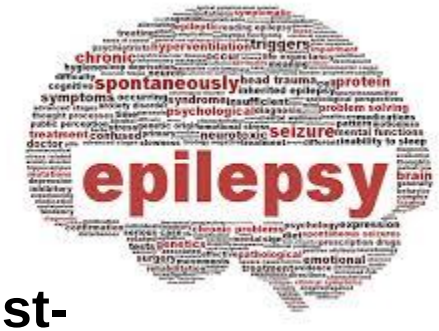
SCN1A and Genetics in Epilepsy

- Migraine and epilepsy are disorders that are common, paroxysmal, chronic and both are strongly heritable disease.

- "Migralepsy" describes a syndrome of migraine with aura immediately followed by an epileptic seizure.



- Co-morbidity - epilepsy patients with two or more first-degree affected relatives a 2-fold increase in the risk of having migraine with aura.

- Mutations in SCN1A gene can cause FHM3 and epilepsy, in particular Dravet syndrome, a common pediatric epilepsy.

Dravet Syndrome

- Important to define causative mutations for pediatric epilepsy to define appropriate treatment
- Some medications specifically anti-convulscants eg tegratol, dilantin can exacerbate Dravet as they are sodium channel blockers and should be avoided if SCN1A loss of function mutations are involved
- Good but expensive treatment, stiripentol can lead to reduced seizures - prescribed if there is a positive genetic and clinical diagnosis
- Hence it is important to determine if SCN1A is implicated to define appropriate treatment for potential Dravet cases
- Also as indicated not all pediatric epilepsies are due to SCN1A and in fact there have been many genes implicated in epilepsy, so it is important to define the gene to personalise the treatment

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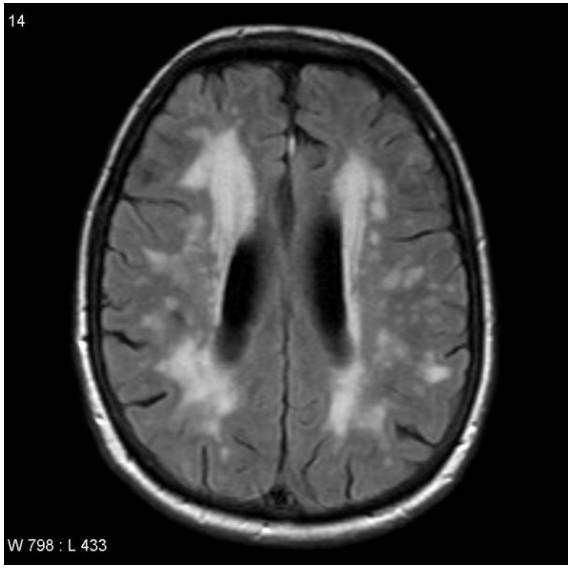
NOTCH3 Gene (CADASIL)

- Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
- A dominantly inherited disorder of small vessels of the brain, leading to cognitive impairment and dementia
- Symptoms include migraine, strokes, white matter lesions.
- Caused by mutations in NOTCH3



FHM

+ Small Stroke episodes (Occasional)

RARE: FHM Associated Seizures

20%: Episodic/permanent cerebellar nystagmus & ataxia

25%: Bilateral sensorimotor disturbances

40%: Prolonged aura attacks

15%: Alternating FHM & MA attacks

Migraine
Nausea
Aura
Numbness
Dysphasia
HEMIPARESIS

CADASIL Treatments:

- Aspirin (75-300mg/day)
- Dipyridamole
- Clopidogrel
- Lifestyle changes
- **CANNOT** take newer anti-migraine drugs i.e. Imigran (reduces blood flow to the brain)

FHM Treatments:

- Tricyclic antidepressants
- Calcium channel blockers
- Antiepileptic medications (topiramate, lacosamide, valproate)

Episodic Ataxia type 2 Treatments:

- Acetazolamide
- Flunarizine
- 4-aminopyridine

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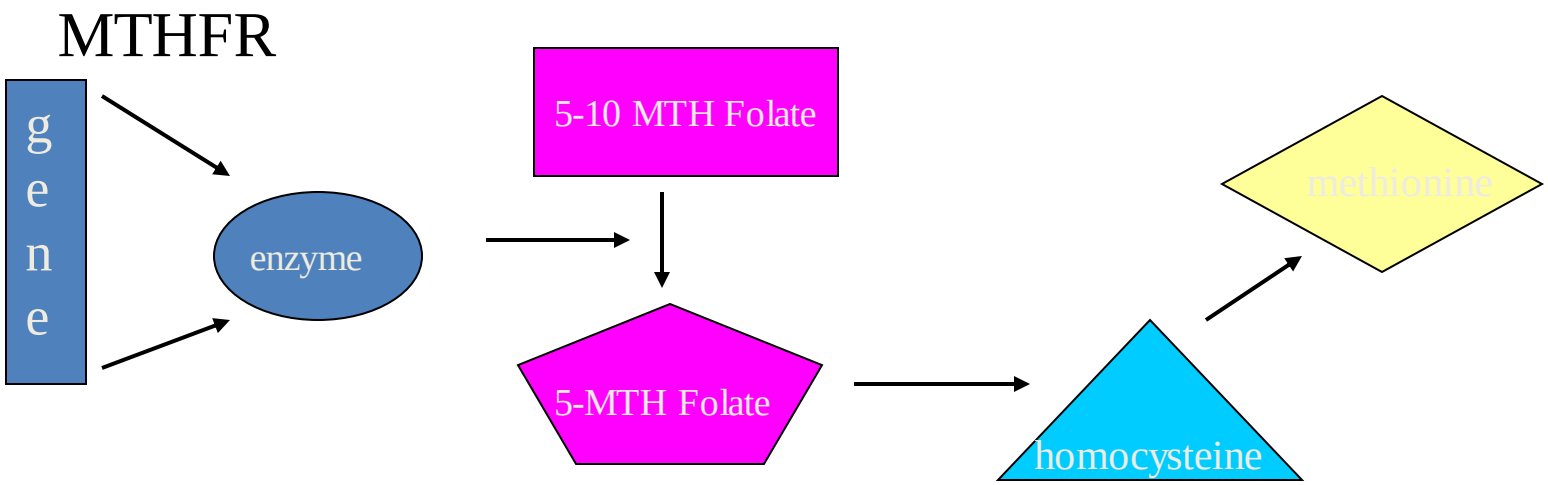
Genomics Research Centre Diagnostics

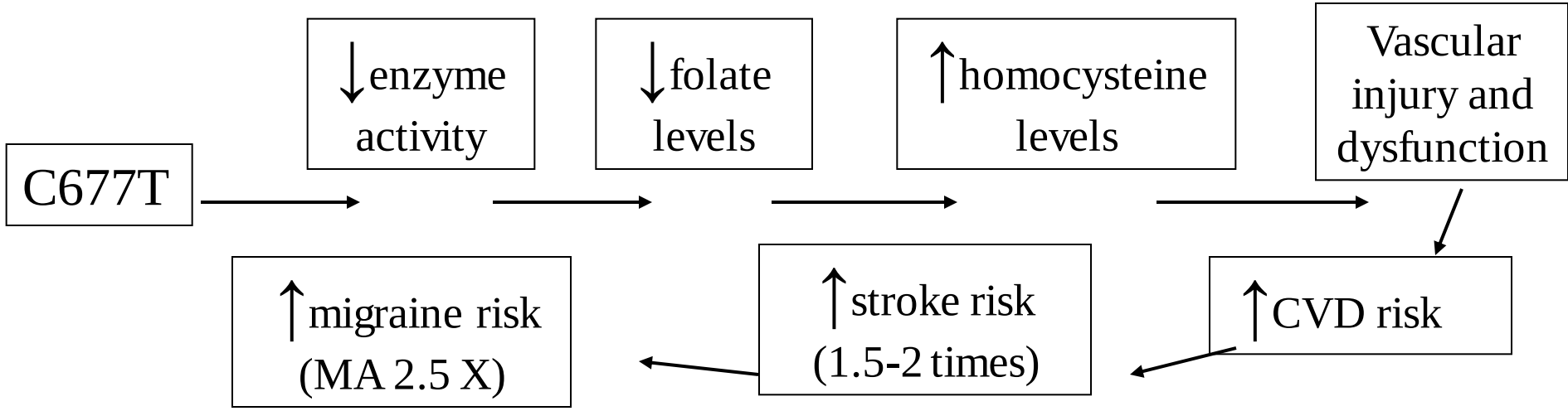
- Adjunct to and grown from our research interest in migraine and familial migraine syndromes.
- Our disorders of interest are:
    - Familial Hemiplegic Migraine (FHM)
    - Episodic Ataxia type 2 (EA2)
    - Spinocerebellar Ataxia type 6 (SCA6)
    - Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts & Leukoencephalopathy (CADASIL)
    - Epilepsy
- Able to diagnose about 21-28% of patients
- Clearly there are mutations we are missing

Current Directions

- Continue to identify new FHM/CADASIL/EA genes and add these to diagnostic testing services
  -hence Whole Exome Sequencing to identify novel genes
- Extend our epilepsy diagnostic testing
  -accredited whole exome approach for epilepsy diagnostics
- Extend testing to potentially related disorders – concussion
- -sample collection and investigation of ion channel genes
- Develop treatments based on genetic targets

MTHFR Gene


MTHFR
gene
enzyme
5-10 MTH Folate
5-MTH Folate
methionine
homocysteine
circulatory folate


C677T
↓enzyme activity
↓folate levels
↑homocysteine levels
Vascular injury and dysfunction
↑CVD risk
↑stroke risk (1.5-2 times)
↑migraine risk (MA 2.5 X)

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Migraine Pharmacogenetic Trial

- MTHFR C677T mutation is associated with enzyme function

  – TT genotype exhibits ~50% reduction in enzyme activity and results in higher homocysteine levels

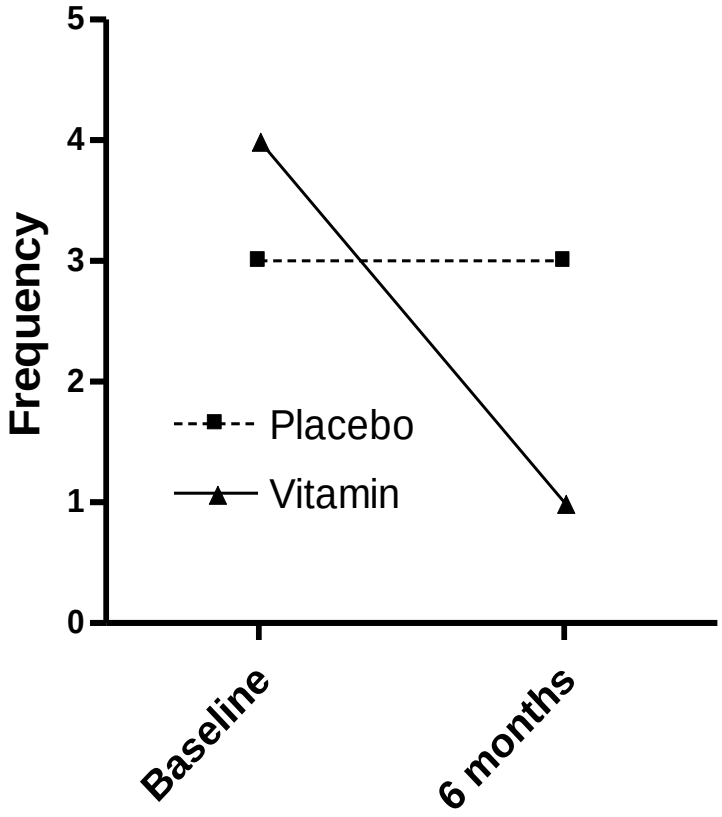
  - and is associated with increased risk of MA

- Plasma homocysteine levels can be lowered by vitamin supplementation with folic acid, vitamin B12 and vitamin B6

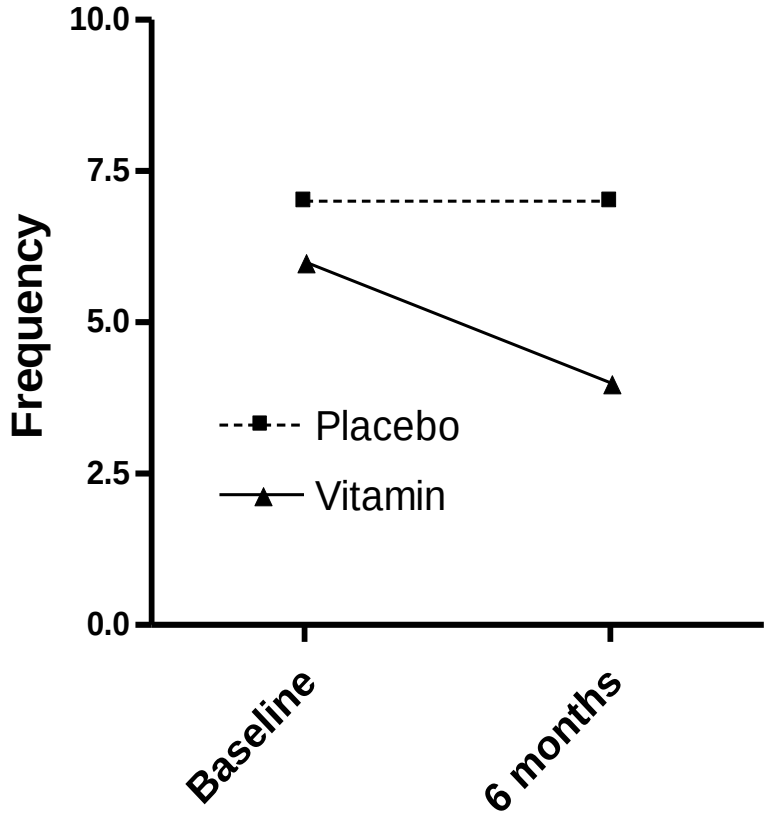
- Double blind, placebo controlled trial of 52 MA patients over 6 month period, seen at baseline, 3 mths and 6 mths

- Vitamin tablets (containing 2mg of folic acid, 25mg vitamin B6 and 400µg of Vitamin B12) or placebo - one tablet daily for 6 months

Effect on Migraine Frequency and Severity



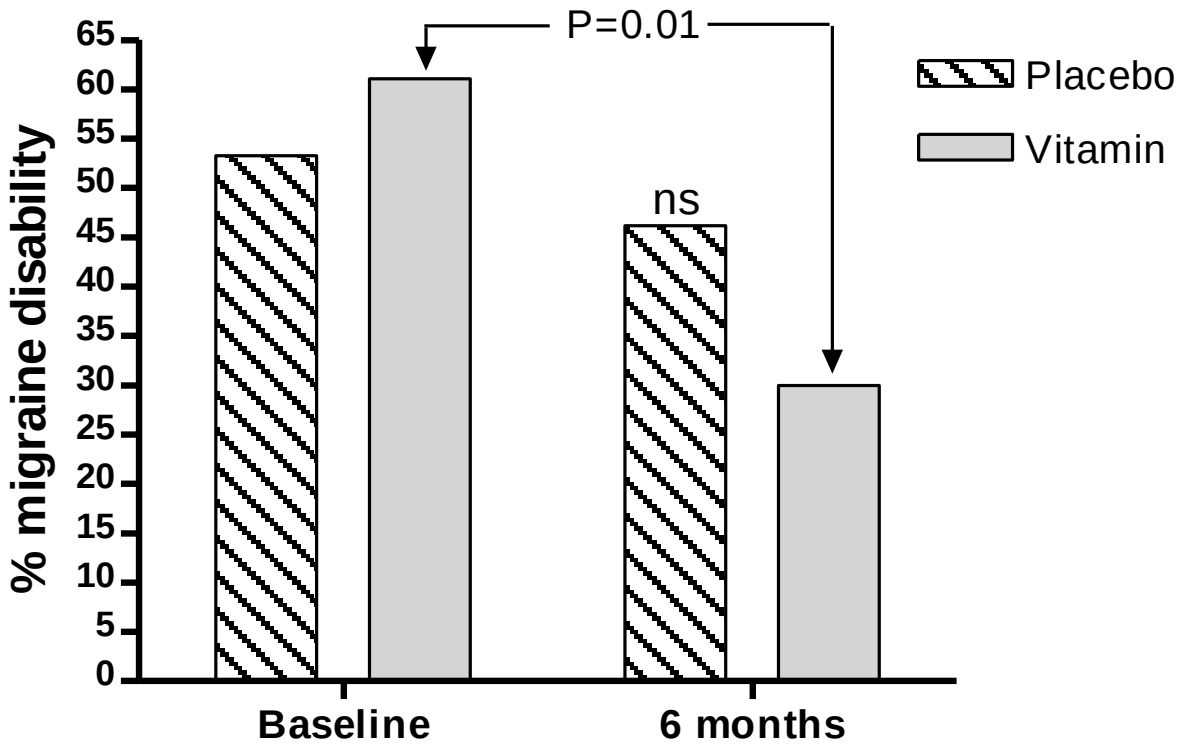
A. Change in headache frequency



B. Change in head pain score

Change in secondary clinical outcomes ie. 6-month migraine frequency (A) and average pain score (B) over the treatment period for vitamin and placebo groups. Values are medians. Quartiles not shown but reductions are statistically significant (P<0.05).

Effect on Migraine Disability



Change in primary clinical outcomes ie. frequency of high level migraine disability (MIDAS >11) over the treatment period in vitamin and placebo groups

-frequency of disease disability decreased 2-fold following 6 months of daily supplementation (61% to 30%, P= 0.01)
-reduction in placebo group not statistically significant (53% to 46%, P=0.3).

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Migraine Clinical Trial

- Disease **disability decreased 2-fold** following 6 months of daily supplementation (61% to 30%, P=0.01)

- **Decrease in headache frequency**, from 4 attacks to 1 per month (P=0.04),
- **Decrease in pain severity**, from an average score of 6 to 4.5 (P=0.002)

  - placebo group, no change either headache variable (P>0.1)

- Effect of vitamin therapy on migraine disability was dependent on MTHFR C677T genotype - reduction in disability occurring predominantly in patients carrying the CC/CT genotype (P=0.002).

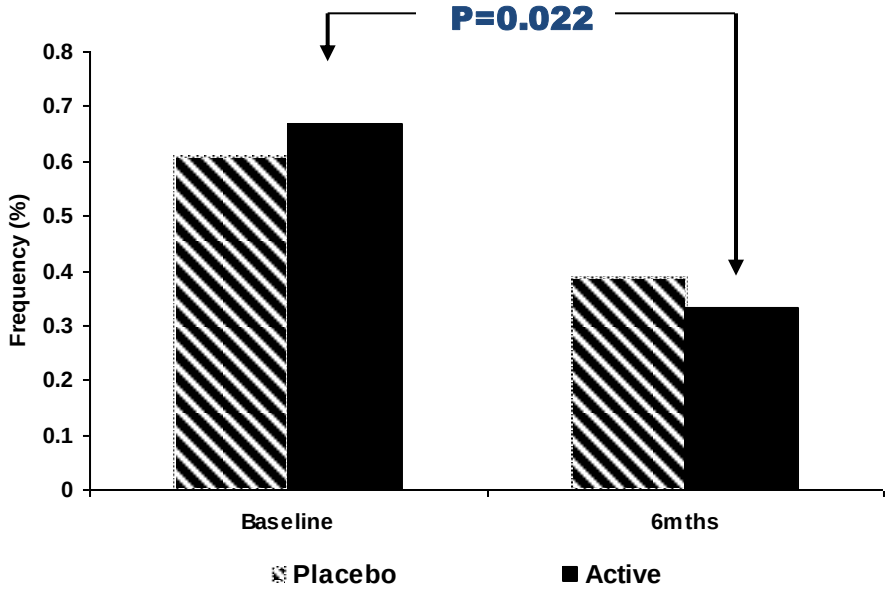
- Results suggest that MTHFR genotype plays a role in migraine response to vitamin supplementation, with a **significant reduction in migraine frequency, severity and disability**

Lea et al 2009 *Pharmacogenetics and Genomics*

Recent RCT of Vitamin Supplementation

- 245 MA patients, female Caucasians
- No statistically significant differences between the vitamin and placebo groups for the test variables at baseline.
- 206 patients completed- treatment well tolerated, no adverse reactions
- At 6 mths, folate, B6 and B12 marked increases, compared to baseline and placebo ($P<0.001$), homocysteine marked decrease compared to placebo

Effect on Migraine Disability



Change in primary clinical outcome - frequency of high-level migraine disability (Migraine Assessment Score > 11) over the treatment period in vitamin and placebo groups.

Menon et al 2012 ***Pharmacogenetics and Genomics***

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Conclusions

- DNA studies can aid in defining genes involved in disease and this can have important diagnostic and treatment implications
- DNA diagnostics -effective way to differentiate the genes involved in familial hemiplegic migraine, episodic ataxia, hereditary stroke and pediatric epilepsy - and hence define personalised treatments
- Not all genes for these disorders have yet been identified and we are undertaking studies to identify new FHM, stroke, ataxia genes
- There are currently ~395 known epilepsy genes and we have recently developed a method to investigate all of these as a potential new diagnostic test
- Concussion genetics study – to investigate ion channel genes in relation to susceptibility.

Acknowledgements

- Peter Brimage, John MacMillan
  - clinical diagnosis

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  -genotyping and analysis

- Saras Menon, Sharon Quinlan
  - clinical collections, trials, phenotype analyses

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