Ethical issues in genetic risk factor research

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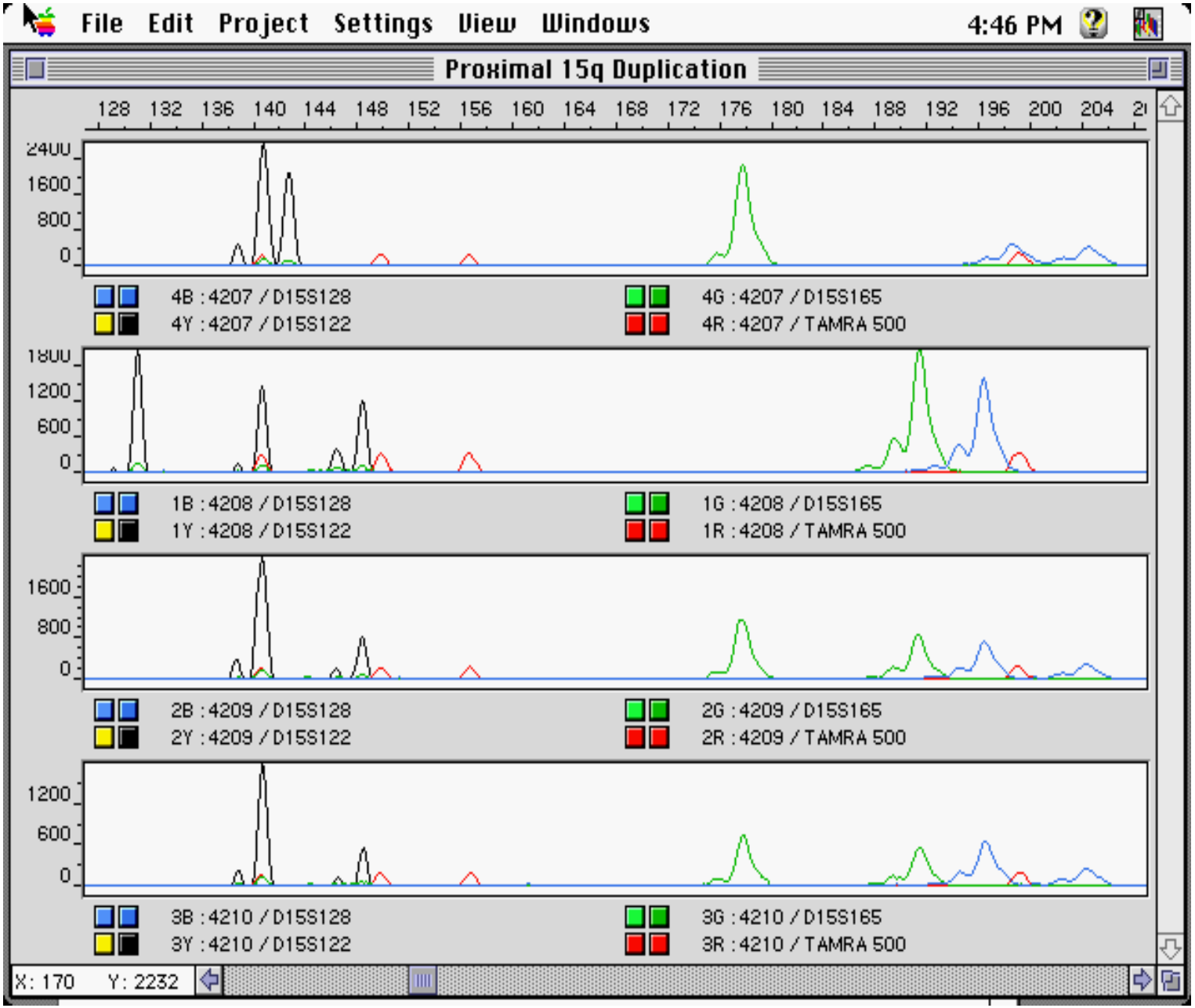
15q11-q13 Maternal Duplication

- Initial goal – map common variants across 15q11-q13 and especially GABA-A gene cluster related to anxiety and epilepsy in autism
- 1995 – consent form had no mention of clinically meaningful findings because frankly not anticipated to have individually meaningful factors
- Then and now, view was that autism etiology was multifactorial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4:46 PM
Proximal 15q Duplication
128 132 136 140 144 148 152 156 160 164 168 172 176 180 184 188 192 196 200 204
2400
1600
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0
4B : 4207 / D15S128
4Y : 4207 / D15S122
4G : 4207 / D15S165
4R : 4207 / TAMRA 500
1800
1200
600
0
1B : 4208 / D15S128
1Y : 4208 / D15S122
1G : 4208 / D15S165
1R : 4208 / TAMRA 500
1600
800
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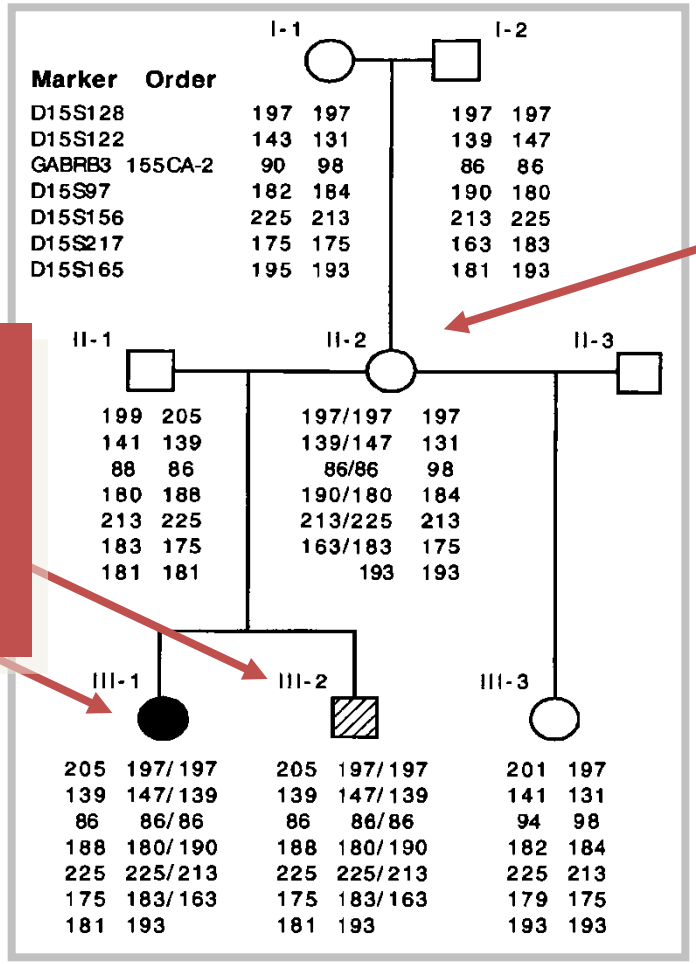
2B : 4209 / D15S128
2Y : 4209 / D15S122
2G : 4209 / D15S165
2R : 4209 / TAMRA 500
1200
600
0
3B : 4210 / D15S128
3Y : 4210 / D15S122
3G : 4210 / D15S165
3R : 4210 / TAMRA 500
X: 170 Y: 2232

15q11-q13 Duplication—Parent of Origin Effect/ 2. Pre-conceptual risk



15q11-q13 dupe from father–no effect

15q11-q13 dupe from mother–autism or Asperger's syndrome

- Bolton and colleagues confirm increased risk for developmental disorders with maternal compared with paternal 15q11-q13 duplication*

*Bolton PF et al. *Am J Med Genet.* 2001;105:675-685.

15q11-q13 Duplication Pre-conceptual Counselling

- Later approached by mother who requested prenatal counseling and would not have become pregnant without the knowledge from fetal testing
- 20% risk for ASD (baby sibs paper in Pediatrics) to 33% after two affected, is 50% risk that much of a difference to a given parent ? – concern was about suffering of her child, not intellectual disability
- No duplication found from chorionic villus sampling (CVS) – parent was unsure what she would have done if duplication had been present
- In this case, the opportunity to know the risk is likely substantially reduced (but not zero)
- Other risks unaffected or paradoxically may have increased
  - e.g. possibly some risks related to having more group social interaction (e.g. drug abuse)

Implications for Identification of Strongly Implicated Findings

- IDEAs, now dup 15q alliance (http://www.idic15.org/)
- Considerable support, among parents and those with dup 15q11-q13 ranging from children to adults
- Identification of risk for sudden unexpected death
- Another ethical concern – duty to warn the group of a pharmacogenetic risk ?

Pros and Cons in the Balance

- Insufficient data – rate of sudden unexpected death higher but about level of refractory epilepsy (but occurring in mostly controlled epilepsy)
- Association with GABA-A agonists in death during sleep which may be associated with failure to restore respiration after seizure or deep sleep
- However, may have been on GABA-A agonists due to their epilepsy – exception – single dose of Ambien and death that night

Sudden Death Statement for Physicians

- Most primary care physicians would have only one patient
- Provided for families to take to their physicians with explicit instructions only to make changes in consultation with their physicians
- Obsessive document (probably so much so interfered with the communication)
- Outcome – sudden unexpected death rate has reduced (but is this the fall of a rare event)

Simons Foundation Approach

- Over 2500 children with ASD and unaffected siblings
- Highest odds ratio is threshold at which 5% of those with ASD have a CNV and 1% of unaffected siblings
- However, which of the 5% at that threshold are likely pathogenic CNVs
- Expert team relying highly on rapidly developing databases such as ISCA database

“Clinical significance”

- For an example of 10 flagged for review, 2 or 3 are undisputed and probably don’t need reference to a database
- About half are uncertain pending additional data although in many cases, the data are sufficient to show modest odds ratio
- About 2 or 3 are likely not “clinically relevant”

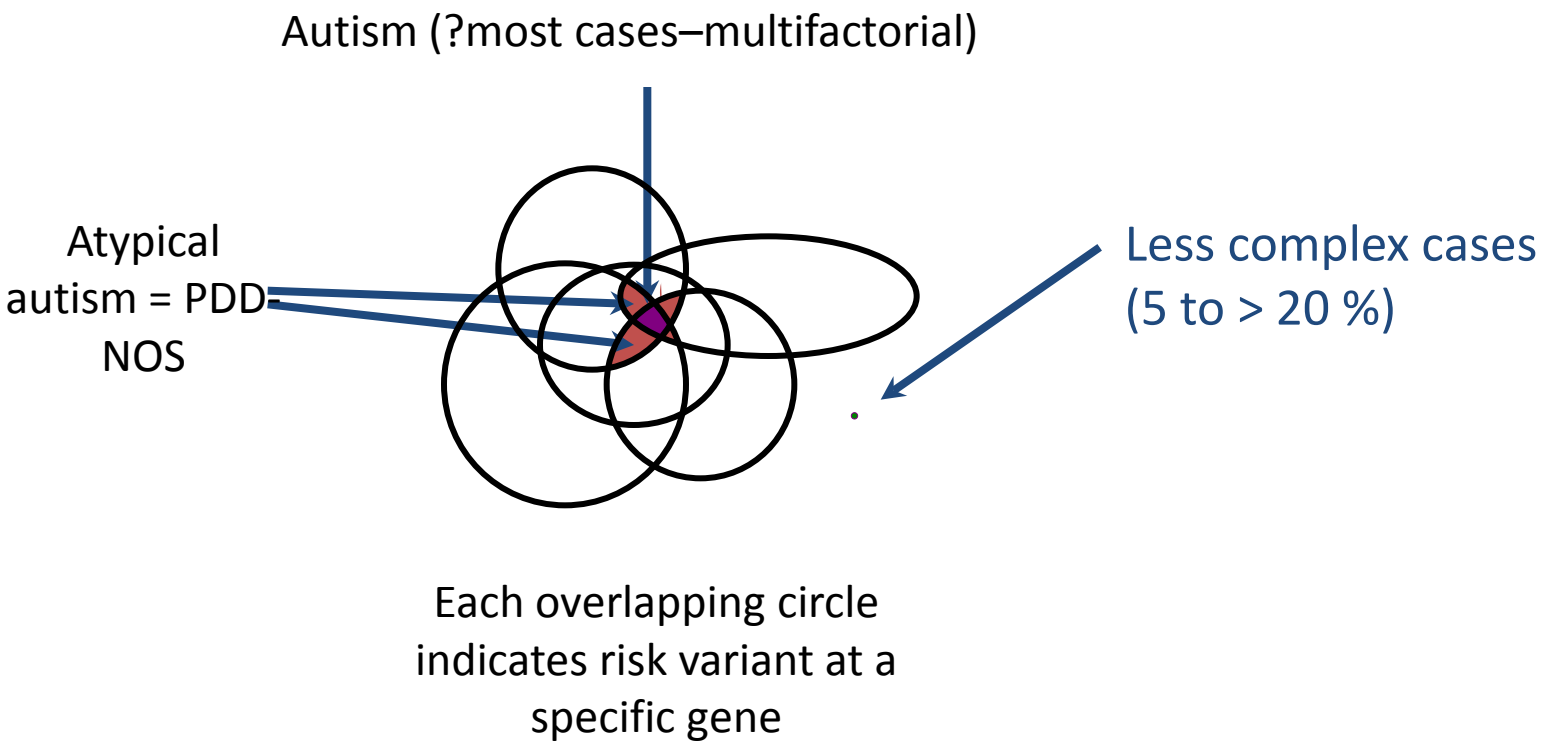
What may be predicted ?

- 16p11.2 duplication and deletion (need to have the precise genetic coordinates and map being used – e.g. hg18 vs. hg19)
- Highly significant risk factor for ASD
- However, if someone was identified early in development with such a deletion the range of outcome could be from obesity without LD to ASD & ID to schizophrenia
- Therefore specific predictions are often limited and are stronger for ID for some findings than for ASD

Language

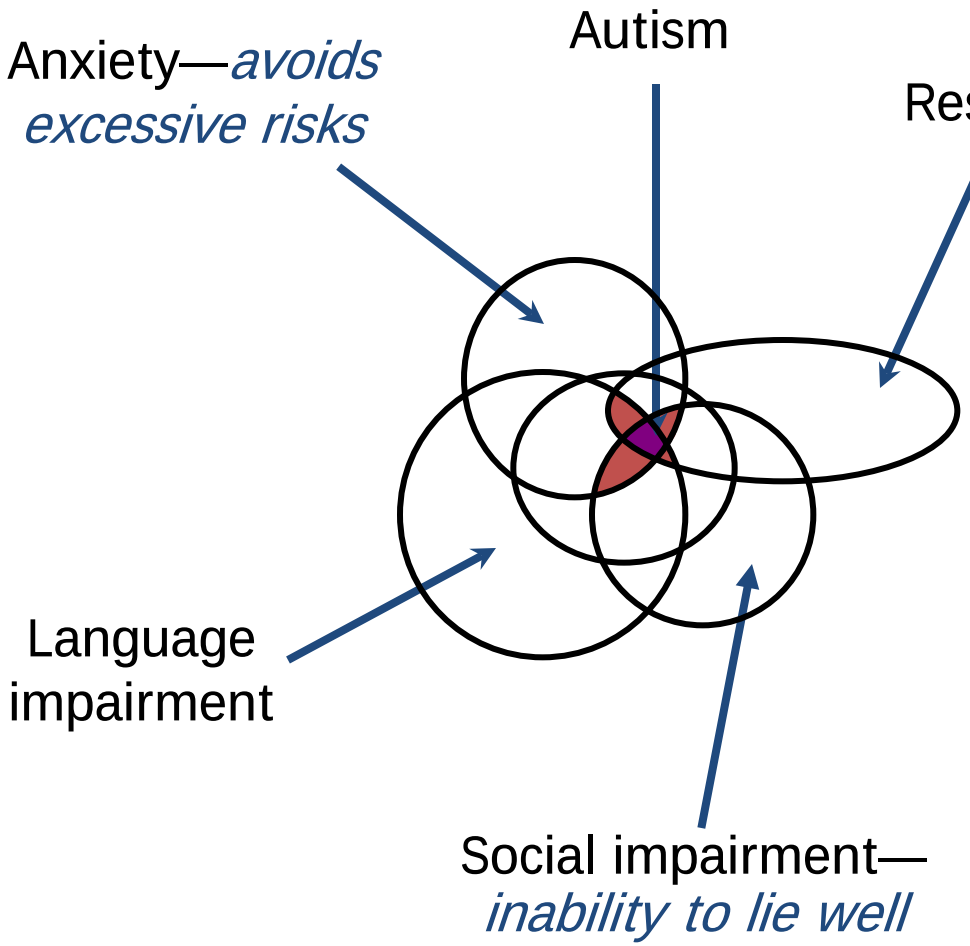
- Most of ASD explained by complex interplay of common genetic and environmental variants and chance
- A very complex multivariate equation
- That equation includes stronger effects but often not present and don’t affect risk
- Almost none of the variants are ASD specific
- Strongly implicated used in the AGP-CNV paper by Pinto and colleagues, 2010, NOT CAUSAL

Genetic Model of Autism



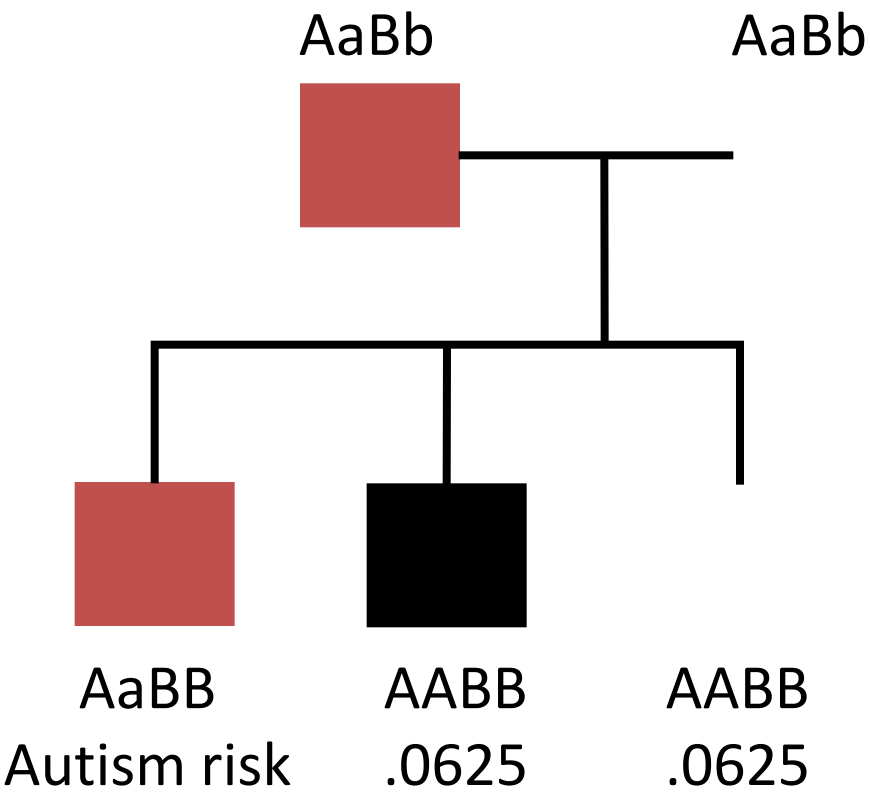
Most likely model is that the “less complex” cases represent situations where the chromosomal or single gene variant is equivalent to a number of smaller effect risk variants

Beneficial Effects of Risk Variants?



- Context is essential
  - Gene-gene interactions
  - Gene-environment interactions

Multiplicative Recessive Genetic Disorder Model—2 Interacting Recessive Loci



- A,B risk alleles;
  a,b protective alleles
- If A and B equally common and population prevalence is 1:500
- Frequency of A and B 21% each
- At least 1 “risk” allele: 61% of population
- Double-carriers 15% of population

Genetic Knowledge & Autism Ethics & Policy

- Insurance discrimination
  - All are at risk for common, developmental neurobiological, and other medical disorders
  - Risk for one illness may decrease risk for others and/or be associated with strengths
- Respect for persons with autism is vital aspect of humanity
- Provision of appropriate education, behavioral intervention, pharmacological management, quality adult placements, family and community supports are essential (but not ubiquitous)

Implications of Genetics of Autism

- Genetic etiology doesn't reduce need for habilitation, education, or any other non-genetic treatment
- Idea is to help empower patient and families
- Inherited risk genes for most diseases likely shared partly by all, has implications for parent blaming (Stop parent blaming, but parental guilt is not an easy thing to stop)

Why genetics remains relevant to ASD

- Predictions of ASD or severity of any given ASD-related dimension based on genetics will be limited in vast majority of cases (multiple protective and risk genetic variants and multiple environmental protective and risk factors)

- Point of genetics:
  - 1) develop new treatments by understanding pathophysiology and developing paths to new interventions (e.g. FRAXA to Seaside trials) or preventative strategies (can we find another PKU?)
  - 2) help to choose available treatments