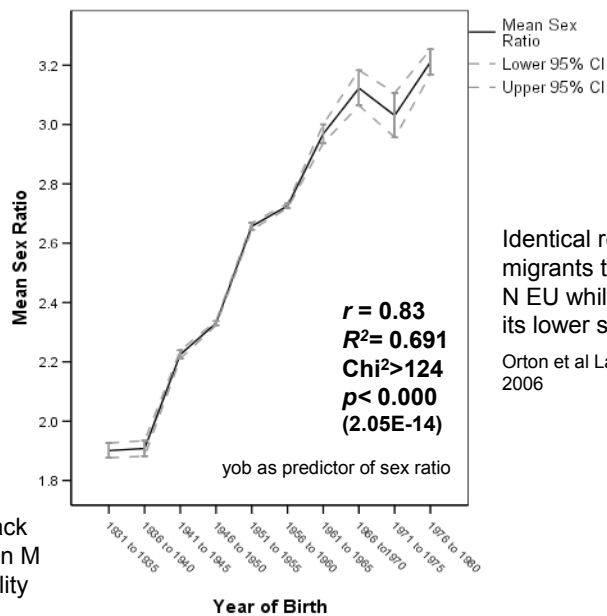


Samuel Stanhope Smith 1787 a vicar -
a "Hartford wit" (not a Harvard twit)

'I've had a look and skin colour is determined by where you live and therefore we must all be one species so what's all this slavery about' - paraphrase

CCPGSMS Sex Ratio by y.o.b in 30K MS patients



Identical results seen in migrants to Canada for N EU while S EU keeps its lower sex ratio)

Orton et al Lancet Neurology 2006

(Extrapolating back (sm #) factoring in M premature mortality takes this to 1/1)

Canadian MS Clinics

a population base of > 30,000 MS patients with all seen by an MS specialist neurologist
repeated complete pedigrees – took 25years.



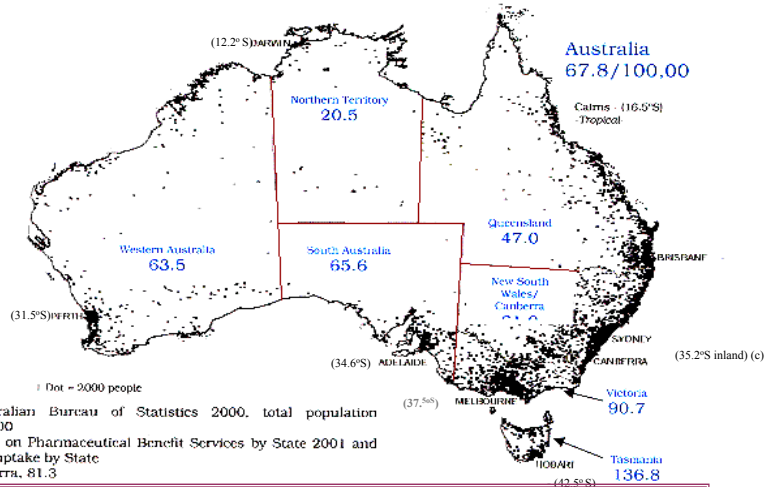
Cumulative effect of adding shared environment

Start with the general population rate of 1/1000 as baseline work back from adulthood in timing of environmental sharing adding as we proceed

- 1) **add** the shared environment of conjugal cohabitation and the rate is still ~1/1000 as **zero** risk is added Ebers et al Ann Neurol. 1999
- 2) **add** shared environment of being raised together as in ½ sibs r.t. subtract the r.a. rate leaving another **zero** to be added Ebers et al Lancet 2004
- 3) **add** in ↑ sharing of adjacent birth order sib vs. sib leaving home before sib to get MS was born – again **zero** Sadovnick et al Lancet Neurology 2005
- 4) **add** in risk attributable to growing up with non biological relatives destined to get MS i.e. adopted at birth – i.e. **zero**. Ebers et al Nature 1995
risk for adopted relatives of MS probands is zero, risk for biol parents sep at birth is ~ as non-sep.
- 5) **add** in risk for stepsibs of MS patient i.e. **zero** Sadovnick et al JNNP 2005
- **Conclusion** : inability to detect *any* effect of the shared familial or cohabitational microenvironment with single exception (DZ>sib risk).

Factors determining geography exert huge effects at a broad pop'n level but don't discriminate among familial microenvironments (climate / diet)

**POPULATION DISTRIBUTION, AUSTRALIA^(a)
AND ESTIMATED MS PREVALENCE BY STATE^(b)**
(Estimated MS Population 13,000)

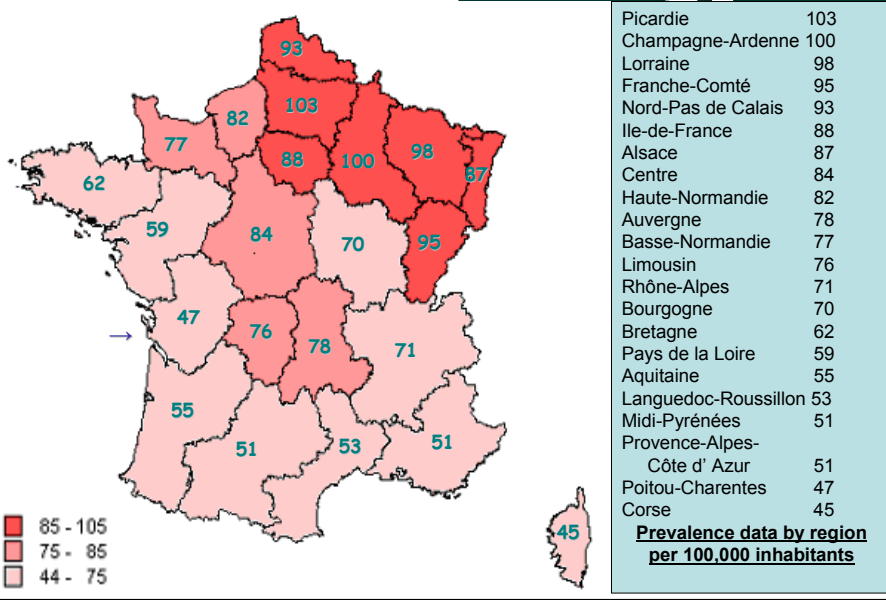


Striking NS gradient in homog. population but not distrib. evenly / focal/urban, migratory - no place of birth data For indep. confirm'n Ideal country - evenly distrib. nonmigratory popul'n, NS extent,

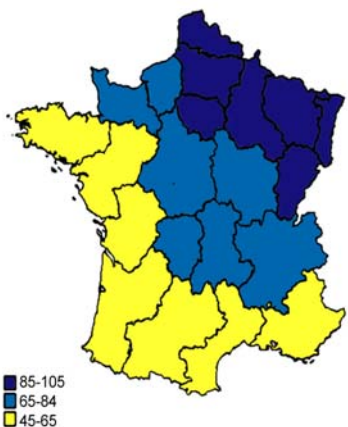
g.c.1

Prevalence of MS

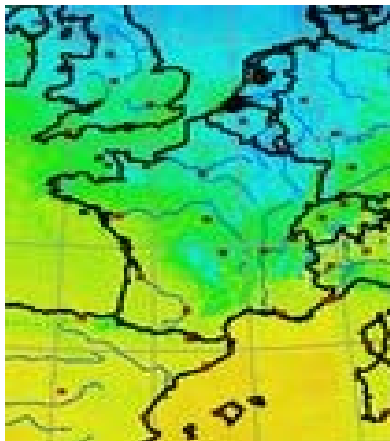
French Farmers/families - evenly distributed non-mobile population



Sunlight in February vs. MS prevalence for France

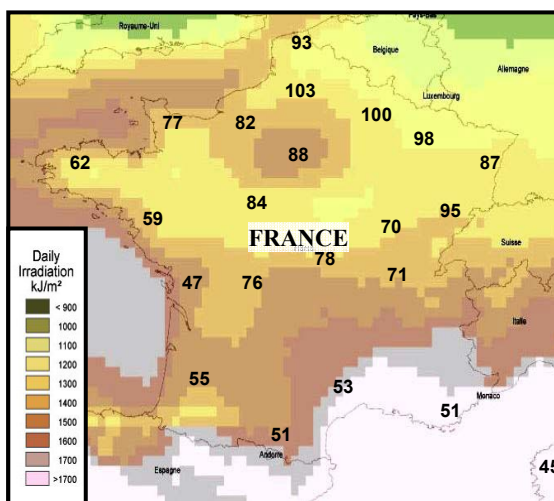


End winter sunlight in France



MS/10⁵ by region - Fr. farm families

UV Irradiation and MS prevalence in France



UV map from Wald et al 2005, Ecole des Mines de Paris, www.sodais.com

August monthly mean, 1993-2002

Vitamin D via UV as a candidate

- Some are chronically deficient through the year
- Some 50-70% of the population are deficient in the UK at winter's end
- The vitamin D-responsive family is the largest in the genome with approx. 1000 members
- Interaction with dietary intake limited here as there are few sources excepting oily fish, shiitake mushrooms and reindeer stomach contents for those with a taste for them
- In many northern communities it is conventional wisdom to take fish liver e.g. cod.
- Acts as a cofactor for epigenetic modifications

Early life events and MS risk

- 1) migration studies (Dean, Alter, McLeod et al confirmed by our own intrafamilial migration study)
- 2) maternal parent of origin effect in $\frac{1}{2}$ sibs (Ebers, Sadovnick et al Lancet 2005)
- 3) month of birth effect (Willer et al BMJ 2004)
- 4) DZ twin rate > sib rate (Willer et al PNAS 2003)
- 5) age onset correlation DZ twins vs sibs (Sadovnick and Ebers - CCPGSMS unpublished)
- 6) space/time clustering in very early life (Pugliatti et al)



An American teen group meeting for the first time – is there any resemblance?
Taken from the NYT some years after the study was suggested by MW

Half sib strategies

Here we have one parent in common not two

Does it matter which is the common parent?

Raised together vs. apart – difference in risk?

How many genes in determining risk?

- 1) $\frac{1}{2}$ sib rate raised together (r.t.) vs. apart (r.a.) (~50/50)
- 2) Parent of origin effect? Mat sig > pat $\frac{1}{2}$ sib rate
- 3) Full sib rate in $\frac{1}{2}$ sib families - 3.5%
($\frac{1}{2}$ sib vs full sib measures complexity)
- 4) Half sib rate of 1.9% implied effect of nonMHC genes on inheritance in families v. small (confirmed byWGAs)

this approach is really near one stop shopping for genetic epi (Ebers et al Lancet 2004)

Cumulative effect of adding in genes

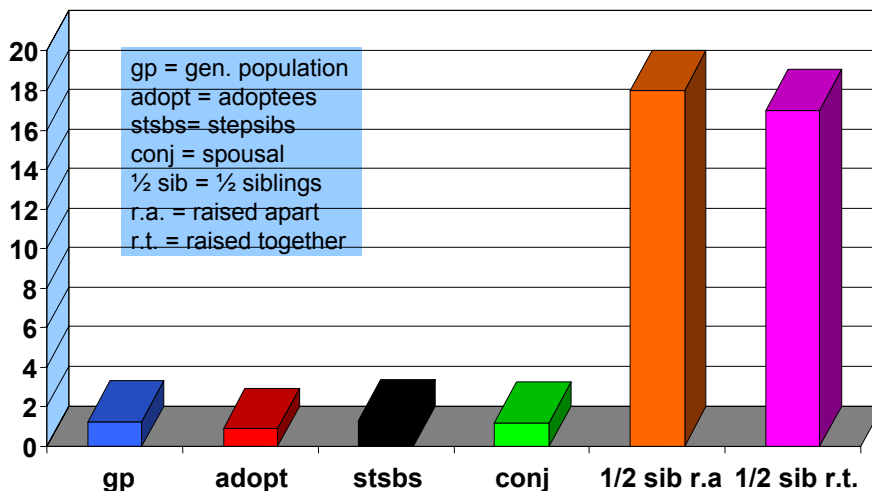
Gen pop'n baseline of 1/1000

• Cousin has MS risk	7/1000
• Pat ½ sib	13/1000
• Half sib risk reared apart	21/1000
• Mat ½ sib	24/1000
• Full sib risk (brother and sister)	35/1000
• Parent/child	35/1000
• HLA identical sib risk	80/1000
• Sib risk in consang mating	90/1000
• Offspring conjugal pair risk	200/1000
• MZ twin risk (~all genes in common)	270/1000
• F MZ with biparental DRB1*1501	450/1000

Contrast to E – serial ↑ genes shared increases risk at each level

could view this as 11 consecutive replications of the hypothesis

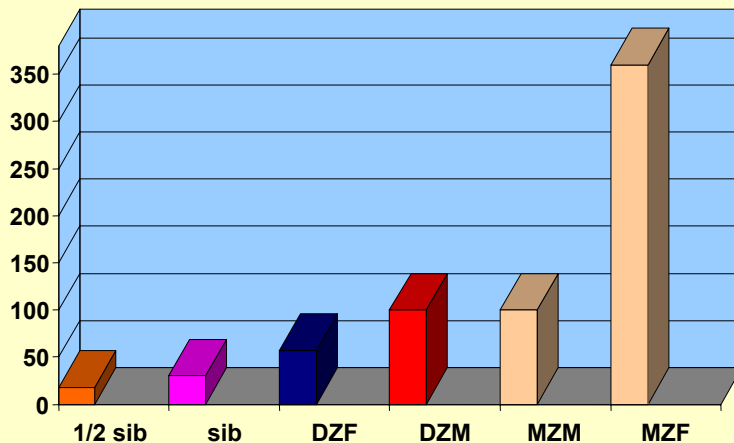
MS prevalence/1,000 in Canada effect of familial environment



none of adopt. stpsbs or conjugals are sig diff from gp

½ sib rate is the anchor point for the next slide, the two spanning a 400 fold diff in risk.

MS prevalence/1000 in Canada
½ sibs r.a. to MZ twins



The inheritance pattern?

- Simple pattern? no but closest to “dominant” just for 2 generations
- Brother/sister very close to that for a child/parent ~ no dominance variance - about 3.5% total - 35x the population rate
- But 3 and 4 generation pedigrees are rare, the latter excessively so.

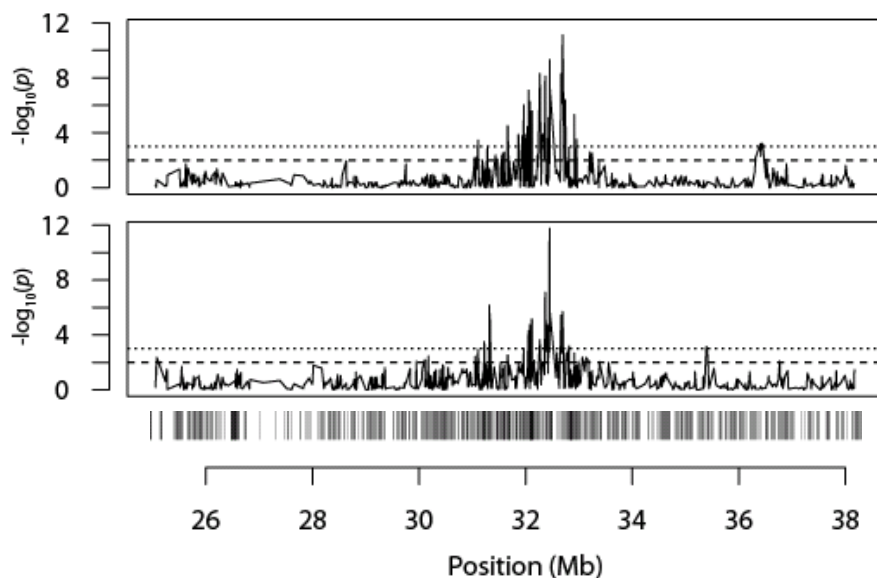


The Ws ? inheritance pattern & Ethnicity of parent of origin matters?
compare risk for offspring of Oriental father vs Caucasian mother and the reverse

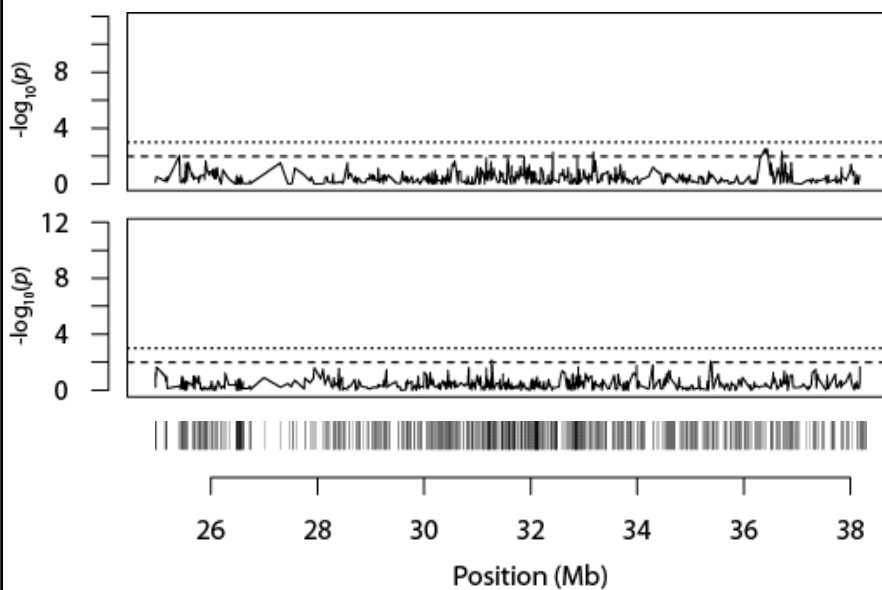


6/18 have MS in the previous generation but one case in the large third generation!

Unconditional SNP Association



SNP Association Conditioned on HLA-DRB1 or Block 63



Lincoln et al Nat Gen. - ironically no SNP haplotype surpassed DRB1 genotyping

An epigenetic effect?

Modification of DNA by E

- 1) maternal parent of origin effect, confirmed in AUNN
- 2) inheritance a conundrum - no dominance variance vs. decay after 2 generations (rising incidence)
- 3) the haplotype sharing excess in concordant sib pairs bearing alleles not overtransmitted - population data
- 4) twin data show F specificity for concordance
similar gender-specificity for epigenetic modifications
- 5) twin data show gender-specificity for inheritance of MHC S/R alleles (MZ cf DZ) imply E-G-G interaction
- 6) twins show marked differences in genome-wide methylation screens -affected MZ vs unaffected twin

Summary

- MS incidence is increasing
- Modifiable E determines approx. 80% of cases
- It acts at a broad population level.
- It interacts with a susceptible genotype
- Inheritance of interaction result volatile & decays
- Best G and best E candidate now united
- G has a VDRE (VDRE is a vitamin D binding site (1/224 regional genes - unlikely coincidental)
- It is time to attend to the practical implications