Suhetest CNV-de ja haiguste vahel

Katrin Männik

Bioinformaatika JClub

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DNA koopiaarvu variatsioonid (CNV-d)

- >1 kb DNA segment, mille genoomsete koopiate arv on suurenenud või vähenenud

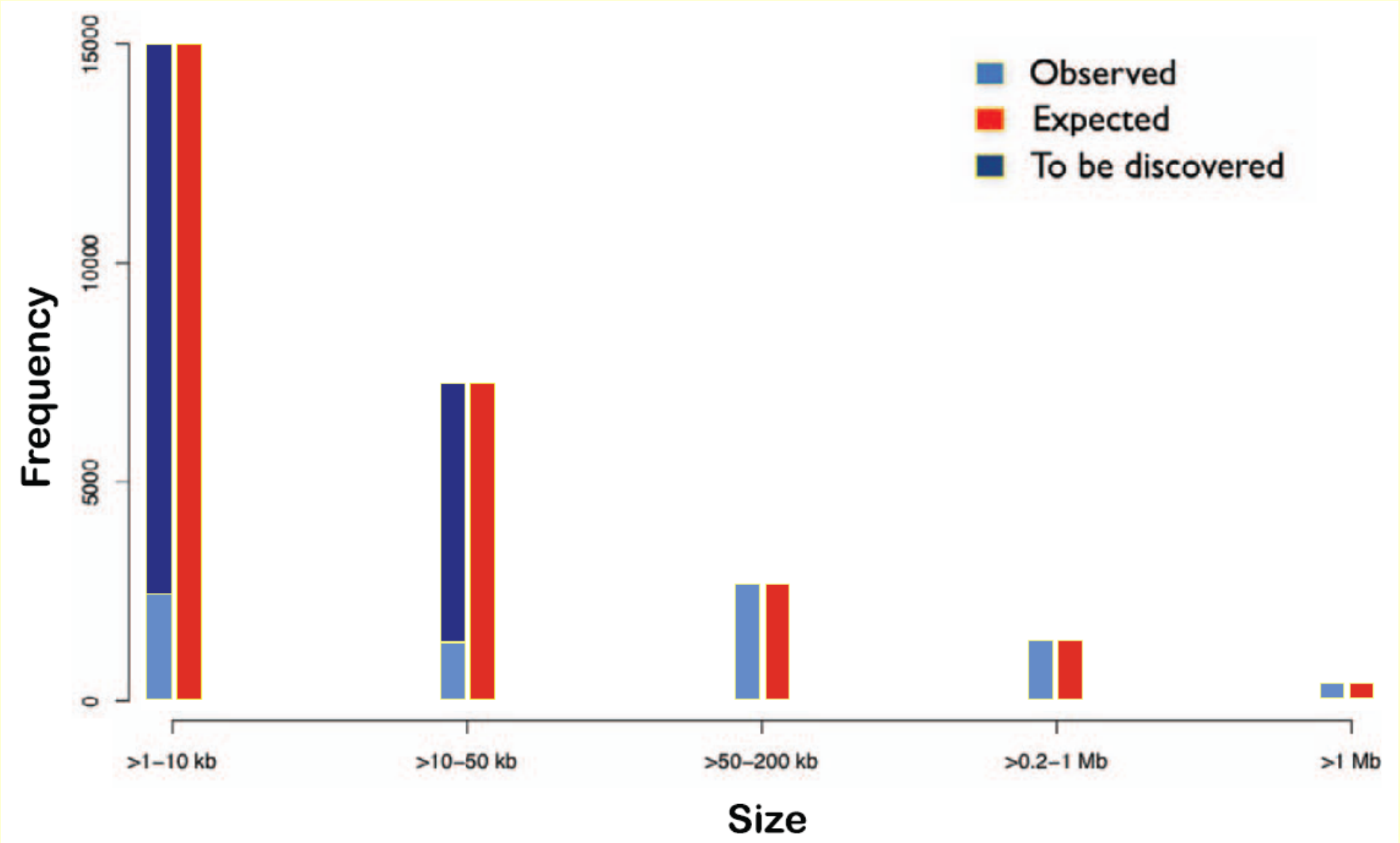
- Kaardistatud 1500 CNV-d → 360Mb = 12% inimgenoomist

Redon *et al* Nature 2006

Konstitutsionaalsed
- kaasasündinud
- üle kogu organismi
- fenotüübiline erinevus
- vastuvõtlikkus haigustele
- arenguhäired

Somaatilised
- elukäigus omandatud
- koespetsiifilised
- tumorigenees

Oodatav vs käesolev olukord



doi:10.1371/journal.pgen.0030190.g003

Figure 3. Expected and Observed Size Distribution of CNV Changes Identified to Date

Estivill & Armengol PLoS Genet 2007

Millest hetkel räägitakse?

- erinevate metoodikate võrreldavaks muutmine
    - hästi uuritud kontrollDNA-d
- detekteeritud/andmebaasides olevate CNV-de valideerimine
    - FISH; RT-qPCR; MLPA
- aberratsiooni murdekohtade täpne kindlaksmääramine
- fenotüübiinfo täpsustamine
- andmebaaside loomine
    - Database of Genomic Variants $\rightarrow$ neutraalsed CNV-d
    - DECIPHER $\rightarrow$ haiguspõhjuslikud CNV-d

Database of Genomic Variants

A curated catalogue of structural variation in the human genome

Hosted by:
The Centre for
Applied Genomics

Please select genome assembly: Build 36 (Mar. 2006)

View Data by Chromosome

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y All

View Data by Genome

Keyword Search

Search

Exact Match? Yes No

Examples: clone name, accession number, cytoband, gene

BLAT Search

Enter sequence in FASTA format here:

BLAT Search

Summary Statistics

Total entries: 29289 (hg18)
CNVs: 11784
Inversions: 182
InDels (100bp-1Kb): 17323
Total CNV loci: 4878
Articles cited: 46

Last updated: Nov 29, 2007
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In citing the Database of Genomic Variants please refer to: Iafrate AJ, Feuk L, Rivera MN, Listewnik ML, Donahoe PK, Qi Y, Scherer SW, Lee C: Detection of large-scale variation in the human genome. Nat Genet. 2004 Sep;36(9):949-51.

DECIPHER - DatabasE of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources - Mozilla Firefox

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http://www.sanger.ac.uk/PostGenomics/decipher/

decipher

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DECIPHER
November News Letter

Welcome to DECIPHER

Guest Access

DatabasE of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources

The DECIPHER database of submicroscopic chromosomal imbalance collects clinical information about chromosomal microdeletions/duplications/insertions, translocations and inversions and displays this information on the human genome map with the aims of:

- Increasing medical and scientific knowledge about chromosomal microdeletions/duplications
- Improving medical care and genetic advice for individuals/families with submicroscopic chromosomal imbalance
- Facilitating research into the study of genes which affect human development and health

About DECIPHER

Background

Chromosome analysis remains the single most useful tool in the diagnosis of children with developmental delay/learning disability and/or multiple congenital anomalies. The limit of resolution of a high quality Giemsa-banded karyotype is ~5Mb, and many such children have a normal result on routine karyotyping.

Challenges

Array-CGH offers the opportunity to detect submicroscopic chromosomal imbalance across the entire genome. With ~3,000 clones on a 1Mb array, and more than 30,000 clones on a whole genome tiling array, a large database is needed to capture this information and relate the location of the submicroscopic chromosome imbalance to the phenotype.

Solutions

Using the Ensembl interface, DECIPHER allows you to:

- Visualise the chromosomal location of the clones which are found to be deleted or duplicated in an array/CGH analysis
- See whether this coincides with a recognized polymorphism or known microdeletion/microduplication syndrome
- See whether a similar deletion or duplication has been reported by any members of the Decipher consortium previously
- Record the phenotype of your patient, and compare this with previous records
- Visualise the known genes and putative genes and expressed-sequence tags (ESTs) within the deleted/duplicated region
- Print out a report, including an ideogram of the chromosomal location of the microdeletion/duplication or inversion

30th Nov 2007

November News Letter

We are pleased to announce our latest DECIPHER News ...

For full details click here...

31st Oct 2007

October News Letter

We are pleased to announce our latest DECIPHER News letter ...

For full details click here

Summary

Data type	Statistics
Patients	1094
Syndromes	49
Array Types	26
Projects	91
Last updated	6th Dec 2007

Mida CNV-d võivad määrata?

- genoomsed haigused

- monogeensed haigused

- pärilike haiguste erinev penetrantsus

- kompleks/multifaktoriaalsed haigused

- indiviididevahelised erinevused
    - vastuvõtlikkus infektsioonidele
    - kasvajaliste protsesside teke
    - reageerimine ravimitele

Beckmann *et al* Nature Rev Genet 2007

Kuidas CNV-d geenieksprессiooni võivad mõjutada?

- 18% geenieksprессiooni muutustest põhjustavad CNV-d

Stranger *et al* Science 2007

- Muutub CNV sisse jäävate geenide ekspressioonitase

- Muutub CNV-ga külgnevates alades paiknevate geenide ekspressioonitase

- Positsiooniline efekt 1 $\rightarrow$ CNV sisse jäävad regulaatorelemendid
  - ümberkaudsete geenide ekspressioonis nii $\downarrow$ kui $\uparrow$

- Positsiooniline efekt 2 $\rightarrow$ muutub kromatiinstruktuur
  - ümberkaudsete geenide ekspressioon $\downarrow$

- Asukoha muutus tuumas/kromosoomterritooriumis

Reymond *et al* Curr Opin Genet Dev 2007

Millised CNV-d võivad olla patogeensed?

Table 1 Factors influencing the risk assessment of a CNV

Major criteria		Characteristic of pathogenic CNVs	Characteristic of benign CNVs
1.	a. CNV is inherited from a healthy parent		×
	b. CNV is inherited from an affected parent	×	
2.	a. CNV is similar to a CNV in a healthy relative		×
	b. CNV is similar to a CNV in an affected relative	×	
3.	a. CNV overlaps a genomic imbalance in a CNV database for healthy individuals (for example, Database of Genomic Variants)		×
	b. CNV overlaps a genomic imbalance in a CNV database for affected individuals (for example, DECIPHER)	×	
4.	CNV contains morbid OMIM genes	×	
5.	a. CNV is gene rich	×	
	b. CNV is gene poor		×

Minor criteria		Characteristic of pathogenic CNVs	Characteristic of benign CNVs
1.	a. CNV is a deletion	×	
	b. CNV is a homozygous deletion	×	
2.	a. CNV is a duplication		×
	b. CNV is an amplification (gain of more than one copy)	×	
3.	CNV is >3 Mb in size	×	
4.	CNV is devoid of known regulatory elements		×

Lee *et al* Nat Genet 2007

CNV-de seos komplekshaigustega

Table 3. Summary of Common Disorders for Which Associations to CNVs Have Been Reported

Disorder	CNV	SD	SNPs[a]	Gene	Effect	Risk Associated	Study Type	Significance
HIV-1/AIDS susceptibility	Common	Yes	No	*CCL3L1*	Dosage	Low CNV	Case control	Varies in populations
Rheumatoid arthritis and Type 1 diabetes	Common	Yes	No	*CCL3L1*	Dosage	High CNV	Case control	OR = 1.34; $p = 0.009$
SLE, microscopic Polyangiitis, and Wegener granulomatosis	Common	Yes	No	*FCGR3B*	Dosage	Low CNV	Case control	$p < 0.001$
SLE	Common	Yes	No	*C4A/C4B*	Dosage	Low CNV	Case control	OR = 6.5; $p < 0.00002$
Crohn disease	Common	Yes	No	*DEFB4*	Dosage	Low CNV	Case control	OR = 3.6 $p < 0.008$
Bipolar disorder	Common	No	Poor	*GSK3B*	Positional	High copy number	Case control	$p = 0.002$
Early-onset Parkinson disease	Rare	No	Yes	*SNCA*	Dosage	Duplication/triplication	Familial	NA
Hereditary early-onset Alzheimer disease	Rare	No	Yes	*APP*	Dosage	Duplication	Familial	NA
Hereditary pancreatitis	Rare	Yes	Poor	*PRSS1*	Dosage	Triplication	Familial	NA
Autism spectrum disorders	Common	NA	Vary	Multiple	Unknown	Higher "de novo" CNVs; multiple CNVs	Familial	NA
Familial breast cancer	Common	No	Yes	*MTUS1* (exon 4)	Positional	Exon deletion confers lower risk	Familial	OR = 0.41; $p < 0.003$

Estivill & Armengol PLoS Genet 2007

CNV-de seos komplekshaigustega

Komplekshaigustega seotud regioonidel ühised tunnused:

- esinevad nii CNV-d kui segmentaalsed duplikatsioonid

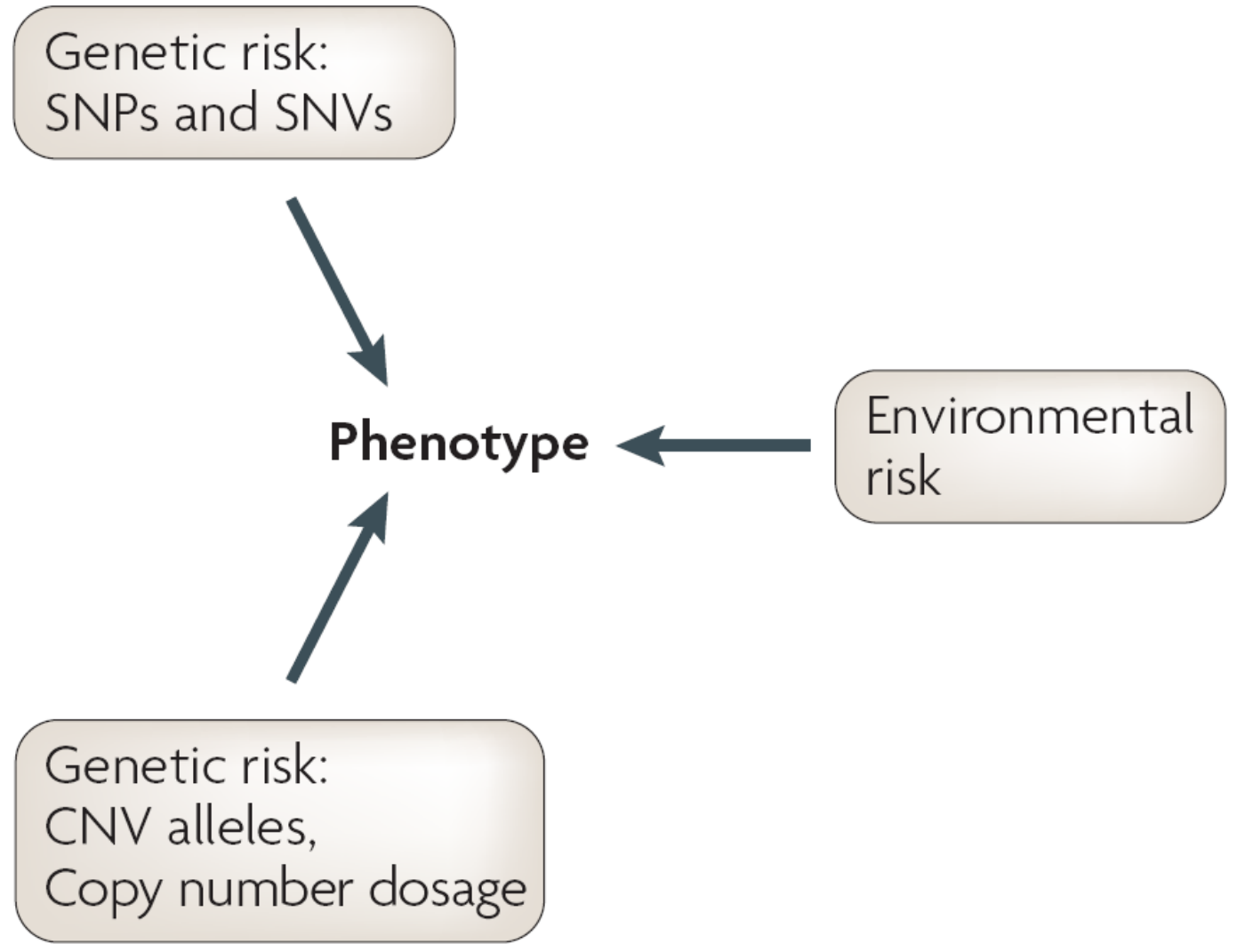
- on kompleksed ja multialleelsed CNV-d

- on juba eelnevates uuringutes leitud CNVR-d

- Affymetrix`i ja Illumina kiipidel halvasti või üldse mitte esindatud

Estivill & Armengol PLoS Genet 2007

CNV-de seos komplekshaigustega



Beckmann *et al* Nature Rev Genet 2007

Laiendame ettekujutust genoomsest varieeruvusest…

Runs of homozygosity (ROH) – suurusega 200kb…15Mb

Human Molecular Genetics, 2006, Vol. 15, No. 5 **789–795**
doi:10.1093/hmg/ddi493
Advance Access published on January 25, 2006

Extended tracts of homozygosity in outbred human populations

Jane Gibson*, Newton E. Morton and Andrew Collins

Human Genetics Research Division, School of Medicine, University of Southampton, Southampton SO16 6YD, UK

PNAS

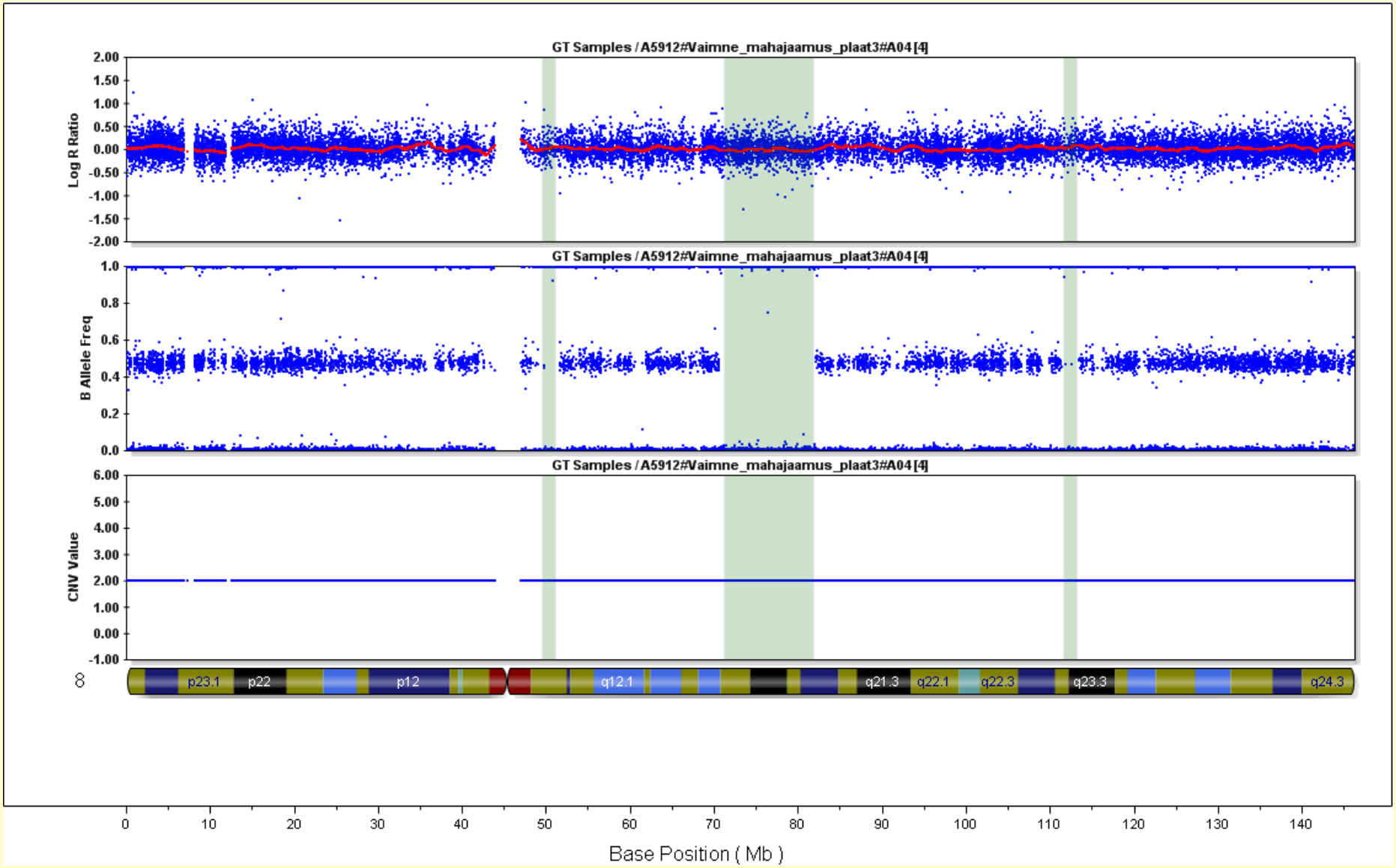
Runs of homozygosity reveal highly penetrant recessive loci in schizophrenia

Todd Lencz*†‡§, Christophe Lambert¶, Pamela DeRosse*, Katherine E. Burdick*†‡, T. Vance Morgan‖, John M. Kane*†‡, Raju Kucherlapati‖, and Anil K. Malhotra*†‡**

*Department of Psychiatry Research, Zucker Hillside Hospital, North Shore–Long Island Jewish Health System, 75-59 263rd Street, Glen Oaks, NY 11004; †The Feinstein Institute for Medical Research, 350 Community Drive, Manhasset, NY 11030; ‡Department of Psychiatry and Behavioral Science, Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Park Avenue, Belfer Room 403, Bronx, NY 10461; ¶Golden Helix, Inc., 716 South 20th Avenue, Suite 102, Bozeman, MT 59718; ‖Harvard Partners Center for Genetics and Genomics, 65 Landsdowne Street, Cambridge, MA 02139; and **Department of Genetics, Harvard Medical School, 77 Avenue Louis Pasteur, Boston, MA 02115

Communicated by James D. Watson, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, October 22, 2007 (received for review July 10, 2007)

Milline ROH välja näeb?



10.7Mb CN-neutraalne LOH Chr8q13.3-21.13