Assessing Genomic Variability using High-throughput SNP Arrays

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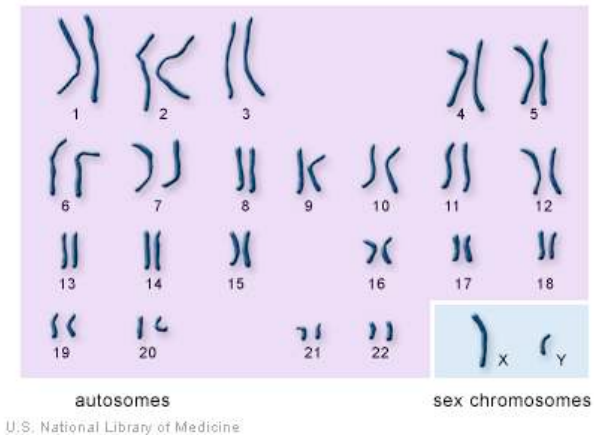
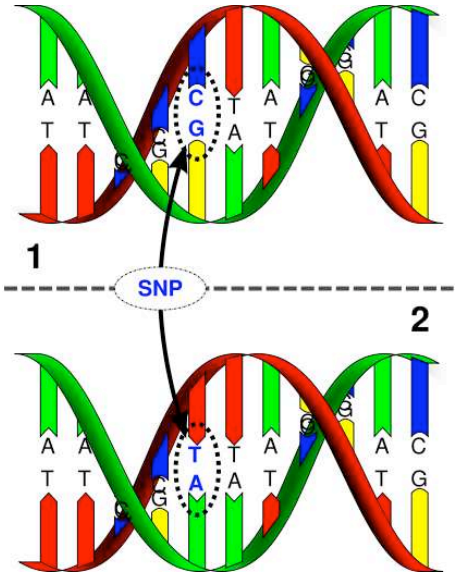
February 17, 2010

Karyotypes



http://ghr.nlm.nih.gov/

Single Nucleotide Polymorphisms



urgi.versailles.inra.fr

Coverage

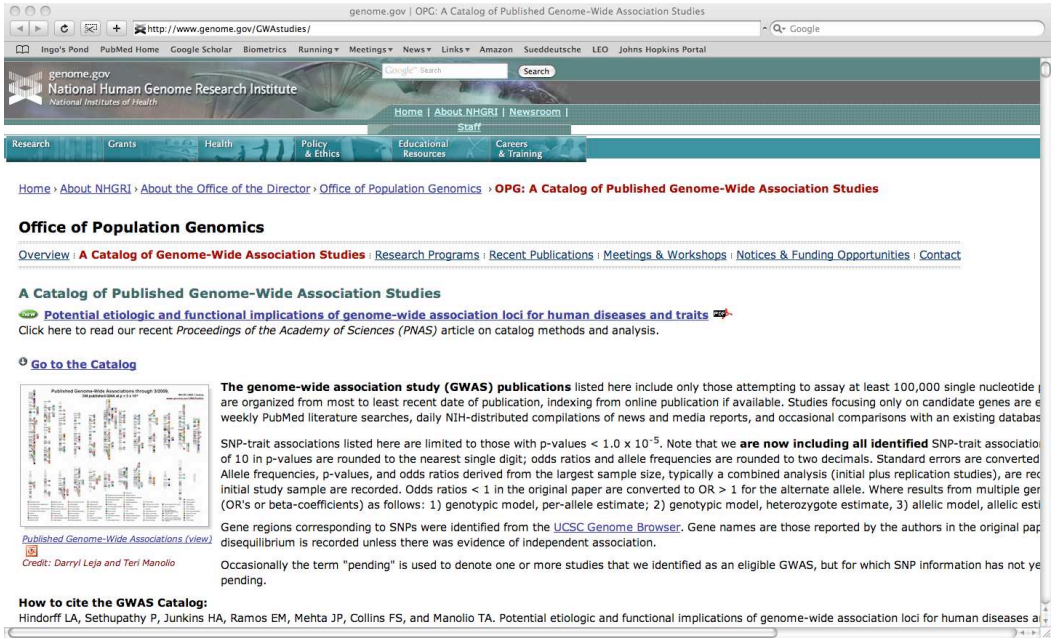
Table 1
Estimated coverage of commercially available fixed marker genotyping platforms

Platform	HapMap population sample		
	YRI	CEU	CHB + JPT
Affymetrix GeneChip 500K	46	68	67
Affymetrix SNP Array 6.0	66	82	81
Illumina HumanHap300	33	77	63
Illumina HumanHap550	55	88	83
Illumina HumanHap650Y	66	89	84
Perlegen 600K	47	92	84

Data represent percent of SNPs tagged at $r^2 \geq 0.8$. Values assume all SNPs on the platform are informative and pass quality control. YRI, Yoruba in Ibadan, Nigeria; CEU, subsample of Utah residents of Northern European ancestry selected from Centre d'Étude du Polymorphisme Humain samples; CHB, Han Chinese in Beijing, China; JPT, Japanese in Tokyo. From the International HapMap Consortium, 2007 (3).

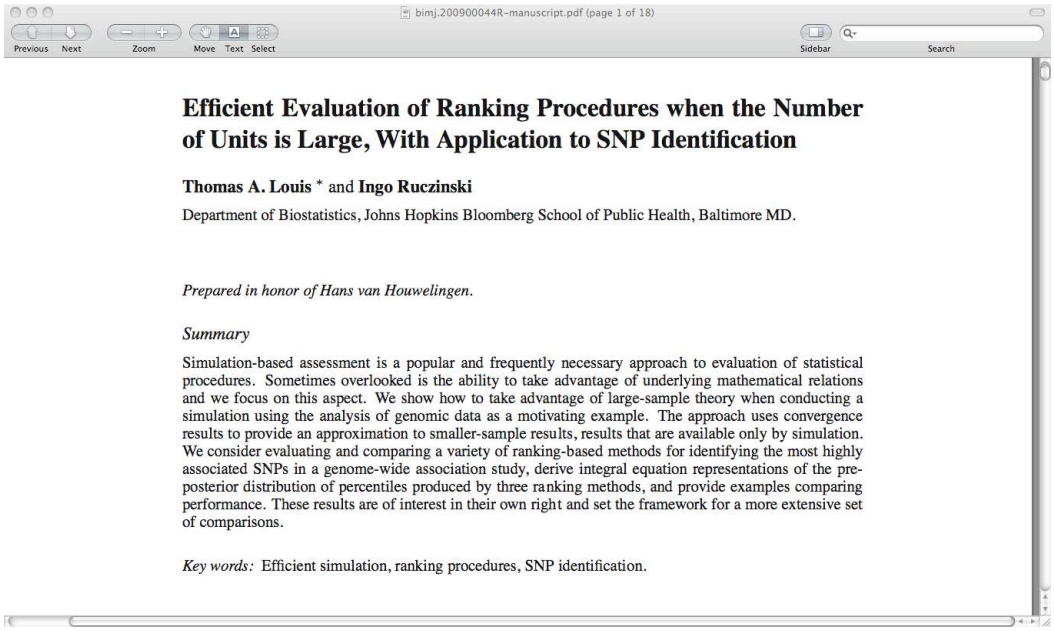
Manolio et al (2008), J Clin Invest 118(5): 1590-605.

Results



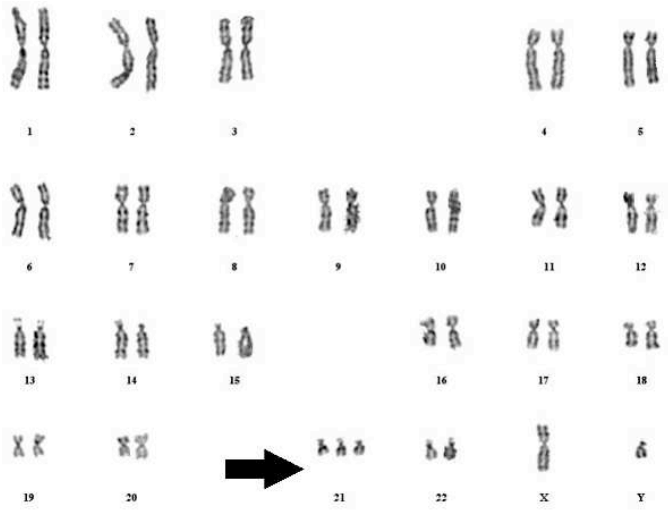
http://www.genome.gov/GWAstudies/

Ranking

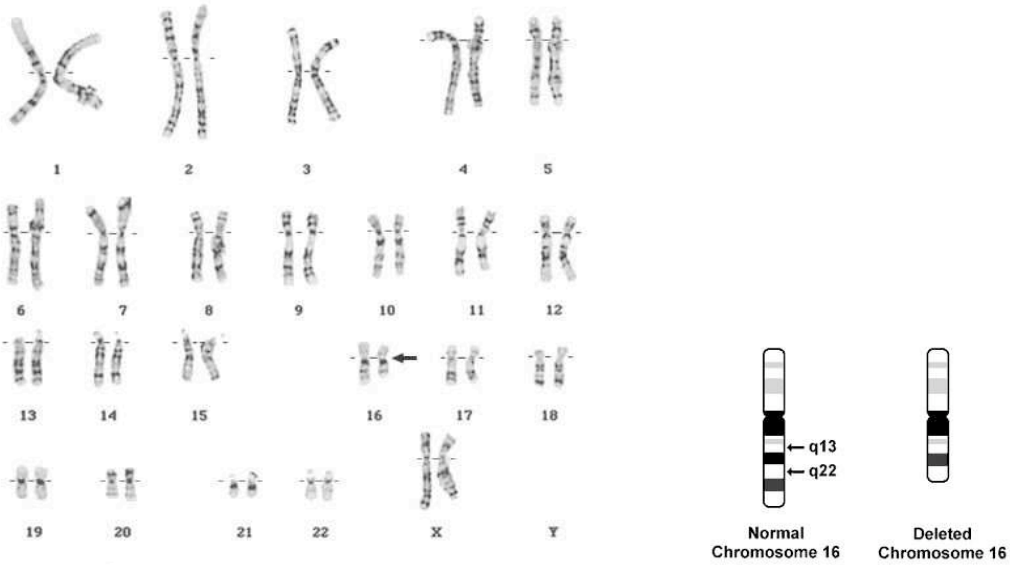


Louis and Ruczinski (2010). Biometrical Journal 52(1), 1-16.

Trisomy

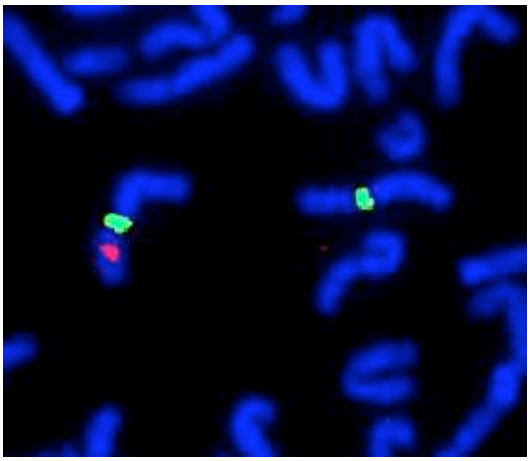


Karyotypes



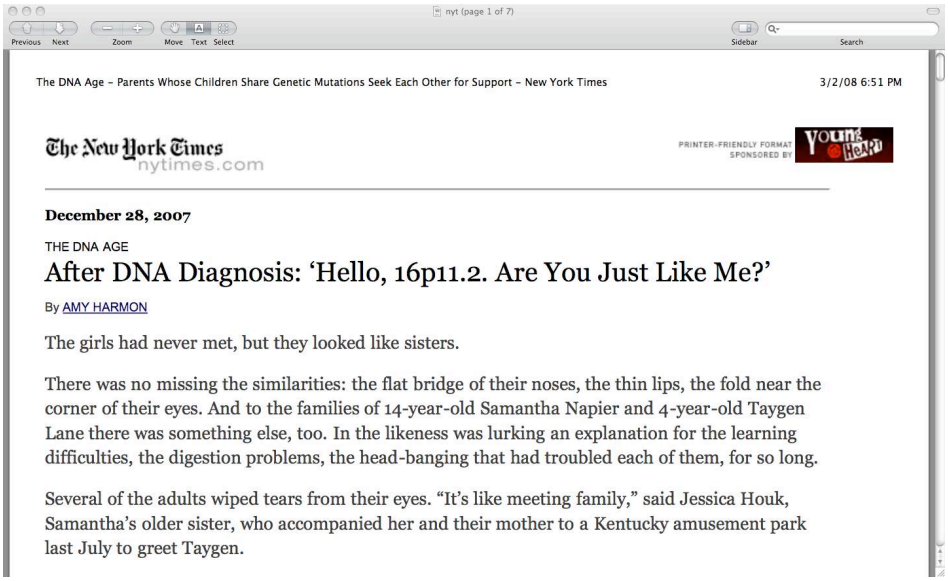
General Cytogenetics Information *http://members.aol.com/chrominfo/*

FISH



Courtesy of the Pevsner Laboratory

Clinical practice



The DNA Age – Parents Whose Children Share Genetic Mutations Seek Each Other for Support – New York Times 3/2/08 6:51 PM

The New York Times nytimes.com

PRINTER-FRIENDLY FORMAT SPONSORED BY Young Heart

December 28, 2007

THE DNA AGE

After DNA Diagnosis: 'Hello, 16p11.2. Are You Just Like Me?'

By AMY HARMON

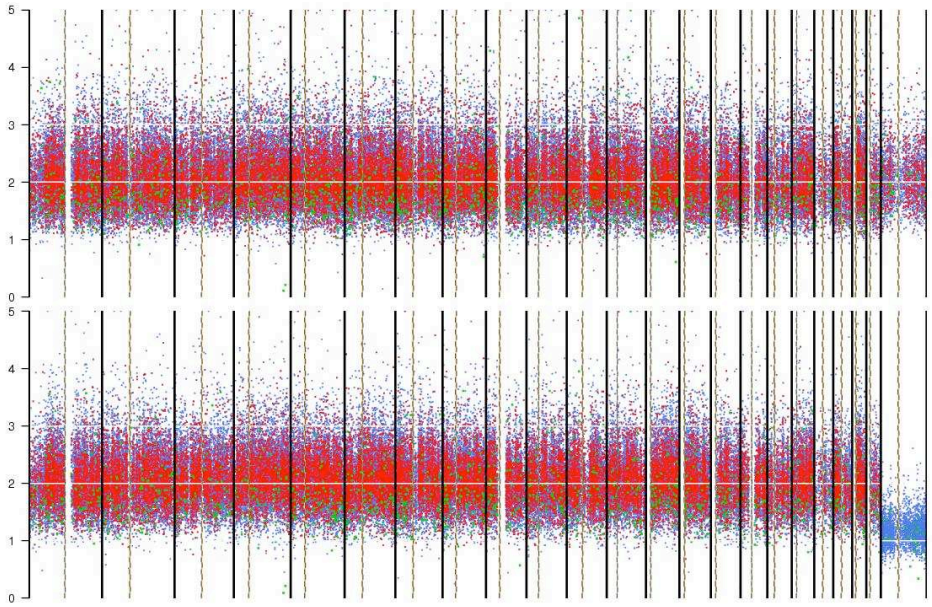
The girls had never met, but they looked like sisters.

There was no missing the similarities: the flat bridge of their noses, the thin lips, the fold near the corner of their eyes. And to the families of 14-year-old Samantha Napier and 4-year-old Taygen Lane there was something else, too. In the likeness was lurking an explanation for the learning difficulties, the digestion problems, the head-banging that had troubled each of them, for so long.

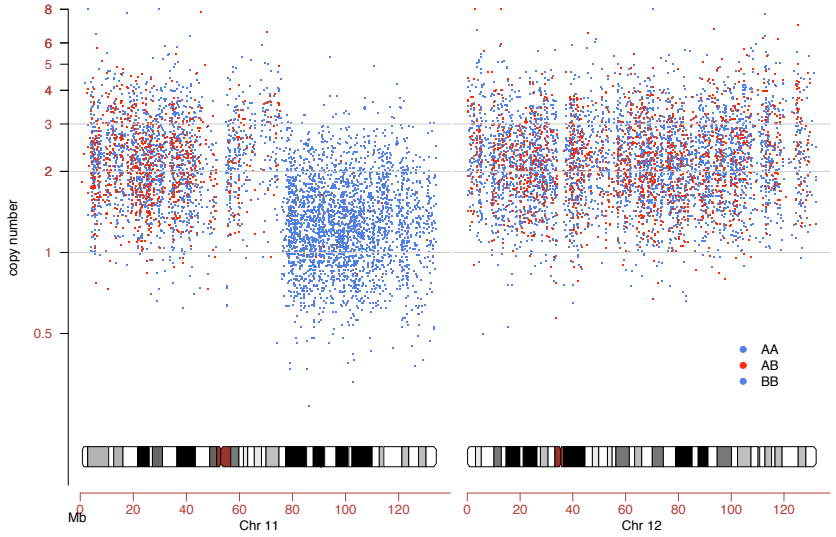
Several of the adults wiped tears from their eyes. "It's like meeting family," said Jessica Houk, Samantha's older sister, who accompanied her and their mother to a Kentucky amusement park last July to greet Taygen.

New York Times, December 28, 2007

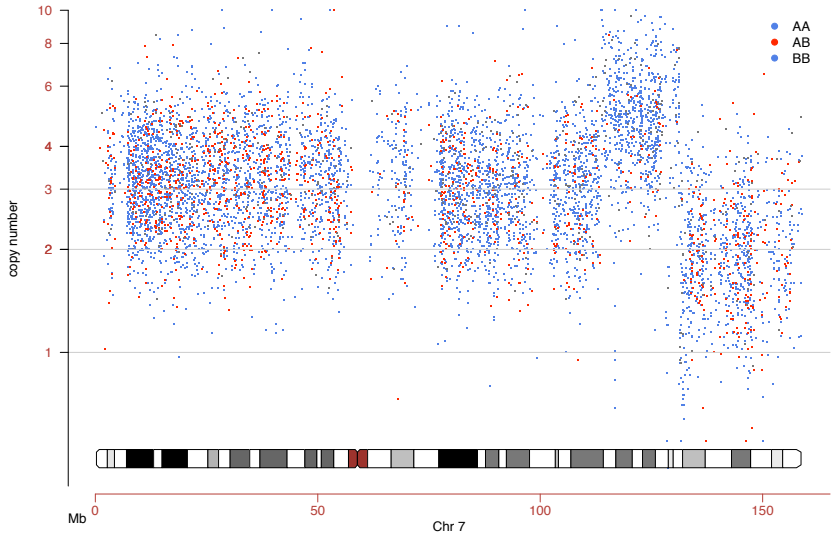
SNP chip data



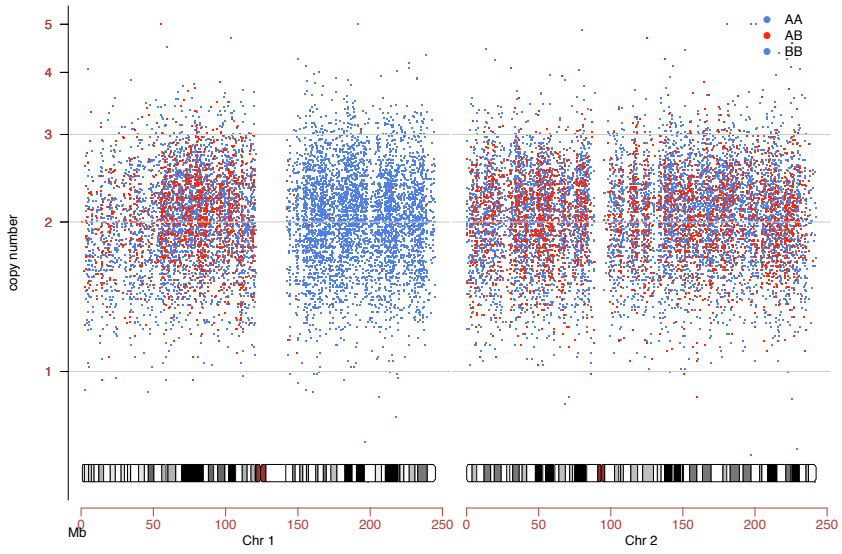
Deletion



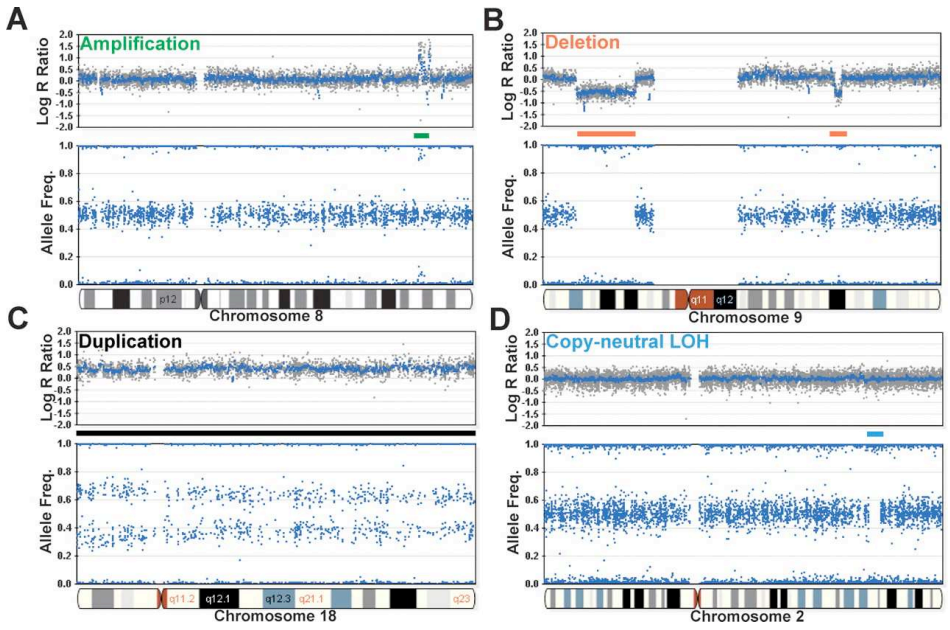
Amplification



Uniparental Isodisomy

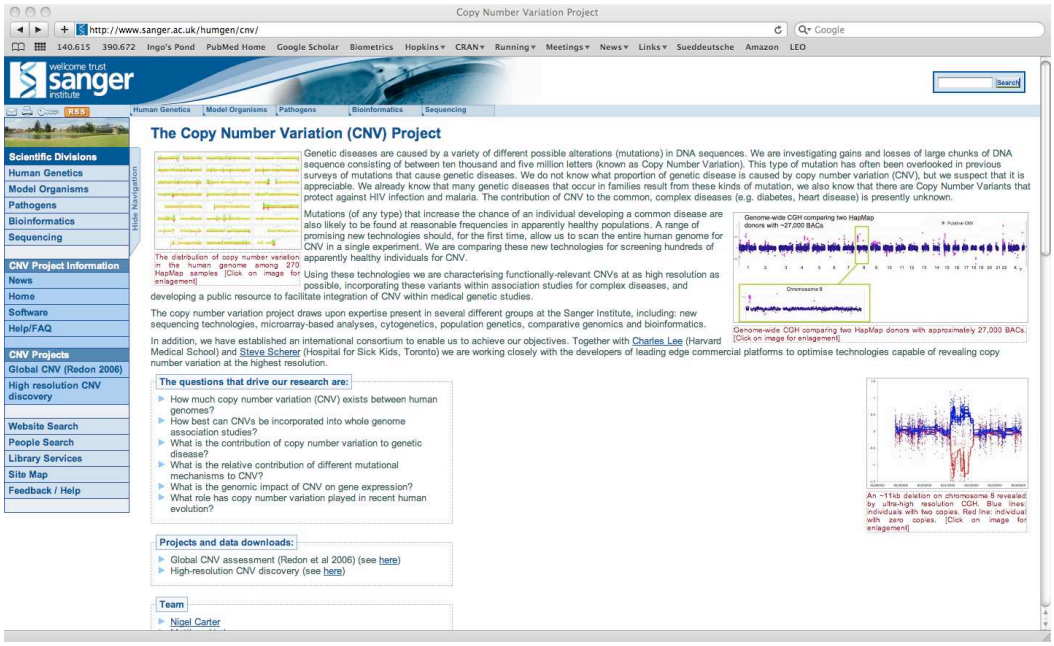


Illumina



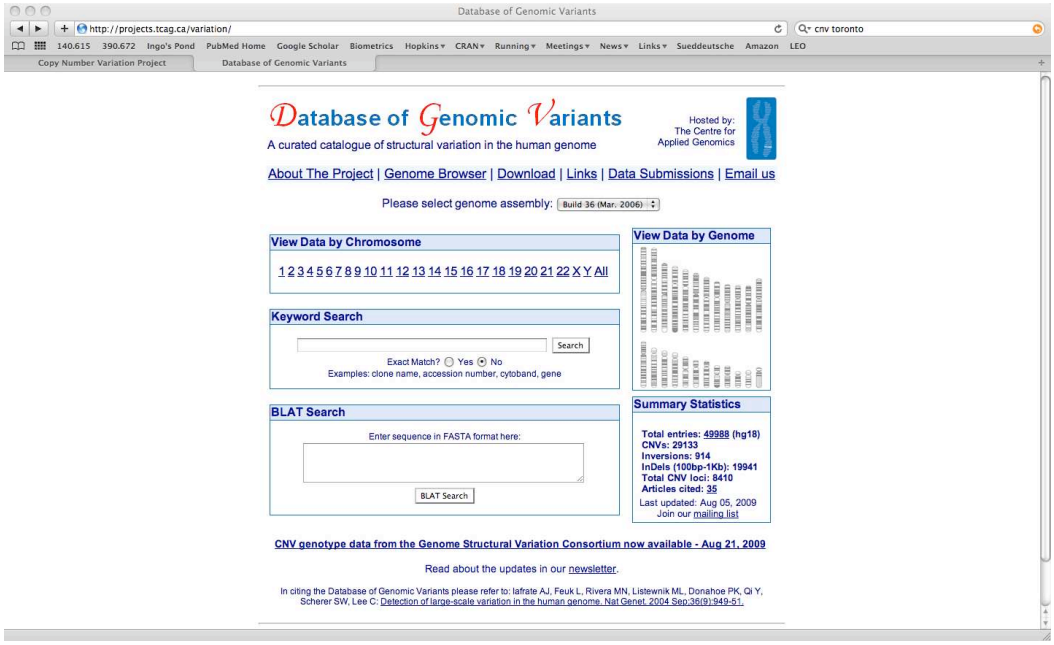
Pfeiffer et al (2006), Genome Res. 2006. 16: 1136-1148.

Structural variation



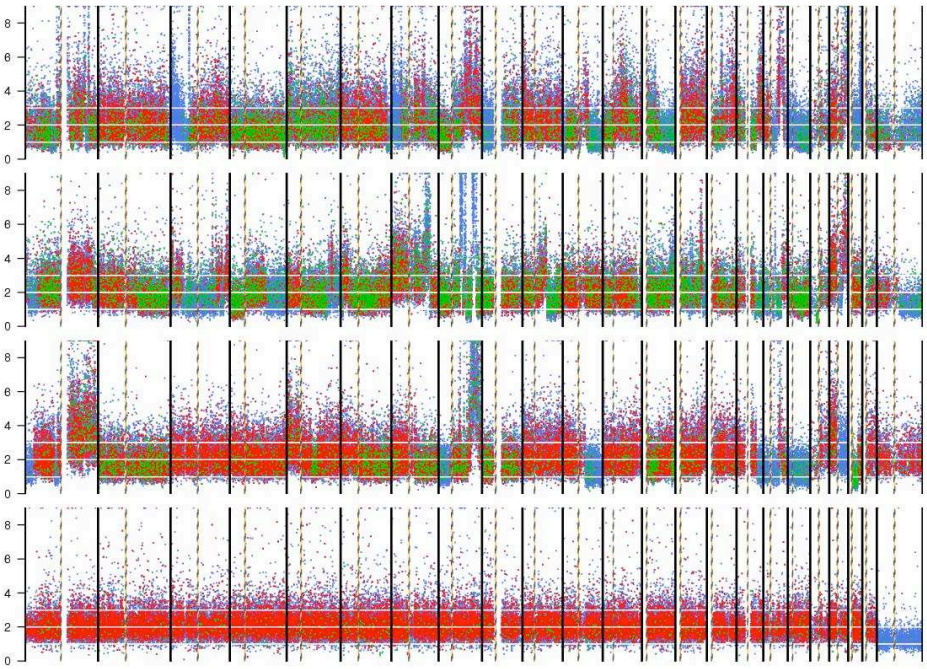
http://www.sanger.ac.uk/humgen/cnv/

Structural variation

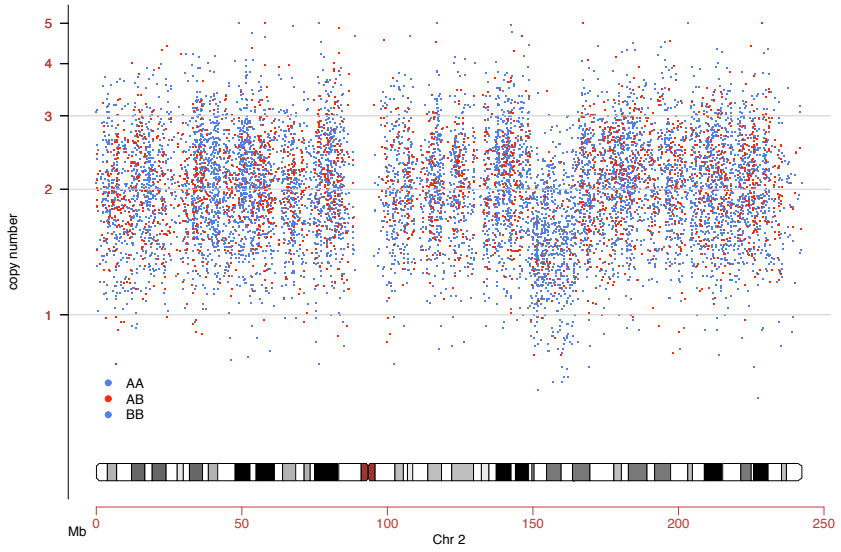


http://projects.tcag.ca/variation/

Cancer samples

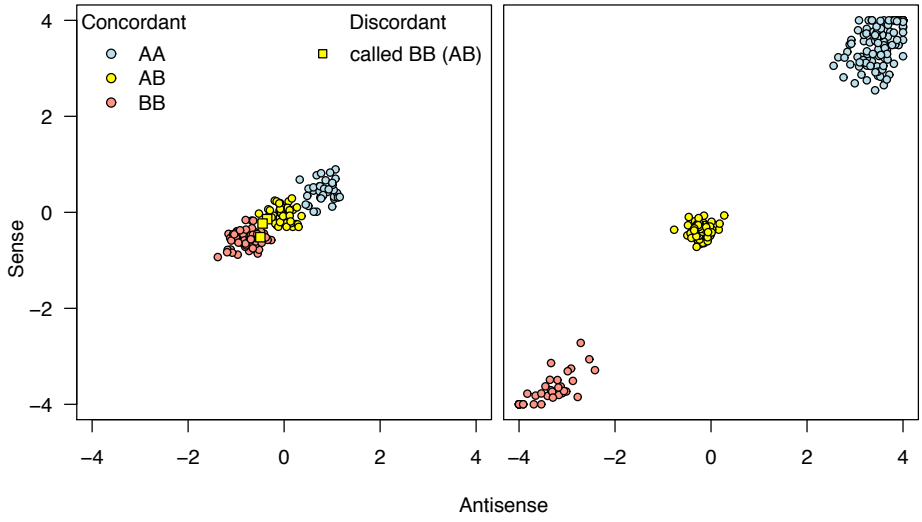


Mosaicism

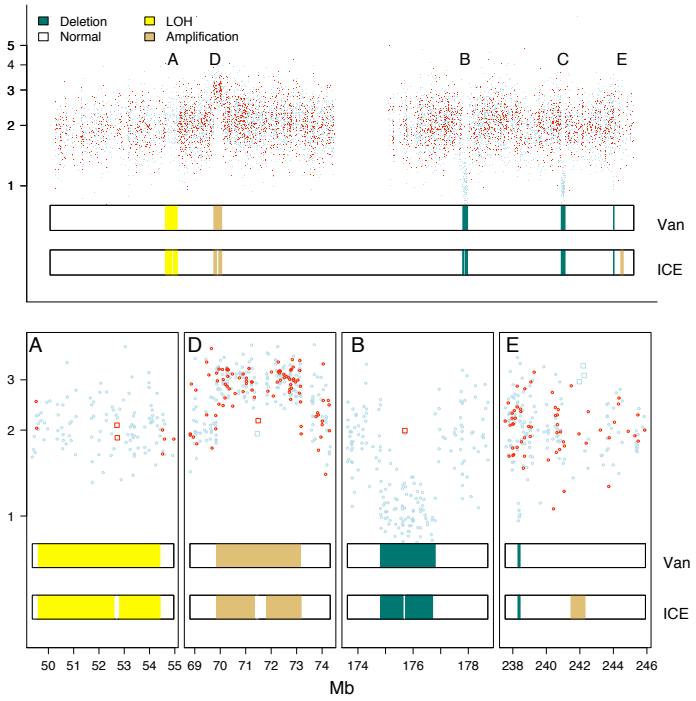


More information

→ The confidence in genotype calls can differ substantially between SNPs!

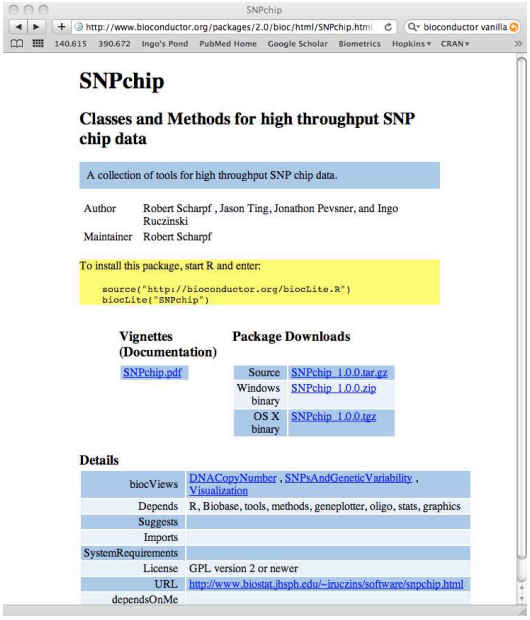


Vanilla and ICE HMMs for genotype and copy number



Scharpf et al (2008). Ann Appl Stat 2(2): 687-713.

Open source software



SNPchip

Classes and Methods for high throughput SNP chip data

A collection of tools for high throughput SNP chip data.

Author	Robert Scharpf , Jason Ting, Jonathon Pevsner, and Ingo Ruczinski
Maintainer	Robert Scharpf

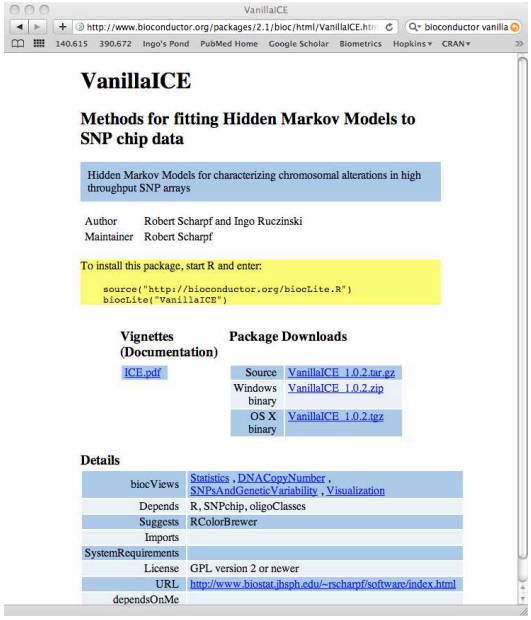
To install this package, start R and enter:

```
source("http://bioconductor.org/biocLite.R")
biocLite("SNPchip")
```

Vignettes (Documentation)	Package Downloads	
SNPchip.pdf	Source	SNPchip_1.0.0.tar.gz
	Windows binary	SNPchip_1.0.0.zip
	OS X binary	SNPchip_1.0.0.tgz

Details

biocViews	DNACopyNumber , SNPsAndGeneticVariability , Visualization
Depends	R, Biobase, tools, methods, geneplotter, oligo, stats, graphics
Suggests	
Imports	
SystemRequirements	
License	GPL version 2 or newer
URL	http://www.biostat.jhsph.edu/~iruczins/software/snpchip.html
dependsOnMe	



VanillaICE

Methods for fitting Hidden Markov Models to SNP chip data

Hidden Markov Models for characterizing chromosomal alterations in high throughput SNP arrays

Author	Robert Scharpf and Ingo Ruczinski
Maintainer	Robert Scharpf

To install this package, start R and enter:

```
source("http://bioconductor.org/biocLite.R")
biocLite("VanillaICE")
```

Vignettes (Documentation)	Package Downloads	
ICE.pdf	Source	VanillaICE_1.0.2.tar.gz
	Windows binary	VanillaICE_1.0.2.zip
	OS X binary	VanillaICE_1.0.2.tgz

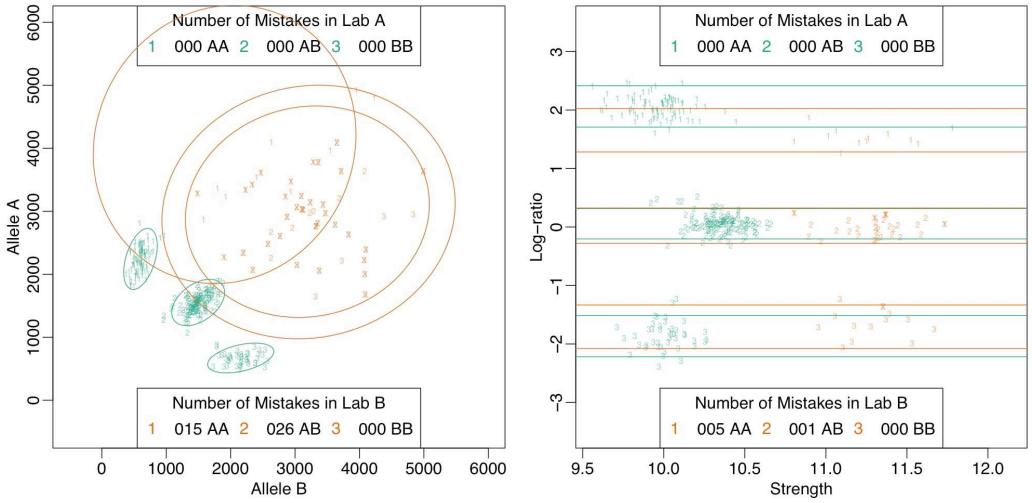
Details

biocViews	Statistics , DNACopyNumber , SNPsAndGeneticVariability , Visualization
Depends	R, SNPchip, oligoClasses
Suggests	RColorBrewer
Imports	
SystemRequirements	
License	GPL version 2 or newer
URL	http://www.biostat.jhsph.edu/~rscharpf/software/index.html
dependsOnMe	

Scharpf et al (2007). Bioinformatics. 23(5): 627-8.

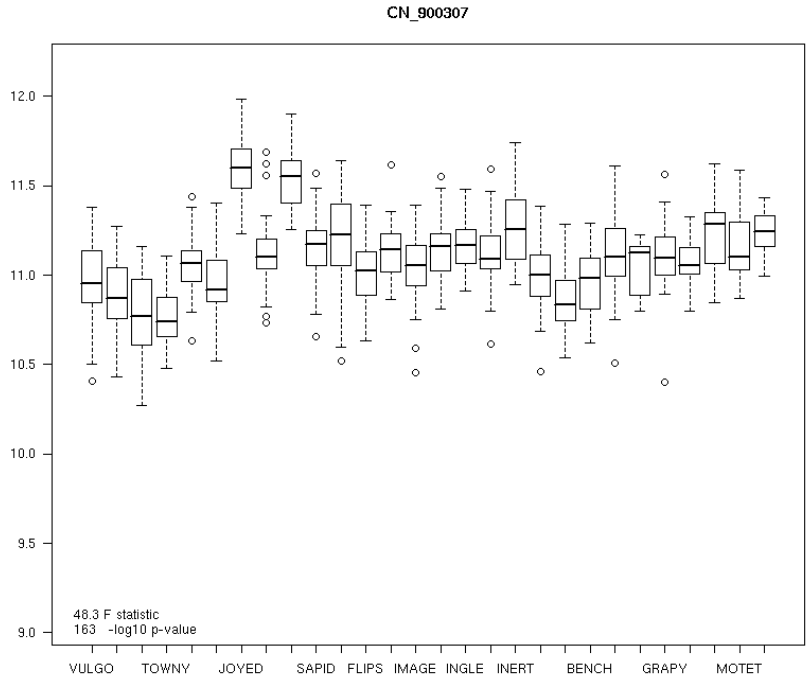
Scharpf and Ruczinski (2010). Methods Mol Biol 593: 67-79.

Genotypes and copy numbers



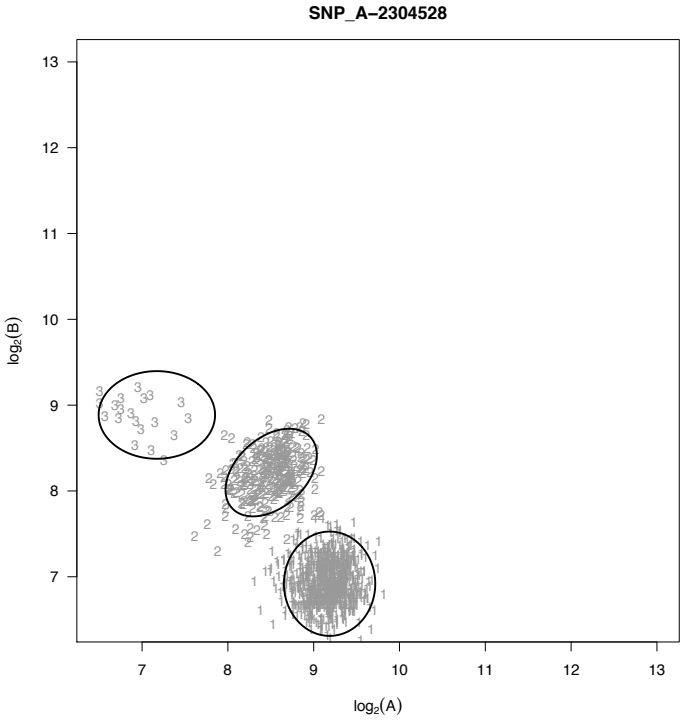
From Benilton Carvalho and Rafa Irizarry

Plate effects



Bipolar GWAS (EA controls) from dbGap

A versus B plots



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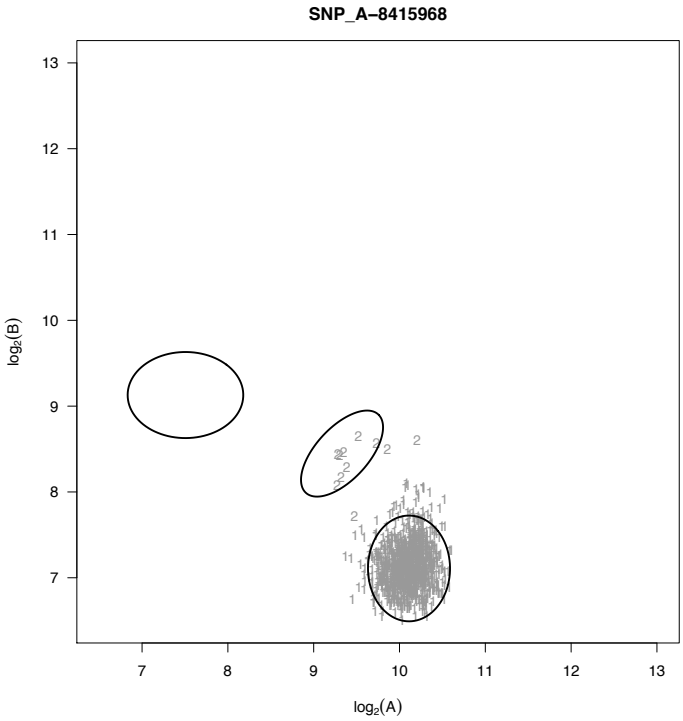

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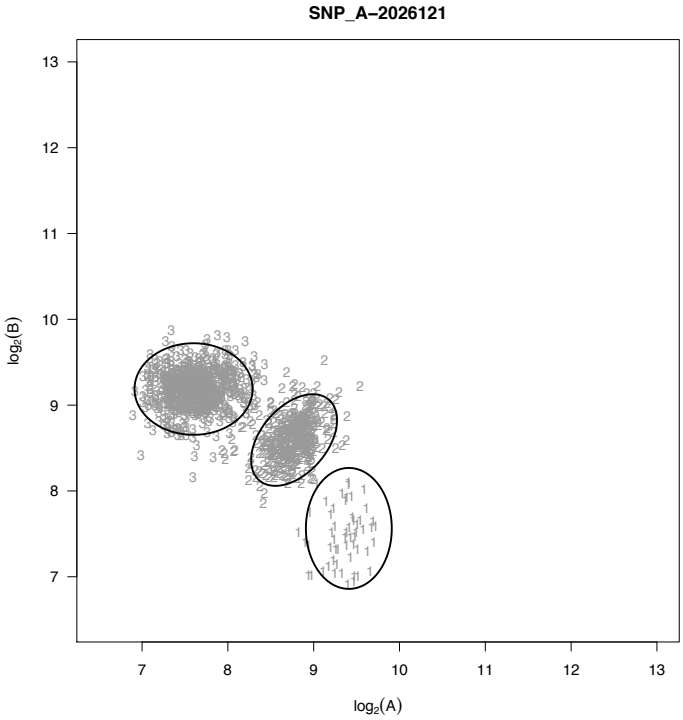

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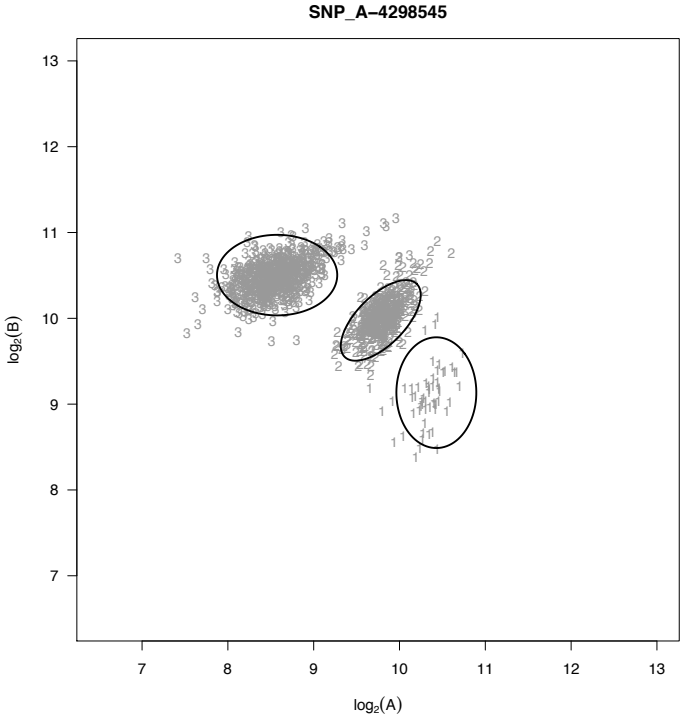

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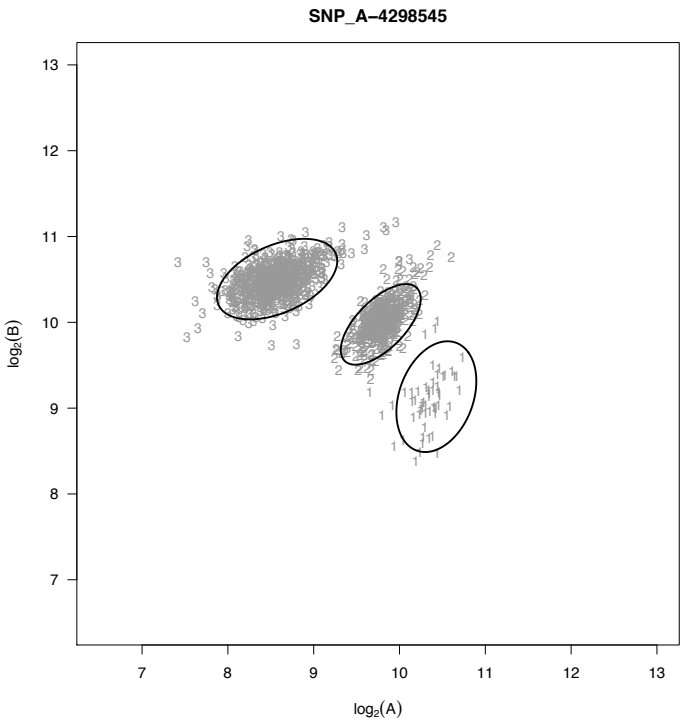

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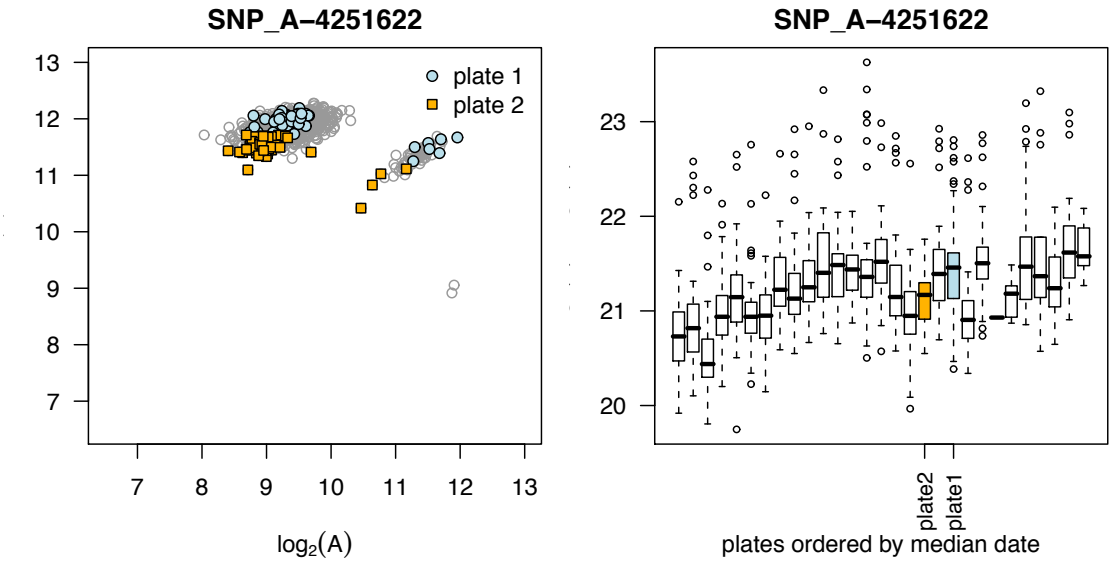

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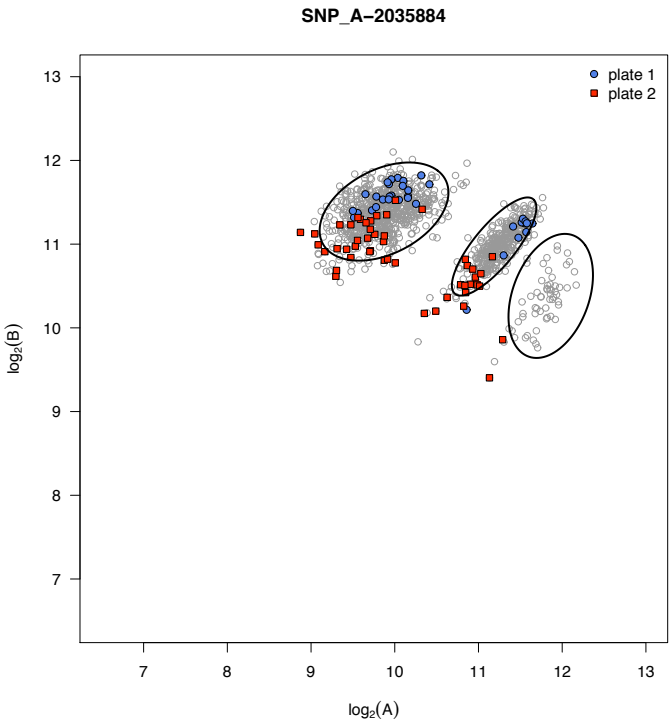

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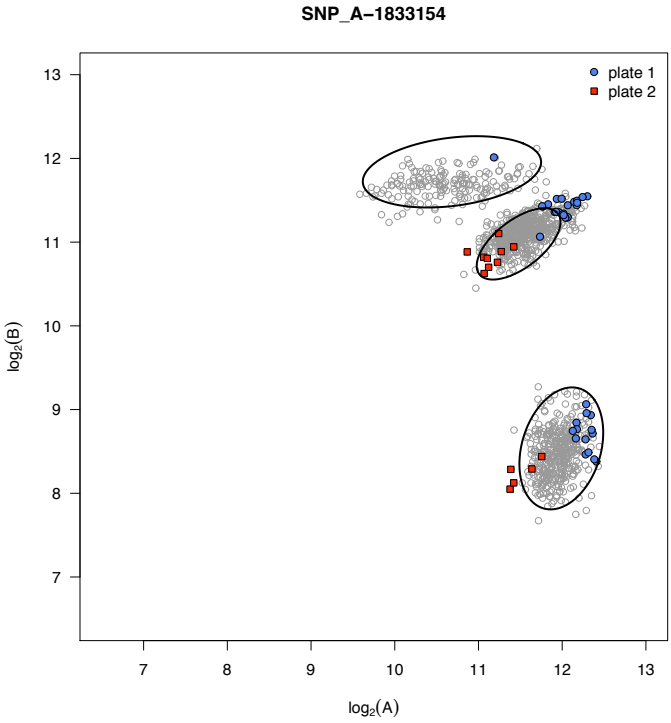

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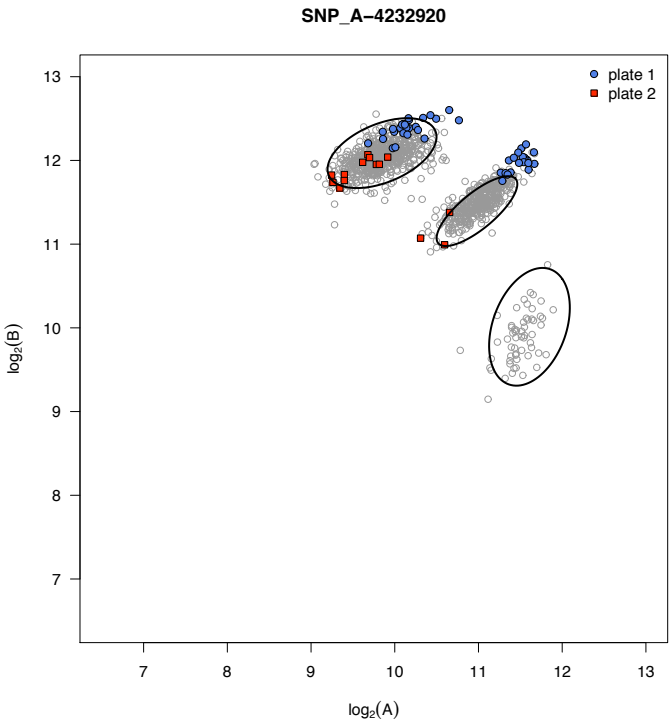

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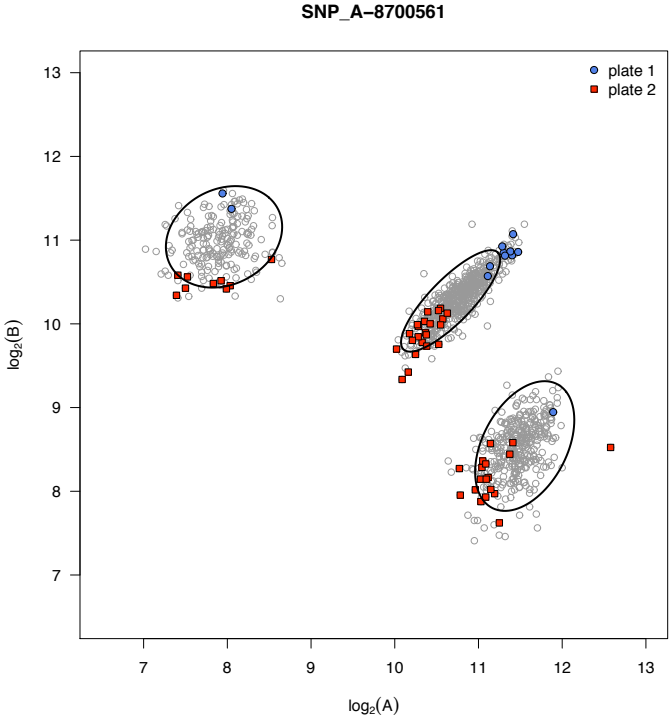

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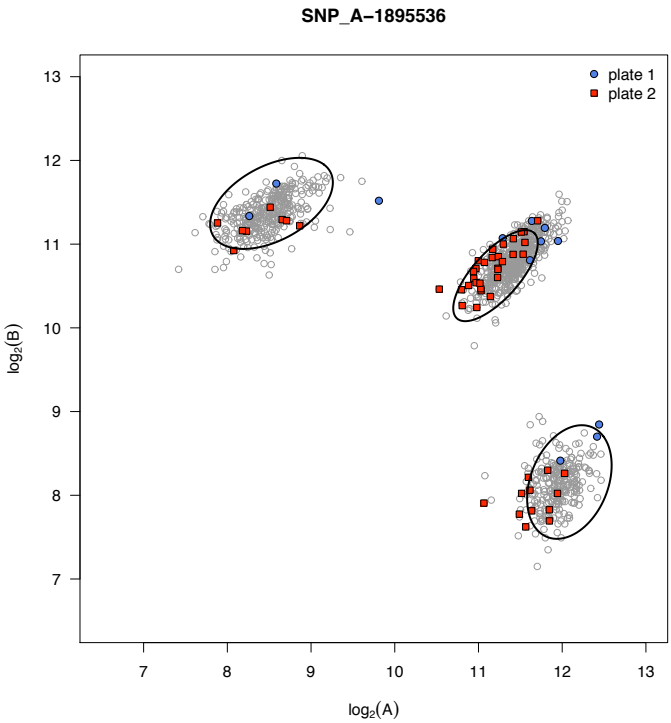

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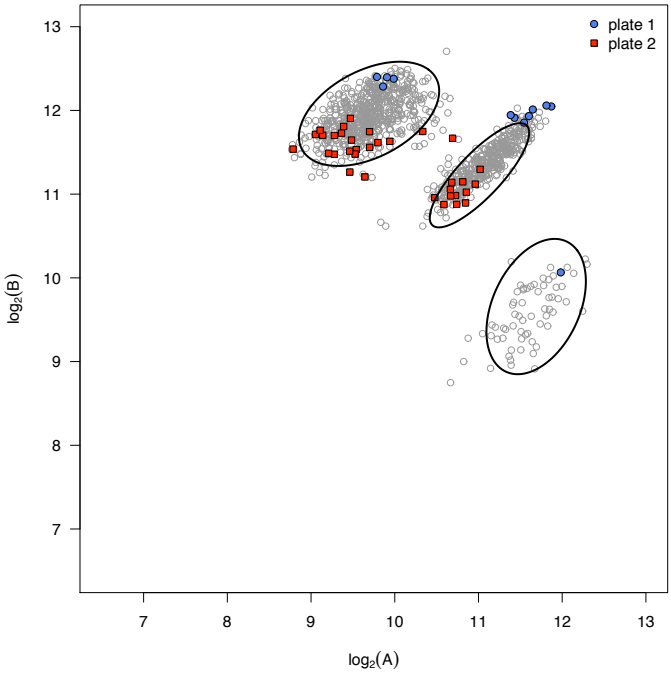

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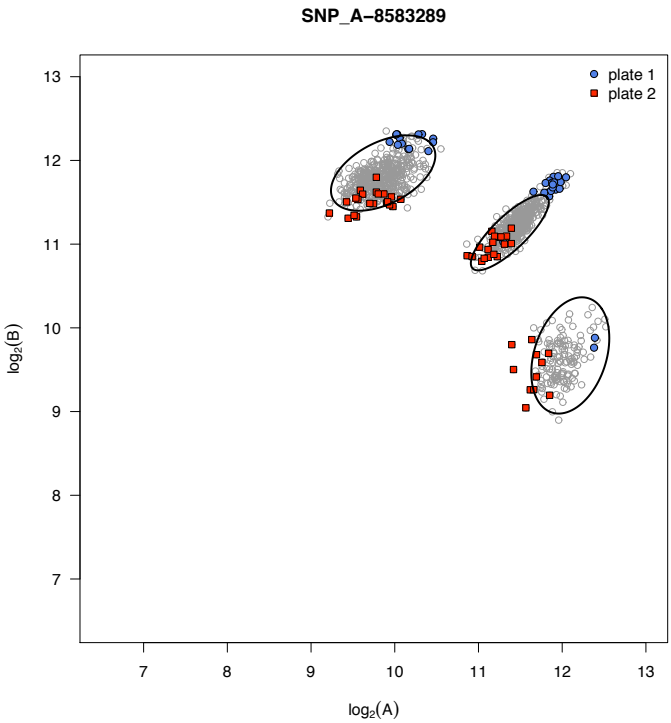

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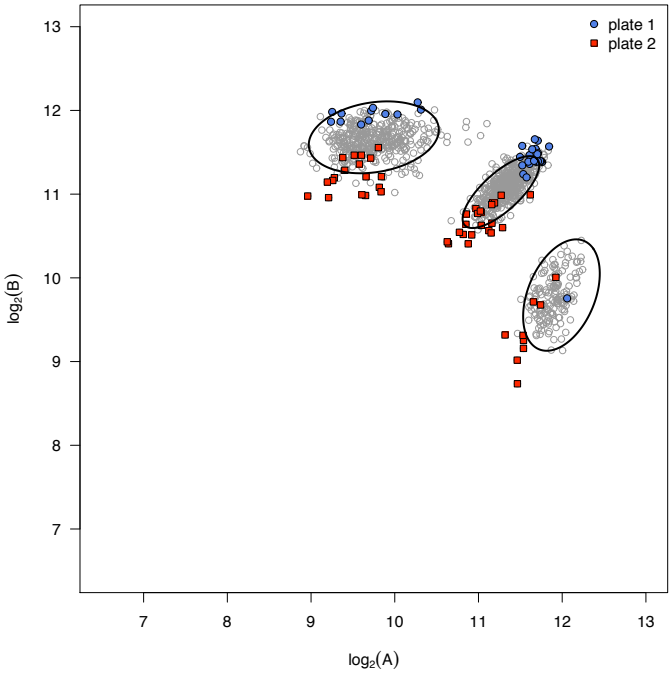
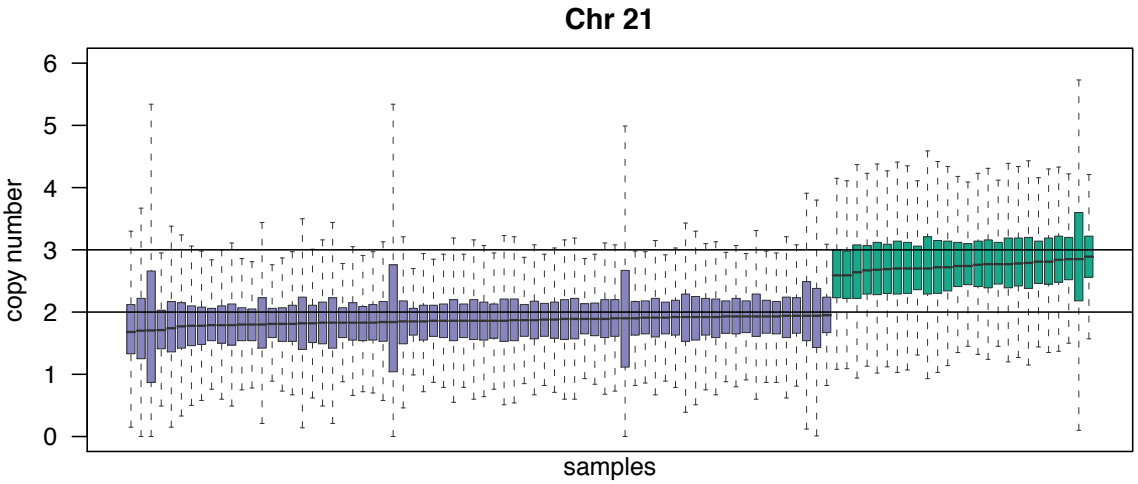
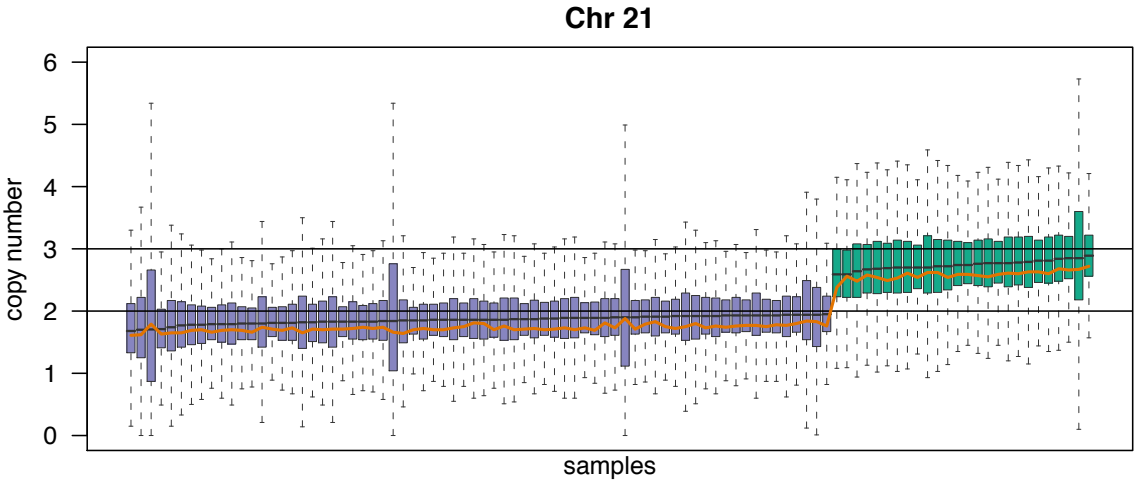


Trisomy 21



Samples from Aravinda Chakravarti and Betty Doan

Trisomy 21



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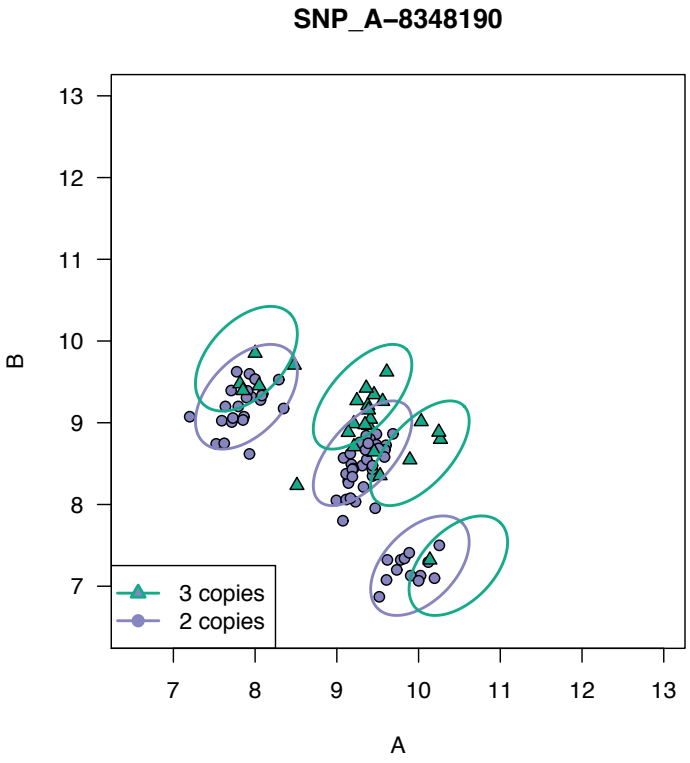
A versus B plots



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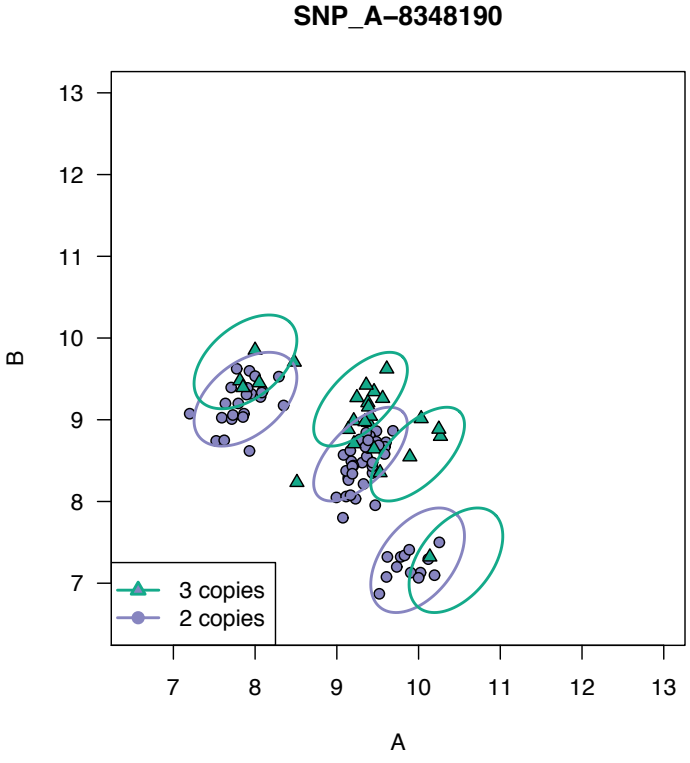

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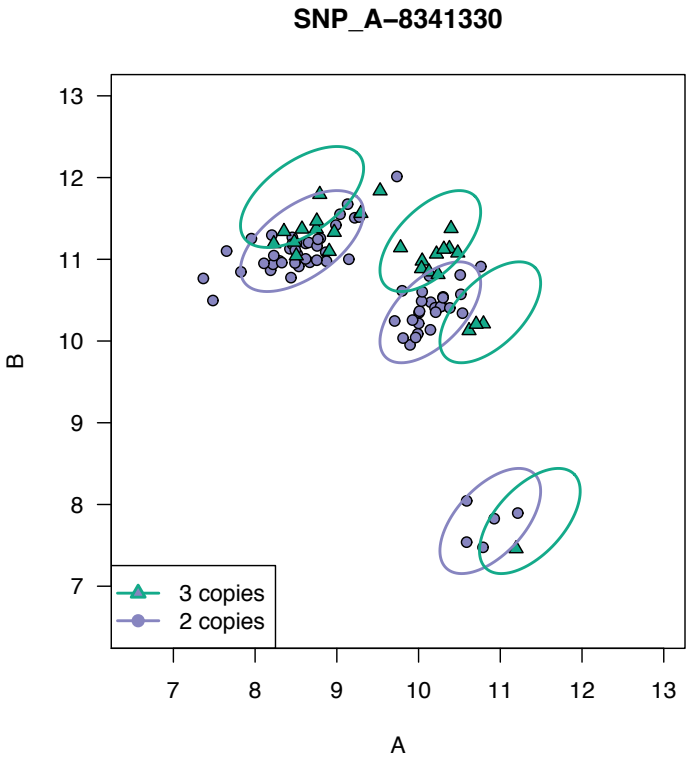

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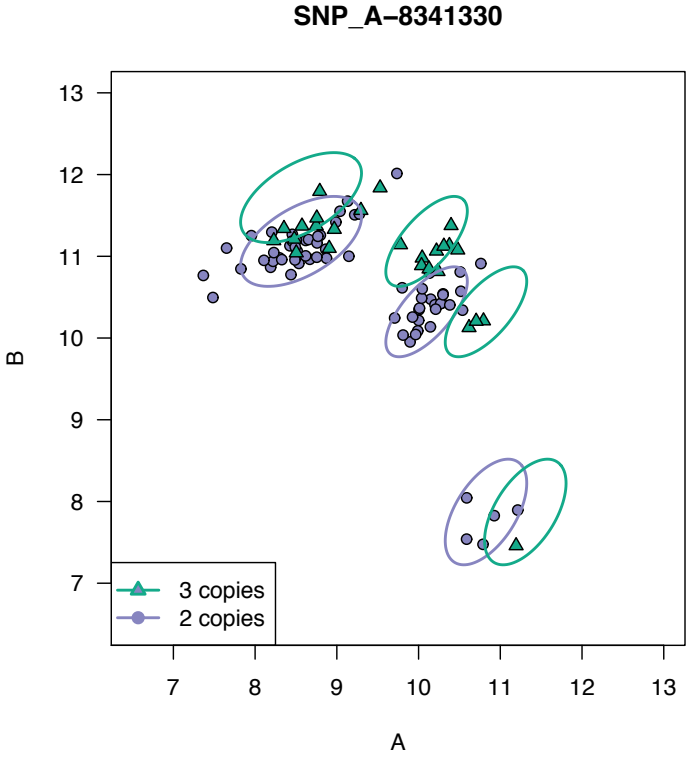

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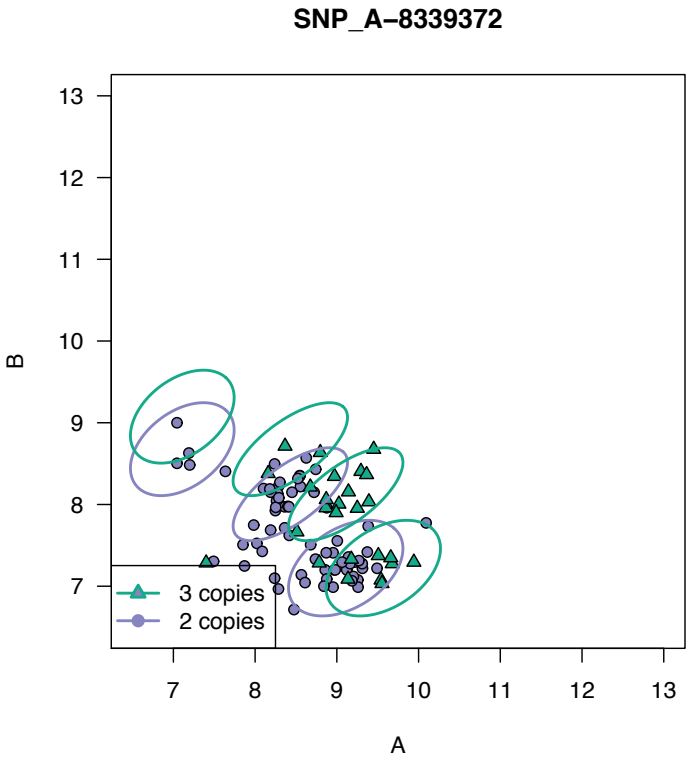

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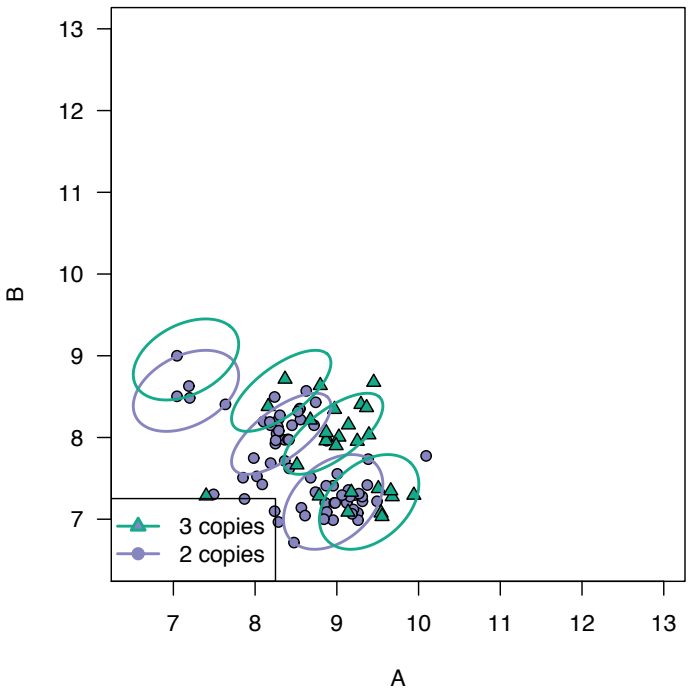

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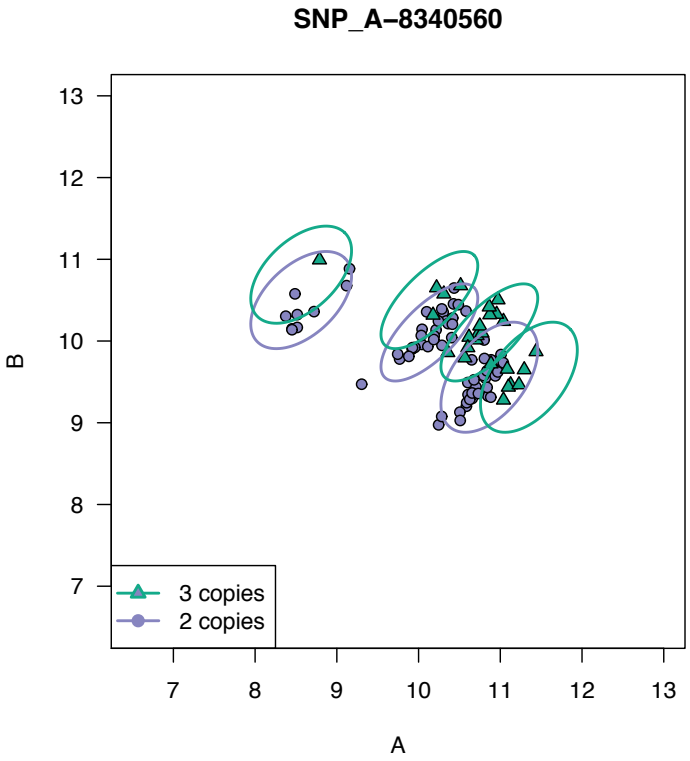

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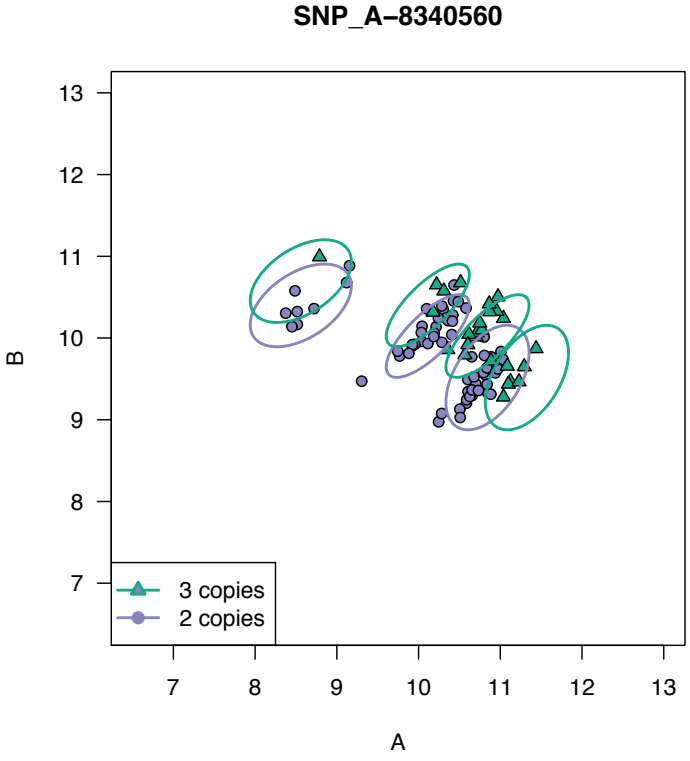

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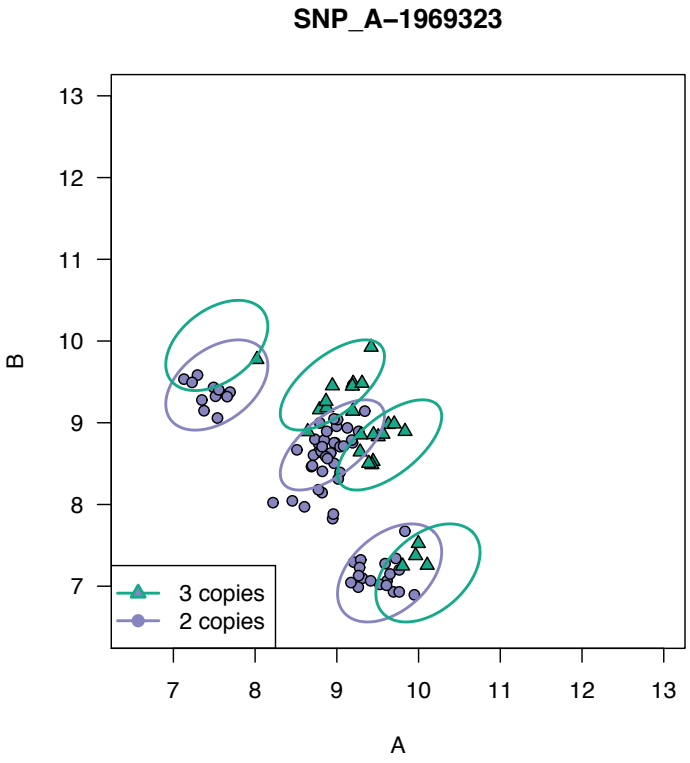

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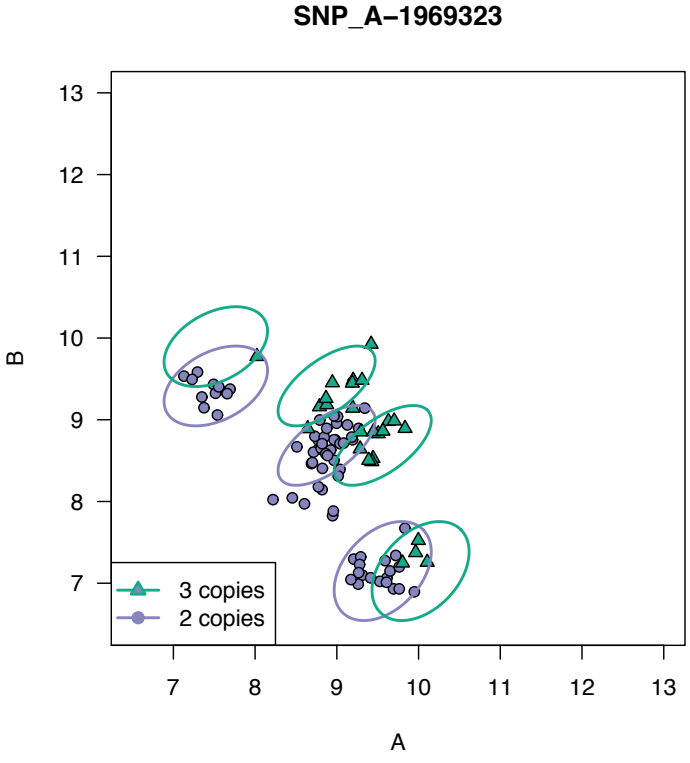
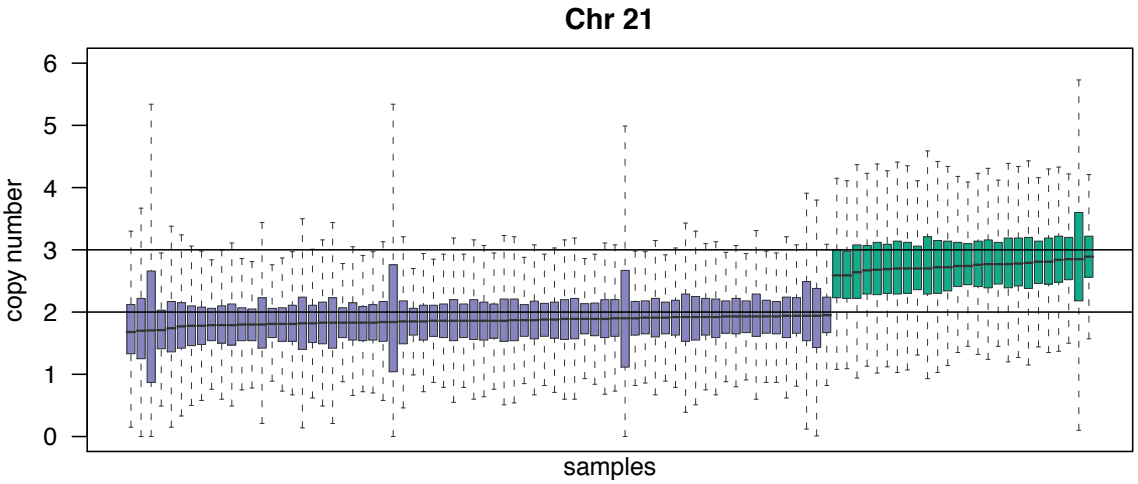
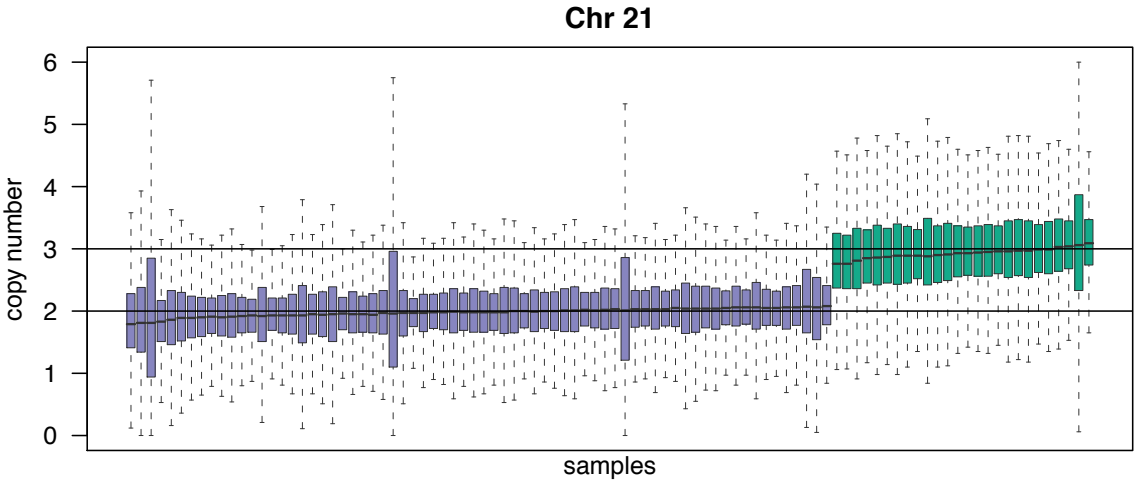


Trisomy 21



Samples from Aravinda Chakravarti and Betty Doan

Trisomy 21



Samples from Aravinda Chakravarti and Betty Doan

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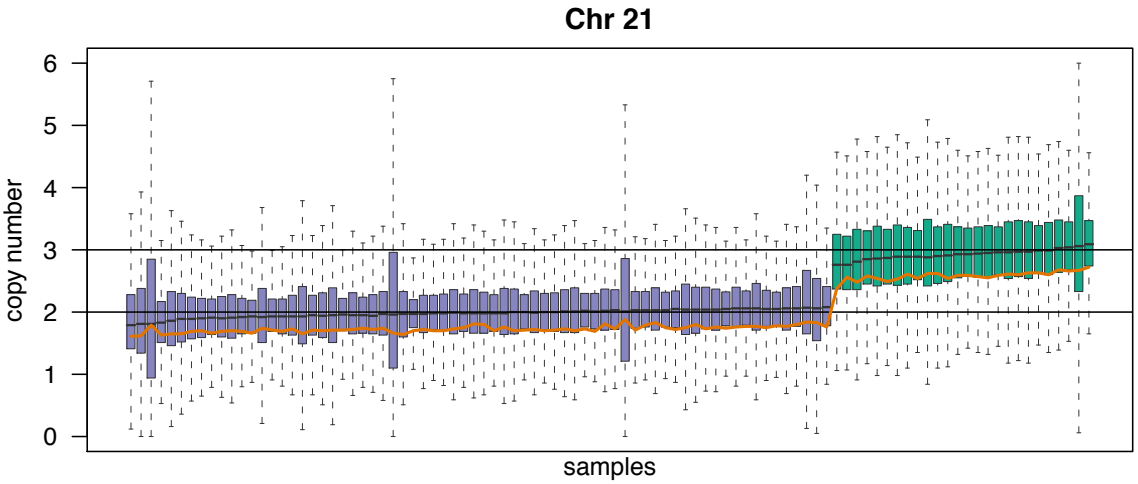
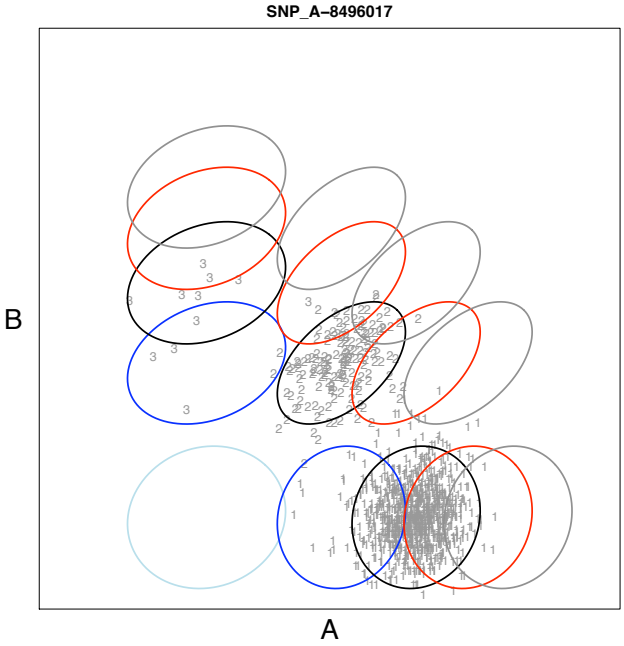


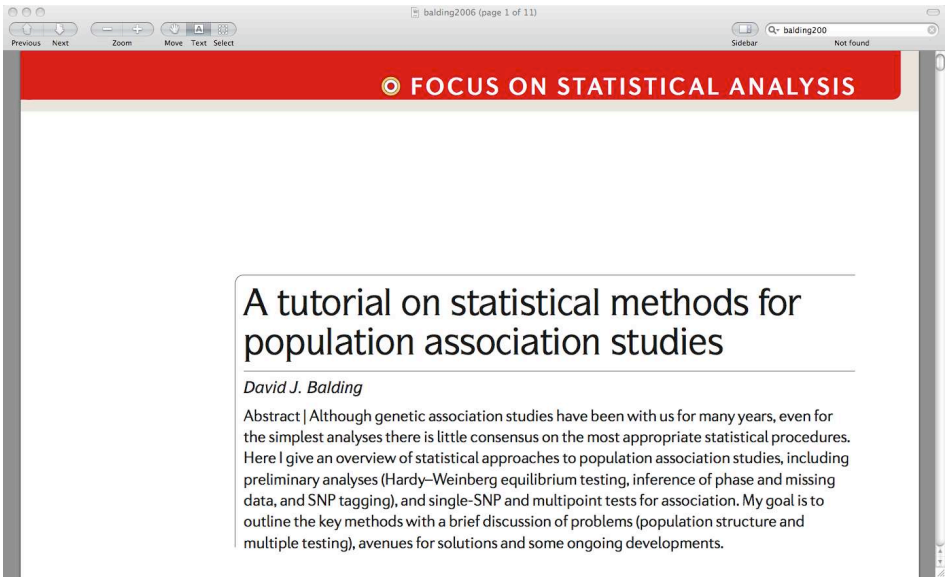
Samples from Aravinda Chakravarti and Betty Doan

Prediction regions for copy number



Scharpf et al (2010), in revision.

Population-based association studies



Balding (2006). Nature Reviews Genetics 7(10): 781-91.

Family-based designs

Laird and Lange (2006), Nature Reviews Genetics 7, 385-94.

Summary

Table 1. Study Designs Used in Genome-wide Association Studies

	Case-Control	Cohort	Trio
Assumptions	Case and control participants are drawn from the same population Case participants are representative of all cases of the disease, or limitations on diagnostic specificity and representativeness are clearly specified Genomic and epidemiologic data are collected similarly in cases and controls Differences in allele frequencies relate to the outcome of interest rather than differences in background population between cases and controls	Participants under study are more representative of the population from which they are drawn Diseases and traits are ascertained similarly in individuals with and without the gene variant	Disease-related alleles are transmitted in excess of 50% to affected offspring from heterozygous parents
Advantages	Short time frame Large numbers of case and control participants can be assembled Optimal epidemiologic design for studying rare diseases	Cases are incident (developing during observation) and free of survival bias Direct measure of risk Fewer biases than case-control studies Continuum of health-related measures available in population samples not selected for presence of disease	Controls for population structure; immune to population stratification Allows checks for Mendelian inheritance patterns in genotyping quality control Logistically simpler for studies of children's conditions Does not require phenotyping of parents
Disadvantages	Prone to a number of biases including population stratification Cases are usually prevalent cases, may exclude fatal or short episodes, or mild or silent cases Overestimate relative risk for common diseases	Large sample size needed for genotyping if incidence is low Expensive and lengthy follow-up Existing consent may be insufficient for GWA genotyping or data sharing Requires variation in trait being studied Poorly suited for studying rare diseases	May be difficult to assemble both parents and offspring, especially in disorders with older ages of onset Highly sensitive to genotyping error

Pearson and Manolio (2008). JAMA. 299(11): 1335-44.

Family-based designs –

- Typically less power per SNP typed than case-control studies.
- Pedigrees maybe hard to get except for childhood diseases, and may not be feasible for late-onset diseases.
- Can be a lot more expensive.
- Highly sensitive to genotyping errors.
- Might be computationally more demanding, especially for studies with large pedigrees.
- Software may be an issue.

Family-based designs +

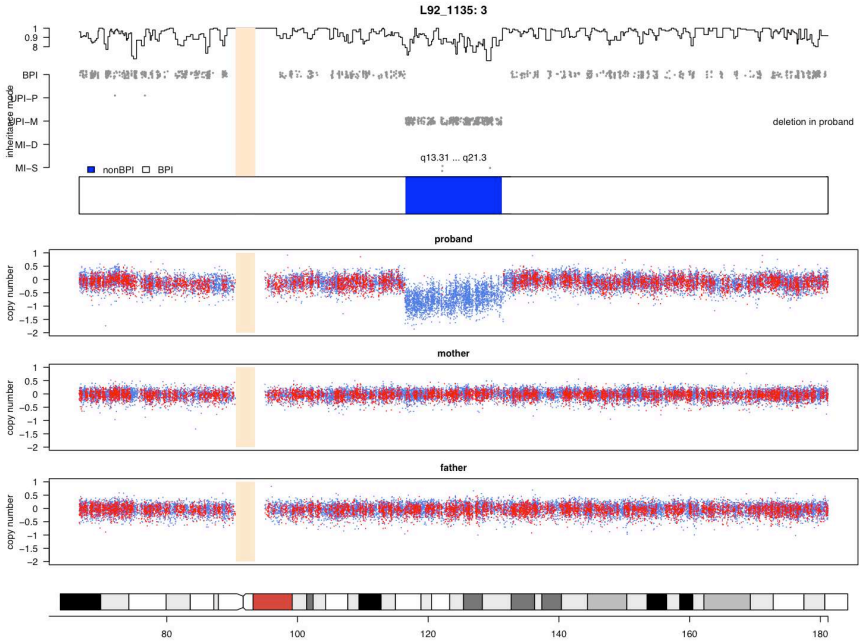
- Robust to possible effects of population stratification and genetic heterogeneity.
- Parent-of-origin effects (imprinting) can be assessed.
- Data quality control is usually more thorough (e. g. genotyping errors and sample swaps are easier to catch).
- Distinction between de-novo and inherited events (copy number changes) is possible.
- Logistically easier for childhood diseases.
- In case-parent data, low minor allele frequencies are of less worry (genotyping errors are still possible).
- Case-parent designs do not require phenotyping parents.
- Linkage information from previous family studies can be employed in association studies.

Parent-of-origin

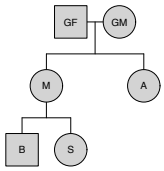
		Paternal				Maternal					
		TAT				TAT				PO-LRT[b]	
No.	SNP name	T	NT	*P*-value	OR[c]	T	NT	*P*-value	OR[c]	OR[d]	*P*-value
1	rs7771980	9	8	0.808	1.13	16	18	0.732	0.89	0.79	0.692
2	rs2677104	25	30	0.500	0.83	22	24	0.768	0.92	1.10	0.811
3	rs2819855	36	34	0.811	1.06	37	25	0.128	1.48	1.40	0.342
4	rs2819854	35	36	0.906	0.97	37	29	0.325	1.28	1.32	0.417
5	rs910586	15	13	0.705	1.15	20	5	**0.003**	4.00	**3.59**	**0.036**
6	rs2819853	14	12	0.695	1.17	18	5	**0.007**	3.60	3.19	0.063
7	rs765724	15	13	0.705	1.15	20	6	**0.006**	3.33	2.97	0.065
8	rs1343799	14	12	0.695	1.17	18	5	**0.007**	3.60	3.19	0.063
9	rs2819861	13	12	0.841	1.08	19	5	**0.004**	3.80	**3.73**	**0.036**
10	rs2790103	16	11	0.336	1.45	20	5	**0.003**	4.00	2.86	0.092
11	rs2790093	15	12	0.564	1.25	18	5	**0.007**	3.60	2.99	0.079
12	rs2790098	15	12	0.564	1.25	19	6	**0.009**	3.17	2.60	0.110
13	rs4714854	15	12	0.564	1.25	19	6	**0.009**	3.17	2.60	0.110
14	rs9472494	15	14	0.853	1.07	22	7	**0.005**	3.14	2.99	0.051
15	rs2396442	17	14	0.590	1.21	24	8	**0.005**	3.00	2.51	0.086
16	rs1934328	41	17	**0.002**	2.41	35	33	0.808	1.06	**0.44**	**0.029**
17	rs7773875	33	21	0.102	1.57	32	32	1.000	1.00	0.65	0.245
18	rs7771889	36	18	0.014	2.00	40	31	0.285	1.29	0.64	0.238
19	rs10485422	15	13	0.705	1.15	17	6	0.022	2.83	2.42	0.135
20	rs6904353	13	14	0.847	0.93	18	11	0.194	1.64	1.78	0.294
21	rs13207392	16	15	0.857	1.07	19	7	0.019	2.71	2.50	0.102
22	rs7748231	13	13	1.000	1.00	18	11	0.194	1.64	1.64	0.373
23	rs10948237	13	14	0.847	0.93	18	11	0.194	1.64	1.78	0.294
24	rs1928533	12	13	0.841	0.92	15	13	0.705	1.15	1.27	0.671

Sull et al (2008), Genetic Epidemiology 32: 505-12.

De-novo deletion

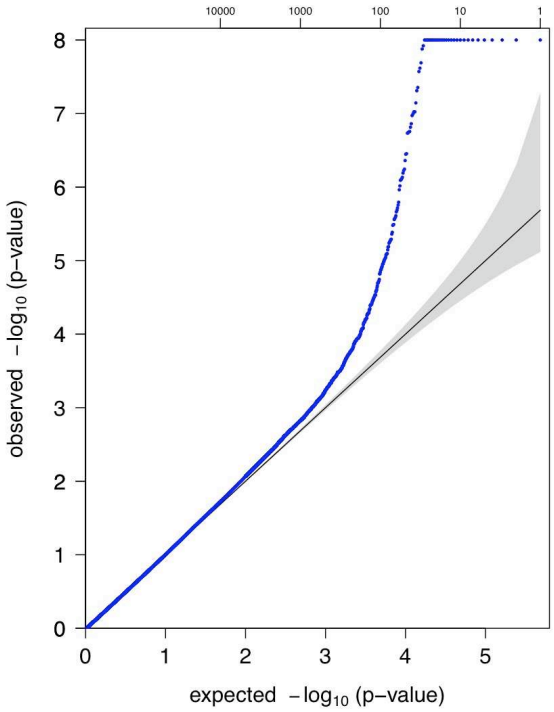


Homozygous and hemizygous deletions



Grandfather		Grandmother		Mother		Aunt		Brother		Sister	
AB	0.01	BB	0.05	AB	-0.11	AB	-0.32	AB	0.06	BB	-0.02
AA	0.27	NC	**-5.52**	AA	**-0.48**	AA	**-0.45**	AB	0.12	BB	**-0.42**
AB	0.15	NC	**-5.04**	AA	**-0.20**	AA	**-0.24**	AB	-0.09	BB	**-0.49**
AB	-0.03	NC	**-4.59**	AA	**-0.40**	AA	**-0.24**	AA	0.30	AA	**-0.72**
BB	0.20	NC	**-2.46**	NC	**-0.38**	BB	**-0.28**	BB	0.22	BB	**-0.45**
AB	0.03	NC	**-6.14**	BB	**-0.28**	BB	**-0.42**	AB	0.09	AA	**-0.70**
AB	-0.05	NC	**-5.02**	BB	-0.17	BB	**-0.34**	AB	-0.22	AA	**-1.06**
BB	0.01	NC	**-4.04**	BB	0.04	BB	**-0.68**	BB	0.14	NC	**-0.98**
AB	0.17	NC	**-4.06**	AA	**-0.27**	AA	**-0.33**	AA	-0.03	AA	**-0.76**
AB	0.01	NC	**-4.70**	AA	**-0.67**	AA	**-0.52**	AA	0.16	AA	**-0.80**
AB	-0.10	NC	**-4.42**	BB	**-0.25**	BB	**-0.62**	AB	0.13	AA	**-0.58**
AB	0.01	NC	**-8.29**	BB	-0.17	BB	-0.15	AB	-0.15	AA	**-0.29**
BB	0.16	NC	**-5.73**	BB	**-0.64**	BB	**-0.46**	BB	0.10	BB	**-0.52**
AB	0.06	NC	**-7.48**	AA	**-0.23**	AA	**-0.33**	AB	0.07	BB	**-0.47**
AA	0.17	NC	**-3.70**	AA	**-0.50**	AA	**-0.52**	AB	-0.06	BB	**-0.48**
BB	0.02	NC	**-5.00**	BB	**-0.34**	BB	**-0.45**	AB	0.13	AA	**-0.55**
AA	0.21	NC	**-6.10**	AA	**-0.43**	AA	**-0.40**	AB	0.20	BB	**-0.40**
BB	0.05	BB	0.11	BB	0.15	BB	0.29	AB	0.13	AB	-0.01

International Cleft Consortium



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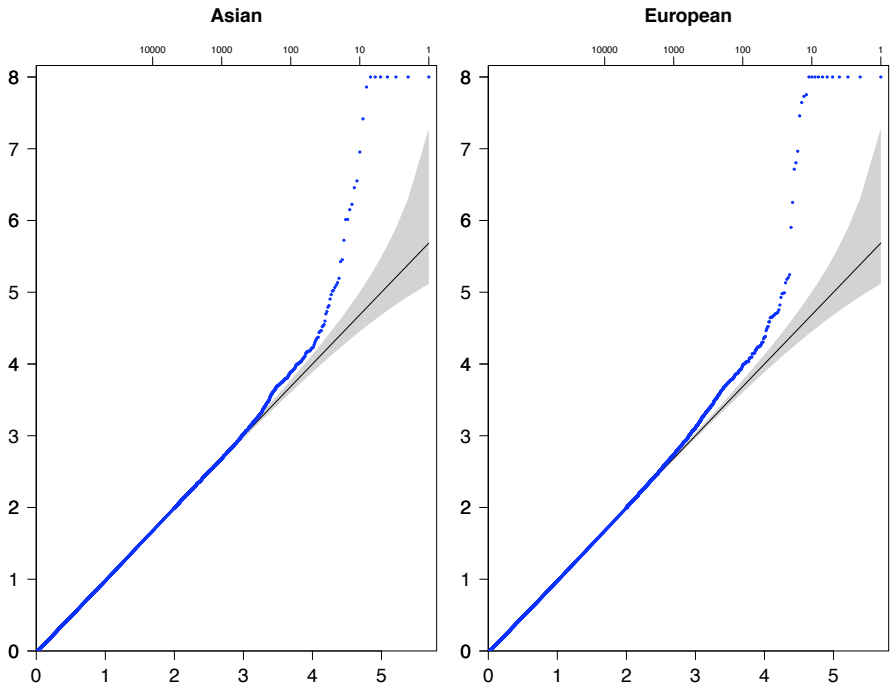

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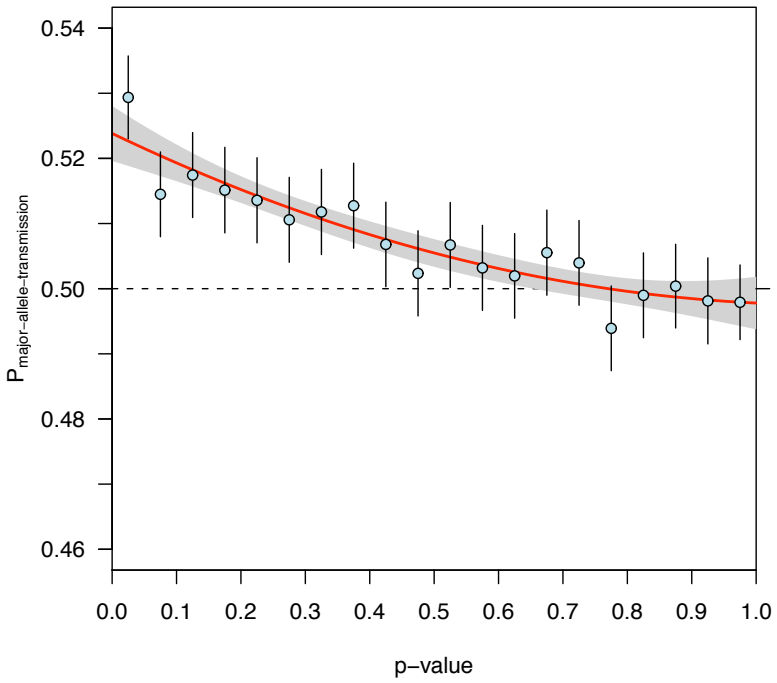
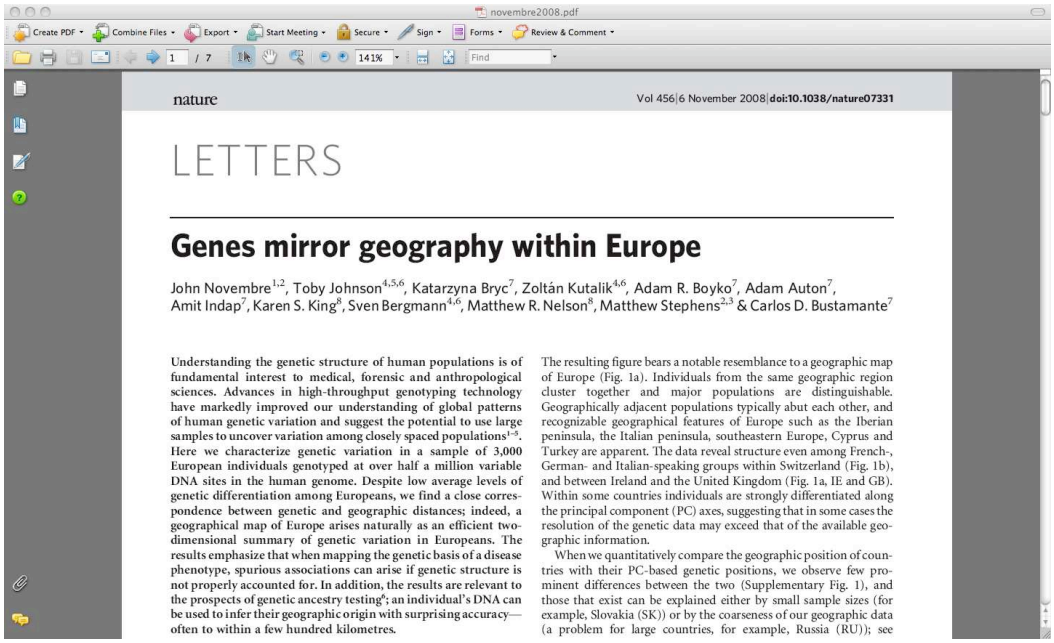


Principal components



novembre2008.pdf

nature Vol 456|6 November 2008|doi:10.1038/nature07331

LETTERS

Genes mirror geography within Europe

John Novembre[1,2], Toby Johnson[4,5,6], Katarzyna Bryc[7], Zoltán Kutalik[4,6], Adam R. Boyko[7], Adam Auton[7], Amit Indap[7], Karen S. King[8], Sven Bergmann[4,6], Matthew R. Nelson[8], Matthew Stephens[2,3] & Carlos D. Bustamante[7]

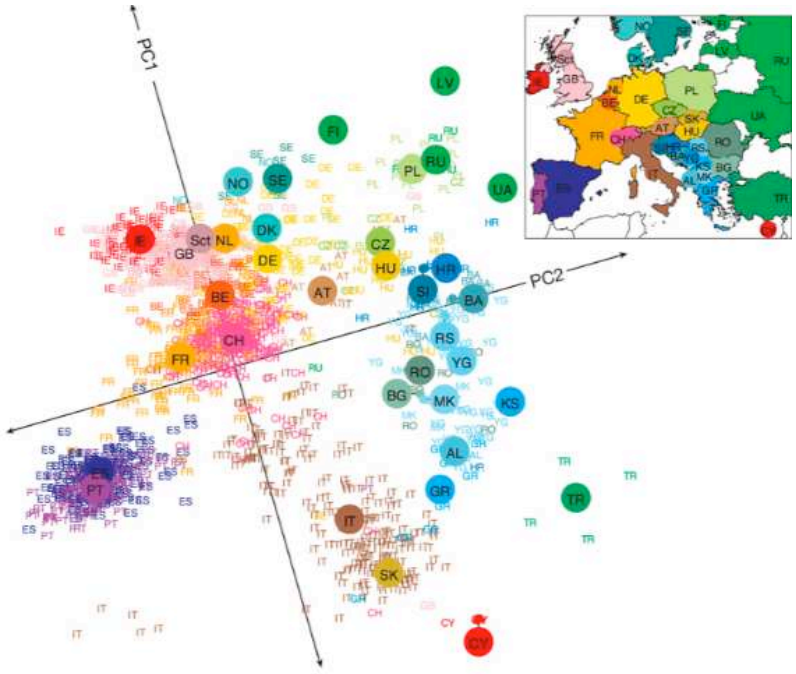
Understanding the genetic structure of human populations is of fundamental interest to medical, forensic and anthropological sciences. Advances in high-throughput genotyping technology have markedly improved our understanding of global patterns of human genetic variation and suggest the potential to use large samples to uncover variation among closely spaced populations[1–3]. Here we characterize genetic variation in a sample of 3,000 European individuals genotyped at over half a million variable DNA sites in the human genome. Despite low average levels of genetic differentiation among Europeans, we find a close correspondence between genetic and geographic distances; indeed, a geographical map of Europe arises naturally as an efficient two-dimensional summary of genetic variation in Europeans. The results emphasize that when mapping the genetic basis of a disease phenotype, spurious associations can arise if genetic structure is not properly accounted for. In addition, the results are relevant to the prospects of genetic ancestry testing[4]; an individual's DNA can be used to infer their geographic origin with surprising accuracy—often to within a few hundred kilometres.

The resulting figure bears a notable resemblance to a geographic map of Europe (Fig. 1a). Individuals from the same geographic region cluster together and major populations are distinguishable. Geographically adjacent populations typically abut each other, and recognizable geographical features of Europe such as the Iberian peninsula, the Italian peninsula, southeastern Europe, Cyprus and Turkey are apparent. The data reveal structure even among French-, German- and Italian-speaking groups within Switzerland (Fig. 1b), and between Ireland and the United Kingdom (Fig. 1a, IE and GB). Within some countries individuals are strongly differentiated along the principal component (PC) axes, suggesting that in some cases the resolution of the genetic data may exceed that of the available geographic information.

When we quantitatively compare the geographic position of countries with their PC-based genetic positions, we observe few prominent differences between the two (Supplementary Fig. 1), and those that exist can be explained either by small sample sizes (for example, Slovakia (SK)) or by the coarseness of our geographic data (a problem for large countries, for example, Russia (RU)); see

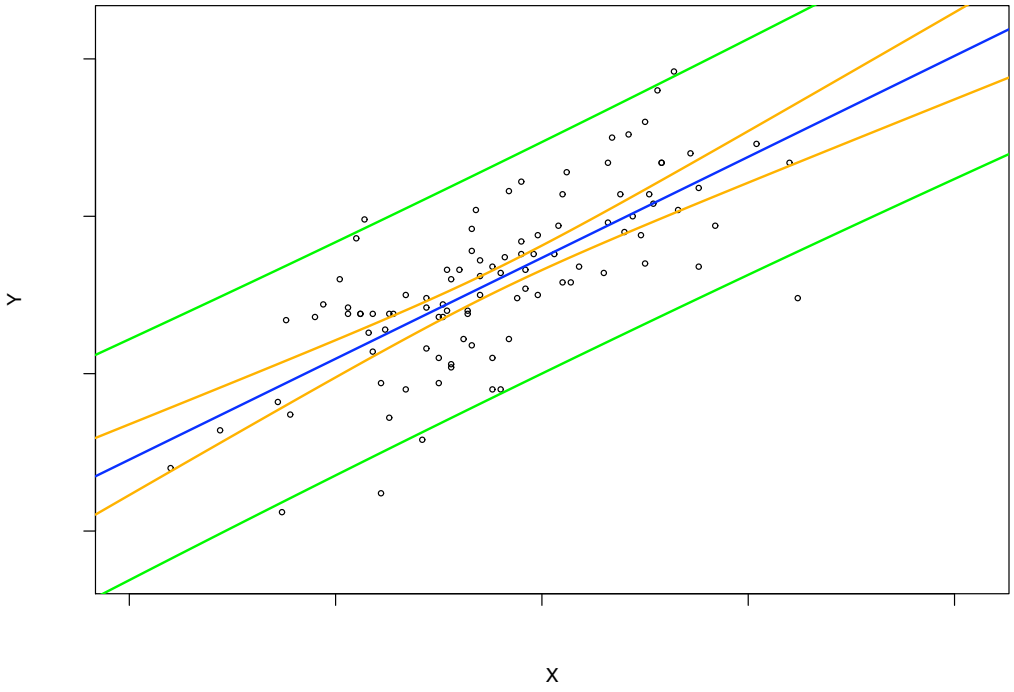
Novembre et al (2008), Nature 456: 98-101.

Principal components



Novembre et al (2008), Nature 456: 98-101.

Prediction



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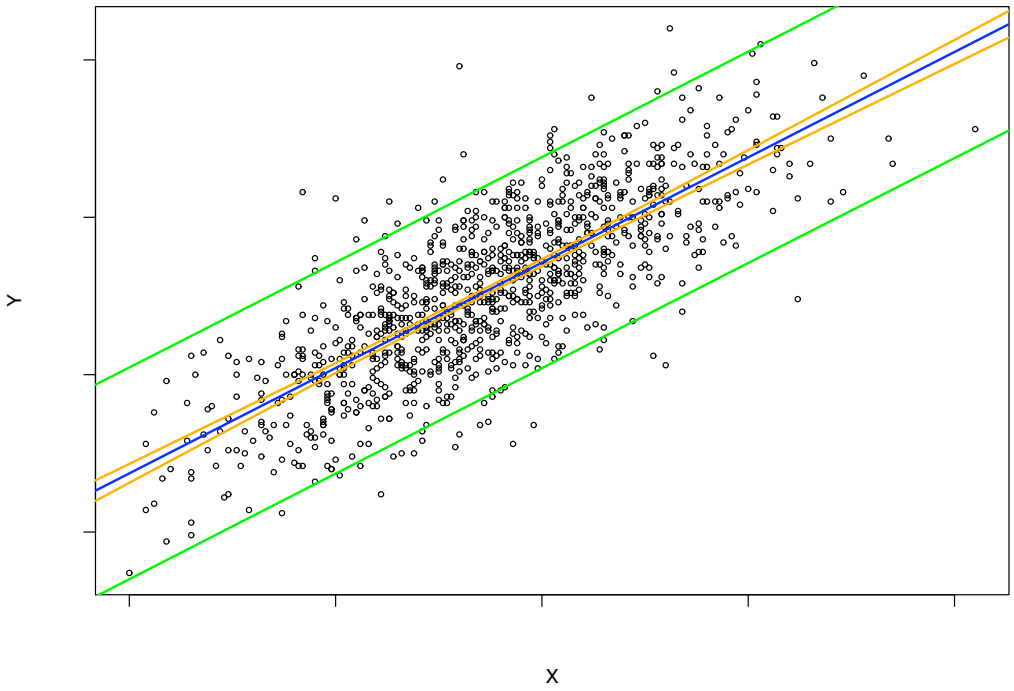

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