Genetics of Schizophrenia – CNVs provide new insight

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TOP

TOP study

" **T**hematic **O**rganized **P**sychosis Research"

- Severe mental illness– schizophrenia and bipolar disorder
- Thematic research study – consist of several subproject
- Study same patient with different methods: TRANSLATIONAL RESEARCH
- Collaboration with all hospitals in Oslo and UiO research groups

Status TOP study

- Inclusion: 760 patients, 397 controls
- MRI: structure: 380, functional 220

Total scanned: 325 pts, 105 cntr

- 31 Res fellows/PhD cand,6 post docs
- 2 project nurses, 1 administrator, 1 database assistant, 1 secretary
- Program for PhD education and training
- http://www2.med.uio.no/tematisk/psykoser/

Copy Number Variants (CNVs)

- Genomic variability 0.2%, SNPs 0.08%, CNVs 0.12%
  - Sebat Nat Gen 2007
- Recent findings implicate CNV in autism
  - Weiss et al NEJM 2008

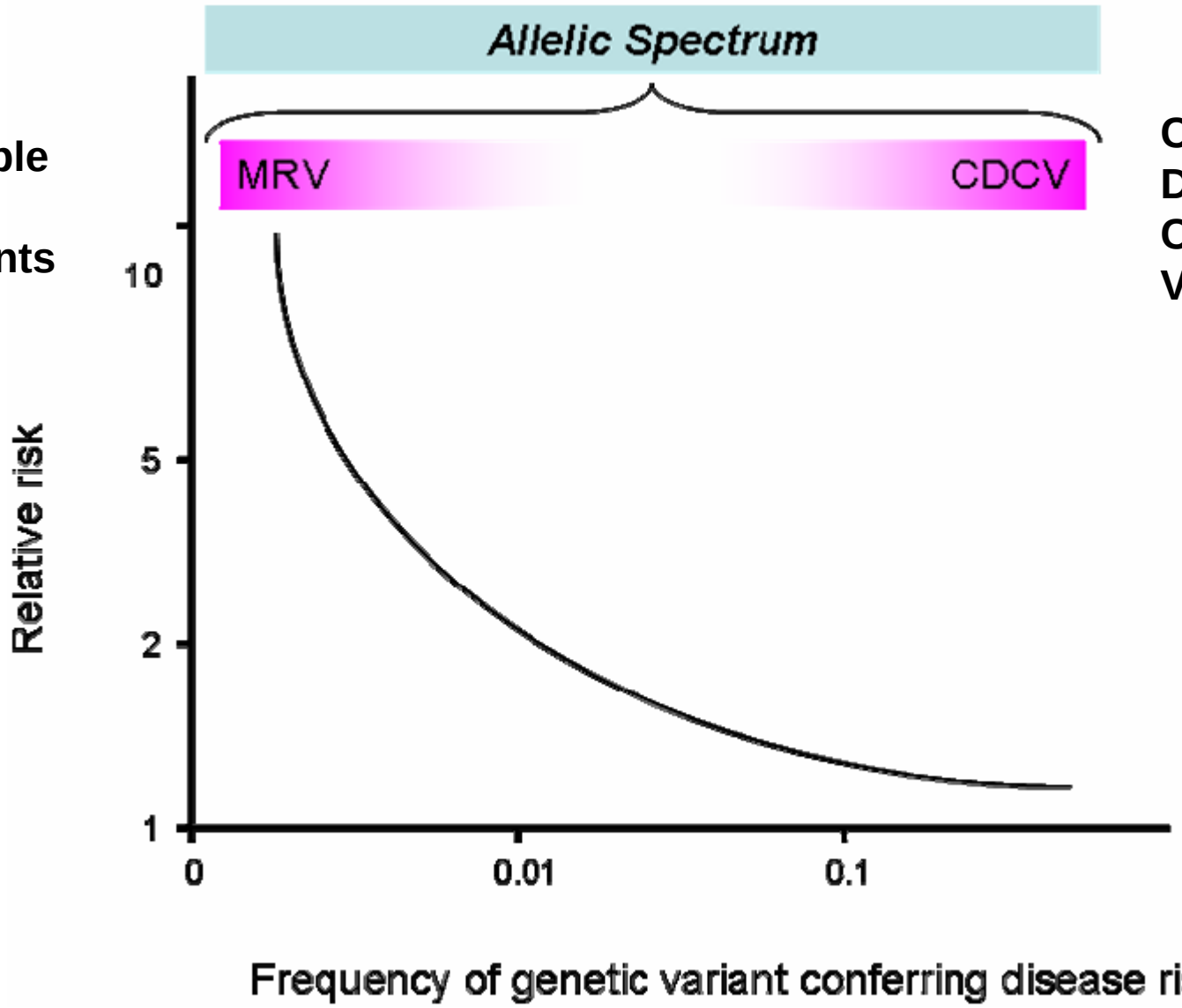
  and mental retardation
  - Lu et al PLoS One 2007
- CNVs in early onset Schizophrenia
  - Walsh et al Science 2008

Schizophrenia

- Severe mental disorder – psychosis
- Life time prevalence 1%
- Heritability 0.6-0.8
- Not mental retardation (but some neurocognitive dysfunction)
- Reduced fecundity
  - Negative selection pressure on risk alleles
- Mechanisms:
  - Common variants – common disorder?
  - Rare variants – common disorders?

Rare variants – higher risk

Multiple Rare Variants



Common Disease, Common Variants

Sample

- Population based sample (Iceland): 9878 transmissions
- Phase I – Schizophrenia 1433, controls 33250
- Phase II – Schizophrenia 3285, controls 7951

Genotyping

- I: Illumina 317 K chip (DeCODE)
- II: Misc. chips (TOP: Affy 6.0), a few TaqMan
- CNV calling: Custom made software

Results

- Identified 66 deNovo deletions
- 1q21.1, 15q11.2 and 15q13.3
- Nominal in first phase, significant in second (controlling for 66 CNVs)

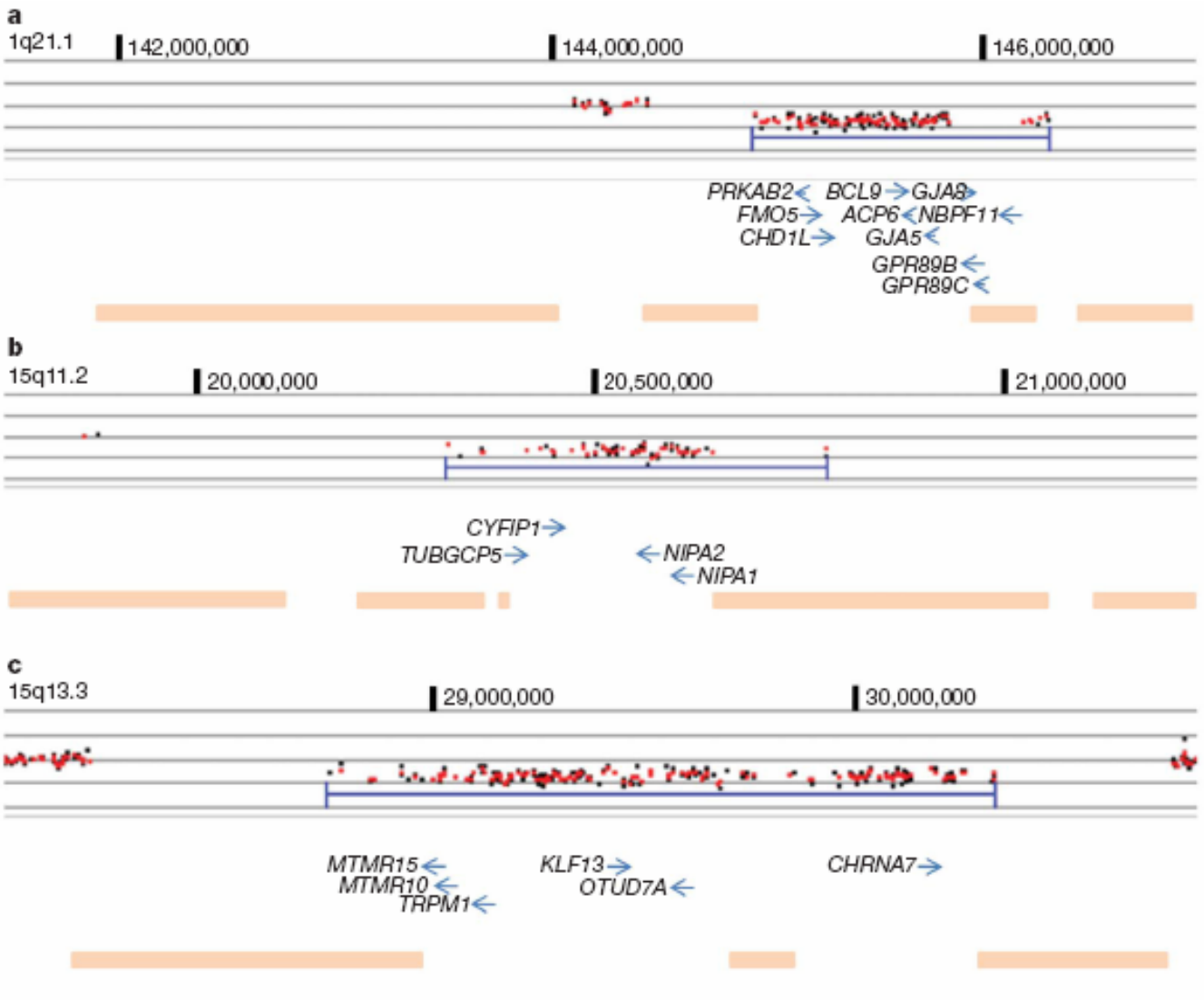
Table 2 | Significant association of deletions at 1q21.1, 15q11.2 and 15q13.3 with schizophrenia and related psychoses in the combined samples

Locus	Chromosome 1: 144.94–146.29 (Mb)		Chromosome 15: 20.31–20.78 (Mb)		Chromosome 15: 28.72–30.30 (Mb)	
	Cases	Controls	Cases	Controls	Cases	Controls
Germany	2 of 911	0 of 1,297	3 of 911	4 of 1,297	0 of 911	0 of 1,297
Scotland	2 of 451	0 of 441	5 of 451	1 of 441	0 of 451	0 of 441
The Netherlands	0 of 806	0 of 4,039	4 of 806	12 of 4,039	3 of 806	1 of 4,039
Norway	0 of 237	0 of 272	0 of 237	0 of 272	1 of 237	0 of 272
Denmark*	3 of 442	0 of 1,437	4 of 442	3 of 1,432	0 of 375	0 of 501
China*	0 of 438	0 of 463	0 of 438	0 of 463	NA	NA
Phase II						
OR		∞ (2.85, ∞)		2.18 (1.01, 4.60)		16.47 (1.52, 833.38)
P-value		5.6×10^{-4}		0.032		7.9×10^{-3}
Phase I and II						
OR		14.83 (3.55, 60.40)		2.73 (1.50, 4.89)		11.54 (2.53, 49.58)
P-value		2.9×10^{-5}		6.0×10^{-4}		5.3×10^{-4}

The three deletions nominally significant in phase I were tested for association in follow up samples from Germany, Scotland, The Netherlands, Denmark, Norway and China. All three deletion associate with schizophrenia and related psychoses in the combined phase I and II samples (the multiple testing significance threshold is $0.05/66 = 7.6 \times 10^{-4}$). *P*-values in the table (uncorrecte for the 66 tests) are from the exact Cochran–Mantel–Haenszel test and are two-sided. Coordinates are based on Build 36 assembly of the human genome. 95% confidence intervals are given with brackets. NA, not analysed.

*Samples were measured using Taqman assays. Samples with CNVs identified by measuring gene dosage by a Taqman assay were verified and confirmed by genotyping the respective sampl using the HumanCNV370 chip. A limited amount of DNA was available for genotyping the Chinese samples.

DosageMiner



99 SNPs
1,38 Mb

54 SNPs
470 Kb

166 SNPs
1,57 Mb

Conclusions

- Three new microdeletions 1q21.1, 15q11.2 and 15q13.3 assoc with Schiz
- High OR (10-14) – mechanisms at the core of the disorder
- Rare – not help in diagnostics (yet)
- Identical finding in same *Nature* (International Shizophrenia Genetics Consortium)

PGC – GWAS
Psychiatric Genetic Consortium - Genome Wide Association

A FRAMEWORK FOR INTERPRETING GENOMEWIDE

ASSOCIATION STUDIES OF PSYCHIATRIC DISORDERS

The Psychiatric GWAS Consortium

(Consortium members are listed in the Acknowledgements.)

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HELSE ØST

PGC – GWAS

Whole genom screening (500-900 K SNPs)

- All present GWAS studies, SCHIZ; BIP; MDD; ADHD; AUT
- TOP: n=750 (900 000 SNPs)
- Total 80 000 subjects, 40 billion genotypes
- 101 researchers, 48 institutions, 11 countries

HELSE ØST

PGC – GWAS

GWAS screening

- SCHIZ; BIP: 10 000 per gr
- CONTROLS: 10 000
- Becomes freely available from NIMH repository
- Data spring 2008

Conclusion

- Psychiatry

– Not Graveyard of Genetics anymore!

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- TOP study group – recruitment team and molecular genetic units
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