Genetics of Schizophrenia

Contents

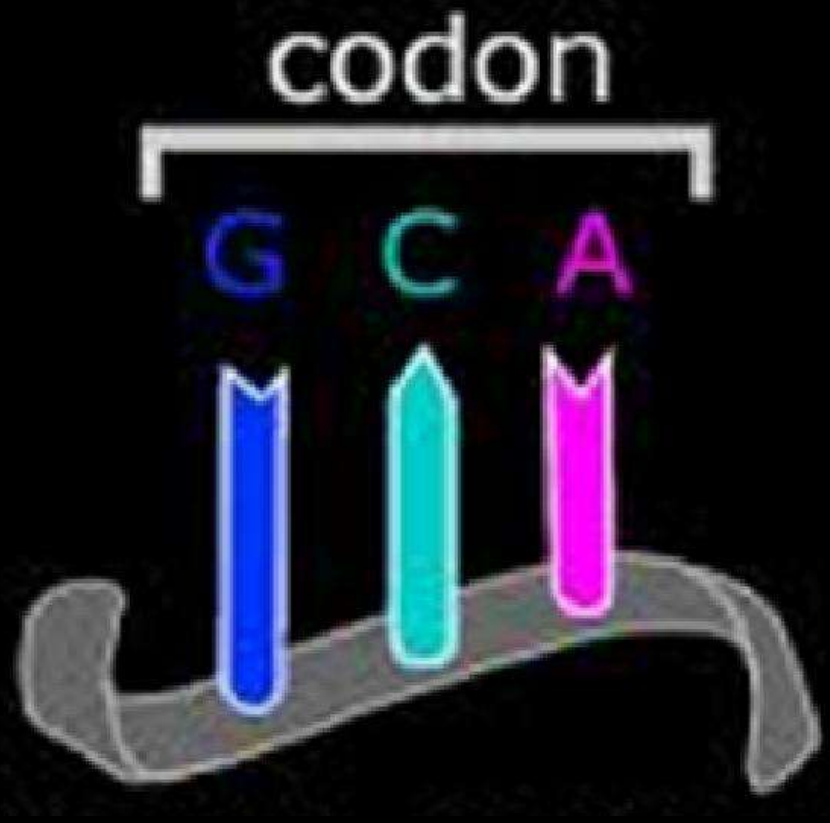
- Familial disorder
- Genetic and environmental factors
- Transmission mechanisms
- Current status
- Predisposing specific genes

Introduction

- Genetics (“genesis”; Origin) - study of heredity
- Molecular structure & function of genes
- Gene behaviour
- Patterns of inheritance from parent to offspring
- Gene distribution, variation and change in populations

Codon

- Genetic information stored as code in DNA
- Codon: sequence of 3 nucleotides
- 1 codon = 1 amino acid
- >1 codon may exist for same AA



Important Terms

- Gene/Cistron: DNA segment carrying codons specific for a particular peptide
- Genotype: Sum total of genes in a cell; includes complete genetic potential of the cell
- Phenotype: Physical impression of the genotype in a given environment

Important Terms

- Concordance: Probability that a pair of individuals (usu. twins) will both have a certain characteristics given that one of the pair has the characteristic
- Heritability: Degree of variation in a phenotypic trait in a population that is due to genetic variation b/w individuals in that population
- Proband: Person serving as the starting point for genetic study of a family

Important Terms

- SNP (Single Nucleotide Polymorphism): specific position in the genome where the chromosomes carry different nucleic acids
- CNV (Copy Number Variant): Chromosomal segment where DNA has been deleted/duplicated
- GWAS (Genome Wide Association Study): Systematic search for common SNPs influencing a disease/trait in a cohort
- Pleiotropy: Single gene controlling/influencing multiple phenotypic traits

Genetic Basis

- Family Studies
- Twin Studies
- Adoption Studies
- Linkage Studies
- Association Studies
- Genomewide Association Studies
- Chromosomal Aberrations & Copy Number Variants

Family Studies

Family Studies

- Proband relatives → increased risk
- 1916: Ernst Rudin; 1st systematic family study
- 1967: Edith Zerbin Rudin
- 1991: Irving I. Gottesman
- Bezugsziffer (BZ):Age adjusted sample size; younger person have not passed through the full period of risk
- Period of risk: 15-39 years

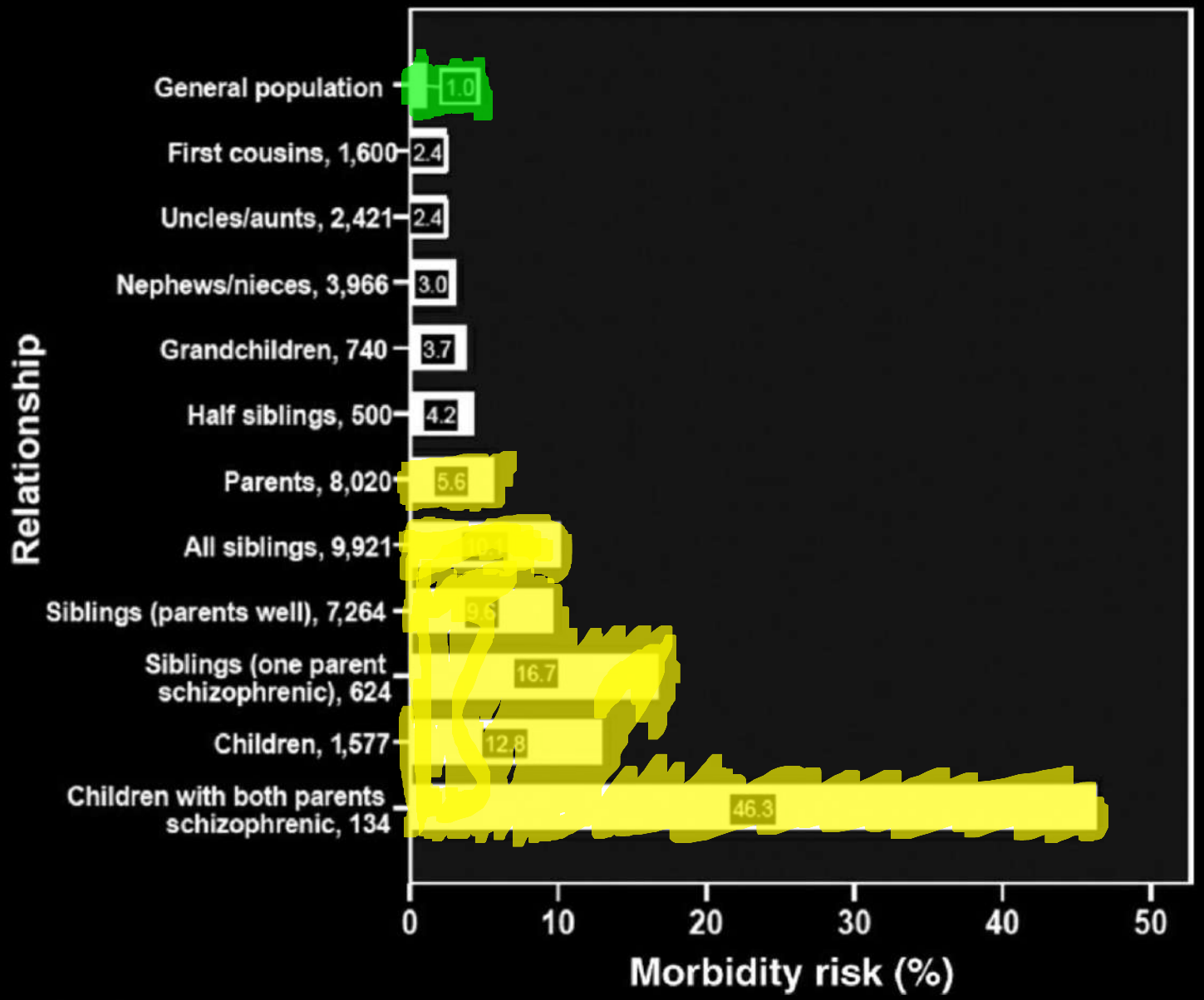


FIGURE 12.4–1. Morbidity risk for schizophrenia in the relatives of schizophrenic probands. The numbers are based on the study by Gottesman and Shields (1982) and used with permission by Irving Gottesman.

Limitations

1. No control groups
2. Non-blind diagnosis
3. Structured personal interviews/operationalized diagnostic criteria not used

Modern Studies

- Lifetime at risk
- Morbid risk
- Correlation liability

Lifetime Morbid Risk

- **C**alculated most easily by dividing the no. of people affected in a population by denominator that has been age corrected for population that has not yet passed through the age of risk
- General population = 1%

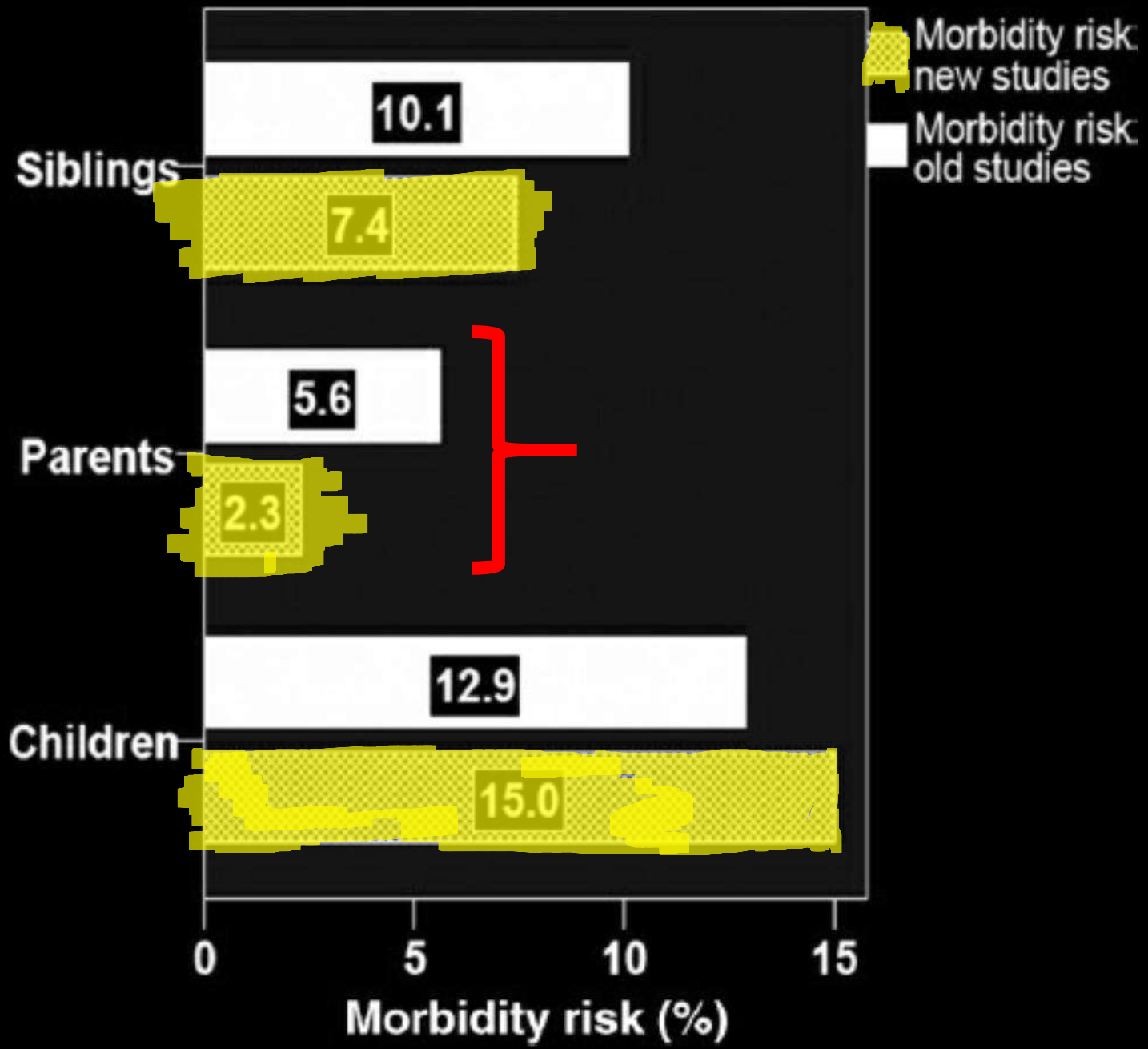


FIGURE 12.4–2. Morbidity risk for schizophrenia in the old and the newer family

Findings

- Findings confirmed
- Smaller morbidity risks (1.4 - 6.5% 1st degree relatives v/s 0 - 1.9% controls)
- High familial loading of schizophrenia (Siblings: 8-10 times increased risk)
- 2010: 27.3% risk in offspring of schizophrenic parents (39.2% - schizophrenia related disorders)

Twin Studies

Twin Studies

- Compares concordance rates in monozygotic (MZ) and Dizygotic (DZ) twins
- MZ twins share all genes; DZ twins share ≈ 50% genes
- Assuming twins share common environment,
  - Higher concordance in MZ twins compared to DZ → Genetic
  - Concordance of < 100% in MZ twins → Environmental

Twin Studies

Pairwise Concordance

- $\frac{C}{C+D}$

Probandwise Concordance

- $\frac{2C}{2C+D}$

C = No. of Concordant Twins
D = No. of Discordant Twins

Gives the risk for the twin of a person suffering from SCZ to become ill him/her self

Twin Studies

Eg: Group of 10 twins preselected with one affected member. During the course of study, 4 other previously non-affected members get affected.

Pairwise Concordance

- $\frac{C}{C+D}$
- $\frac{4}{4+6} = \frac{4}{10} = 40\%$

Probandwise Concordance

- $\frac{2C}{2C+D}$
- $\frac{2 \times 4}{2 \times 4 + 6} = \frac{8}{14} = 57\%$

Discordance

1. Affected member of the pair suffers from an environmentally determined form of the disorder, a so-called phenocopy
2. Both twins inherited the same increased genetic liability, but this is only expressed in the affected twin

Summary

- Strong evidence for importance of genetic factors
- Lack of 100% concordance among MZ twins - Nongenetic factors are also important

Adoption Studies

Adoption Studies

- Role of genetic and environmental factors in transmission of schizophrenia
- 2 important relationships studied:
  1. Individuals who are genetically related but do not share familial-environmental factors
  2. Individuals who share familial–environmental factors but are not genetically related

Adoption Studies

- Genetic component:
- Similarity b/w adopted children + biological parents > Similarity b/w adopted children + adoptive parents
- Adoption – doesn’t increase risk for developing SCZ among children

Adoption Studies

Study	Design	Genetic Relatives of a Schizophrenic Person	Not Genetically Related to a Schizophrenic Person
Heston 1966, Oregon, US	Subjects born mostly in psych. hosp. to schizophrenic/psychotic mothers, separated from birth	5 (10.6%) of 47 adopted away children - SCZ 4 - low IQ <70	No cases - 50 control children adopted away from healthy mothers
Higgins 1976, Denmark	Comparison of 25 children separated from SCZ mothers at age 0–36 months with 23 children reared by SCZ mothers	Children separated: 4 (16%) – chronic SCZ 2 suicide 4 SA/Acute psychotic episodes Children reared by their schizophrenic mothers: 4 - SCZ 4 - Schizoid personality disorders	--

Adoption Studies

Study	Design	Genetic Relatives of a Schizophrenic Person	Not Genetically Related to a Schizophrenic Person
Rosenthal 1971, Denmark	Compared 52 adopted away children of SCZ parents most of whom became ill after the adoption, with 67 control adoptees	14 (26.9%) of 52 children of SCZ parents - broad SCZ-spectrum illness	12 (17.9%) of 67 control adoptees - broad SCZ-spectrum illness
Wender 1974, Denmark	Cross-fostering: 28 children of normal parents raised by SCZ parents and 69 adopted children of SCZ parents	13 (18.8%) of 69 children of SCZ parents - “probable borderline or more severe” disorders.	3 (10.7%) of 28 children of normal parents raised by SCZ - “probable borderline or more severe” disorders

Adoption Studies

Study	Design	Genetic Relatives of a Schizophrenic Person	Not Genetically Related to a Schizophrenic Person
Kety 1994, Denmark	Compared the biological and adoptive relatives of 47 adopted SCZ patients with the relatives of 47 control adoptees	14 (5%) of 279 biological relatives - chronic SCZ 30 (10.8%) - "latent" SCZ	2 (1.8%) of 111 adoptive relatives - "latent" SCZ 1 (0.3%) - SCZ 6 (1.7%) of 351 biological and adoptive relatives of control adoptees - "latent" SCZ
Mirsky 1995, Israel	25 Kibbutz-reared children compared with children reared by their families	3 (12%) - SCZ 3 (12%) - SCZ-spectrum disorders	25 control children reared in kibbutz: no case of SCZ

Adoption Studies

Study	Design	Genetic Relatives of a Schizophrenic Person	Not Genetically Related to a Schizophrenic Person
Tienari 2000, Finland	Compared offspring of schizophrenic or paranoid mothers with offspring of healthy mothers	17 (10.4%) of 164 affected: 11 – SCZ 1- SA 1- SP/ST 4 - Narrow spectrum SCZ	4 (2%) of 197 control adoptees - SCZ

Conclusion

- Children of parents with SCZ - 10% risk of developing SCZ, SCZ affective disorder, or other narrow spectrum SCZ disorders when adopted very soon after birth
- Study supports the results of family and twin study in demonstrating significance of genetic factors in SCZ.

Linkage Studies

Linkage Studies

- Linkage – tendency for genes & other genetic markers to be inherited together as they are located closely on the same chromosome
- Identify genomic regions containing predisposing/protective genes
- Logarithm of odds scores (LoD):

$$\log_{10} \frac{\text{Likelihood of the observed data given linkage}}{\text{Likelihood of the data given no linkage}}$$

- Mendelian disorders: LoD score > 3 - linkage

Linkage Studies

- Certain regions with statically significant LoD Scores

1. 22q11 - q13
2. 6p24 - p22
3. 8p22 - p21

- Regions for with data are suggestive include

1. 1q21 - q22
2. 5q21 - q31
3. 10p15 - p11
4. 13q14.1 - q32

Linkage Studies

- 2 novel genes on chromosome I - disrupted by translocation DISC 1 & DISC 2 in SCZ; may represent candidate genes for susceptibility to Psychiatric illness including SCZ
- Evidence was also obtained for linkage to regions on chromosomes 1q, 3p, 5q, 6p, 8p, 11q, 14p, 20q, and 22q
- The 8p and 22q regions were supported by meta-analyses
- Conclusion: no single gene for schizophrenia exists


CAPON
RGS4
1,2
3
DISC1
3,4,5
1
2
7
6
7
8
3
6
4
5
9,10
2
8,11
DTNBP1
12,13
14,15
16
6
7
PPP3CC
NRG1
2,17,
18
8
9
7
19
16
20
10
11
2
6
DAO
12
DAOA
16,21
13
14
15
16
17
18
19
6
20
21
22
Y
X

Association Studies

Association Studies

- Implicate specific gene by identifying correlation between a disease and alleles at a specific genetic locus
- Compares frequency of marker genotypes in cases with an appropriate control group.
- SNPs - MC source of genetic measurement

Dystrobrevin-Binding Protein 1

- Richard E. Straub et al 2002
- Chr. 6p22.3
- Significant associations found b/w SCZ and several SNPs and multimarker haplotypes spanning DTNBP1
- Support from other large studies (Germany, UK, Ireland, Bulgaria)
- Some studies showing no associations

Neuregulin 1

- Chr. 8p21-22
- Encodes multiple proteins with diverse range of functions in the brain.
- First implicated in SCZ following a linkage study in an Icelandic sample, supported by studies from UK, Ireland, Chinese, Bulgarian and South African population
- Only 3 studies of Icelandic, Scottish, and UK have replicated the specific Icelandic haplotype, suggesting difference in linkage disequilibrium

TABLE 3–3. Evidence supporting variation in specific genes in the etiology of schizophrenia

Gene	Gene product or effect	Location	Linkage evidence, bin (of 120)	Association evidence, box score	Other evidence
NRG1	Neuregulin 1	8p12	55	6 of 7 samples	Altered expression in dorsal lateral prefrontal cortex in schizophrenia, known to be involved in the developing nervous system
DTNBP1	Dystrobrevin binding protein 1	6p22.3	10	6 of 8 samples	Involved in multiple neuronal functions (e.g., synapse formation and maintenance); colocalizes with postsynaptic γ-aminobutyric acid receptors
G72 and *G30*	Produces *PLG72*	13q33.2	62	1 sample	Protein product not yet well characterized; expressed in brain and interacts with D-amino acid oxidase (DAO), which is independently associated with schizophrenia; association of *G72* and *G30* with bipolar disorder replicated in several samples
RGS4	Regulator of G-protein signaling 4	1q23.3	14	2 of 3 samples	Altered brain expression in schizophrenia via microarray studies of postmortem samples
COMT	Catechol-*O*-methyl-transferase	22q11.21	9	Inconsistent	Deletion associated with schizophrenia; functional variant implicated in schizophrenia by neuroimaging and neuropsychological testing
PRODH	Proline dehydrogenase	22q11.21	9	1 of 4 samples	Deletion associated with schizophrenia; mouse model suggests its importance as an endophenotype
DISC1 and *DISC2*	Disrupted in schizophrenia 1 and 2	1q42.2	38		Balanced translocation associated with schizophrenia
HTR2A	Serotonin$_{2A}$ receptor	13q14.2	81	Meta-analytic support	Target for multiple antipsychotic drugs
DRD3	Dopamine$_3$ receptor	3q13.31	68	Meta-analytic support	Implicated via dopaminergic theory of schizophrenia

Genome-Wide Association Studies (GWAS)

GWAS

- Common variant SNPs
- Minor allele frequency of SNP > 0.05
- The effect sizes of the associations likely to be very small – 100s and even 1000s of genes might contribute small effects to the pathogenesis of SCZ

GWAS

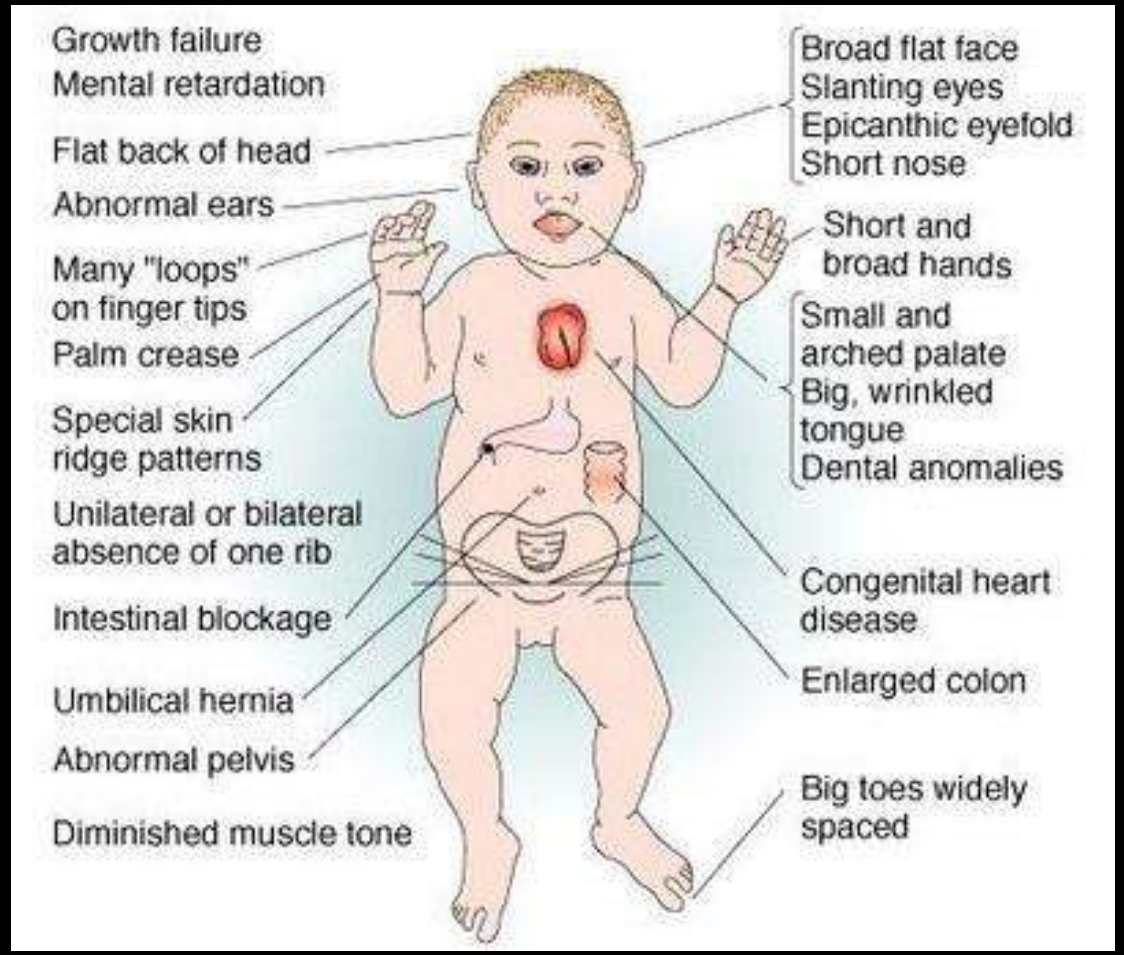
- Thousands of common polygenic variants with very small individual effects explain about 1/3rd of the total variation in genetic liability to SCZ
- Remaining heritability - missing even after the well powered GWAS studies
- The strongest finding was on chromosome 2 around the putative zinc finger protein (ZNF804a)

Chromosomal Aberrations/ Copy Number Variants

Chromosome 22q11.2 Deletion Syndrome

- 1st and best replicated findings
- MC human deletion syndrome (1 in 3900-9700 children)
- aka DiGeorge/VeloCardioFacial syndrome
- Carriers - Phenotypic heterogeneity
- High risk of SCZ – 24%
- Accounts for 0.3 - 0.6% of SCZ cases

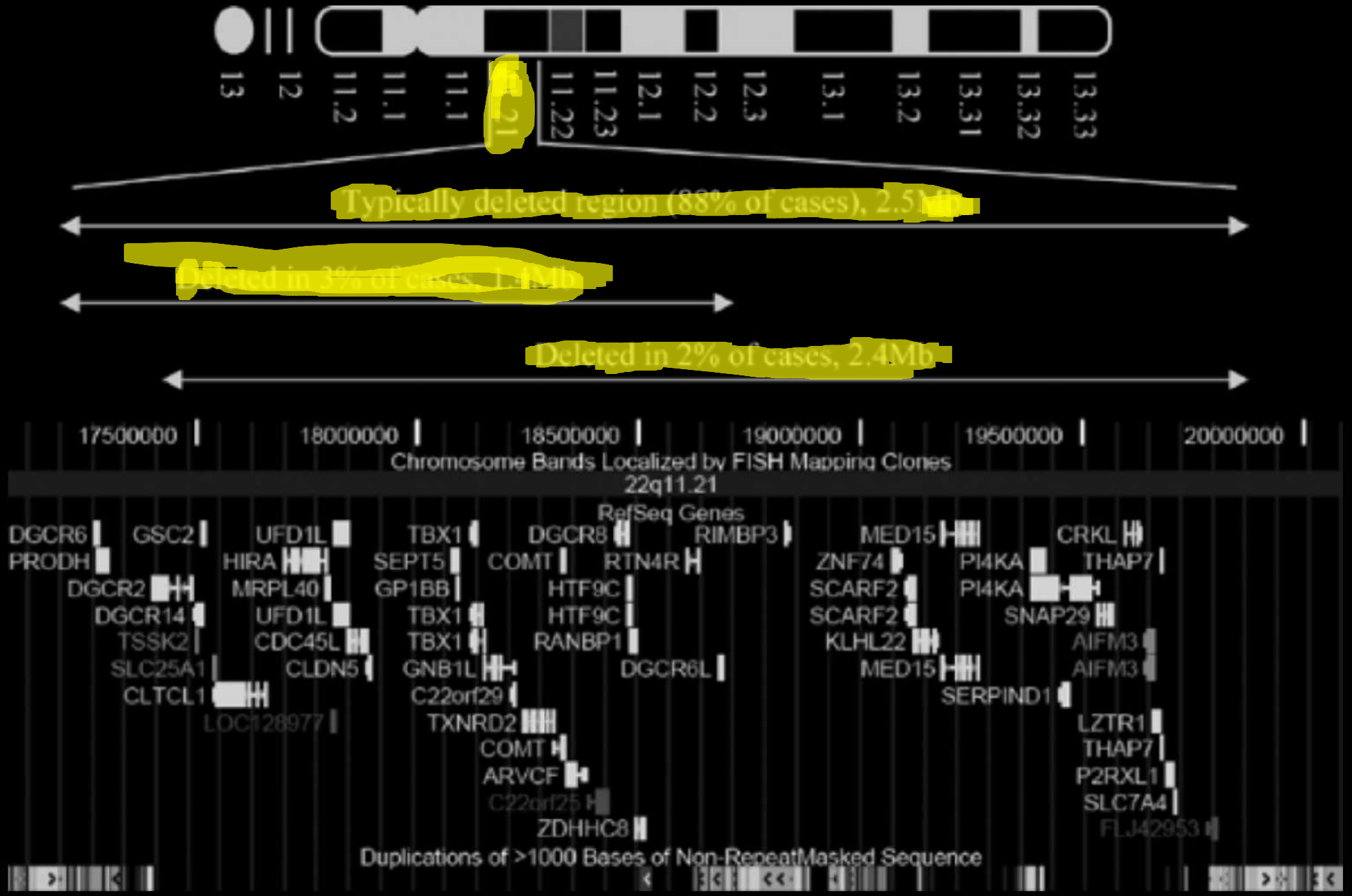
Features



- **C**ardiac anomalies
- **A**bnormal facies
- **T**hymic Hypoplasia
- **C**left Palate
- **H**ypocalcaemia
- Others: Renal and skeletal abnormalities, developmental & speech delay
- Behavioral and psychiatric disorders

Chromosome 22q11.2 Deletion Syndrome

- Largest known individual risk factor for SCZ second only to having an identical twin with SCZ.
- Likely to have larger phenotypic effects than SNPs.
- Other genes implicated: COMT, TBXI, GNBIL, PRODH, and ZDHHC


13
12
11.2
11.1
11.1
21
11.22
11.23
12.1
12.2
12.3
13.1
13.2
13.31
13.32
13.33
Typically deleted region (88% of cases), 2.5Mb
Deleted in 3% of cases, 1.4Mb
Deleted in 2% of cases, 2.4Mb
17500000
18000000
18500000
19000000
19500000
20000000
Chromosome Bands Localized by FISH Mapping Clones
22q11.21
RefSeq Genes
DGCR6
GSC2
UFD1L
TBX1
DGCR8
RIMBP3
MED15
CRKL
PRODH
HIRA
SEPT5
COMT
RTN4R
ZNF74
PI4KA
THAP7
DGCR2
MRPL40
GP1BB
HTF9C
SCARF2
PI4KA
DGCR14
UFD1L
TBX1
HTF9C
SCARF2
SNAP29
TSSK2
CDC45L
TBX1
RANBP1
KLHL22
AIFM3
SLC25A1
CLDN5
GNB1L
DGCR6L
MED15
AIFM3
CLTCL1
C22orf29
SERPIND1
LOC128977
TXNRD2
LZTR1
COMT
THAP7
ARVCF
P2RXL1
C22orf25
SLC7A4
ZDHHC8
FLJ42953
Duplications of >1000 Bases of Non-RepeatMasked Sequence

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Copy Number Variants

- 2p16.3 Neurexin (NRNX1) deletion
- Neurexin - presynaptic cell adhesion molecule; interacts with post synaptic cell adhesion molecules including neuroligins
- Role in release of NTs from presynaptic vesicles
- Along with neuroligins, involved in synapse formation and neural circuits
- SCZ, MR, Autism

Other CNVs

- 15q13.1 duplication
- 1q21.1 deletion
- 15q13.2 deletion
- 15q13.3 deletion – MR & seizures
- 16p11.2 duplication

Pleiotropy

- Genes positive for SCZ, also positive for BPAD, autism and vice versa
- BPAD: DISC 1, NRG 1, RELN, ANK3
- Autism: Neurexin 1

Hurdles in Research

- Lack of operational phenotypes
- Presence of large no. of common variants of small effects
- Cost, expertise and manpower

Conclusion

Purposes of genetic studies:

1. Understand etiology
2. Pharmacogenetic approaches for individualized treatments
3. Understand clinical heterogeneity

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- Internet

Thank you