Finding Genes for ASD in Extended Pedigrees

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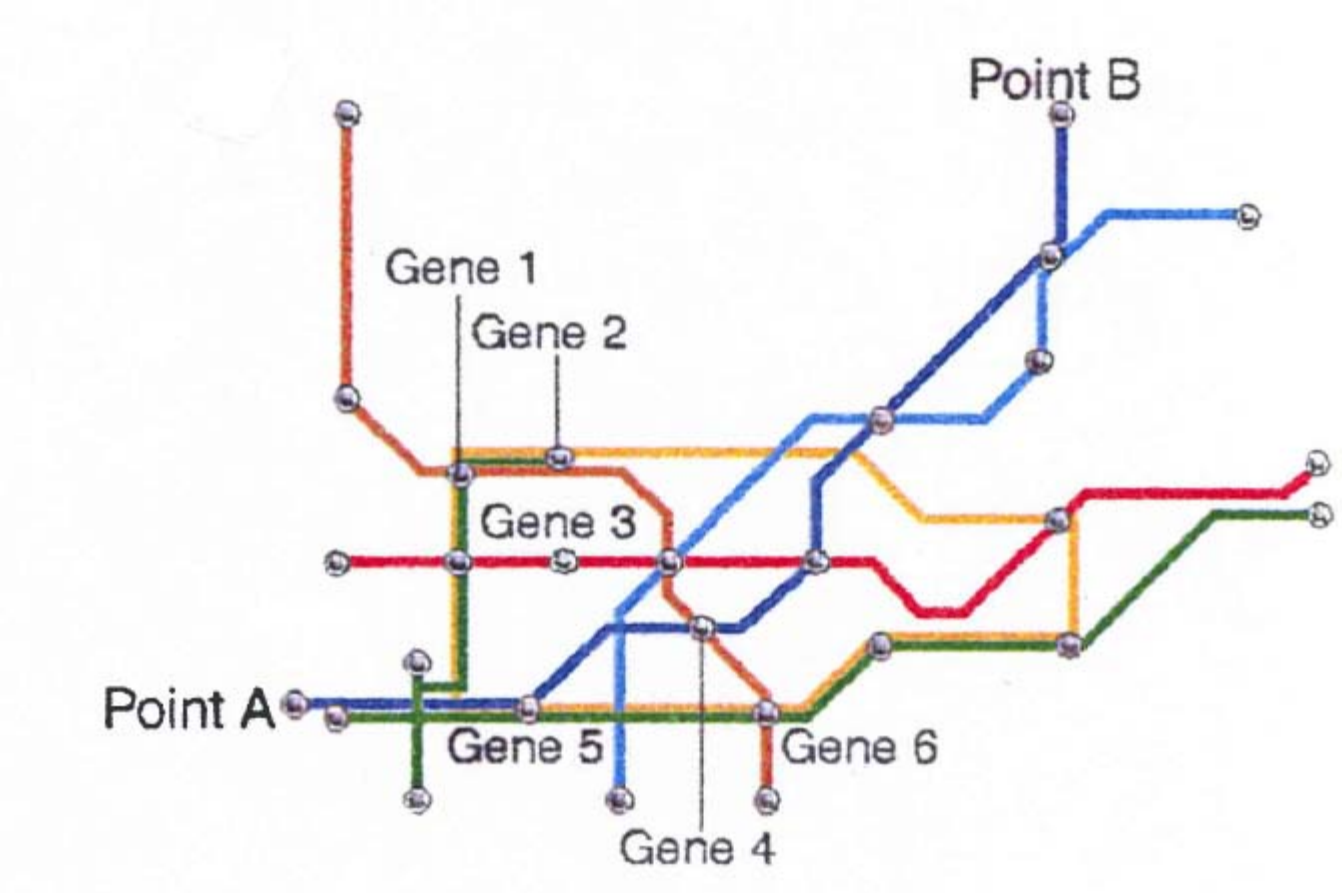
ASD Runs in Families

- Risk in Siblings; 5%-9%; pop prev=0.5%
- Risk in MZ twins; 60%-80%, DZ=0%
- Very low rates of ASD in extended family (cousins, uncles etc)
- Disorder is strongly genetic and runs in families
- But this does not rule out environmental risk factors

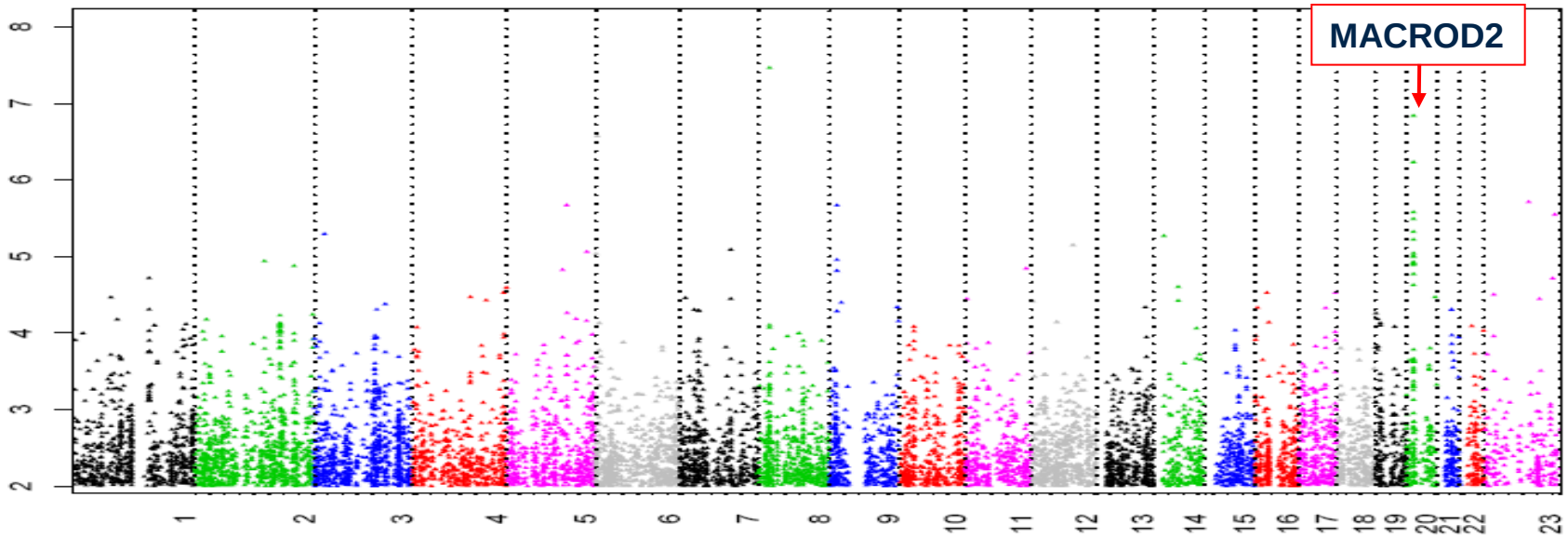
Common Disease-Common Variant model

- ASD is a common disease, therefore it might be caused by common genetic variants that are inherited
- Each variant has a small impact
- Several variants act together to cause the disorder
- Comparing cases and controls can find inherited genetic variants of small effect



The London Underground; de Vries Nature Medicine 15 (8) August 2009

All Ancestry – Autism Dx – Additive Model



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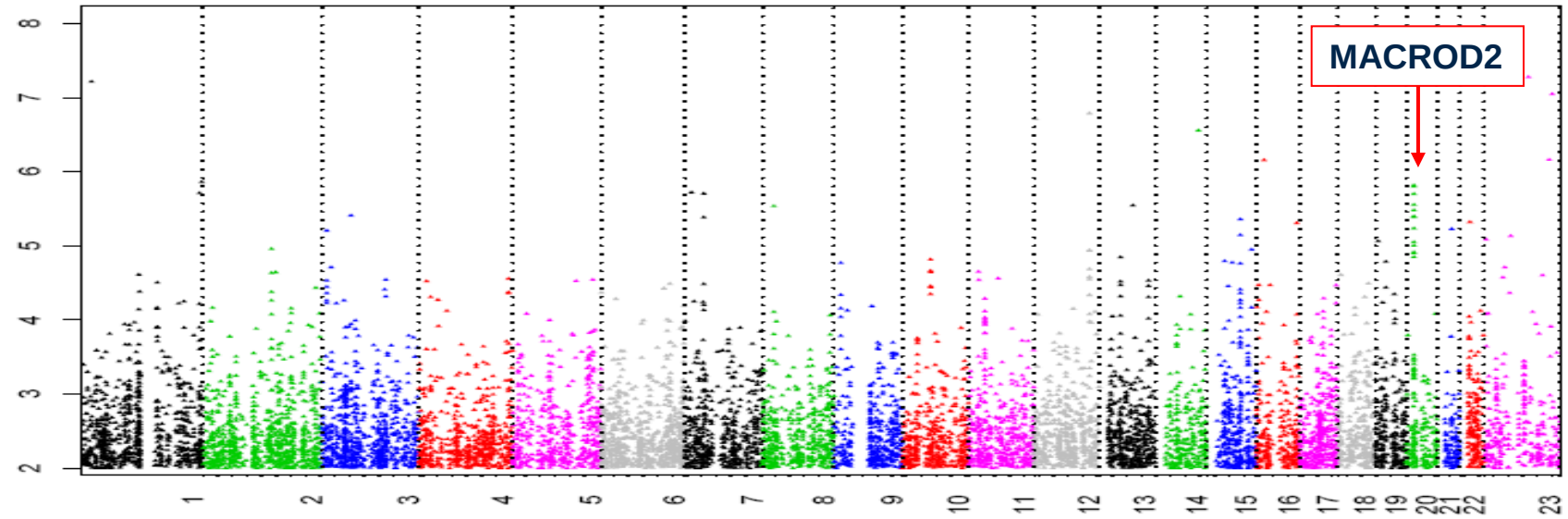
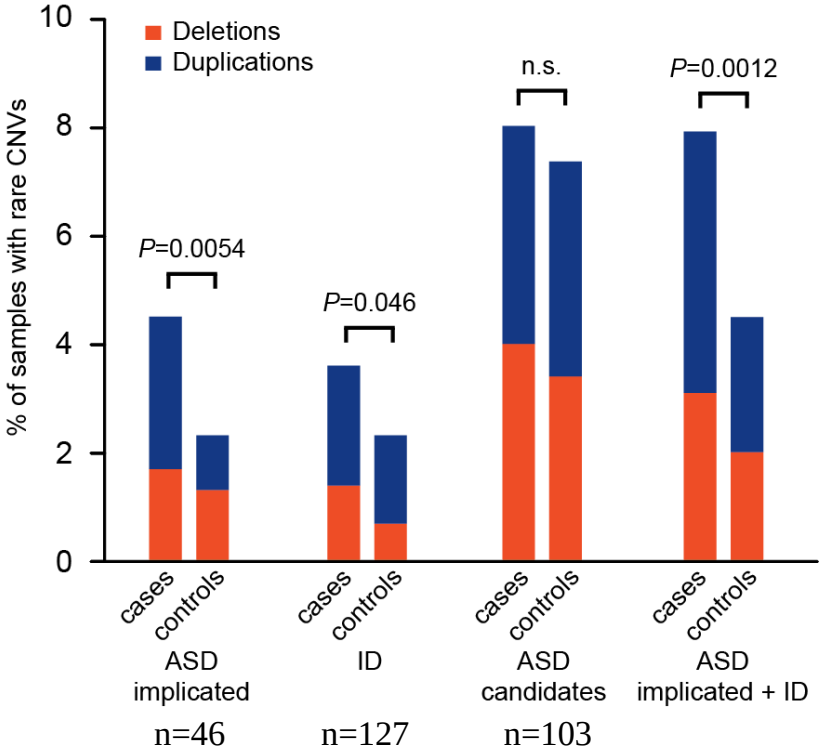
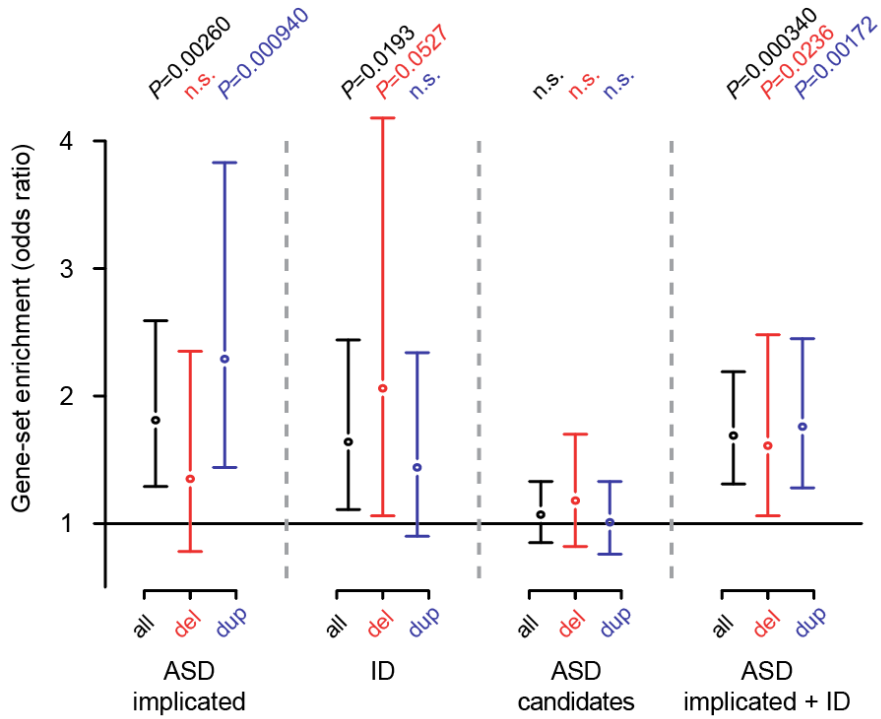


Bottom Line of GWAS?

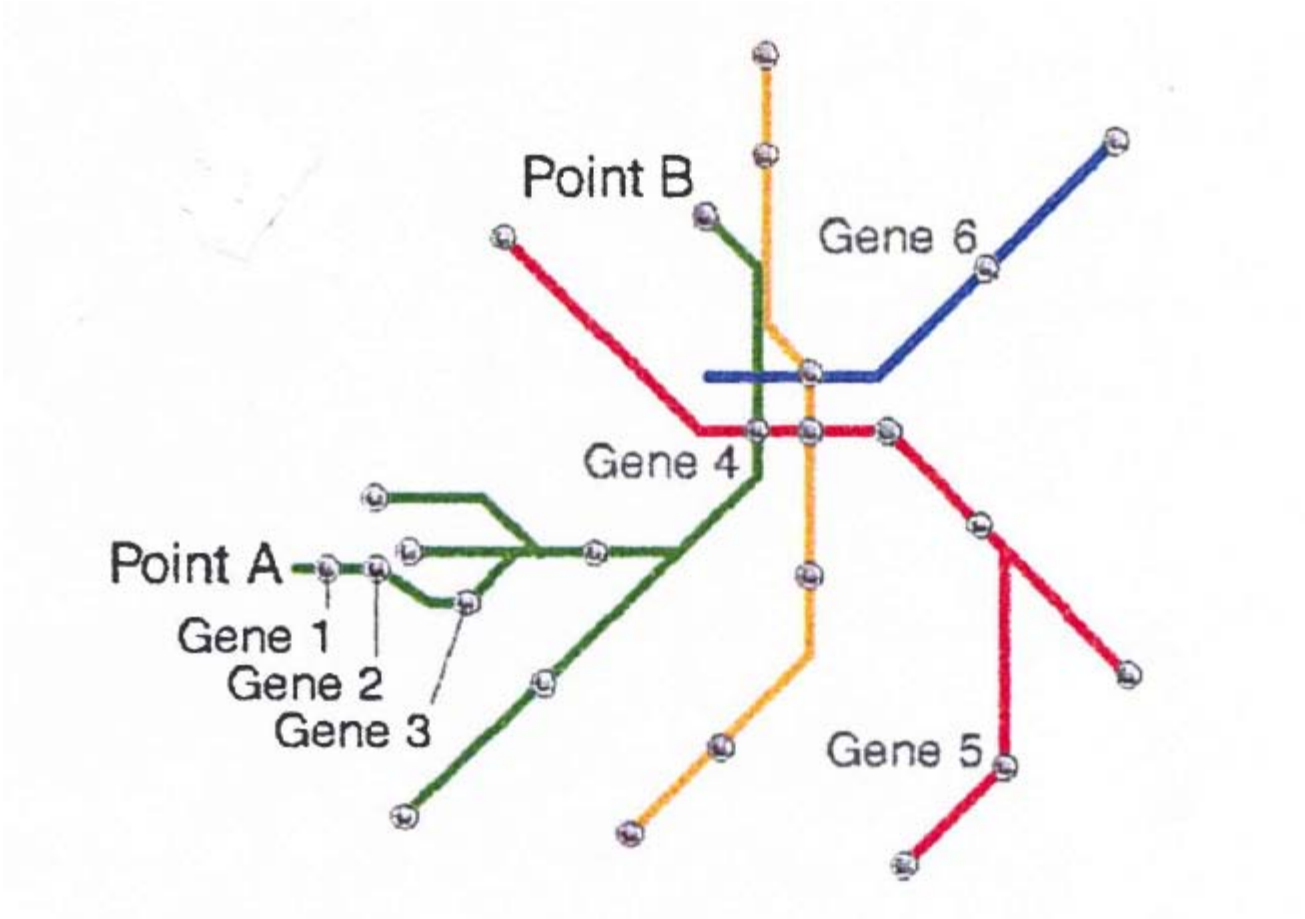
- One common inherited genetic variant barely reaches significance
- None of the other results can be replicated
- So what happened?
- Common inherited genetic variant model may not be the right one
- The genetic variants that we have discovered are rare and mostly arise de novo

CNV burden in known ASD and/or ID genes





Enrichment of genic-CNVs in known ASD and ID loci (1.69 fold, $P = 3.4 \times 10^{-4}$)



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Rare Genetic Variants in ASD

- More de novo rare genetic variants that are expressed in brain, implicated in ASD and ID,1.69 X more likely in ASD
- Seen in 7% of cases vs 4% of controls
- Many more to be discovered
- But if they are de novo, what about the inherited forms of ASD?

Dense Extended Pedigree Project

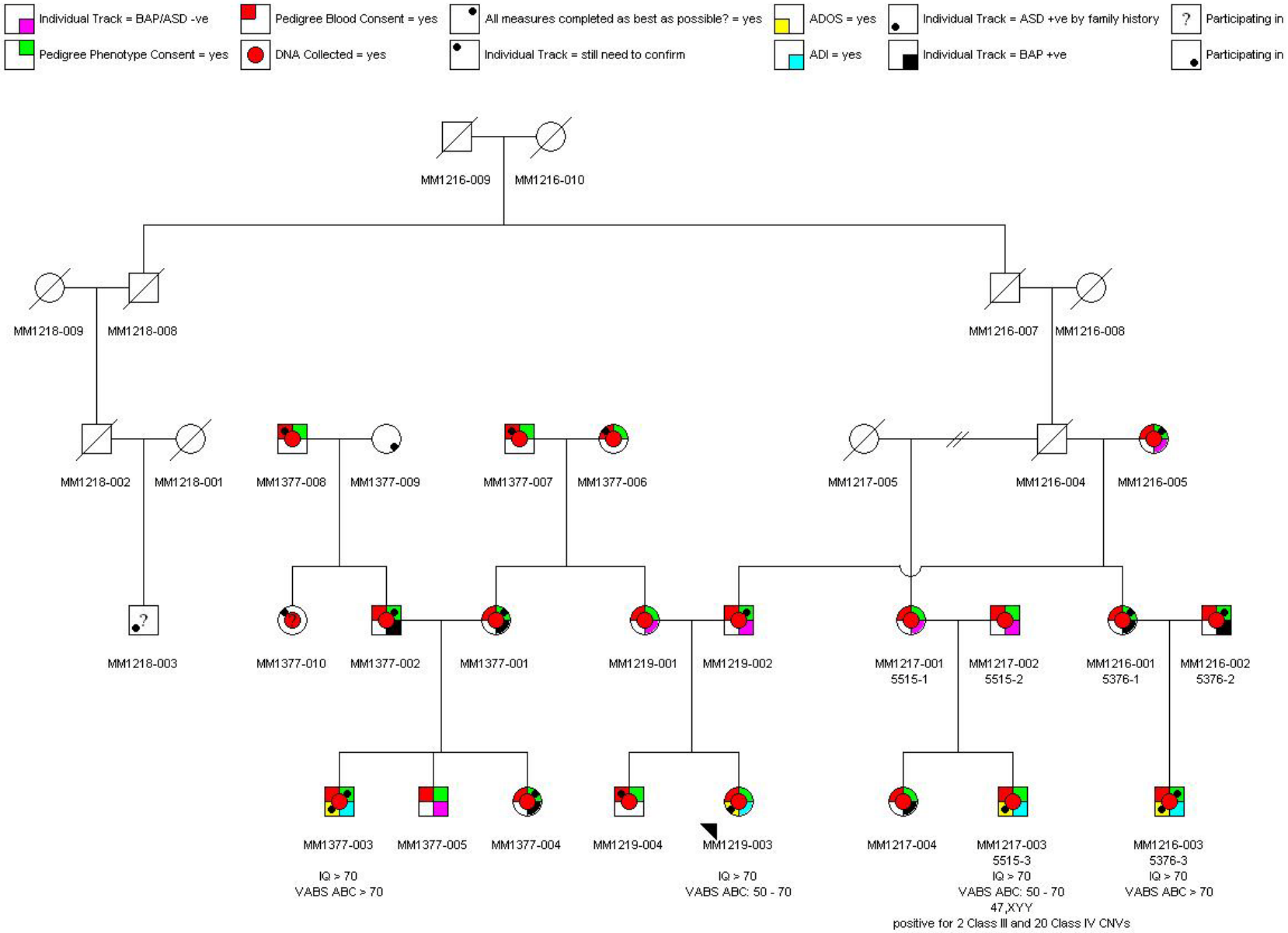
- Collection of highly “familial” cases to identify rare inherited genetic variants that cause ASD
- 3 Nuclear families with ASD within a pedigree
- Phenotype data on affecteds and their first degree relatives

Dense Extended Pedigree Project

- Phenotype data on affecteds and their first degree relatives
- On adults and children with ASD; ADI, ADOS, IQ etc
- On parents and sibs; traits that might be related to autism

Mac1comp

06/12/2010



Mac3comp

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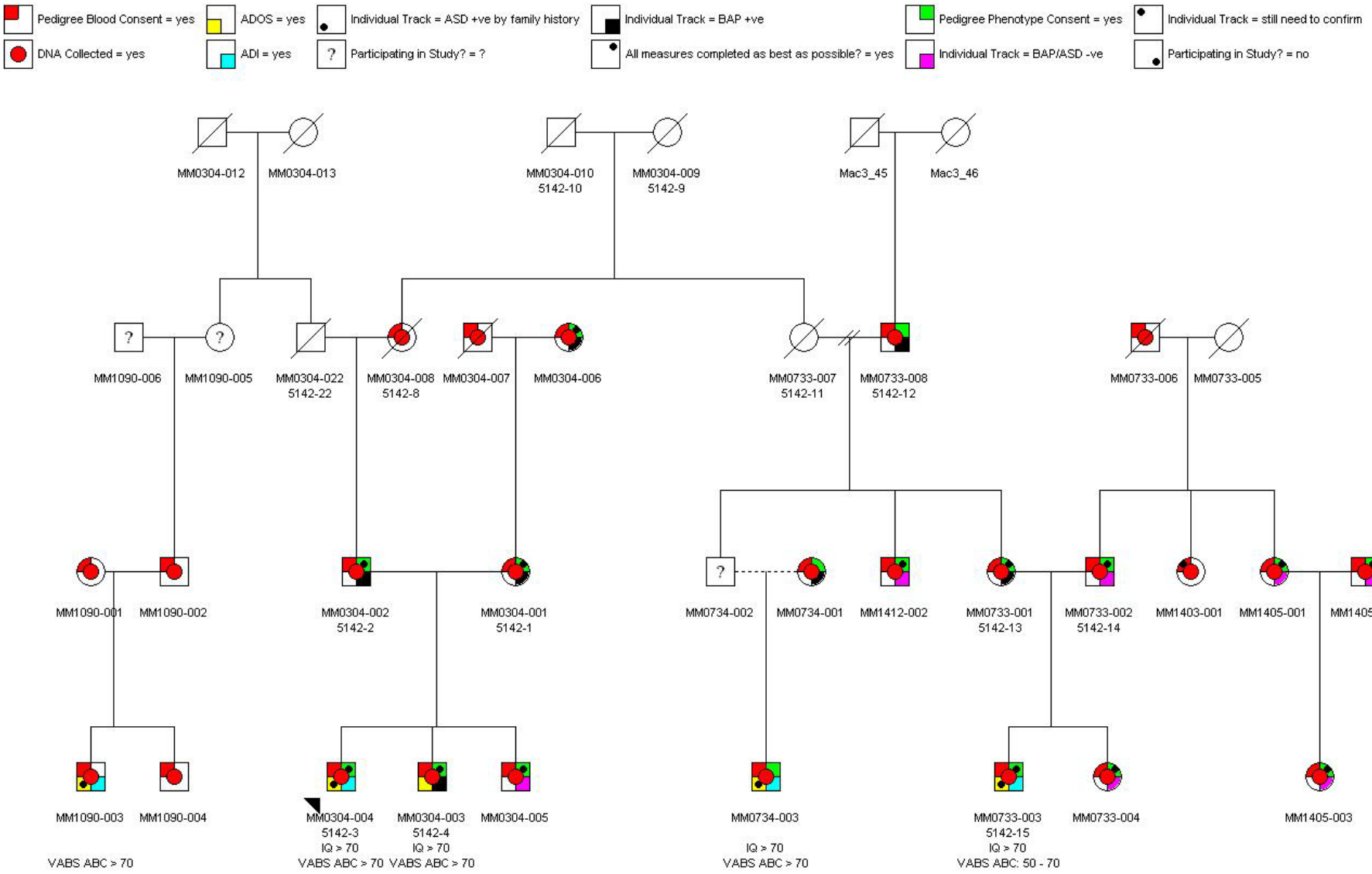

Initial thoughts

- Who are the affected cases in these dense pedigrees?
  - Almost all with autism
  - Sex ratio 4 to 1
  - Almost all (21/25) with IQ>70
- No cases of epilepsy, severe ID, or schizophrenia among affecteds or relatives

Con’t

- One third of parents and sibs have traits related to ASD
- These are equally distributed among males and females
- Some affected children carry the same rare genetic variants we have seen in our other studies

We are we now?

- 26 Pedigrees with many affected relatives across several generations (add 13 with our American colleagues)
- Been funded (CIHR) for another 4 years! Three for data collection and 1 for analysis
- Only funded study of its kind in the world

The CAN-A-GEN Team

- At McMaster;
- Irene O’Conner, Ann Thompson, Ellie Deveau
- Trios; Christina Chrysler, Carolyn Noakes
- In the office; Joan Whitehouse, Bev da Silva, Mike Chalupka
- But a special thanks to all the families who are participating in all these studies

The CAN-A-GEN Team

- At NFLD; Bridget Fernandez, Kathy Whitten
- At HSC: all the people in the room plus John Vincent, Andrew Paterson
- American colleagues; Veronica Vieland, Joe Piven