Gene-environment interaction in migraine

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Migraine has an enormous impact

- 7th cause of years of life lost to disability worldwide
- 3rd cause of disability in under 50s
- Top cause of disability among neurological disorders
  - accounting for over half of all years lived with disability (GBD, 2015)
- In high-income countries like Australia, the total disability due to migraine is
  - >1.5 times that due to multiple sclerosis and Parkinson disease combined, and
  - ~3 times that due to epilepsy (Collins, 2011)
- The economic burden due to migraine is the highest of all neurological conditions in Europe (Linde, 2012; Leonardi, 2014)
Figure 4. Relationship Between NIH Disease-Specific Research Funding and Burden of Disease for Selected Conditions

(Moses, 2015)
Despite its huge impact the causes of migraine are unknown and there are no recognisable, diagnostic, pathological changes.
We do know that migraine is genetic!..

- 1st-degree relatives of migraine cases have 50% greater risk of migraine, compared to relatives of unaffected controls (Russell and Olesen, 1995; Stewart, 1997)
  - relative risk (RR) > 1.5

- Twin studies indicate genetic factors contribute to migraine susceptibility ($h^2 \sim 40-60\%$) (Mulder 2003)
Basis of twin design

Monozygotic (MZ) twins
(identical twins)

Share 100% of their genes

Dizygotic (DZ) twins
(non-identical twins)

Share 50% of their genes

Heritability \((h^2) = 2 \times (r_{MZ} - r_{DZ})\)

*Twin studies indicate females and males have a similar genetic risk*
Hormones

- Migraines similarly affect boys and girls before puberty, but about two to three times more women than men.

- Propensity for migraines usually decreases during pregnancy.

- 50% of women report a relation between their migraine headache and menstruation (Couturier et al 2003).
Incidence of migraine and urinary oestrogen and progesterone concentrations on each day of the menstrual cycle in 120 cycles from 38 women. (MacGregor et al 2006)
Other environmental triggers for migraine

- Migraine attacks rarely occur spontaneously in the absence of possible environmental triggers

- 76% of migraineurs reported triggers when asked, and this figure rose to 95% when individuals responded to a specific list of triggers (Kelman 2007)
The most common headache triggers

- Stress and negative emotions;
- Sensory triggers (flicker, glare, eyestrain, noise, odours);
- Hunger;
- Lack of sleep or excess of sleep;
- Food (particularly chocolate, cheese) and drink;
- Alcohol;
- Menstruation; and
- Weather (cold, heat, high humidity).

Many other factors have been noted including exercise, fatigue, and head and neck movement.  

(Peroutka 2014)
Importance of gene-environment (G×E) interaction

- Common complex diseases such as migraine are the result of the combined effect of genes, environmental factors, and their interactions.

- Given an individual’s genotype remains constant throughout life, the fact that individual migraine patients have a great variation in headache frequency and characteristics during their lifetimes, provides further support for the importance of an interplay between genes and environment (i.e., triggers) in migraine.
Finding genetic risk factors for migraine

Single Nucleotide Polymorphisms (SNPs)

- >34 million
- Most with 2 alleles (up to 4)
- Evenly distributed
Case-control study for genetic association

Cases (n=1,000) (express the trait) vs. Controls (n=1,000) (do not express the trait)

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<thead>
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<th>C</th>
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<tbody>
<tr>
<td>Cases</td>
<td>62%</td>
<td>38%</td>
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<tr>
<td>Controls</td>
<td>49%</td>
<td>51%</td>
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$\chi^2 = 34.2$, p-value $= 4.9 \times 10^{-9}$

$$OR = \frac{P(\text{case}|C)/P(\text{control}|C)}{P(\text{case}|T)/P(\text{control}|T)}$$

$$OR = \frac{0.62/0.49}{0.38/0.51} = 1.7$$
Genome-wide association studies (GWAS)

- Made possible by advances in genotyping technology and determination of correlation patterns between SNPs on a genome-wide scale
- Genotype 300,000 to millions of SNPs
  - so called tagSNPs, because they ‘tag’ (are correlated) with the majority of known SNPs across the genome
- Test each SNP for association with a trait of interest
IHGC: a collaboration between researchers at over 60 centres from around the world
2016 IHGC Migraine GWAS

59,674 cases vs. 316,078 controls

- 44 independent SNPs significantly associated with migraine risk ($P < 5 \times 10^{-8}$)
- 38 distinct genomic loci, including 28 loci (34 SNPs) not previously reported
- The first implicated locus on chromosome X

(Gormley et al. 2016)
Pathways enriched by migraine genes – a ‘word cloud’:

- red = vascular-related pathways;
- blue = metal-ion-related pathways;
- magenta = KEGG pathways;
- green = Reactome pathways; and
- black = remaining pathways.

The font size is related to their enrichment (larger font indicates greater significance).
Gene-environment interaction in migraine

- The migraine risk SNP rs1024905 on chromosome 12 is associated with expression of the TIGAR gene

- The TIGAR gene encodes an enzyme which functions as a regulator of glucose breakdown (glycolysis)

- Decreased expression of TIGAR will result in increased glucose breakdown
Gene-environment interaction in migraine

- The migraine risk allele rs1024905-G is associated with increased glucose breakdown (glycolysis) in human cells

- Low blood glucose (hypoglycemia), also known as low blood sugar, can be responsible for triggering or exacerbating migraines and headaches, and

- Many migraine sufferers report food-related triggers associated with their migraines

- G×E interaction between SNP rs1024905 and food-related triggers in migraine
Thank you for your attention.
My contact email: d.nyholt@qut.edu.au

“You don’t look anything like the long haired, skinny kid I married 25 years ago. I need a DNA sample to make sure it’s still you.”