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Statistical genetics: A Swiss army tool for understanding melanoma risk and outcome

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Includes data presented on behalf of the melanoma meta-analysis and Breslow analysis group

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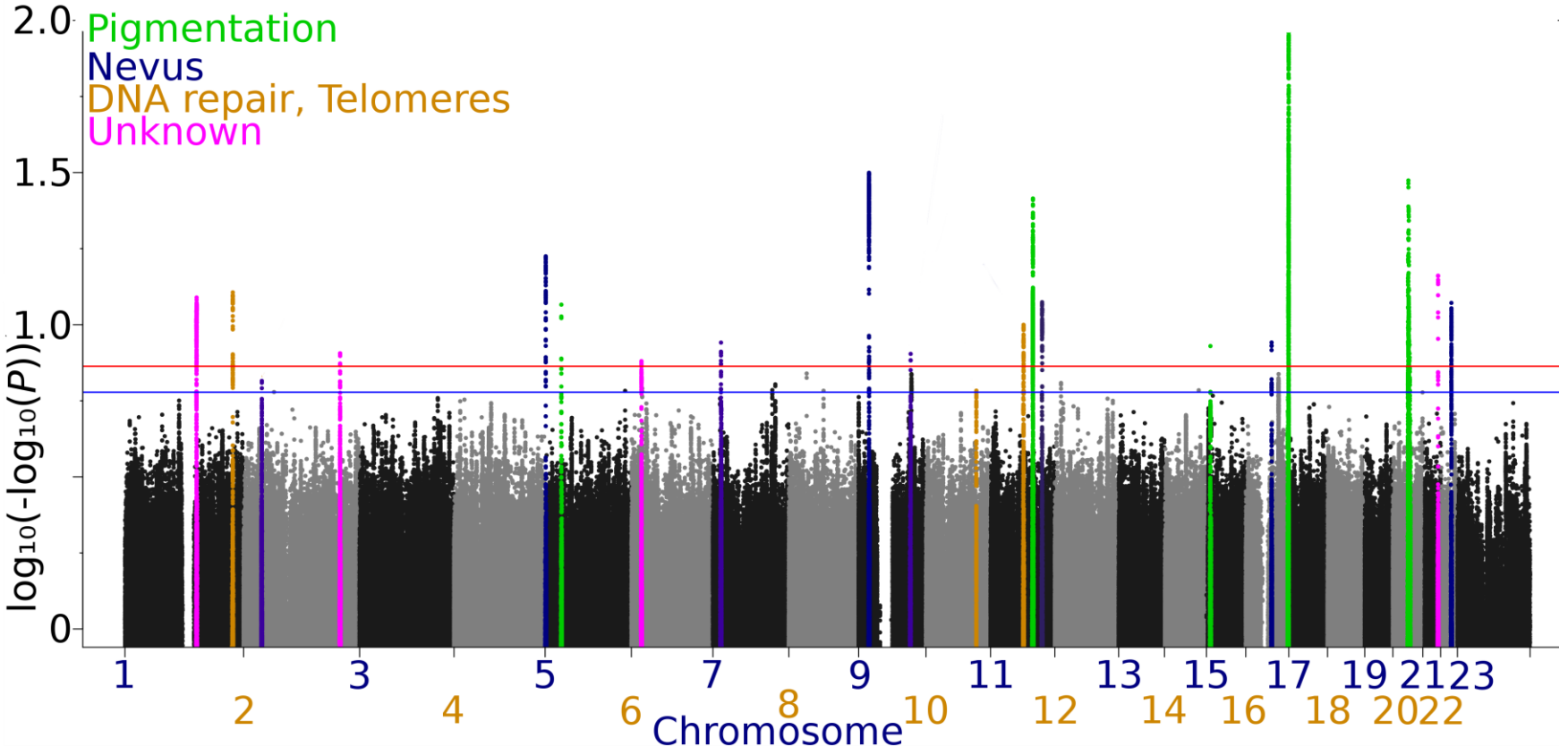
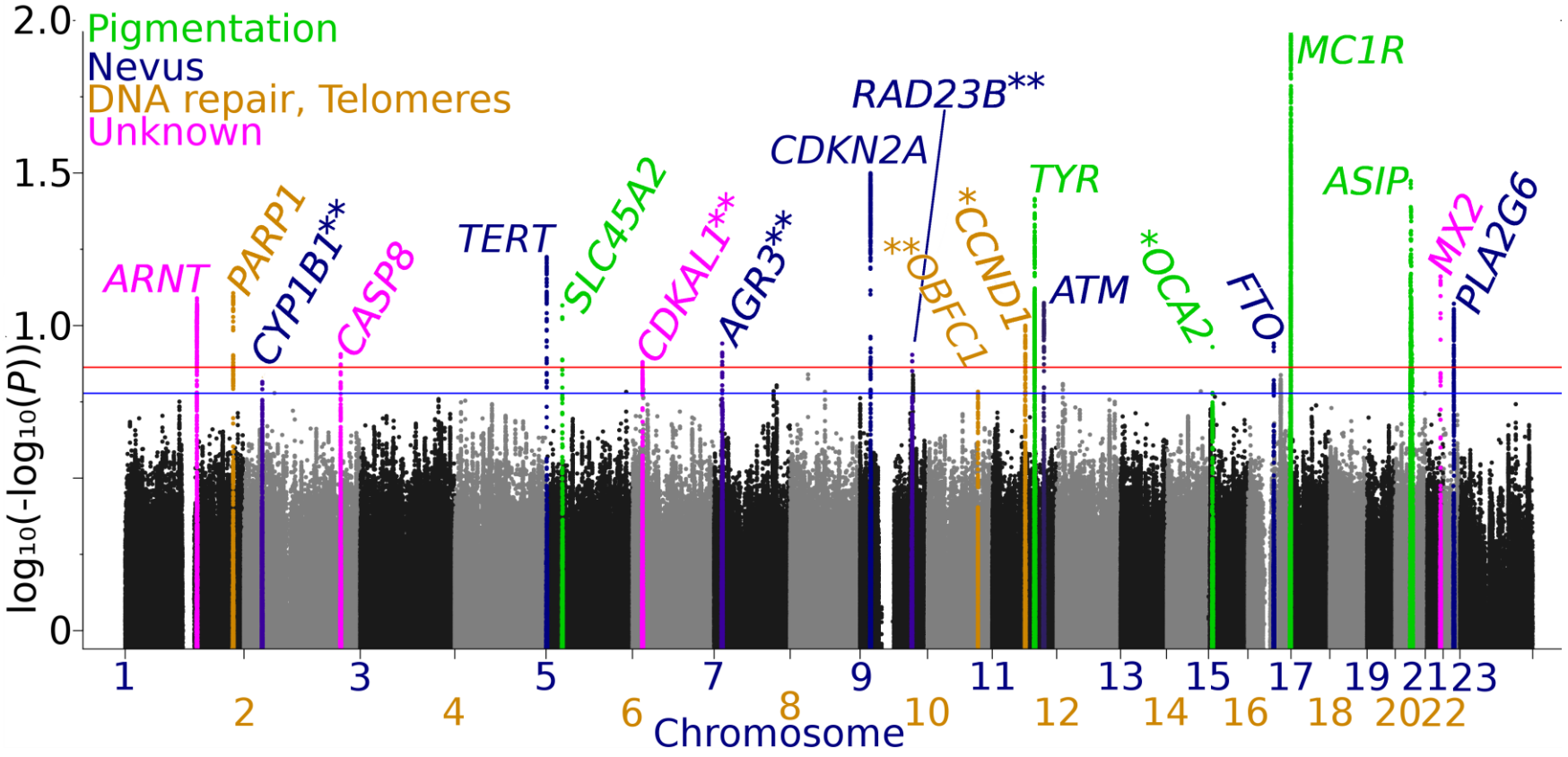
Melanoma meta-analysis



Law et al, *Nature Genetics*, 2015

Melanoma meta-analysis



Law et al, *Nature Genetics*, 2015

Meta-analysis phase 2

- **Updated imputation with HRC[1,2]**
  - Will include all SNPs with imputation quality > 0.5
- **Previous effective sample size was 14,451 cases and 14,451 controls (adjust to 1:1)**
  - Found 20 loci; % FRR from 16.9% to 19.2%
- **Additional new datasets (MIA, Melanostrum, 23andMe, UK Biobank, Kaiser-Permanante)**
- **~40,000 cases and 40,000 controls**
  - Loci discovery scales with N

[1]McCarthy *et al, Nat Gen,* 2016
[2]Das *et al* , *Nat Gen,* 2016

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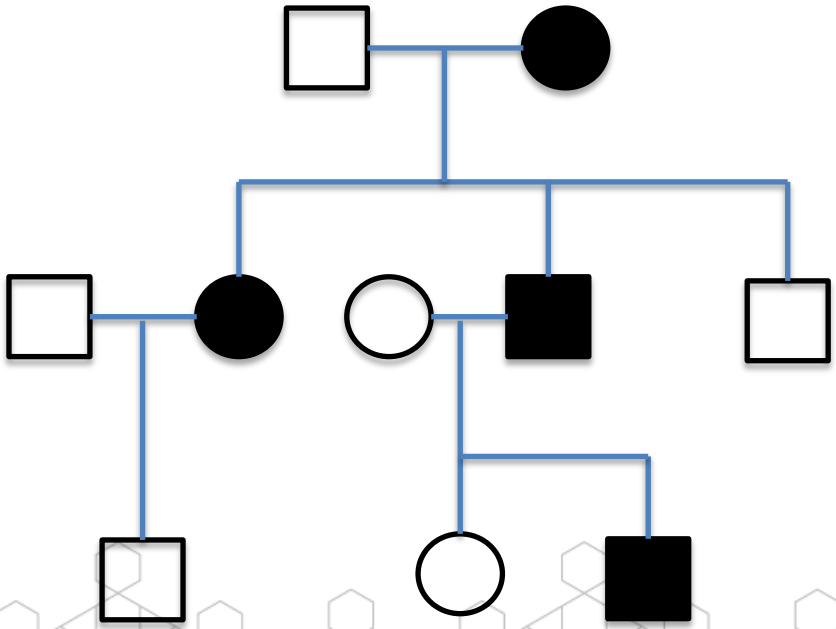
Post (risk) GWAS

- **Kevin Brown (NIH) undertaking functional characterisation of some loci**
- **Aim is to characterise additional loci here (NHMRC)**
  - Looking for local collaboration
- **Apply these same tools to other components**
  - Familial melanoma
  - Risk phenotypes
  - Survival
  - Survival phenotypes

Prioritising families for sequencing

- **Work in progress with NH, NM, DD**
- **Familial clustering of melanoma may be due to a high risk, rare variant (e.g. *CDKN2A*)**
  - But we've shown polygenes important for risk[1] (~30% h^2) so may just be high polygenic load in some families



- **Generate a polygenic risk scores (PRS) to prioritise which families we sequence**

[1] **Lu et al, *HMG*, 2014**

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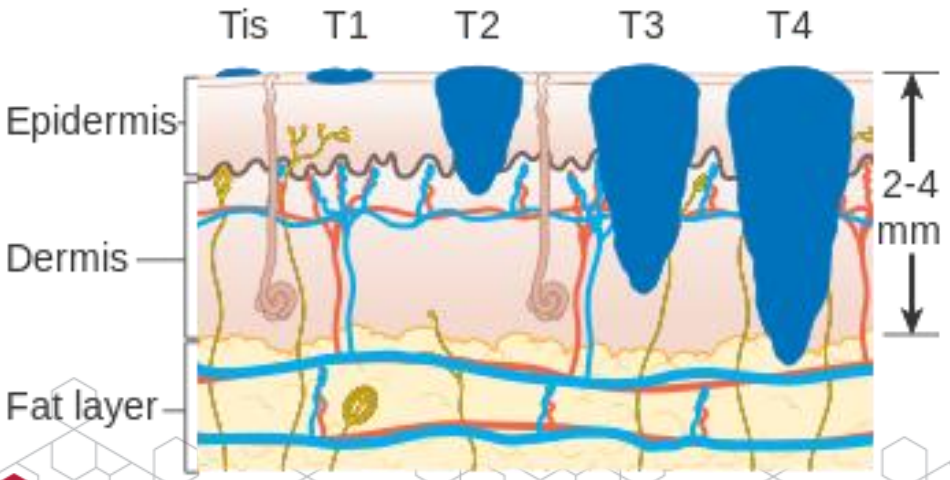
Is survival from melanoma heritable?

- **The Swedish Family Cancer database shows familial aggregation of mortality (sibs vs. general population ratio > 3)** [1]
- **We and others have shown a number of risk SNPs are associated with survival**[2,3,4]
- **Estimation of heritability from twin/family data confounded by negative correlation**
  - Unbiased approach may be better

[1]**Brandt., *et al;. Br J Dermatol* 2011**
[2]**Rendleman, *et al., J Med Genet*. 2015**
[3]**Davies, *et al. Int J Cancer* 2014**
[4]**Law, *et al., Int J Cancer* 2014**

Heritability of Breslow's depth 1

- **GREML method, as implemented in Genome-wide Complex Trait Analysis (GCTA) software**
- **Requires 'unrelated' (IBD ~0.005 to ~0.025)**
- **Estimates the proportion of trait variation attributable to genotyped SNPs**

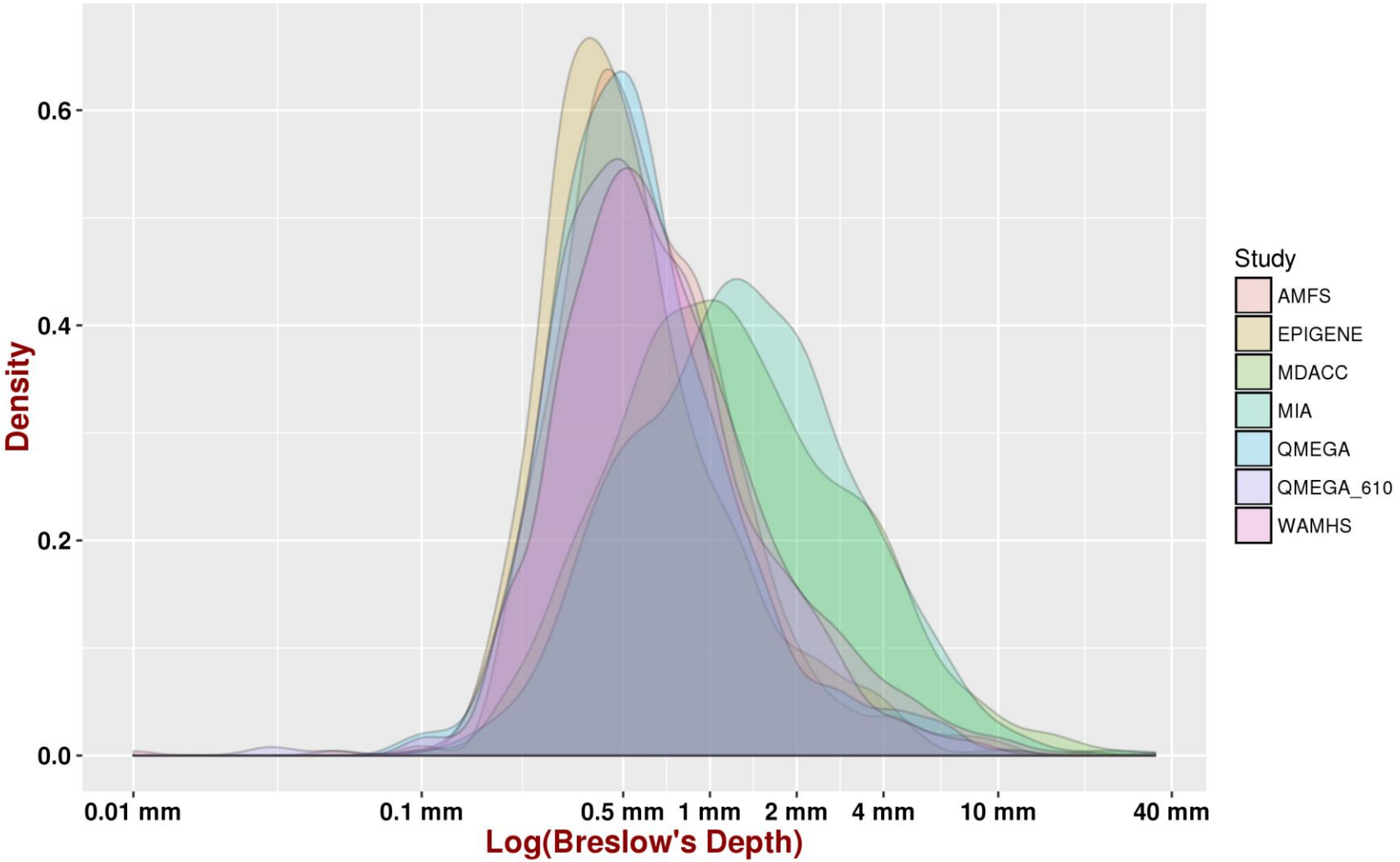


- array heritability, h^2_{array}; lower bound
- P value for $h^2_{array} > 0$ vs $h^2_{array} = 0$

Heritability of Breslow's depth 2

- **Mega-analysis of 101,190 SNPs common to all arrays; N = 5,778 cases**
- **Breslow's depth correlated with sex and age**
  - Covariates age, sex, the principal components 1-6
- **We explored the robustness of this finding**

logN Breslow's depth distribution



Mendelian Randomisation

- **Allows causal inference using natural randomisation (needs a good instrument)**
  - Valid even if the proportion of variance explained by the SNP(s) is small (~1%)
- **MR derived decrease of 20 ηmol/L of vitamin D level has OR 1.44 for all cancer mortality[1]**
- **Phase 1 MA - a 20nmol/L decrease in vitamin D increased melanoma risk by 1.13 (C.I. 0.86, 1.48)**
  - Phase 2 will have sufficient power
- **Now considering additional modifiable risk/protective factors – coffee, fatty acids, BMI**

[1]Afzal, S., *et al.*. *BMJ , 2014*

Summary

- **Ongoing GWAS with collaborators to include additional melanoma datasets for risk + surv**
  - Ideally will double sample size → will double loci
  - imputed platform to cover rarer variants
- **Functional characterisation underway**
- **Germline factors influence Breslow's depth**
  - h^2 5% - 12 %
  - Denser genotype coverage will improve h^2 estimates
- **MR: can leverage large scale GWAS data to make more robust causal inference**
- **Need additional local collaborations…**

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MELANOMA FOCUS

Melanoma Research Alliance

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Melanoma meta-analysis

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