Autism is a Complex Genetic Disorder

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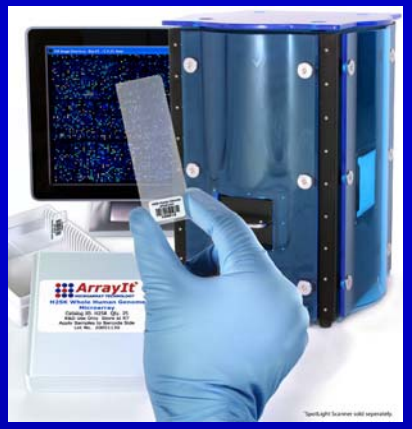
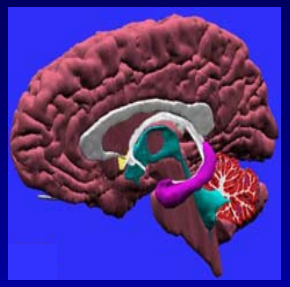
1. ***Why Genetics?***
2. What does it mean autism is genetic?
3. Finding the Gene/s - Linkage
4. Finding the Gene/s - Association
5. How many genes?
6. Reducing Heterogeneity
7. Outlook

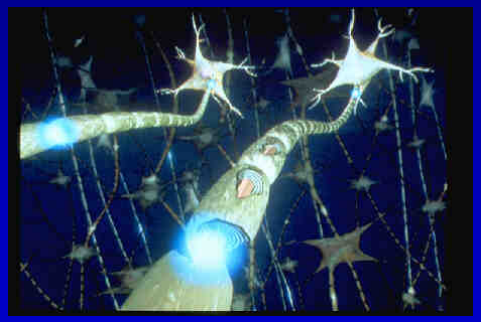

ArrayIt

Why Genetics?

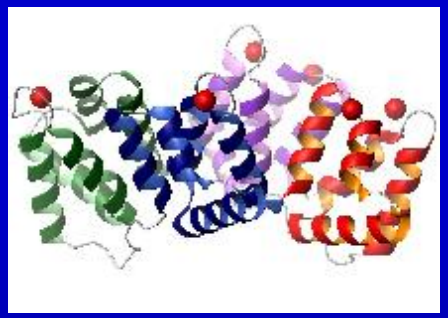
- Child Psychiatric Disorders
  - Run in Families
  - MZ concordance > DZ concordance
- Heritability estimates
  - Autism > 0.9
  - ADHD 0.6-0.8
  - Early onset Bipolar Disorder 0.8
  - Conduct Disorder 0.5



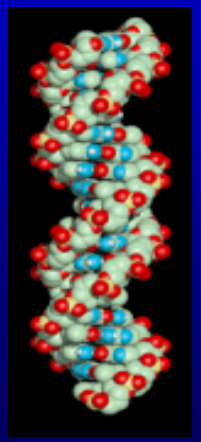
Brain



Neuron



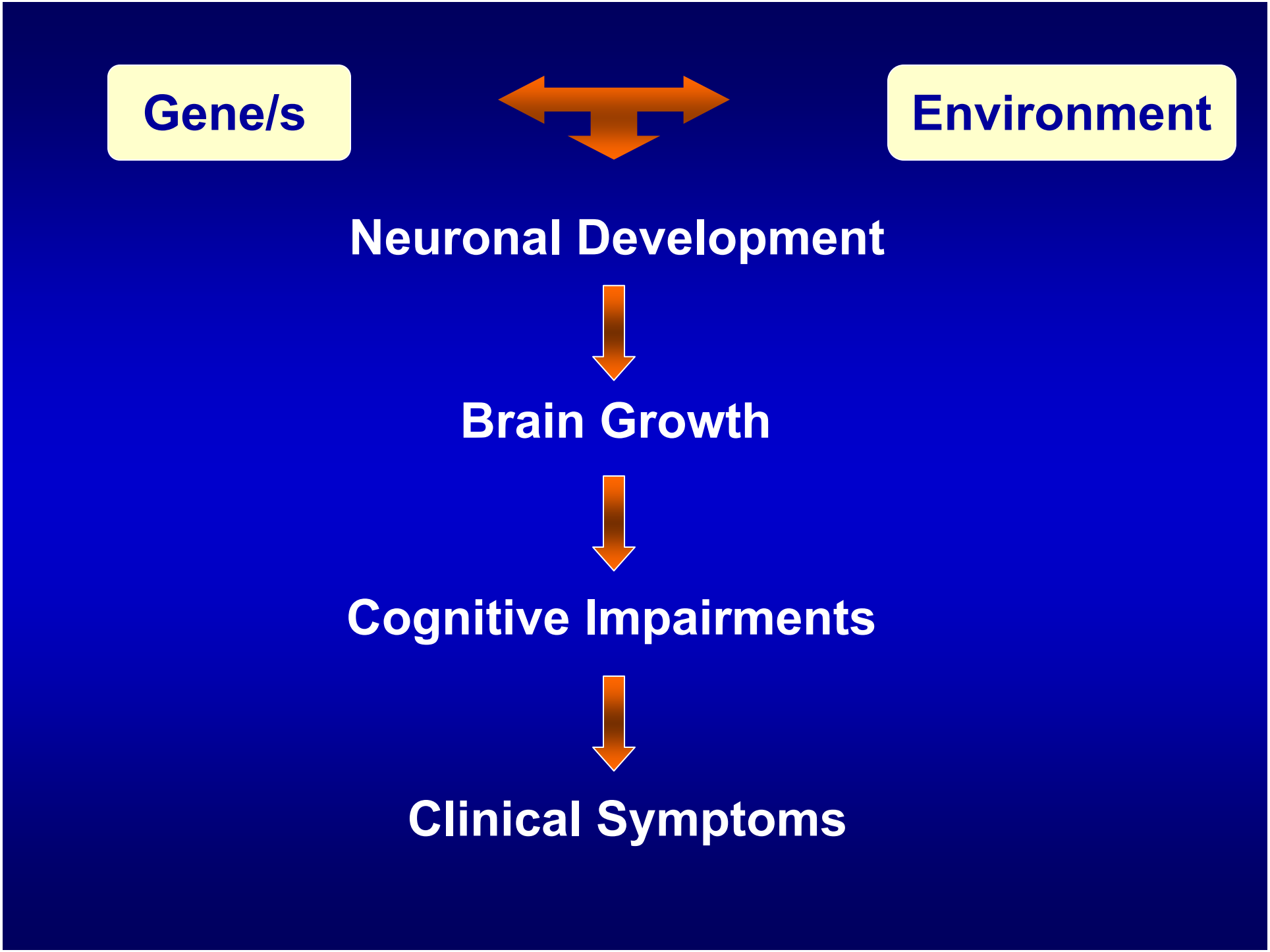
Protein



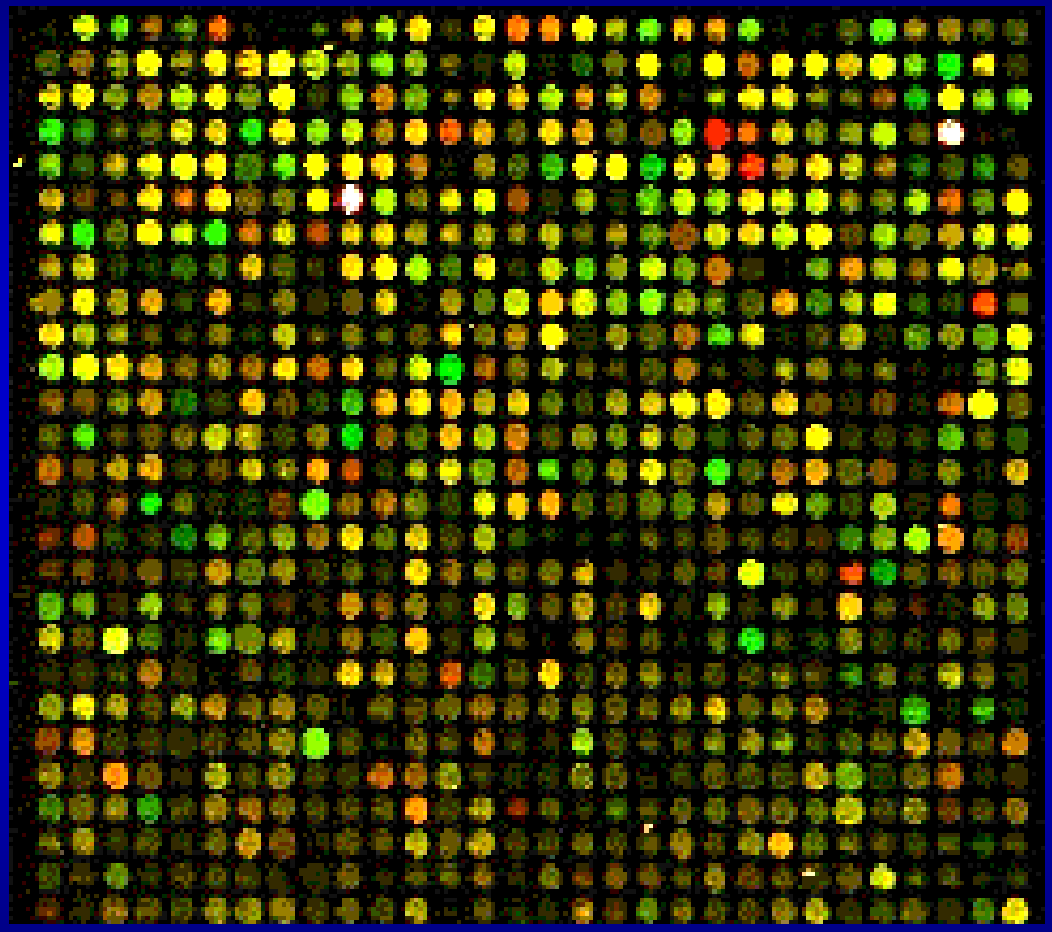
DNA

Complexity

45.000 Genes


Gene/s
Environment
Neuronal Development
Brain Growth
Cognitive Impairments
Clinical Symptoms

Technology



CHEAP GENOTYPES

1. Why Genetics?
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Genes are

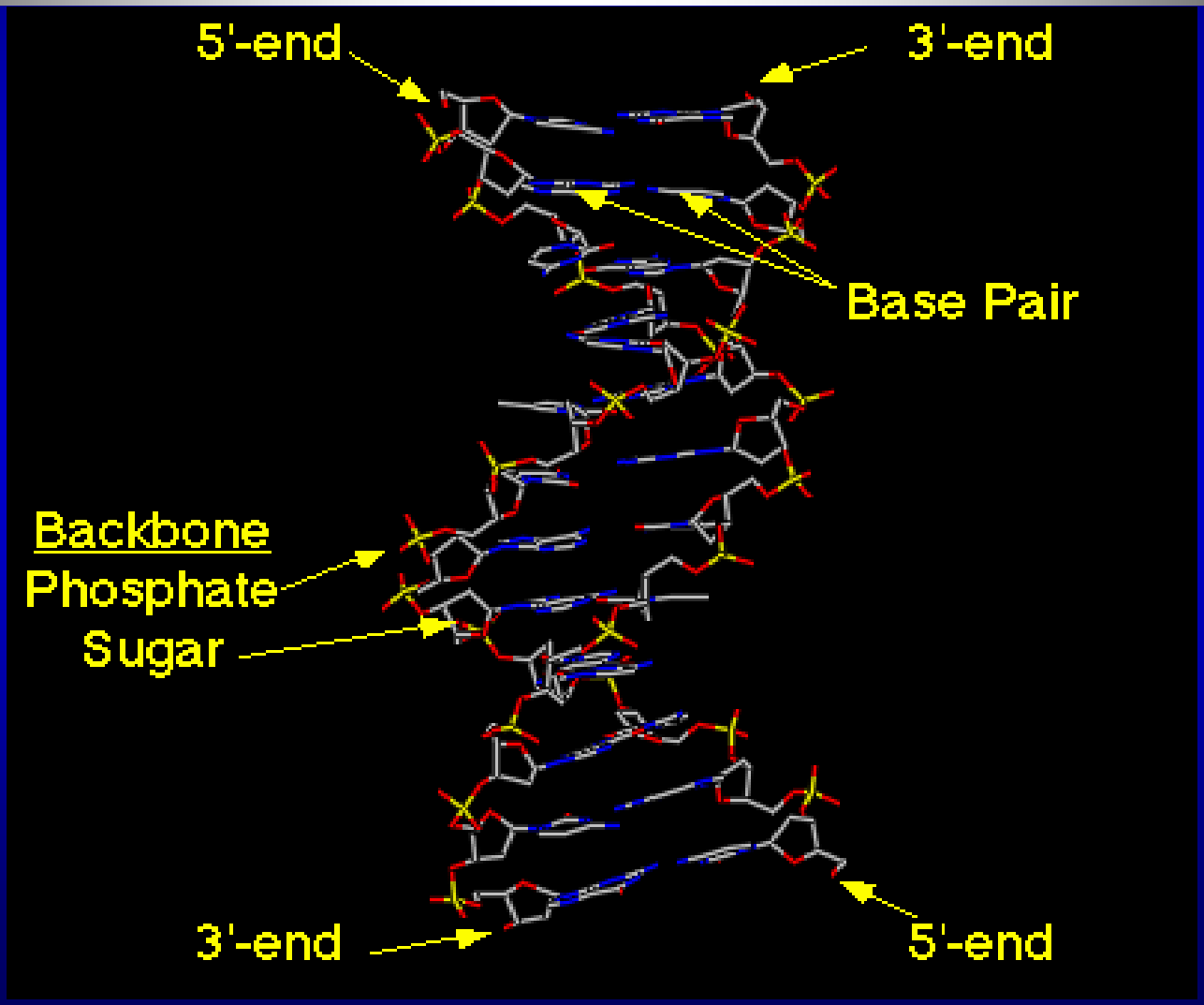
Molecules

Interacting with

Other

Molecules

DNA



Genes and Development

- “The very meaning of DNA sequence is relational” (Keller, 2005)
- Any phenotype is the result of interactions between a specific set of genes and specific environments
- Phenotype product of Development
- Prediction of the Future presence of a trait is not accomplished by identifying the trait with genes, but by understanding the developmental system
- A simplified Nature-Nurture Dualism is not tenable

Why Find the Gene/s?

- Better understanding of pathophysiology
  - Function of gene/s
  - Develop models
- Psychiatric Disorders are not monogenic
  - Targeted Research
  - Targeted Treatment
- Environmental Factors
- Final Goal – Gene x Environment

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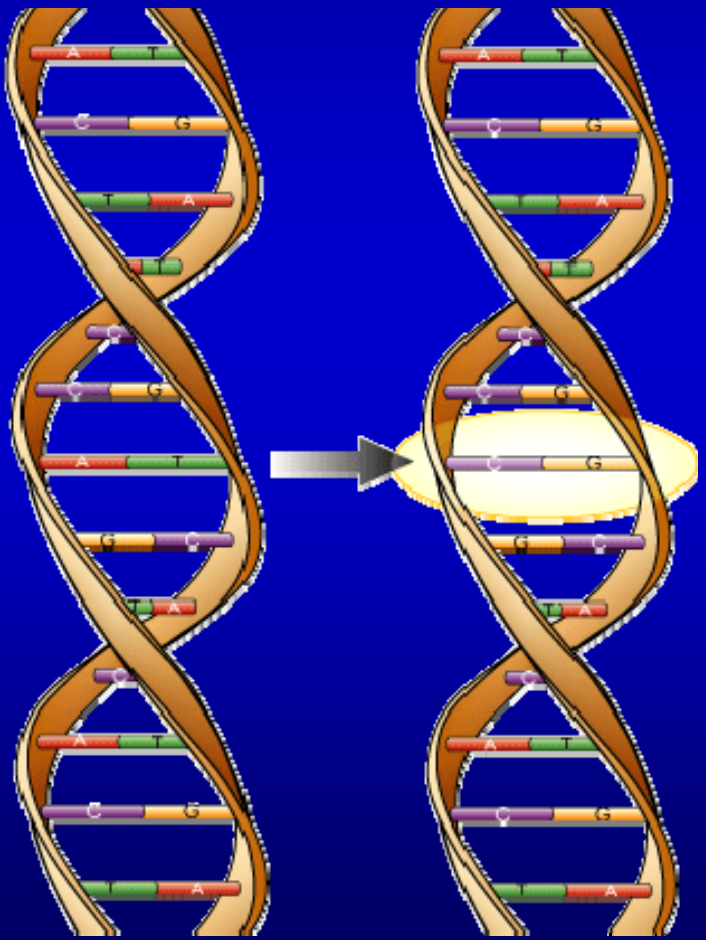
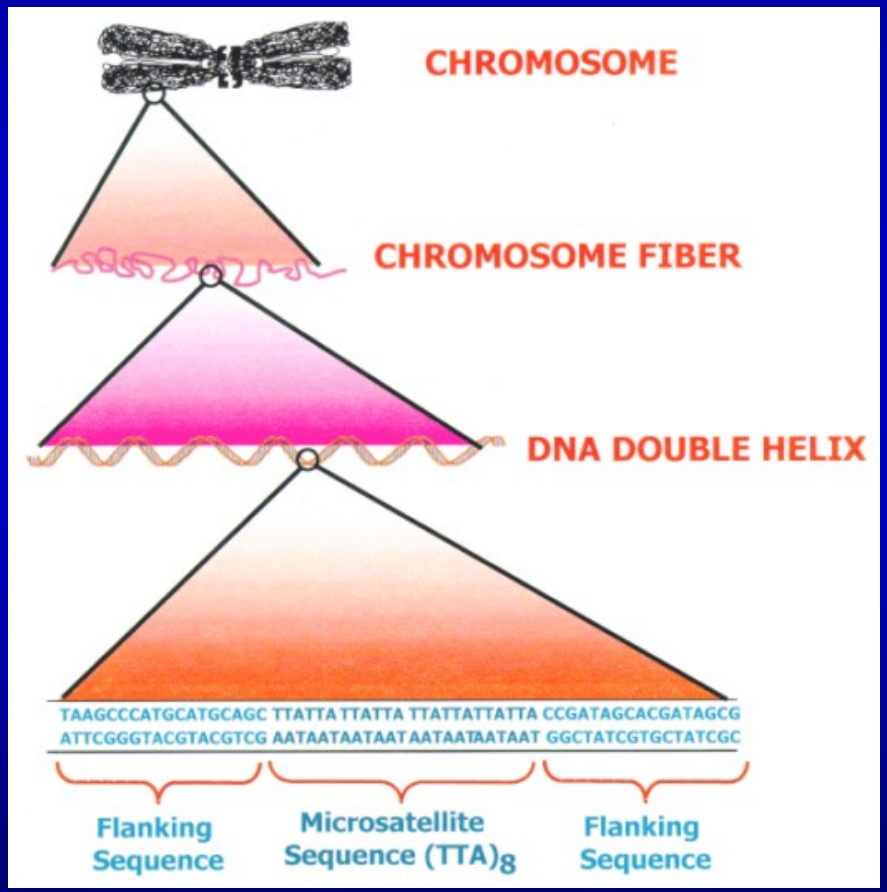
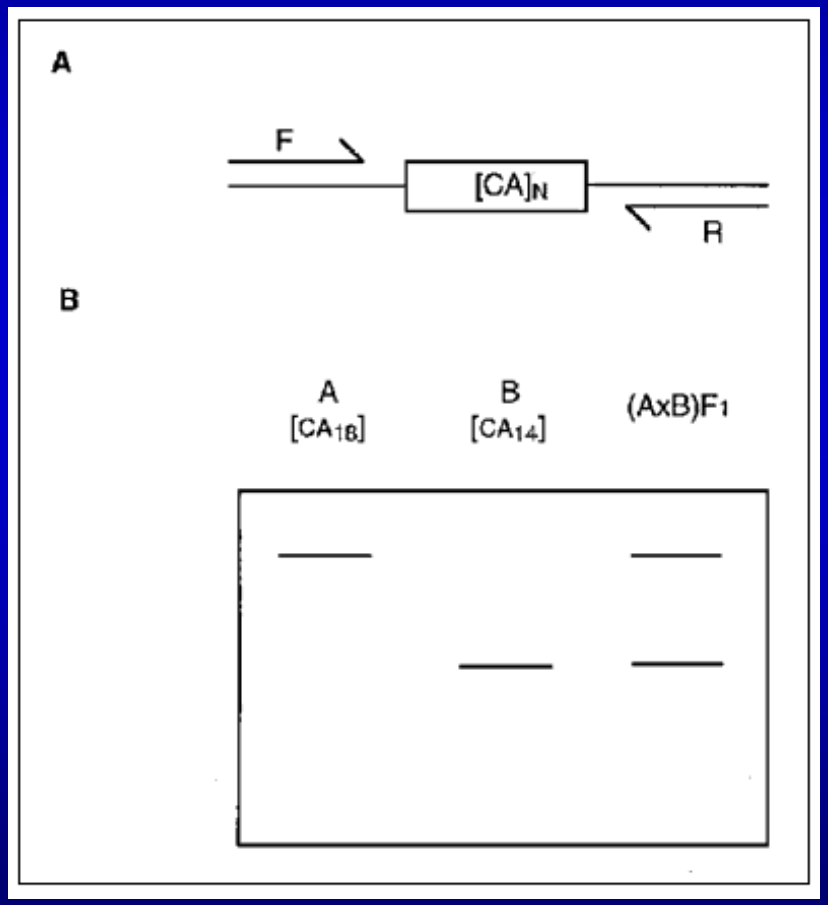
Single Nucleotide Polymorphism



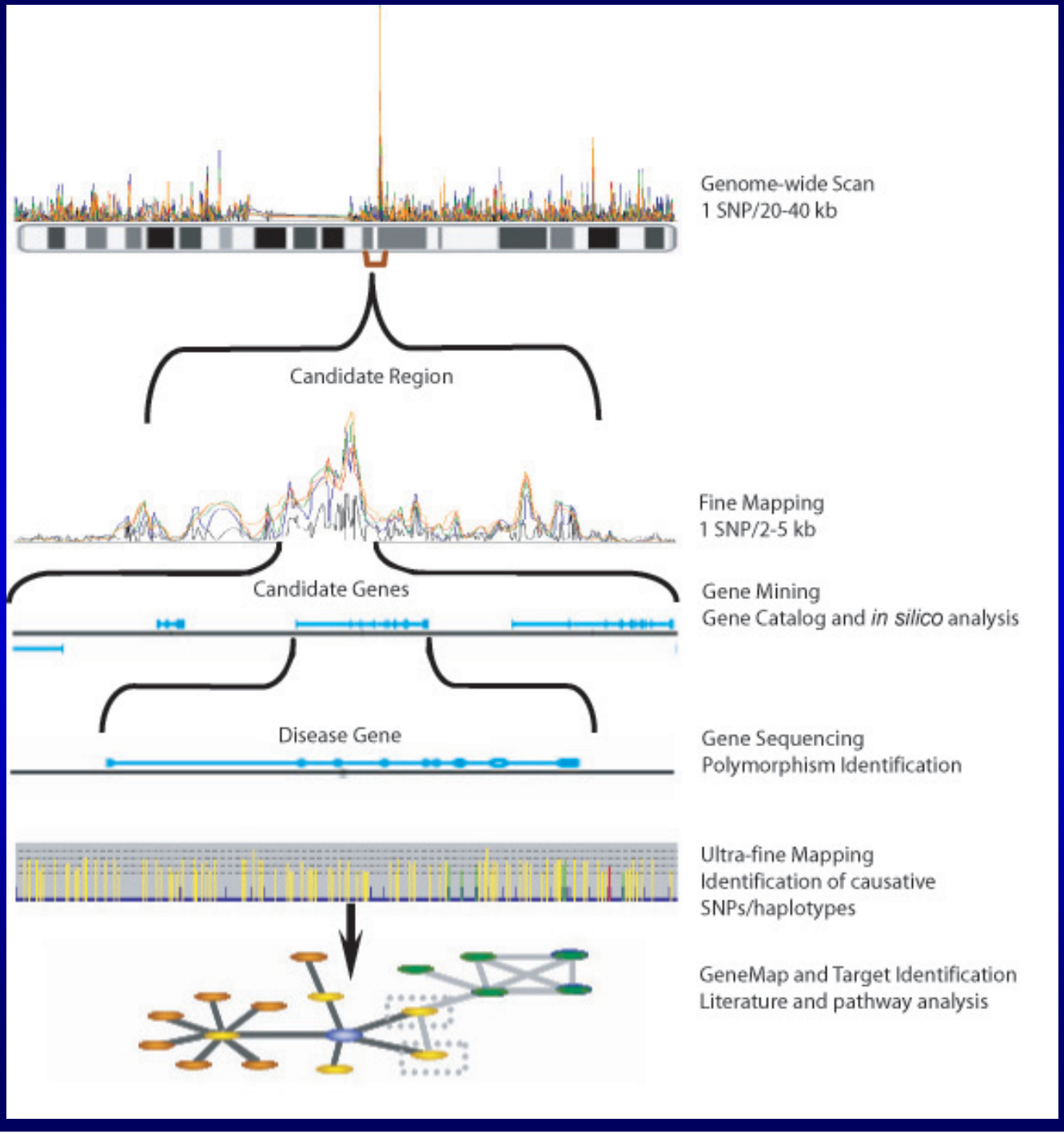
Microsatellite





Human Genome

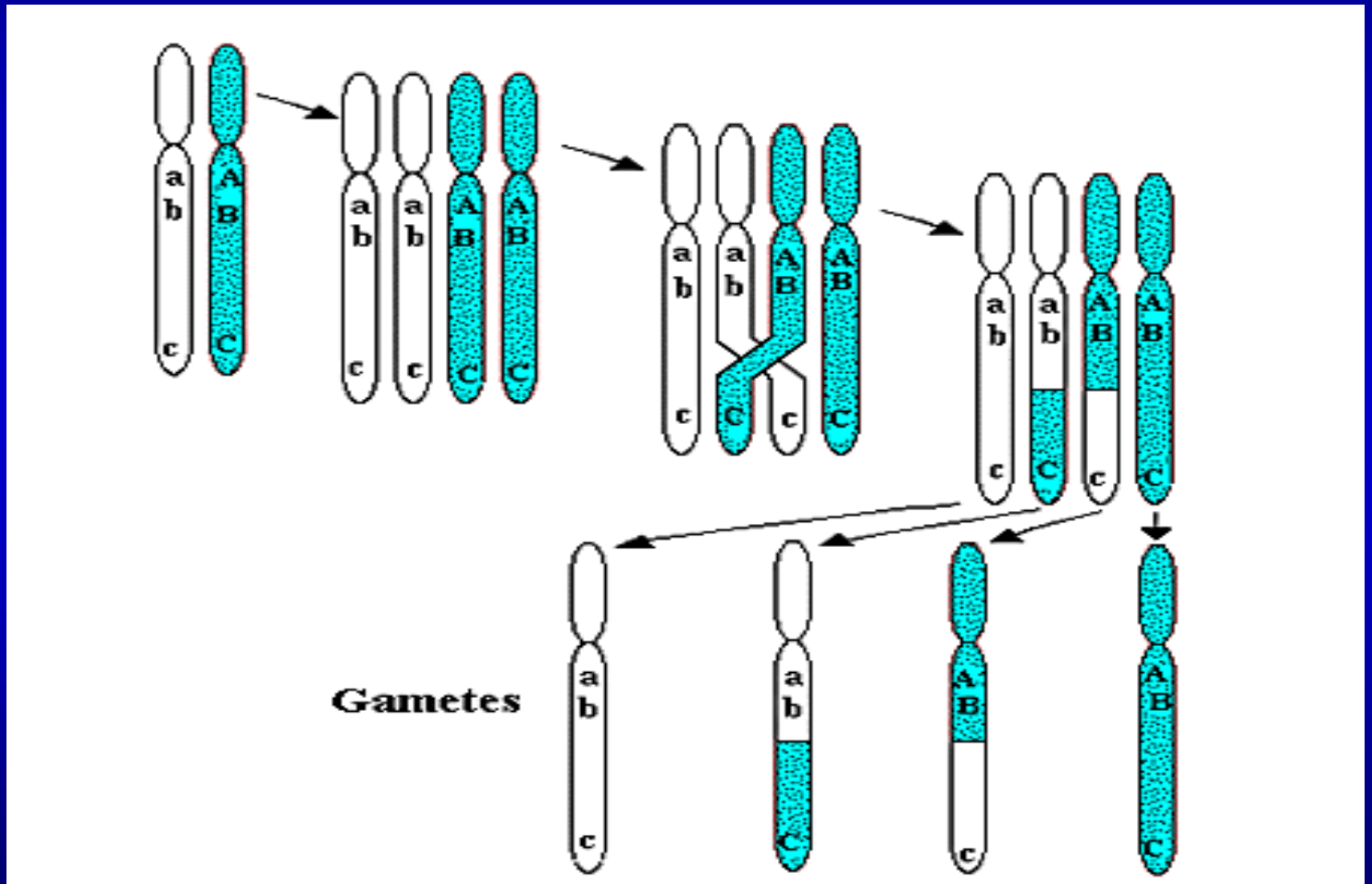
- ~3,300 million base pairs
- <1.5% are typical genes
- Number of genes
  - Estimates vary between 28,000 and 120,000
  - Best estimate - ~41,000-45,000
- 43% repetitive elements (>4.1 million)
- Locations of ~ 6 million SNPs known


Genome-wide Scan
1 SNP/20-40 kb
Candidate Region
Fine Mapping
1 SNP/2-5 kb
Candidate Genes
Gene Mining
Gene Catalog and *in silico* analysis
Disease Gene
Gene Sequencing
Polymorphism Identification
Ultra-fine Mapping
Identification of causative
SNPs/haplotypes
GeneMap and Target Identification
Literature and pathway analysis

Finding the Gene/s - Linkage

- More than one affected family member
- Based on Recombination
- Power dependent upon increase in risk to relative
- Genome-wide
  - ~500 markers evenly spaced microsatellites
  - 5-10,000 SNPs
- Results have not been unequivocal

Linkage – Recombination

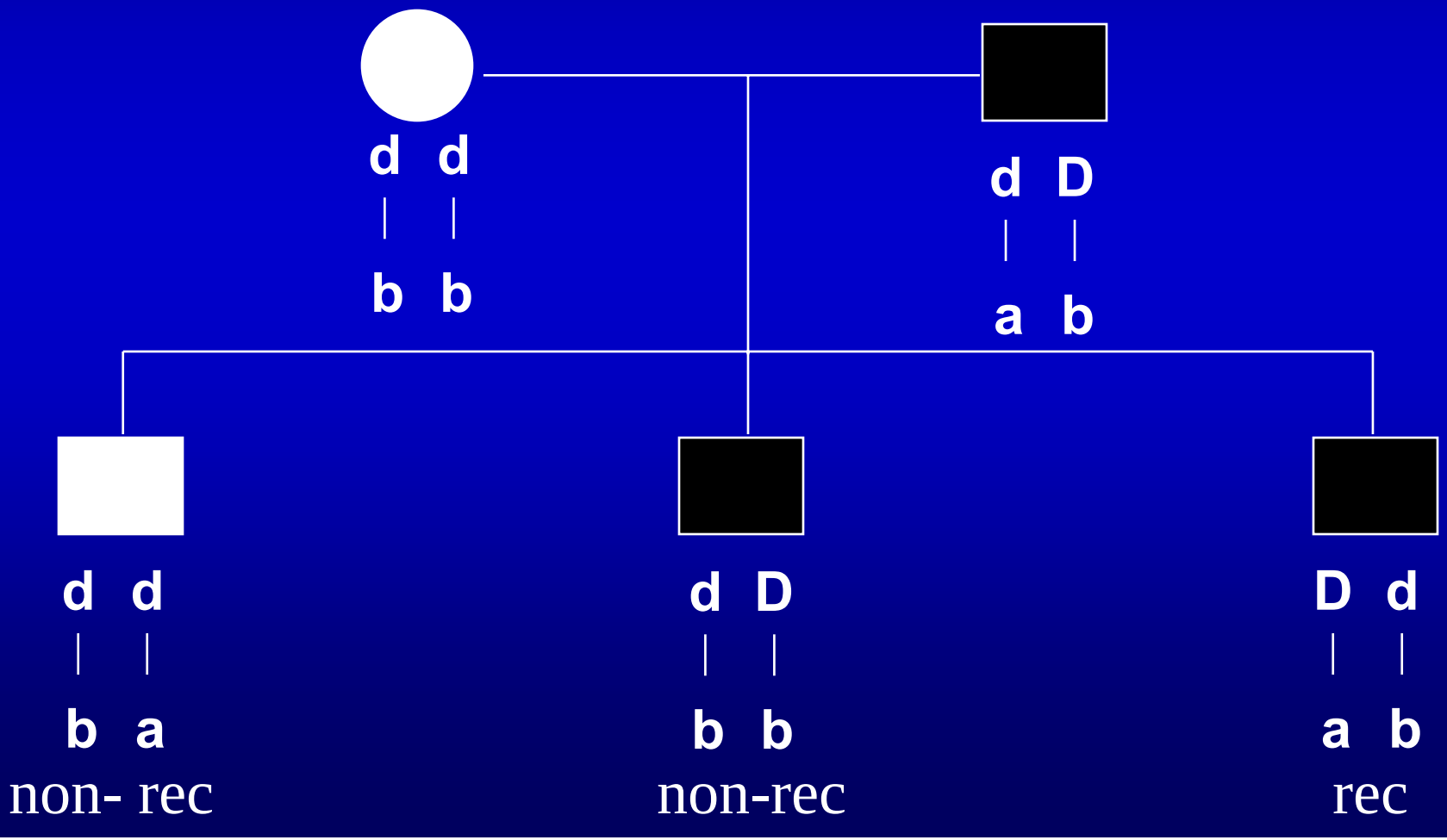


Crossing-over and recombination during meiosis

Linkage

- Tests the co-segregation between a marker and a disease
- Requires families with more than one affected family member (multiplex - MPX)
- Based on Recombination
- Power dependent upon increase in risk to relative
- Markers are tested evenly spaced across the entire genome
- Lod score serves as summary statistics
- Lod>3 considered evidence for linkage

Linkage Analysis – Dominant Allele D



Linkage Analysis – What to expect

- Small number of markers
- Chromosomal Region
  - Can be large
    - >50 million base pairs
- Requires follow-up studies
- Results are restricted to multiplex families

Linkage Studies - Autism

Chr.	LOD score >2.0	References
1	D1S1675 (p13.2)	Risch, Am J Hum Genet 1999; 65: 493–507.
	D1S1653 (q23.2)	Auranen M, Am J Hum Genet 2002; 71: 777–790.
	D1S1656 (q42.2)	Buxbaum JD, Mol Psychiatry 2004; 9: 144–150.
2	D2S2188 (q31.1)	IMGSAC. Am J Hum Genet 2001; 69: 570–581.
	D2S364 (q31.3)	Buxbaum JD, Am J Hum Genet 2001; 68: 1514–1520.
3	D3S3037 (q26.32)	Auranen M, Am J Hum Genet 2002; 71: 777–790.
	D3S3680 (p25.2)	Shao Y, Am J Med Genet 2002; 114: 99–105.
4	D4S1647 (q23)	Buxbaum JD, Mol Psychiatry 2004; 9: 144–150.
5	D5S2494 (p13.1)	Liu J, Am J Hum Genet 2001; 69: 327–340.
	D5S1473 (p14.3)	Yonan AL, Am J Hum Genet 2003; 73: 886–897.
		Buxbaum JD, Mol Psychiatry 2004;9: 144–150.
6	D6S283 (q16.3)	Philippe A, Hum Mol Genet 1999; 8: 805–812.
	D6S261 (q22.1)	Buxbaum JD, Mol Psychiatry 2004; 9: 144–150.
	D6S1270 (q14.3)	
7	D7S1813 (q21.2)	Barrett S, Am J Med Genet 1999; 88: 609–615.
	D7S483 (q36.1)	Liu J, Am J Hum Genet 2001; 69: 327–340.
	D7S477 (q22.1)	IMGSAC. Am J Hum Genet 2001; 69: 570–581
	D7S2462 (q36.2)	and: Hum Molecular Genetics 2001; 10: 973–982.

Linkage Studies - Autism

Chr.	LOD >2.0	References
10	D10S1412 (p14)	Buxbaum JD, Mol Psychiatry 2004; 9: 144–150.
11	D11S1392 (p13) D11S1993 (p12) D11S1392 (p13)	Yonan AL, Am J Hum Genet 2003; 73: 886–897. Buxbaum JD, Mol Psychiatry 2004; 9: 144–150.
13	D13S1229 (q12.3)	Barrett S, Am J Med Genet 1999; 88: 609–615.
16	D16S3102 (p13.13)	IMGSAC, Am J Hum Genet. 2001; 69: 570–581.
17	HTTINT2 (q11.2) D17S1800 (q11.2) SLC6A4 (q11.2)	IMGSAC, Am J Hum Genet 2001; 69: 570–581. Yonan AL, Am J Hum Genet 2003; 73: 886–897. McCauley JL, Am J Med Genet 2004; 127B: 104–112.
19	D19S433 (q12) D19S714 (p13.12)	Liu J, Am J Hum Genet 2001; 69: 327–340. Buxbaum JD, Mol Psychiatry 2004; 9: 144–150.
X	DXS1047 (q25)	Liu J, Am J Hum Genet 2001; 69: 327–340.

Increasing Sample Size

- Power in Linkage Studies
  - λ_r = Risk increases in siblings/Risk in population
- Risk increase of conferred by mutations in specific gene may be low due to heterogeneity
- Solution – Increase Sample Size

Finding the Genes

- Large-Scale Collaborative Studies
  - AGP – Consortium of 13 Groups (>20 Universities)
    - >1500 Multiplex families
    - ~ 2000 Trios
    - Phase 1: Affymetrix 10k SNP Chip
    - Phase 2: Fine Mapping

AGP – Phase 1

- Genotypes from TGEN (contract service)
- 10,112 SNPs
  - Completion rate of genotypes/SNP ≥ 90%
  - Completion of genotypes/individual ≥ 80%
- Hardy Weinberg tested in “Europeans”
- Discordant call rate: ≈ 5/10,000 (from duplicates)

AGP – Phase 1

- Diagnostic Groups
  - Narrow: ADI + ADOS = Autism (all)
  - Broad: ADI + ADOS = Autism for ≥ 1 sib
  - hASD: ADOS missing or both sibs ASD by ADI and ADOS
  - Broad + hASD families = Total MPX families

Lod Scores and Sample Size

- Replication - the “holy grail”
- Reality for complex disorders
  - “Strong evidence” diminishes with more data
- Many genes
  - Different samples will maximize at different locations
  - Very large sample sizes are required
- Large samples allow to subdivide phenotype

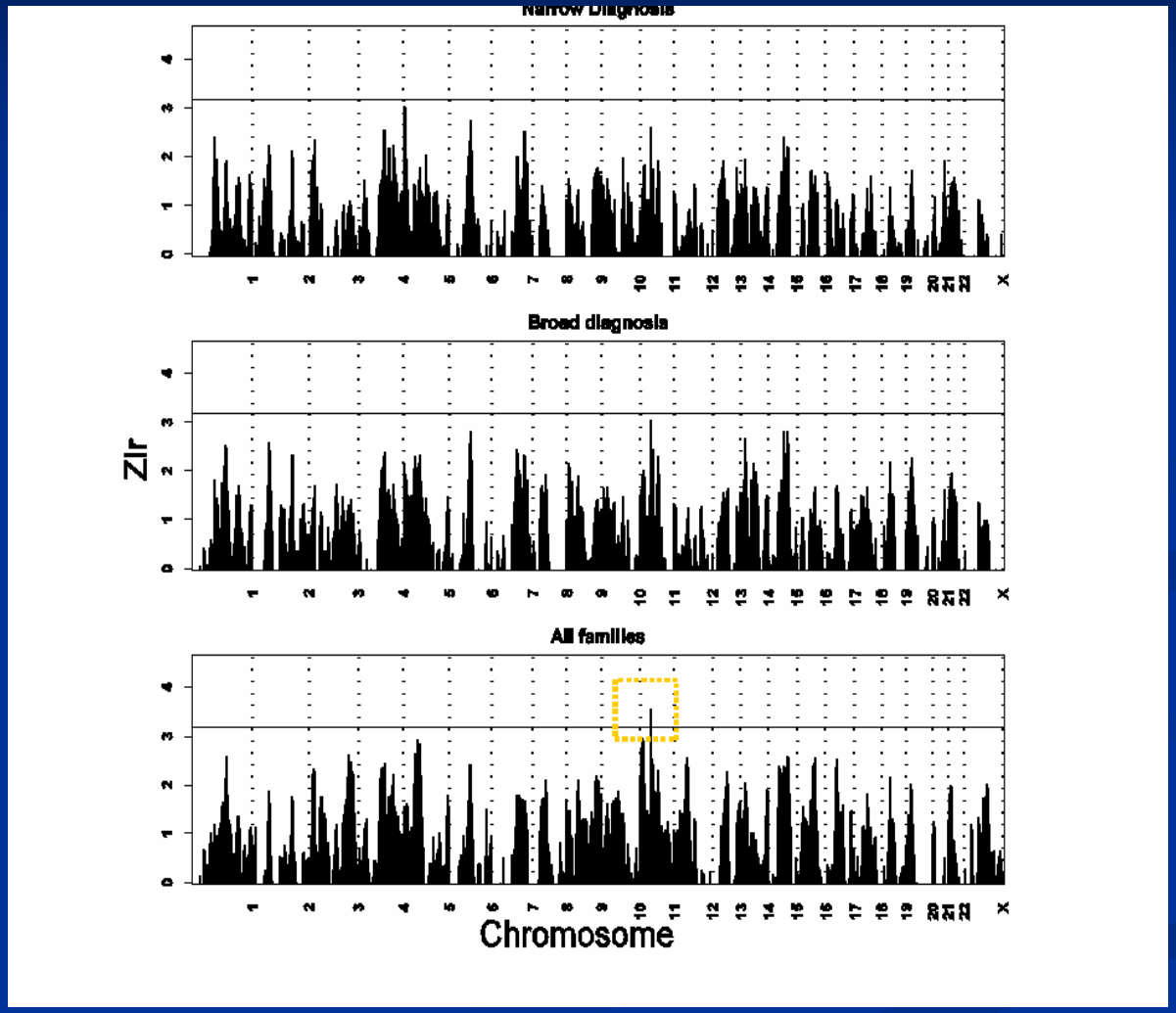
Linkage analysis by diagnostic group.

multiplex

N = 522

N = 739

N = 1168



11p12-p13

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Finding the Gene/s - Association

- Singleton Families
- Based on increased number of allele in disease population compared to control population
- Power dependent upon increase of risk conferred by the allele
- To cover genome
  - 500,000 to 1,000,000 markers
  - Under way - None published for child psychiatric disorder
  - Most studies so far - Candidate Genes

Candidate Genes - Autism

Chr.	Association	References
1	MTF1 (p34.3) - Metal-regulatory transcription factor 1(MTF1)	Serajee FJ, J Child Neurol 2004; 19: 413–417.
2	INPP1 (q32.2) - Inositol polyphosphate-1-phosphatase (INPP1) SLC25A12 (q31.1) - Mitochondrial aspartate/glutamate carrier	Serajee FJ, Journal of Medical Genetics 2003; 40: e119 Ramoz N, Am J Psychiatry 2004; 161: 662–669.
6	HLA-DRB1 (p21.32)	Torres AR, Hum Immunol 2002; 63: 311–336.
7	WNT2 (q31.2) - Wingless-type MMTV integration site family member 2) UBE2H (7q32) - E2 enzyme of the ubiquitin-dependent proteolytic system Glutamate receptor 8 gene (q31) PIK3CG (q22) - Phosphatidyl 3-OH-kinase gene (PIK3CG) RELN (q22) - Reelin LAMB1 (q31.1) - Laminin Beta-1 NRCAM (q22.3) - Neuronal Cell Adhesion Molecule Engrailed2 (En2) (q36) - Homeobox transcription factor Engrailed2 FOXP2 (7q31) - Forkhead Box P2	Wassink TH, Am J Med Genet 2001; 105: 406–413. Vourc'h P, Psychiatr Genet 2003; 13: 221–225. Serajee FJ, J Med Genet 2003; 40: e42 Serajee FJ, J Med Genet 2003; 40: e119 Skaar DA, Mol Psychiatry 2005; 10: 563–571. Persico AM, Mol Psychiatry 2001; 6: 150–159. Zhang H, Mol Psychiatry 2002; 7: 198–207 Bonora E, Eur J Hum Genet 2005; 13: 198–207. Hutcheson HB, BMC Med Genet 2004; 5:12. Gharani N, Mol Psychiatry 2004; 9: 474–484. Gong X, Am J Med Genet 2004; 127B: 113–116. McCauley JL, Am J Med Genet 2004; 131B: 51–59.
15	GABA (A) receptor sub-units GABRB3 and GABRA5 (q12) ATP10C (q12) - Aminophospholipid-transporting ATPase gene UBE3A-gene (q12) - E6-AP ubiquitin ligase	Buxbaum JD, Mol Psychiatry 2002; 7: 311–316. Cook EH, Am J Hum Genet 1998; 62: 1077–1083 Menold MM, J Neurogenet 2001; 15: 245–259. Martin ER, Am J Med Genet 2000; 96: 43–48. Nurmi EL, Mol Psychiatry 2003; 8: 624–634, 570. Numri EL, Genomics 2001; 77: 105–113.
16	TSC2 (p13.3) - Tuberous sclerosis complex	Serajee FJ, et al., Journal of Medical Genetics 2003; 40: e119
17	Serotonin transporter gene (5-HTT)	Cook EH, Mol Psychiatry 1997; 2: 247–250

Association - ADHD

Table 1.

Significant Pooled Odds Ratios for Gene Variants Examined in Three or More Case-Control or Family-Based Studies[a]

Gene	Study Design	Pooled OR	95% CI
Dopamine D4 Receptor (exon III VNTR, 7-repeat)	Family	1.16	1.03–1.31
Dopamine D4 Receptor (exon III VNTR, 7-repeat)	Case-control	1.45	1.27–1.65
Dopamine D5 Receptor (CA repeat, 148 bp)	Family	1.24[a]	1.12–1.38
Dopamine Transporter (VNTR, 10-repeat)	Family	1.13	1.03–1.24
Dopamine β-Hydroxylase (TaqI A)	Case-control	1.33	1.11–1.59
SNAP-25 (T1065G)	Family	1.19	1.03–1.38
Serotonin Transporter (5-HTTLPR long)	Case-control	1.31	1.09–1.59
HTR1B (G861C)	Family	1.44	1.14–1.83

OR, odds ratio; CI, confidence interval; VNTR, variable number of tandem repeats.

From Lowe et al., 2004; Faraone et al., 2006

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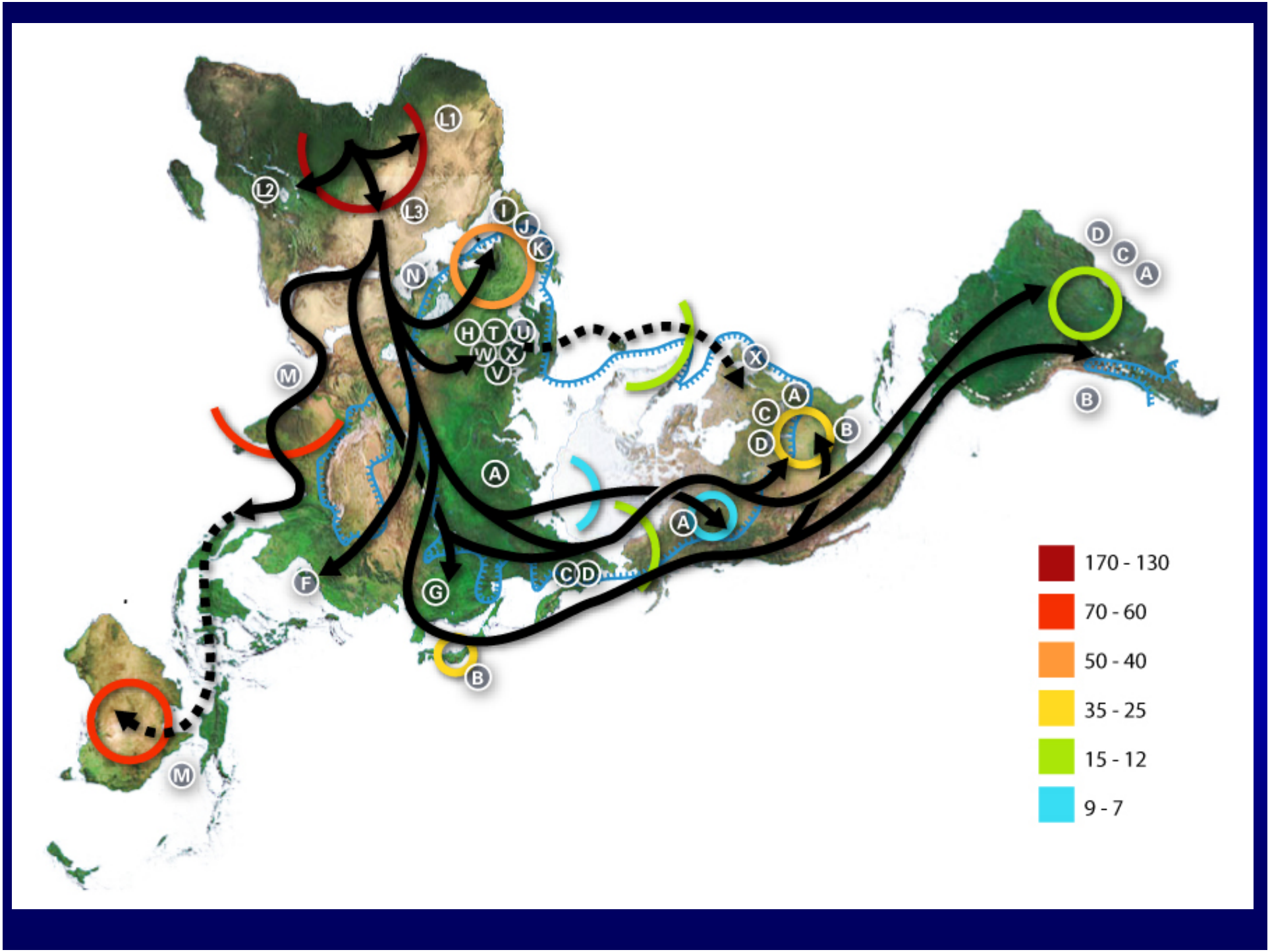
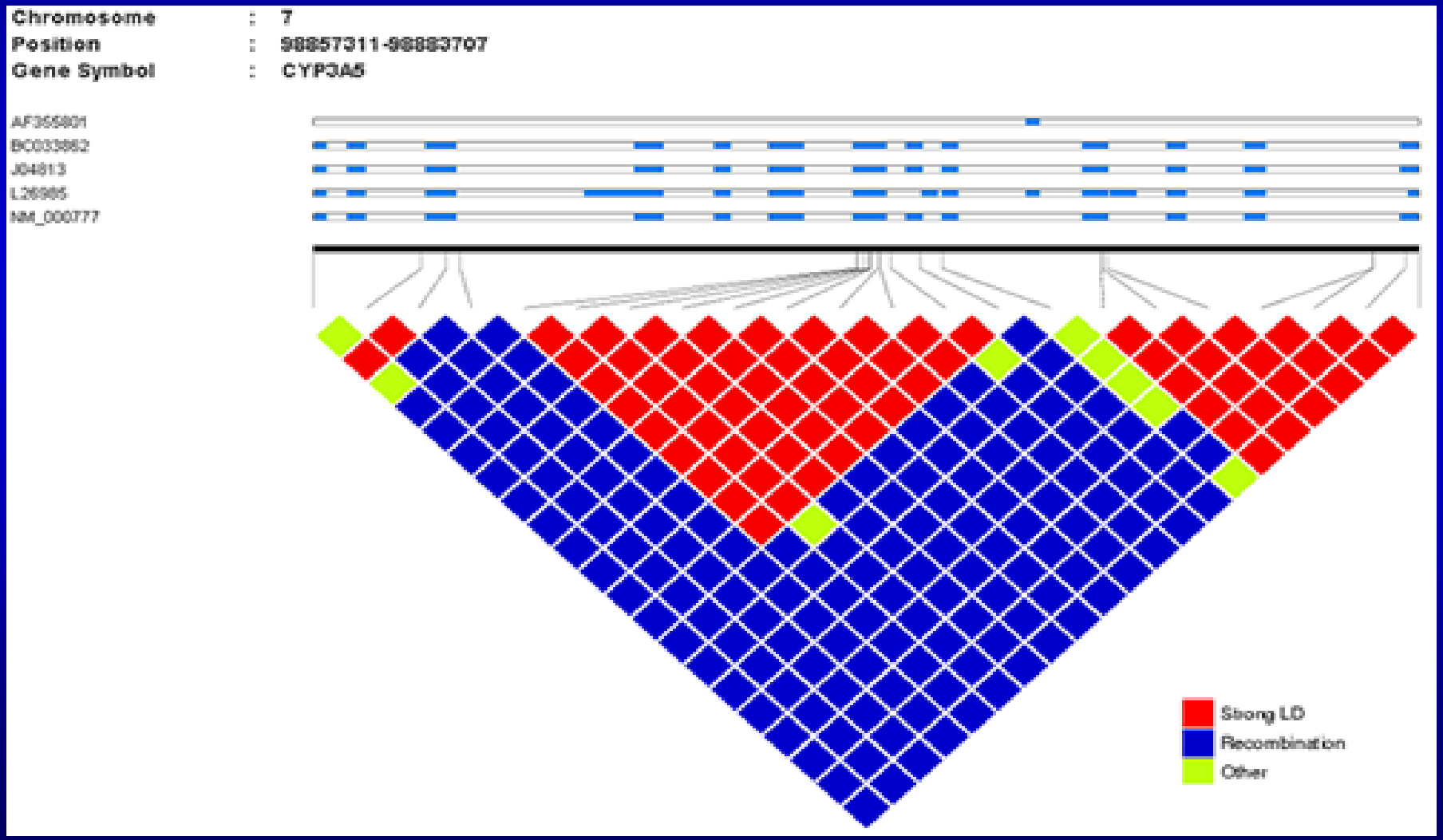
How Many Genes?

- Mapping genes - complex diseases
  - depends on number and frequency of susceptibility alleles
  - only feasible if common diseases influenced by one or a few susceptibility alleles at each locus, but not so if there is a high degree of allelic heterogeneity.


L1
L2
L3
I
J
K
N
H
T
U
W
X
V
M
A
C
D
B
X
D
C
A
B
A
C D
F
G
B
M
170 - 130
70 - 60
50 - 40
35 - 25
15 - 12
9 - 7

Linkage Disequilibrium



Common Disease – Common Variant

- Common disease-common variant hypothesis predicts
  - Common disease causing alleles will be found in all populations
  - Complex polygenic diseases
    - which are evolutionary neutral
    - Caused by common variants
    - Each variation will have a small effect
    - additive or multiplicative effect of many alleles
  - Examples
    - ApoeE (Alzheimer Disease)
    - IL23R (Crohn Disease)

Common Disease – Common Variant

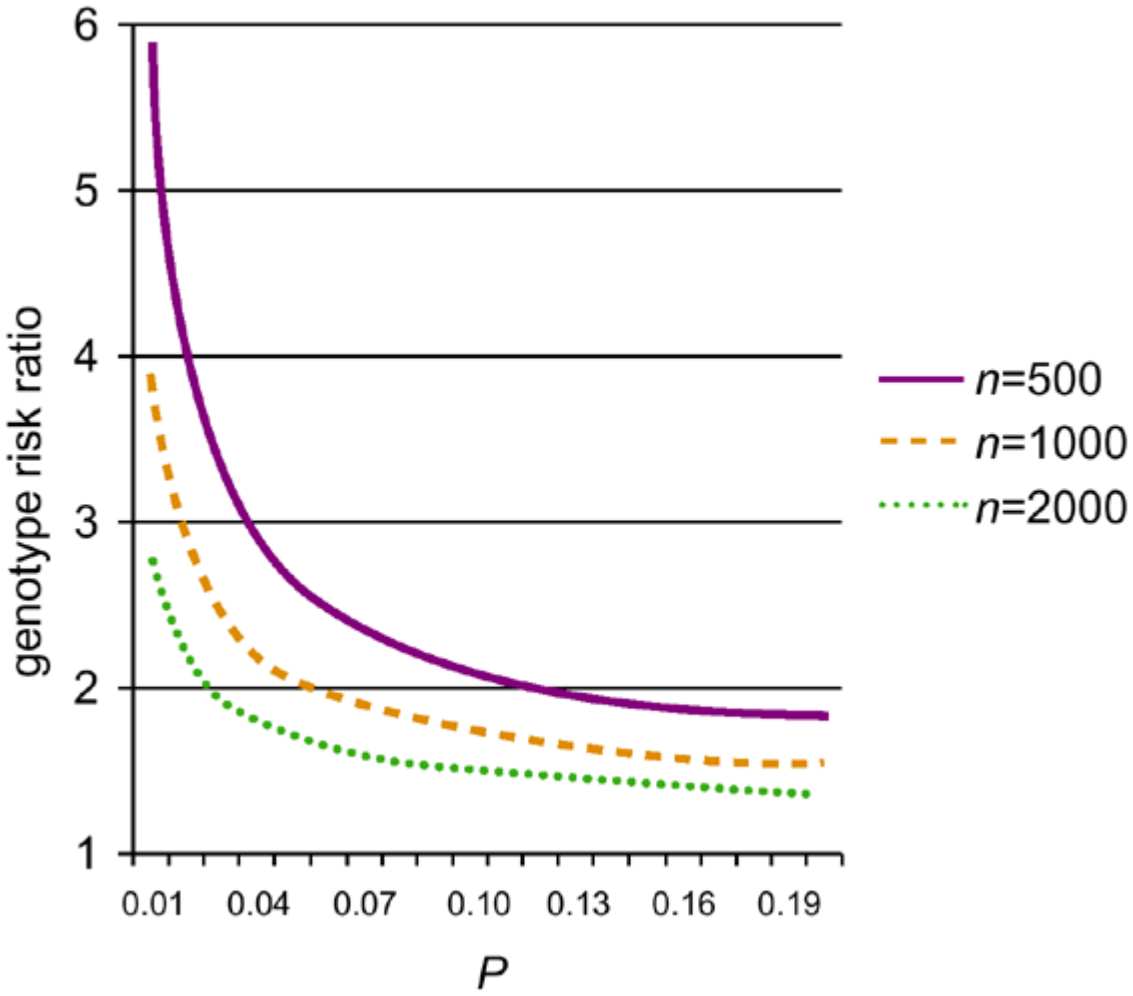
- Strongest Argument in favor of the CD-DV hypotheses
  - Milder Phenotypes in first degree relatives
  - Endophenotypes

Parents of Children with Autism

- Experimental
  - Bias towards detail-focus
  - This is seen across tasks of
    - Perceptual judgment
    - Visuo-spacial construction
    - Problem solving
    - Verbal semantics
- Real-life Skills
  - Preference for solitary pastimes
  - Less interest in social interaction
  - Detail-focus interests

Autism Spectrum Quotient

	Index		Control		
Subscale	**Mo**	**Fa**	**Mo**	**Fa**	**p**
	(65)	*(46)*	*(48)*	*(37)*	
Social skills	**2.2**	**3.8**	**1.8**	**2.3**	**.004**
Attention switching	**3.6**	**3.9**	**3.3**	**4.3**	**.891**
Attention to detail	**3.9**	**3.8**	**4.5**	**3.6**	**.538**
Communication	**2.1**	**3.4**	**1.8**	**2.4**	**.015**
Imagination	**2.0**	**3.2**	**1.9**	**3.5**	**.663**



Botstein and Risch (2003)

Autism and Single Gene Disorders

- Single Gene disorders associated with autism
  - Rett syndrome
  - Tuberous sclerosis
  - Timothy syndrome
  - Many more

Autism and Single Gene Disorders

- Cytogenetic abnormalities
  - Many individual case reports
    - Most often
      - Fragiles X
      - Duplication chromosome 15q11-q13
      - 22q11 deletion syndrome
    - Turner syndrome

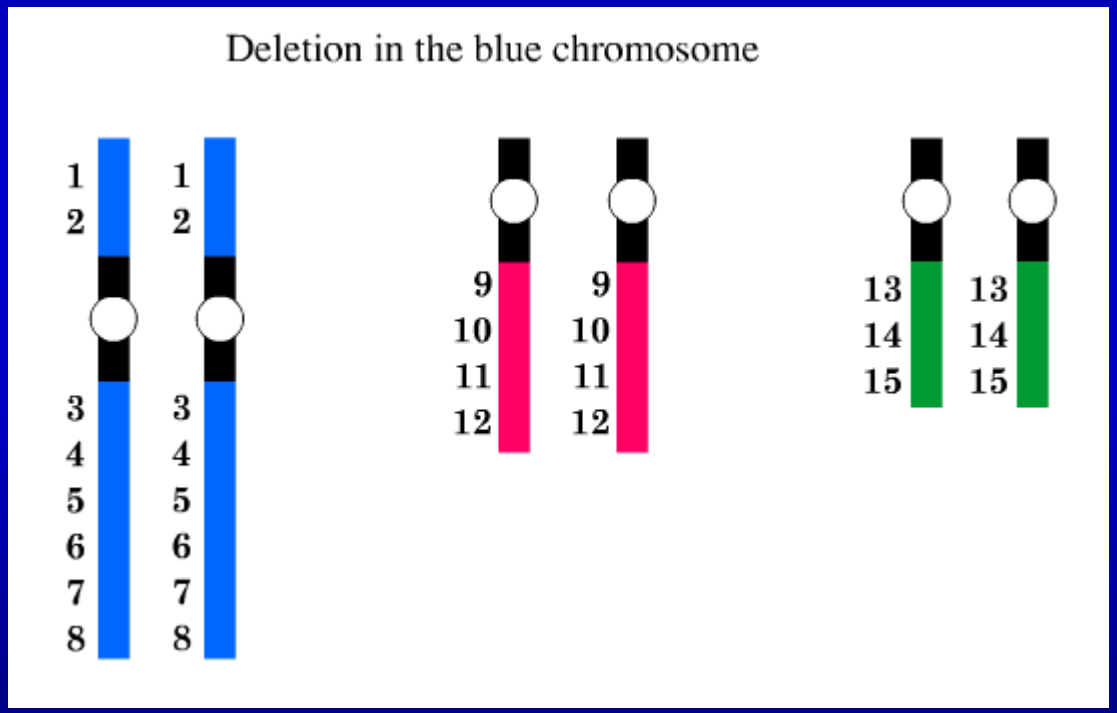
Autism Phenotype

Can the autism phenotype be explained by multiple single gene mutations?

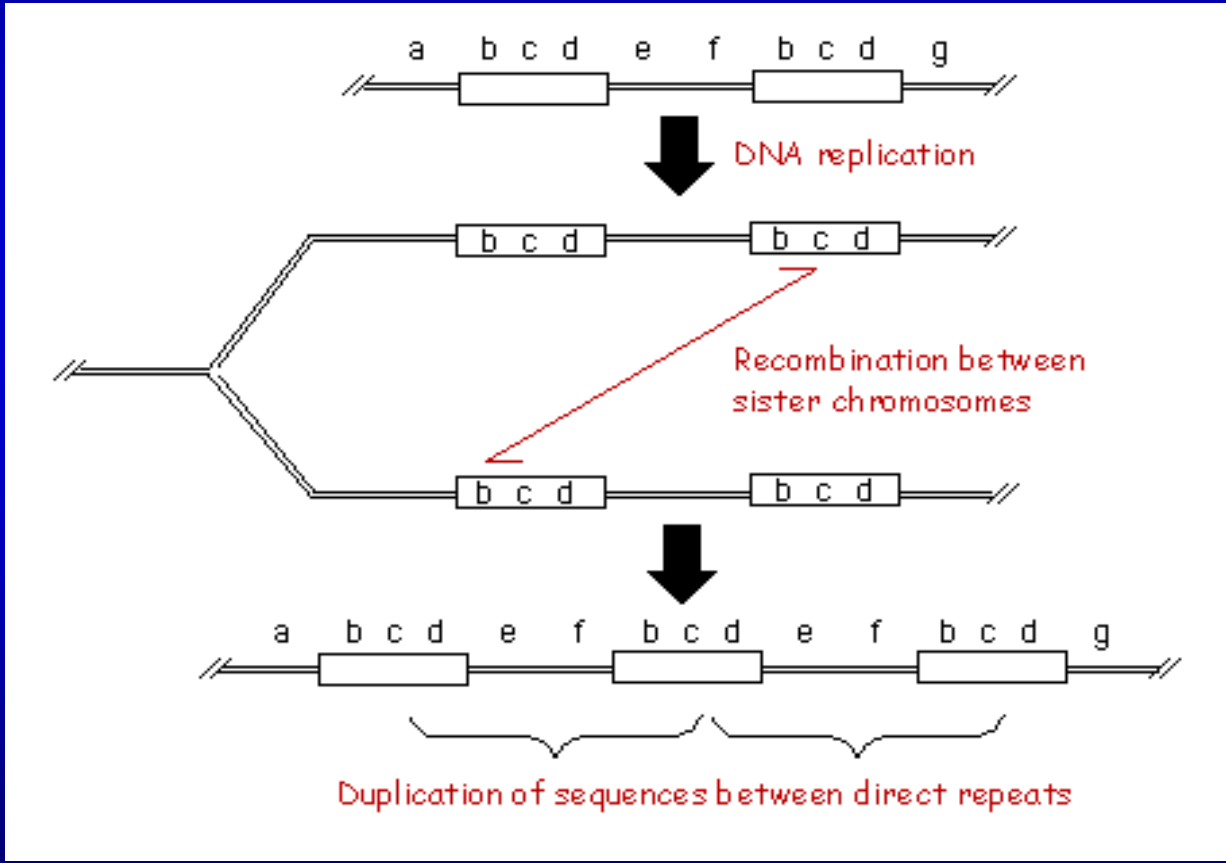
Copy Number Variation

- CNV
  - Gains and Losses of pieces of DNA sequence consisting of between ten thousand and five million base pairs
  - Loss = Deletion
  - Gain = Insertion

Deletion


Deletion in the blue chromosome
1
2
3
4
5
6
7
8
1
2
3
4
5
6
7
8
9
10
11
12
9
10
11
12
13
14
15
13
14
15

Insertion


a b c d e f b c d g
DNA replication
b c d
b c d
Recombination between
sister chromosomes
b c d
b c d
a b c d e f b c d e f b c d g
Duplication of sequences between direct repeats

High Frequency CNVs

- Wong et al. (2007)
  - Genome-wide search using BAC array
    - Sensitivity 40kb
    - Minimum of 40 Mb
    - 1.5% of mapped human autosomes
  - 800 loci
  - 77% are novel
  - Greatest difference between two individuals
    - 228 clones
    - > 9Mb

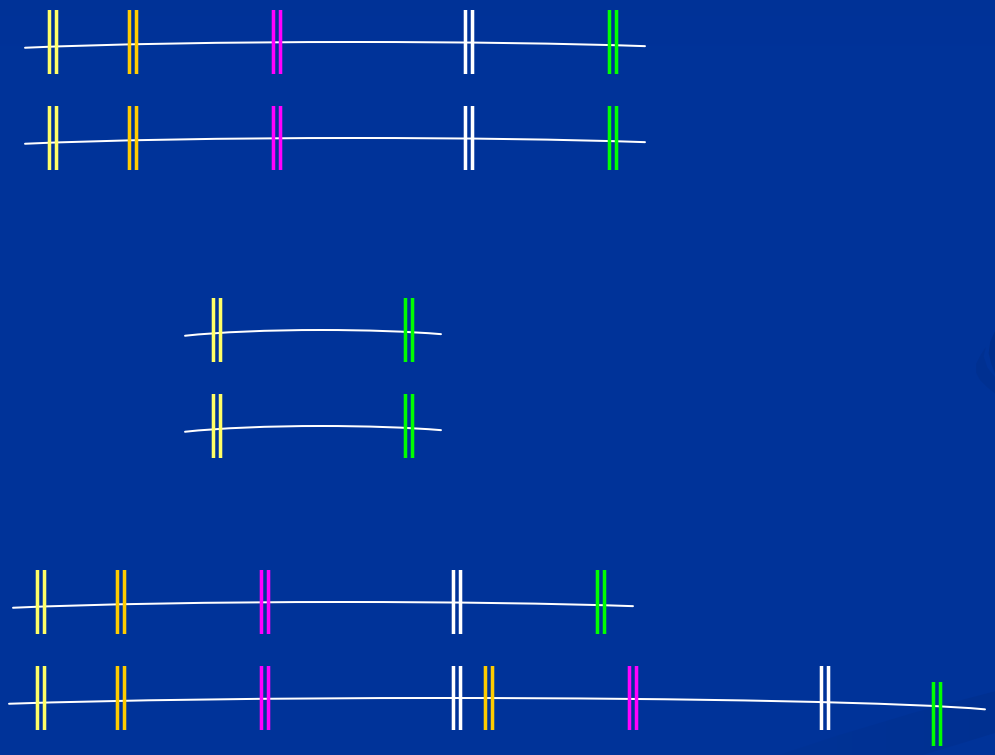
High Frequency CNV - Genes

- Olfactory receptor genes
- Genes affected with taste
- Cancer-related Genes
- Others
  - Diabetes mellitus
  - Alzheimer Disease
  - Coronary artery disease
  - Schizophrenia (COMT)
- 21 microRNAs reside within 14 of CNVs

Copy Number Variants by signal intensity

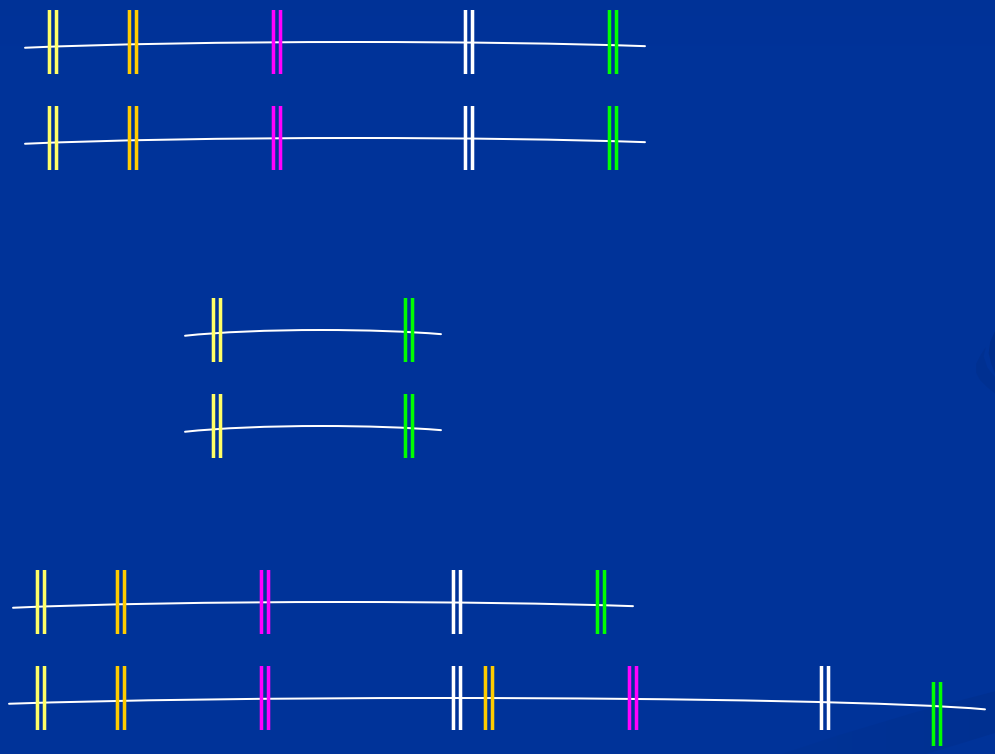
Chromosome fragment with SNP locations |

Signal Intensities

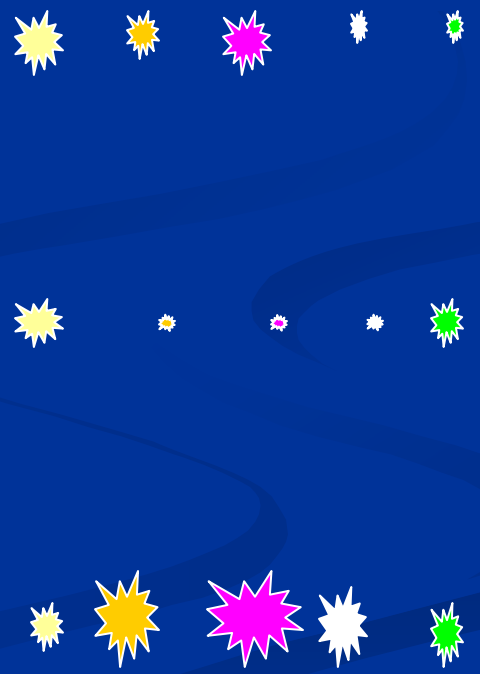


Copy Number Variants by signal intensity

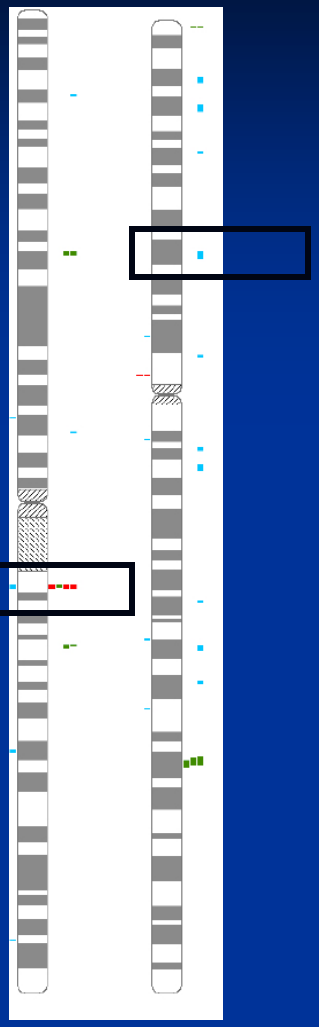
Chromosome fragment with SNP locations |



Signal Intensities ARE NOISY

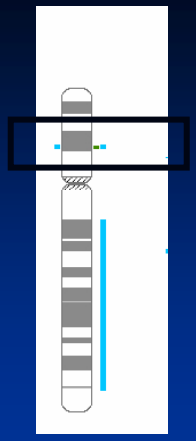


Copy Number Variants

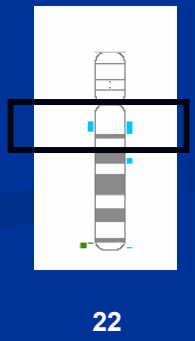


2p16: 2 affected siblings
NRX1

1q21: three families
Previously implicated in MR



17p12: three families
Smith Magenis,
Charcot-Marie Tooth

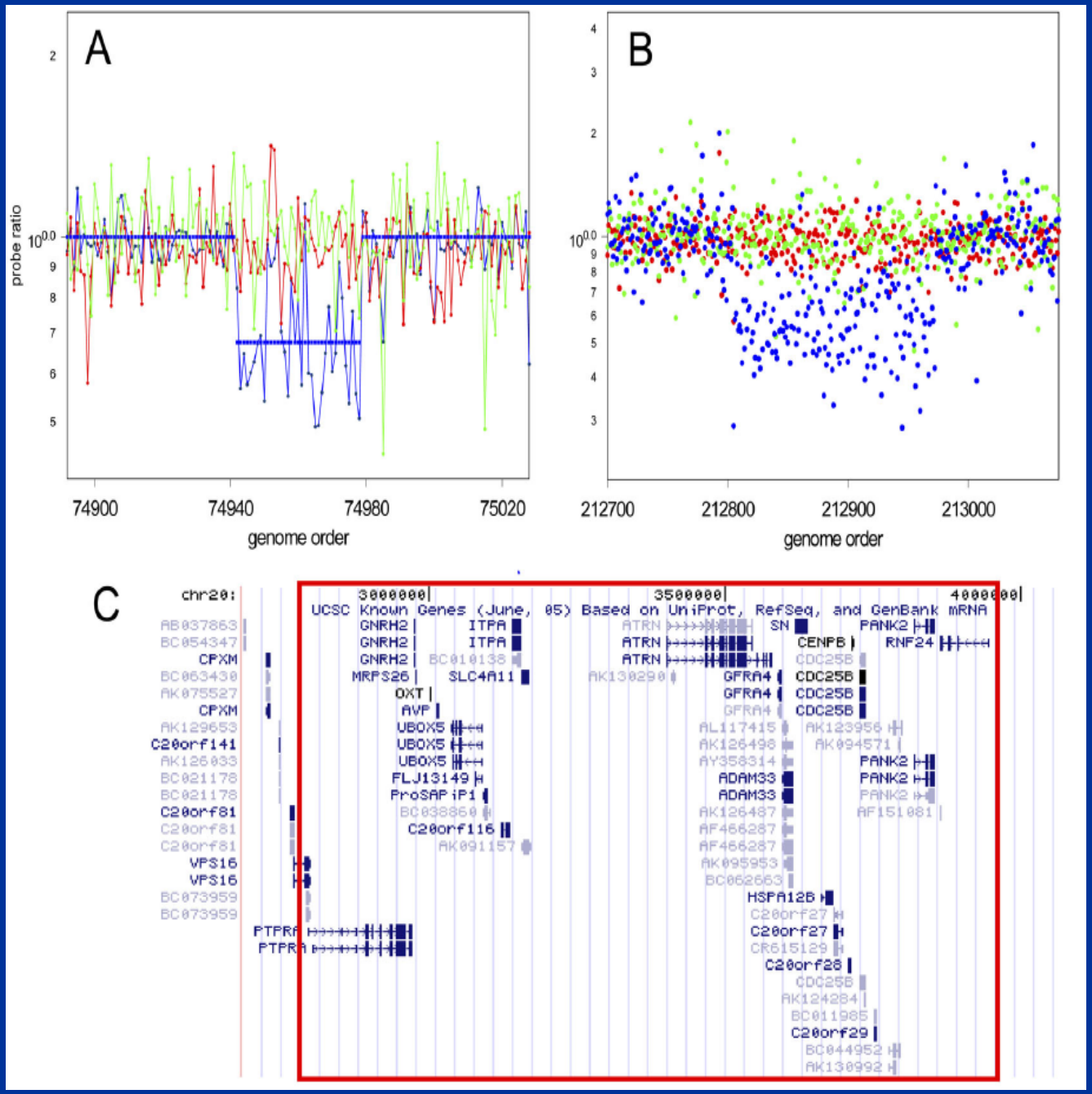


22q11.2: two families
Interpretation complicated

- 14 de novo CNVS found in both ASP
- 18 CNVs overlap ASD-related rearrangements
- Numerous overlapping/recurrent CNVs
- Families with transmission of maternal 15q gains

Sebat et al. (2007)

	No Indiv.	CNV	Proportion	P value	
				x^2	Mplx vs. Splx
Simplex Autism	118	12	0.102	0.0005	0.043
Multiplex Autism	77	2	0.026	0.59	
Splx/Mplx Combined	195	14	0.072	0.0035	
Controls	196	2	0.010		



1.1 Mb Deletion
20p13
27 genes
Incl. Oxytocin

Individual	Locus	Start position	Length	change	Family type	Diagnosis	Gender	Validation	# Genes	Single gene
63-144-2575 & 2667	2q24.2	162,212,720	99,252	loss	Simplex	Autism	female	A	1	SLC4A10
61-2710-3	2q37.2-q37.3	236,414,455	6,286,648	loss	Simplex	Autism	male	A,B,D	50	
Van69 258900	2q37.3	238,217,066	4,484,037	loss	Simplex	Autism	male	A,D	43	
89-3507-1	3p14.2	60,746,033	101,507	loss	Simplex	Autism	male	A	1	FHIT
63-562-6612	3p14.2	61,072,100	293,096	gain	Simplex	Autism	male	A	1	FHIT
AU010604	6p23	13,997,280	1,264,651	loss	Multiplex	Autism	male	A,D	2	
	13q14.12 q14.13	44,199,441	1,943,737	loss				A,D	13	
AU072203	7p21.1	15,160,118	151,880	loss	Simplex	Autism	male	A	1	FLJ16237
AU032903	10q11.23 q21.2	50,562,149	10,916,362	gain	Multiplex	Autism	male	A,B	23	
60-3061-4	15q11-q13.33	18,526,971	12,229,800	gain	Simplex	Autism	male	A, B	30	
AU077504	16p13.3	5,992,836	207,980	loss	Simplex	Autism	female	A, B, C,D	1	A2BP1
CG2061	16p11.2	29,578,715	502,574	loss	Simplex	Aspergers	female	A,C,D	27	
71-259100	20p13	75,912	291,959	loss	Simplex	Autism	female	A C,D	7	
SK-135-C	20p13	2,785,194	1,169,205	loss	Simplex	Aspergers	male	A,D	23	
	22q13.31									
89-3524-100	q13.33	45,144,027	4,321,856	loss	Simplex	Autism	female	A,B,C,D	30	
NA10857	2p16.1	58,394,177	2,786,284	gain	Control	Unaffected	Unaffected	A	7	
AU070807	20p13-p12.3	111,824	5,316,286	gain	Simplex	Unaffected	Unaffected	A	69	

Table 1. Spontaneous CNVs detected by ROMA. A description of 17 de novo CNVs in 16 subjects is provided, along with the methods used for its validation. The number of unique RefSeq genes within each CNV region are indicated, and when the locus apparently encompasses only a single gene, the gene symbol is listed. Types of validation included (A) Higher-resolution microarray scans by 390K ROMA or Agilent 244K CGH, (B) G-banded karyotype, (C) FISH, and (D) microsatellite genotyping. References are listed for four cases where similar de novo CNVs were previously reported in the literature.

FLJ1647 – Sterol desaturase
SLC4A10 – Sodium bicarbonate cotransporter
FHIT – Fragile Histidine Triad
A2BP1 – Ataxin-2 binding protein 1
All four genes are in the top 3% of the human genes by length

Autism – How many Genes

- 10-20%
  - CNVs
  - Large number of different genes
- Is there a more common allele predisposing to autism?

1. Why Genetics?
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6. ***Reducing Heterogeneity***
7. Outlook

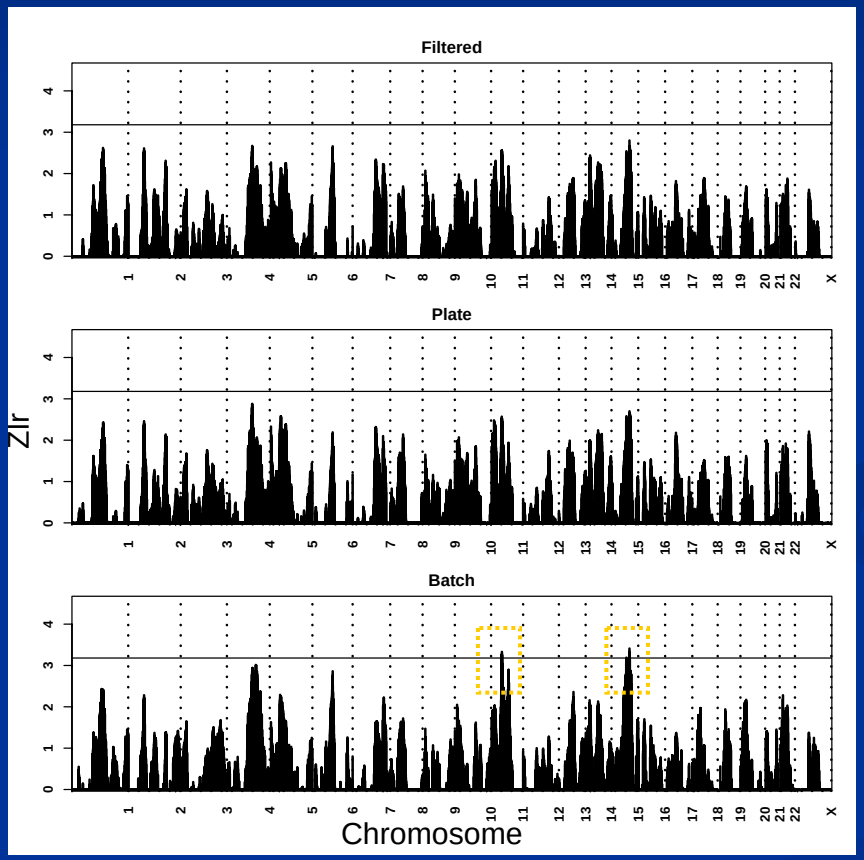
Removing MPX families with CNVs.

Broad Sample:
N= 739 MPX

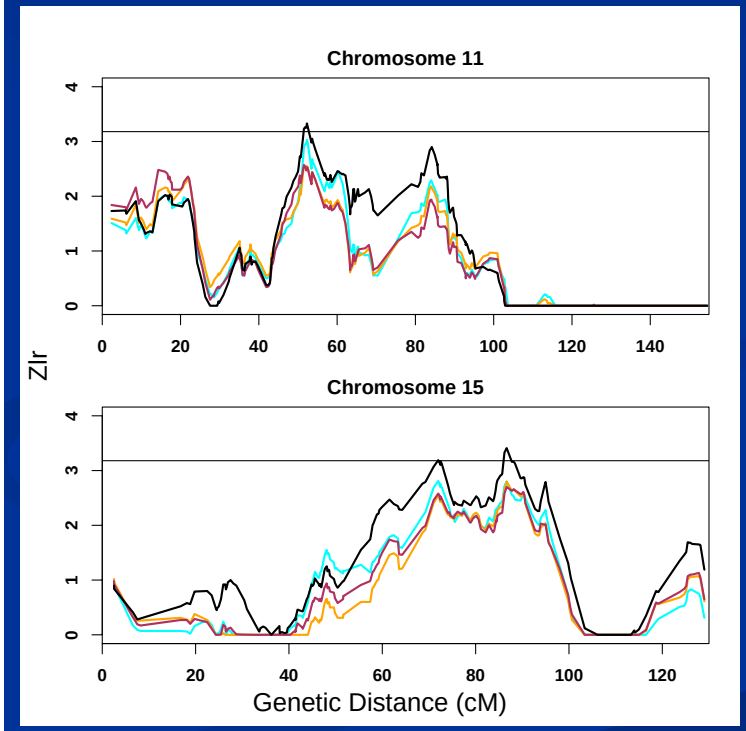
N= 641

N= 603

N= 567

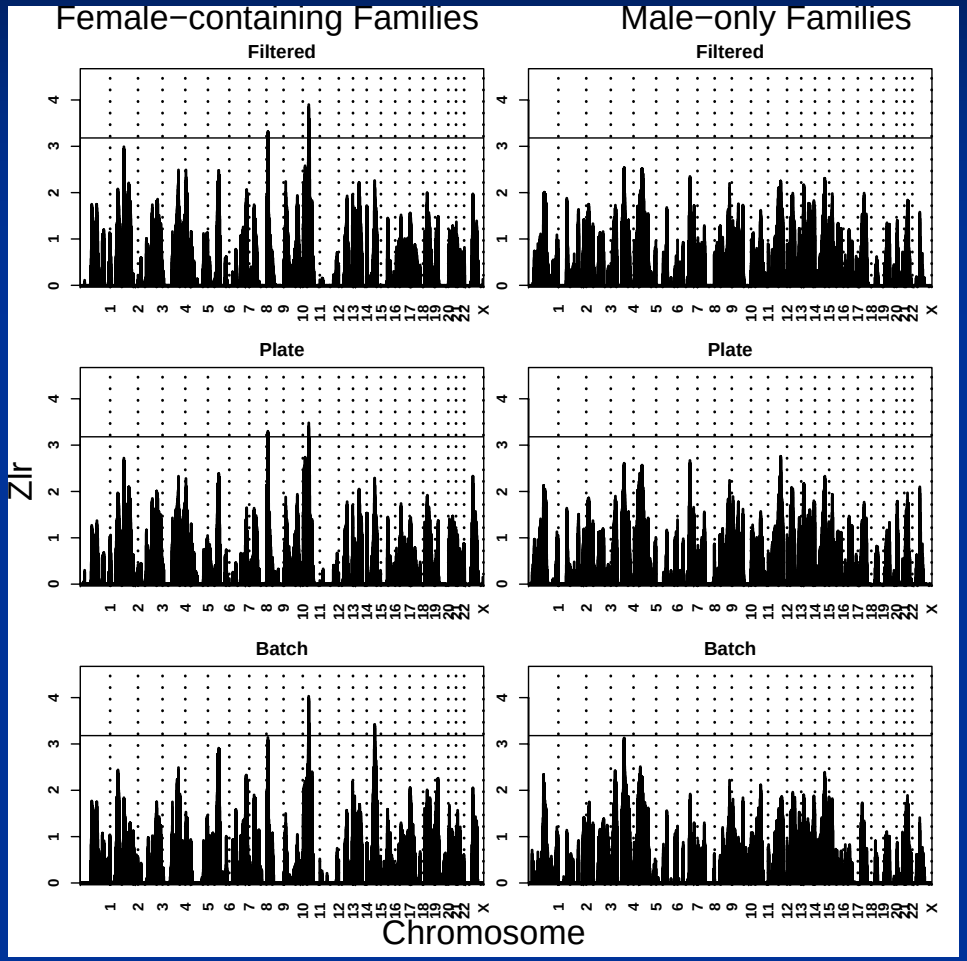


11p13



15q23 & 15q25.3

Removing MPX families with CNVs & Partitioning by sex



No. of Broad MPX families	
233	408
221	382
208	359

FC families	MO families
9p24.1, & 11p12-p13	
9p24.1, 11p12-p13	
11p12-p13, 15q23	

Autism

Impairment in the Development of

Social Interaction	Communication including Language	Stereotypies Restricted Interests

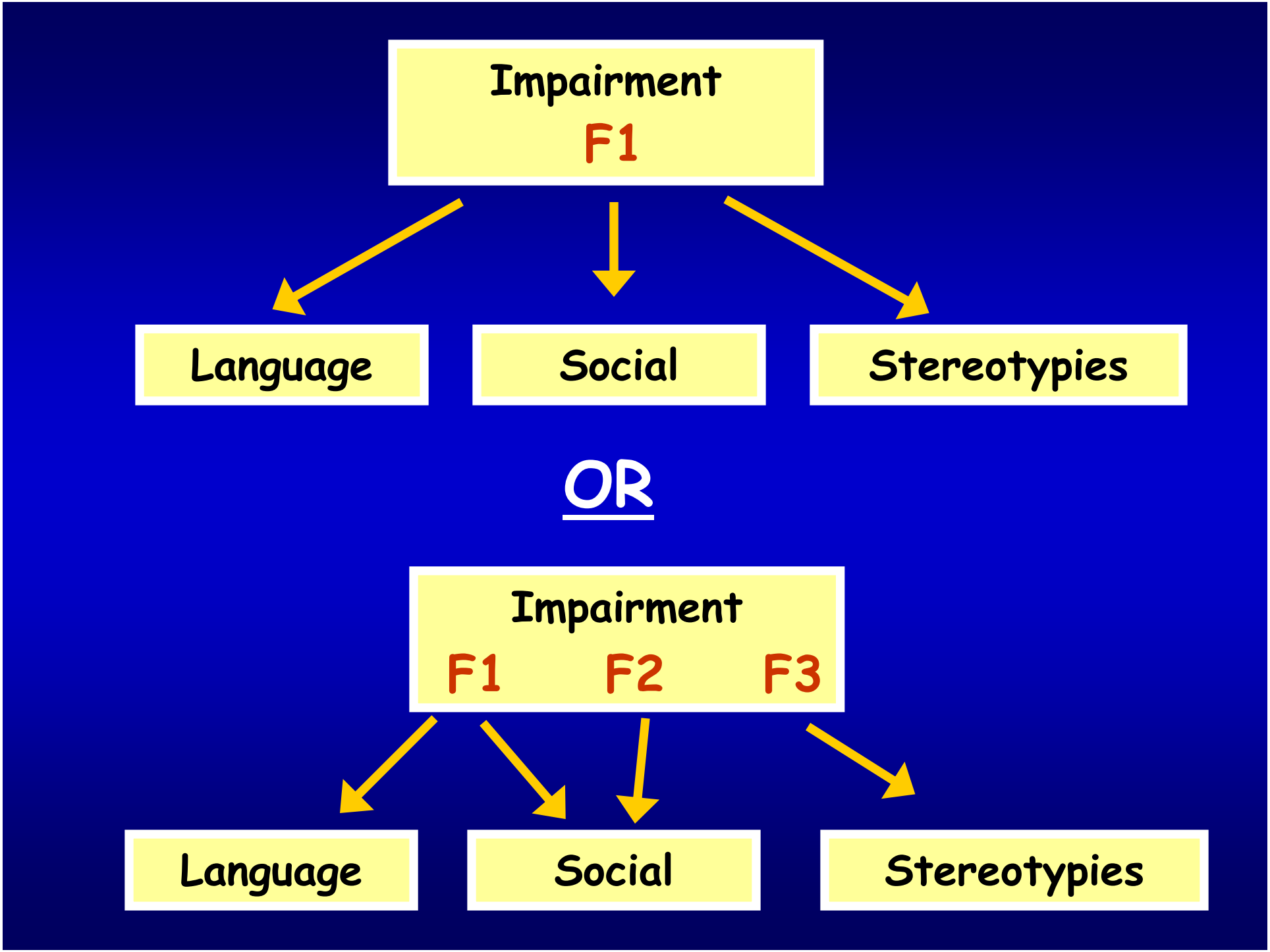

Impairment
F1
Language
Social
Stereotypies
OR
Impairment
F1
F2
F3
Language
Social
Stereotypies

Table I. Summary of Peaks in Stratification Analysis in ALL and DELAYED Families

	Region	All families	Stratified by PD	Stratified by WD
Chr	cM	NPL	NPL	NPL
1	131.34	1.12	1.70*	2.2**
2	136.34	0.48	2.07*	ni
2	153.65	-0.039	1.78*	ni
2	191.87[a]	0.14	1.82*	ni
2	255.7	1.20	1.81*	ni
4	33.42	2.53**	ni	ni
4	104.94	2.42**	ni	ni
4	167.55	1.67*	ni	ni
4	181.93	0.35	ni	1.69*
6	187.23	-0.08	ni	1.76*
7	10.68	0.50	1.68*	ni
8	127.23	1.22	1.90*	ni
9	14.23	0.08	1.69*	ni
9	33.09	0.61	ni	1.89*
10	65.23	1.89*	2.32**	ni
11	32.95	2.43**	ni	ni
11	54.02	2.11*	ni	ni
12	48.7	1.64*	ni	2.41**
12	68.16	2.34**	ni	ni
15	12.2[b]	0.94	2.35**	2.28**
16	28.3	2.36**	ni	ni
17	50.74	2.10*	ni	ni
19	85.19	1.64*	2.16**	2.34**

ni, no increase.
* $P \leq 0.05$.
** $P \leq 0.01$.

Spence et al. (2006)

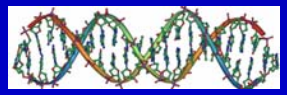
Nature modifies Nuture

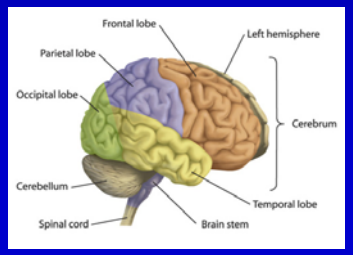
G x E interactions = genes modify environmental effects

Caspi & Moffitt (2006), Legrand et al. (2005)

Environment → Neural substrate reactivity → Behavior

Genotype → Neural substrate reactivity

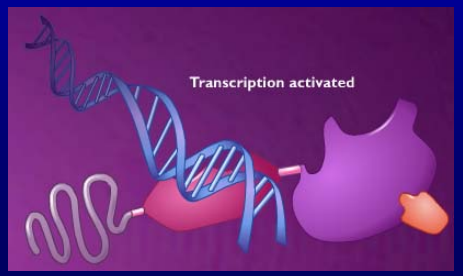


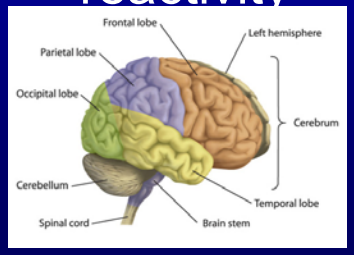


Nuture modifies Nature

Epigenesis = environments modify gene expression

Environment → Gene expression → Neural substrate reactivity → Behavior





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Genetics the Second Wave

- The Bigger – The Better
- Large number of markers to cover genome
  - 500,000 – 1,000,000
- Very close to disease related mutation
- Several Studies Ongoing
  - BROAD
  - Johns Hopkins
  - AGP
- Combined with Genome-Wide Search for CNVs

Genetics the Second Wave

- **Ongoing Studies are based on Common Disease – Common Variation Model**
  - **Low hanging fruits – Common alleles**
  - **Genes implicated will not account for autism in a substantial fraction**
  - **Predisposing alleles on its own will only contribute a small increase in risk**
  - **Risk will be unspecific and overlap with other disorders**
  - **It will require major efforts to define the predictive value of each one of the variants**
- **A better understanding of the relationship between genetic factors, cognitive deficits, neuropathology and clinical symptoms will be paramount**

Conclusions

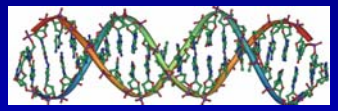
- Autism is a complex genetic disorder and most likely influenced by a combination of mutations in single genes, deletions and duplications, and by more common alleles

- Linkage: 11p13-12 is a good place to look for liability loci (Also, All: 15q; FO: 9p, 5p, 6q, 15q, 2q; MO: 7q, 5q)

Conclusions

- **Could dysregulated glutamate be a major pathway to risk for ASD?**
  - **Linkage results → Any striking coincidences?**
    - **11p13-12: *SLC1A2 – Glutamate transporter member 2***
    - **9p24.2: *SLC1A1 - Glutamate transporter member 1***
    - **2q31: *SLC25A12 - Mitochondrial aspartate/glutamate carrier***
    - **4q28.3: *SLC7A11 - Cystine-glutamate transporter***
    - **7q21.3: *SLC25A13 - Aspartate-glutamate transporter in mitochondria***
- **Striking pattern of CNVs**
  - **Chromosomal abnormalities not rare**
  - **10k does not cover genome.**

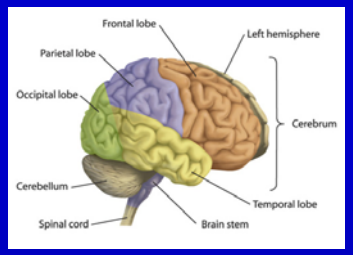
Genotype



Gene expression

Synapse

Neural substrate reactivity



Autism Genome Project

Autism Genetics Collaborative (AGC)

Duke (Margaret Pericak-Vance, Michael Cuccaro, John Gilbert); Mt. Sinai School of Medicine (Joseph Buxbaum, Jeremy Silverman, Christopher Smith); Paris Autism Research International Sibpair Study (Catalina Betancur, Thomas Bourgeron, Marion Leboyer); Stanford University (Joachim Hallmayer); University of Iowa (Veronica Vieland, Thomas Wassink); University of North Carolina (Joseph Piven); University of Toronto/Hospital for Sick Children - McMaster University (Steve Scherer, Peter Szatmari, Andrew Paterson); Vanderbilt University (James Sutcliffe, Jonathan Haines)

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University of California - Los Angeles (Dan Geschwind, Stan Nelson, Rita Cantor, Maricela Alarcon, Kenneth Lange, Sarah Spence); Emory University (David Ledbetter, Christa Lese-Martin); University of Chicago (Conrad Gilliam)

Collaborative Programs of Excellence in Autism (CPEA)

University of Washington (Gerard Schellenberg, Geraldine Dawson, Ellen Wijsman); University of Utah (William McMahon, Hilary Coon); University of Pittsburgh (Bernie Devlin)

International Molecular Genetic Study of Autism Consortium (IMGSAC)

Oxford University (Anthony Monaco, Anthony Bailey, Janine Lamb); University of Bologna (Elena Maestrini); Deutsches Krebsforschungszentrum, Heidelberg (Annemarie Poustka, Sabine Klauck); University of Illinois – Chicago (Ed Cook); University of Michigan (Catherine Lord)

Autism Speaks, CIHR, CAN, Genome Canada, HHMI, Hospital for Sick Children Foundation, INSERM, MRC, NICHD, NIDCD, NIMH, NINDS, NLM Family Foundation, Swedish National Medical Council, Wellcome Trust, EU