

**Clinical Implications of Arrays & Next Generation Sequencing
Technologies Seminar**

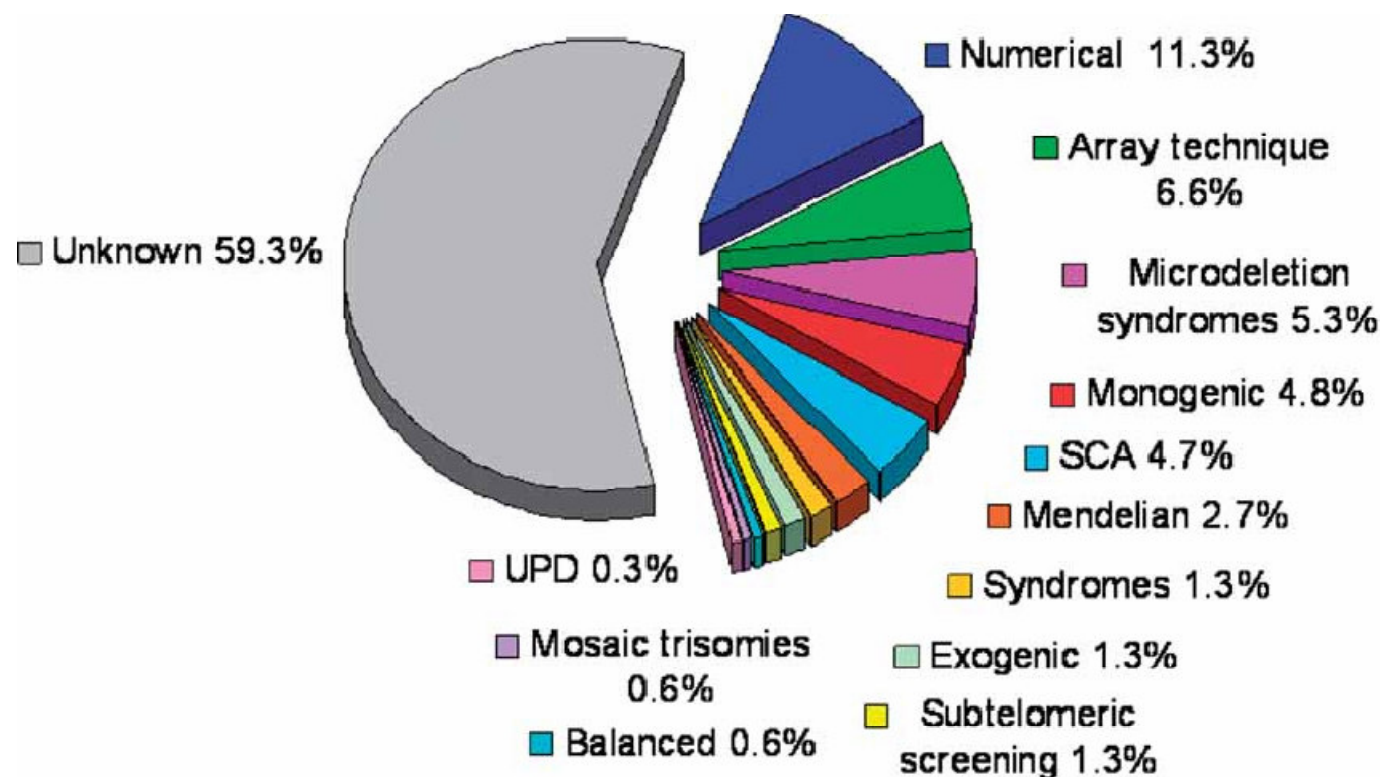
**Analysis of patients suffering
from mental deficiency**



ASSISTANCE
PUBLIQUE  HÔPITAUX
DE PARIS

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UF de Génétique Chromosomique

Mental retardation etiologies



Rauch et al. (2006)

Clinical guidance in mental retardation

- non specific phenotype
- phenotype suggesting a known chromosomal pathology
- phenotype suggesting a known non chromosomal pathology

Diagnostic guidance in mental retardation

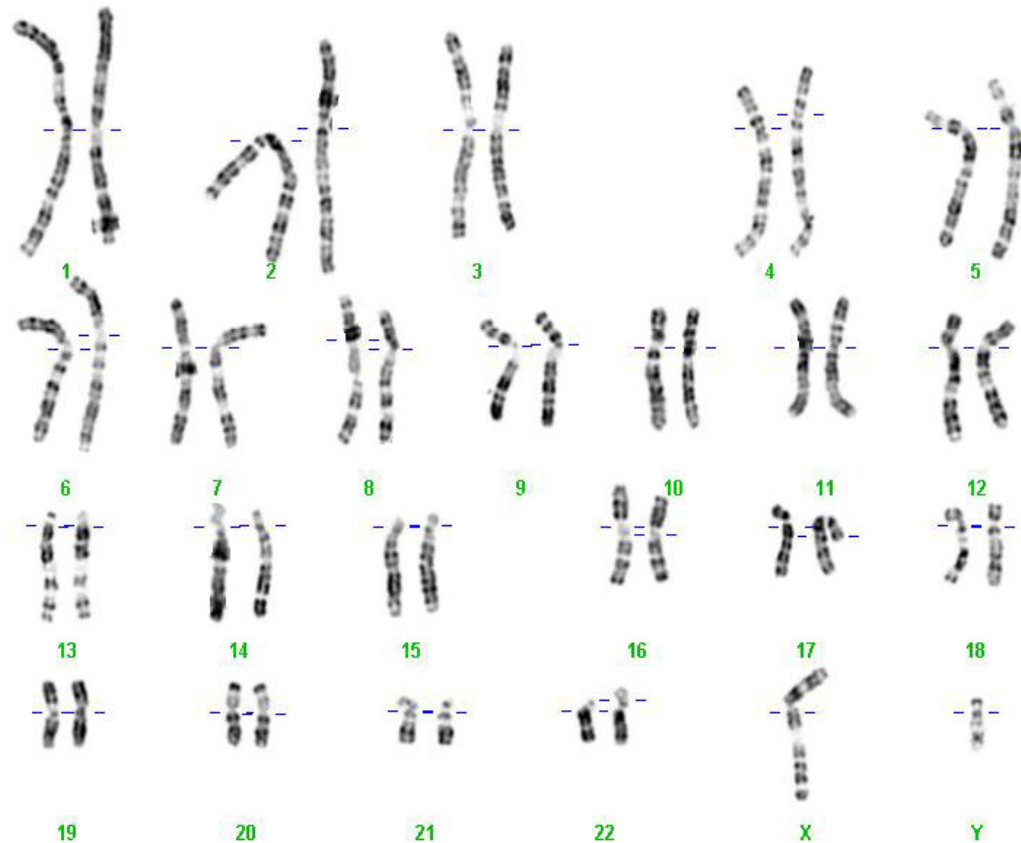
- non specific phenotype
- phenotype suggesting a known chromosomal pathology

➤ Constitutional cytogenetics

~~phenotype suggesting a known non chromosomal pathology~~

Non specific phenotype

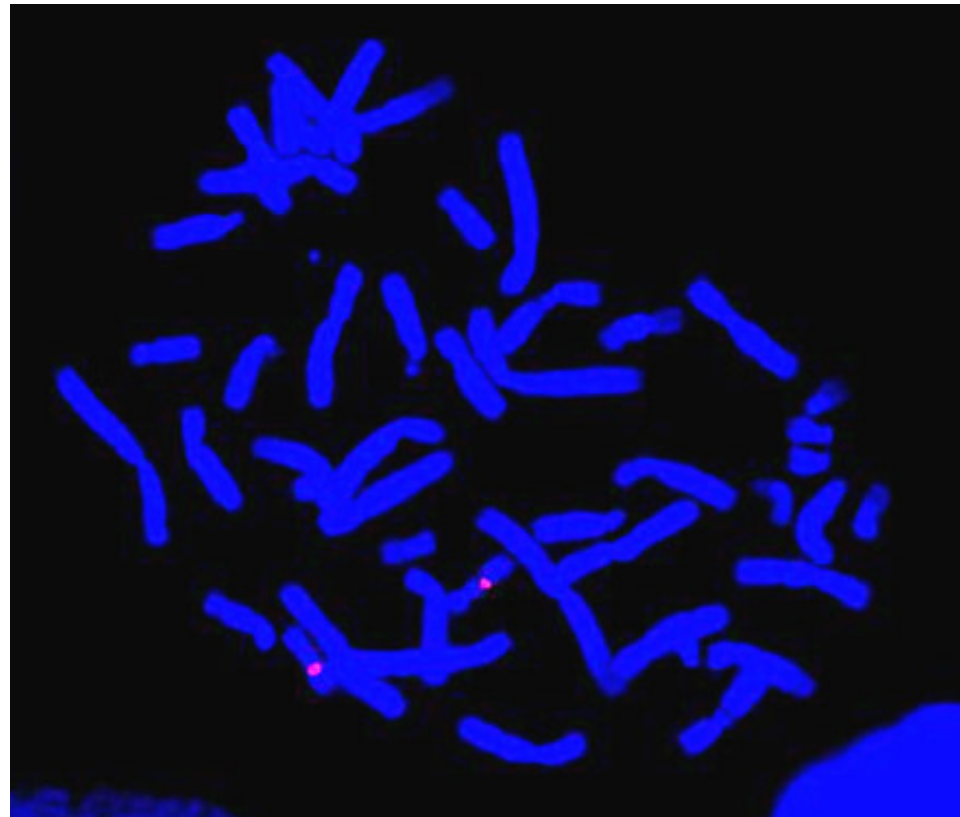
karyotype



- whole genome analysis
- low resolution (~10 Mb)

Phenotype suggesting a known chromosomal pathology

FISH



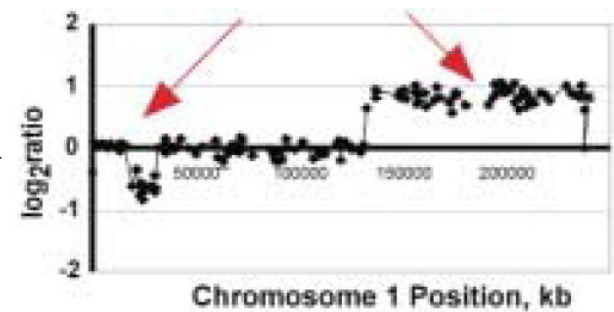
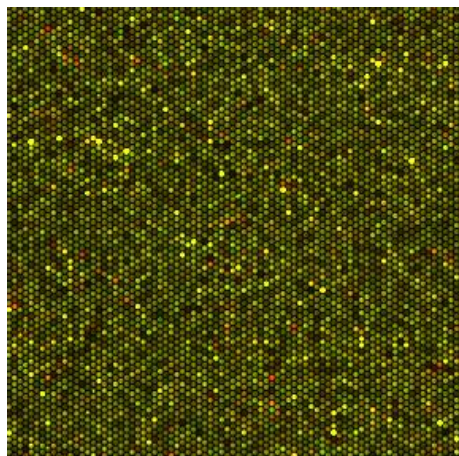
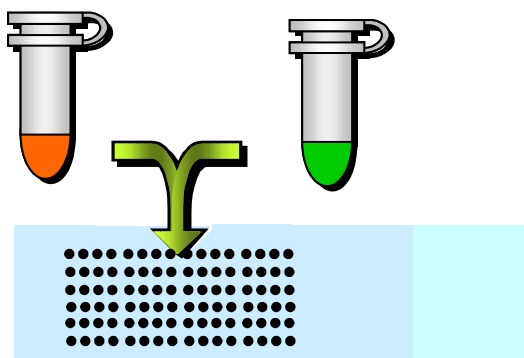
- Targeted analysis
- Higher resolution (2Mb-100kb)

Cytogenetics goals

- Increase resolution
 - Keep a whole genome analysis
-
- CNV detection on arrays

Cytogenetics on array

Array CGH

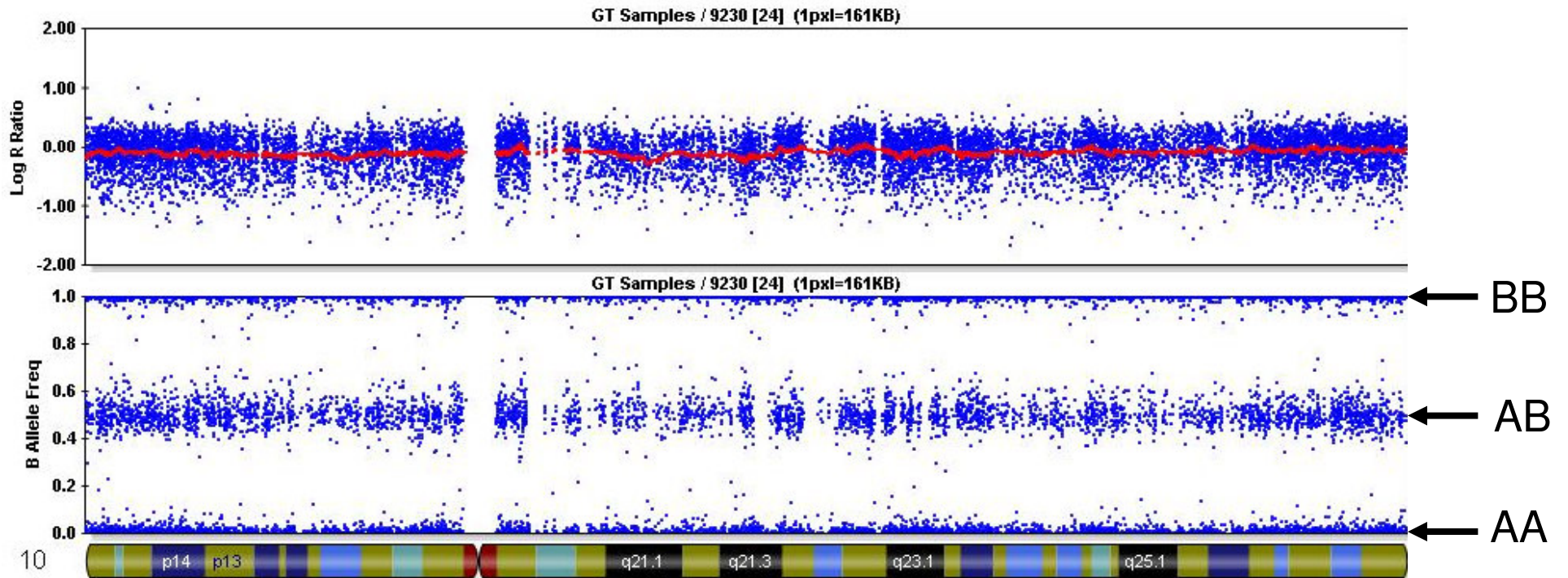


SNP Arrays

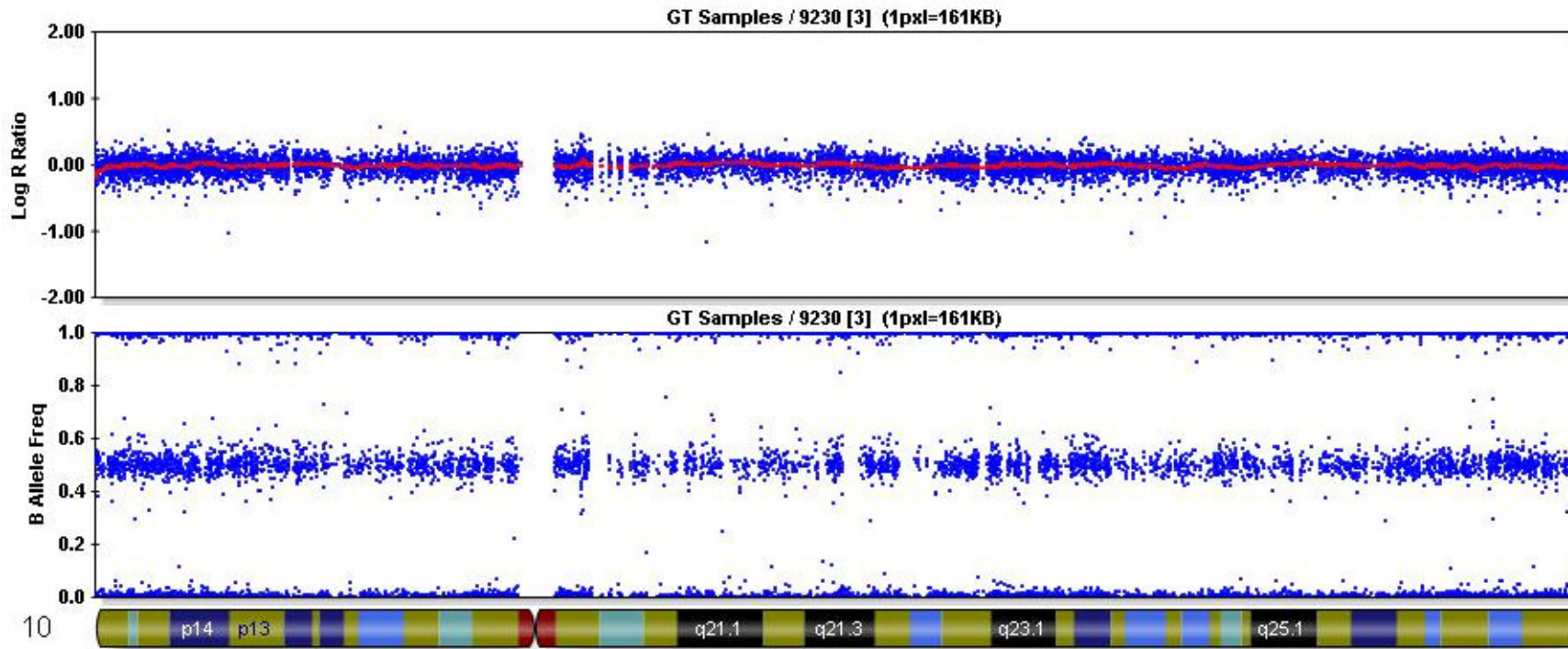
- 2 informations on each marker :
 - Copy number
 - SNP genotype



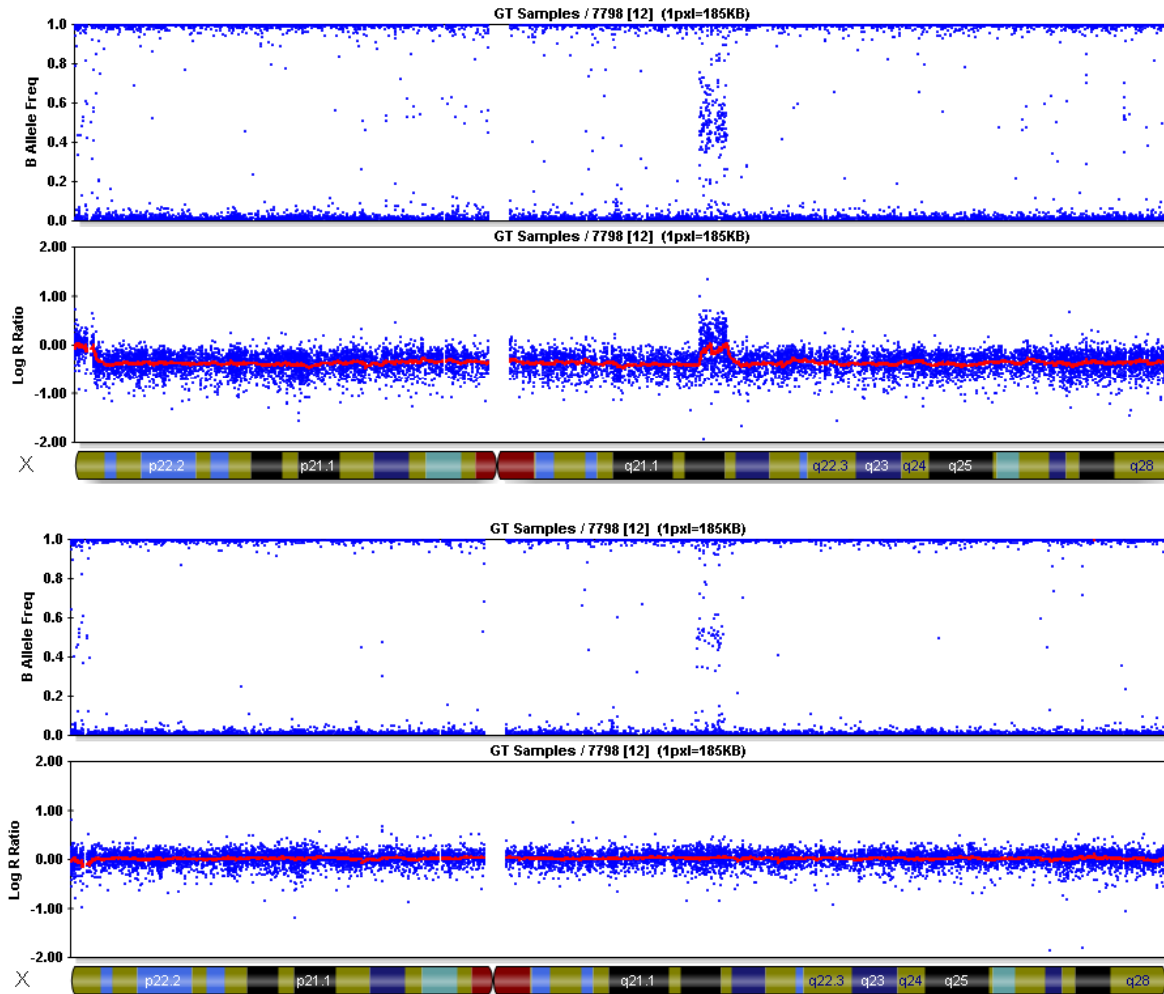
Analysis : BeadStudio



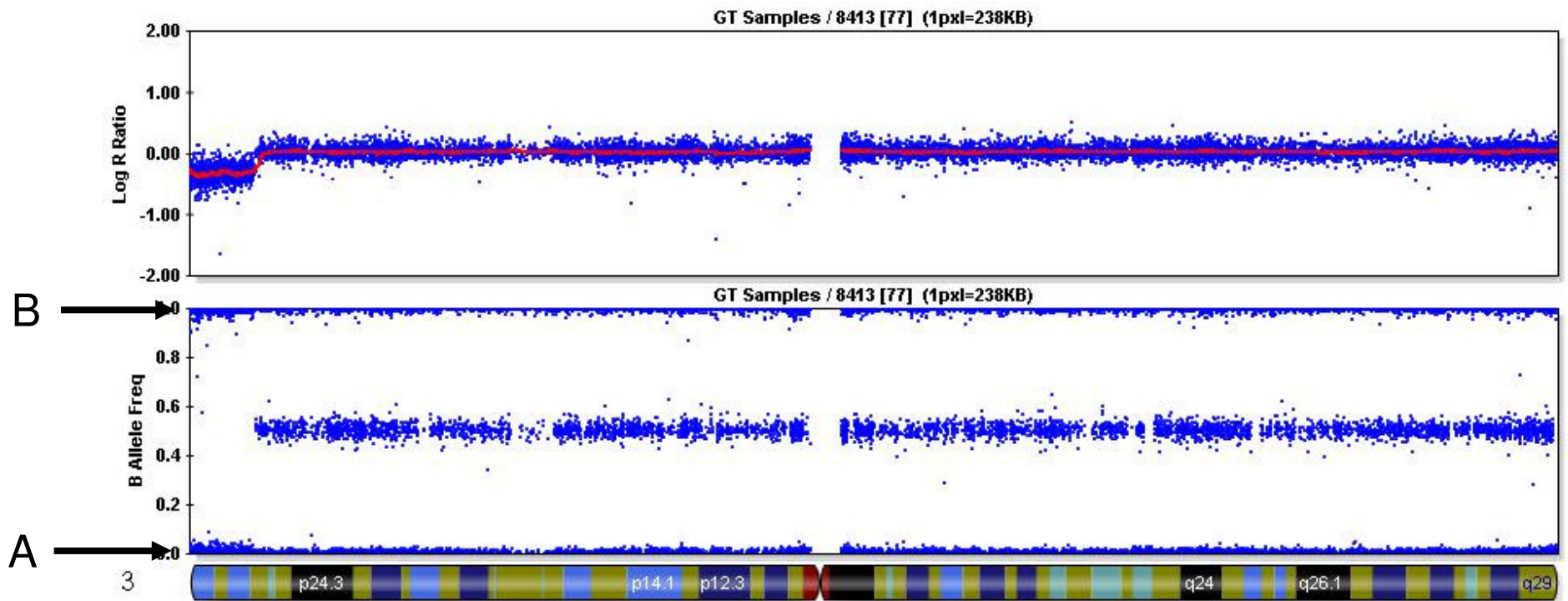
Clustering



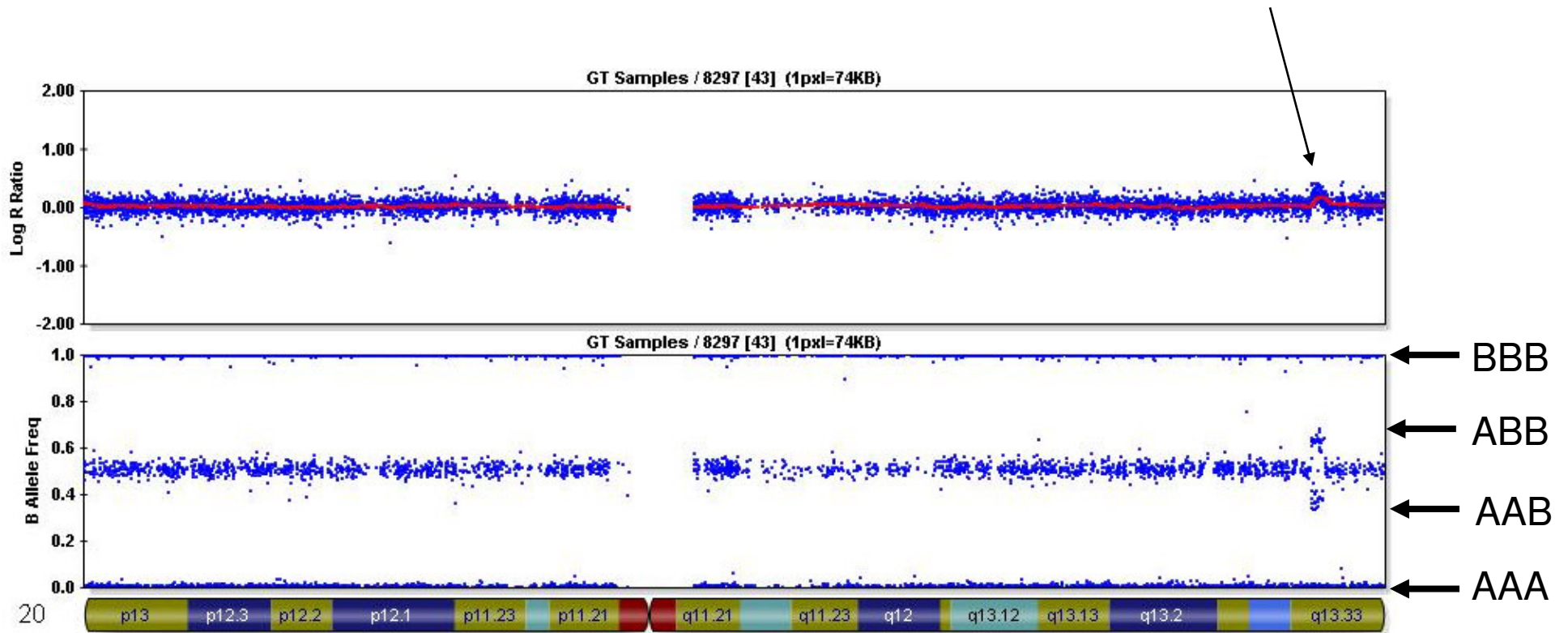
X analysis



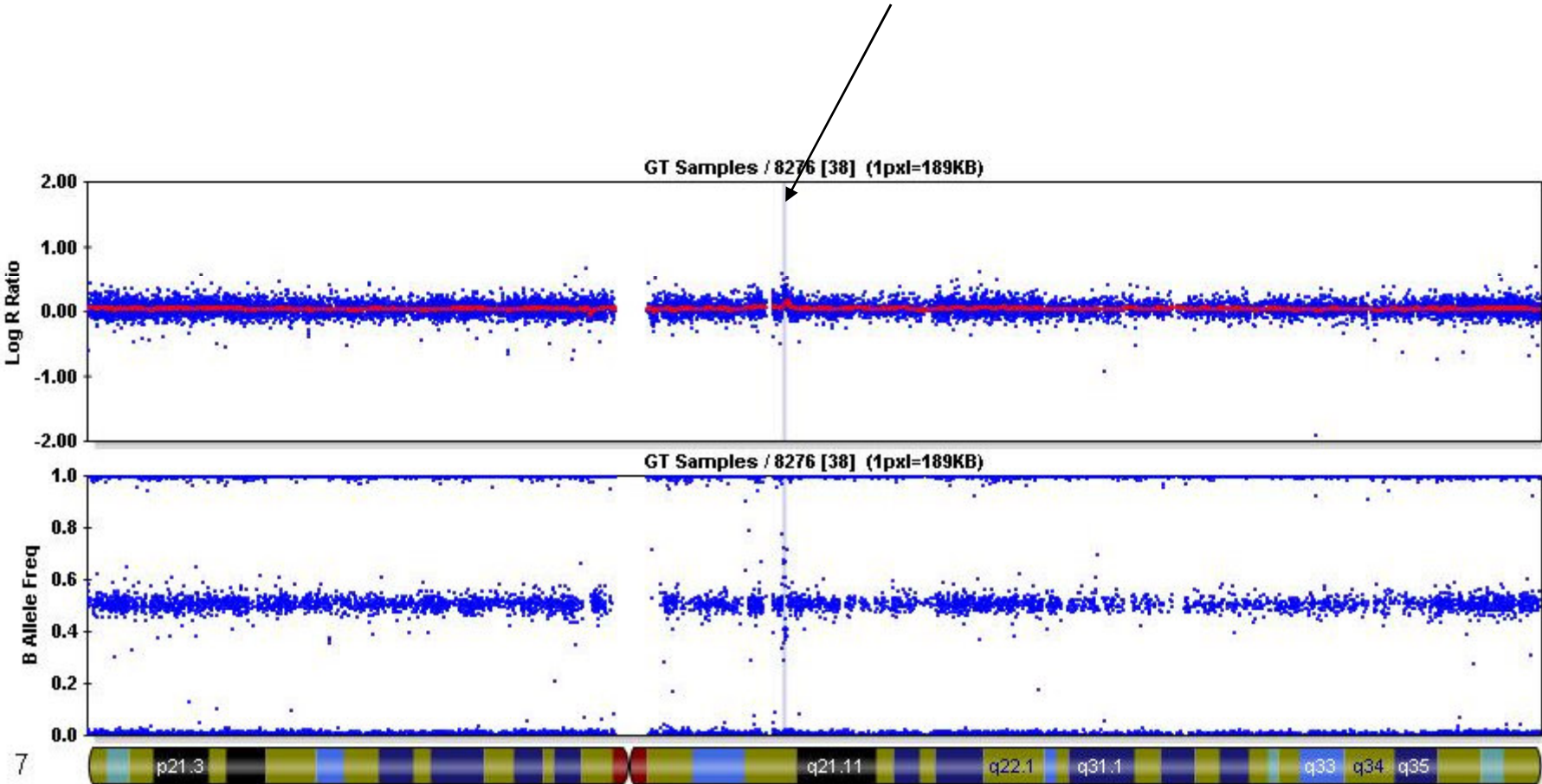
Copy number loss



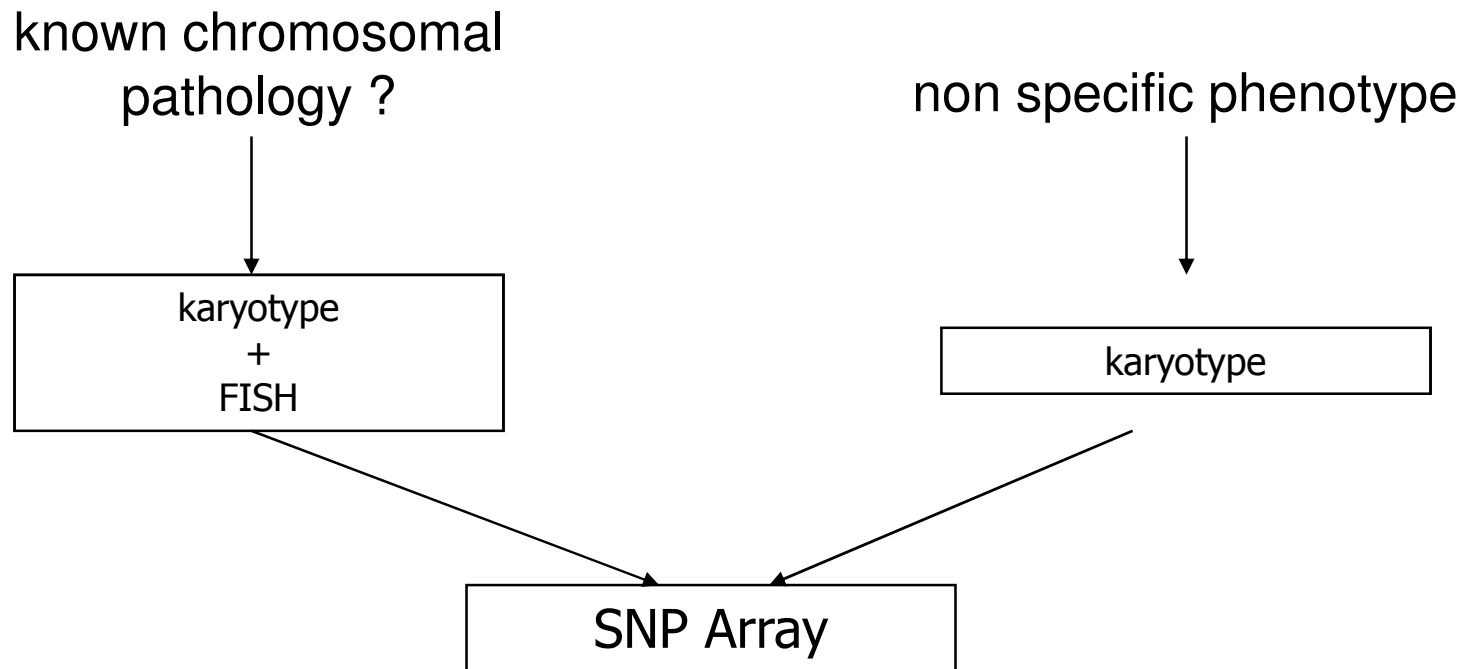
Copy number gain



cnvPartition



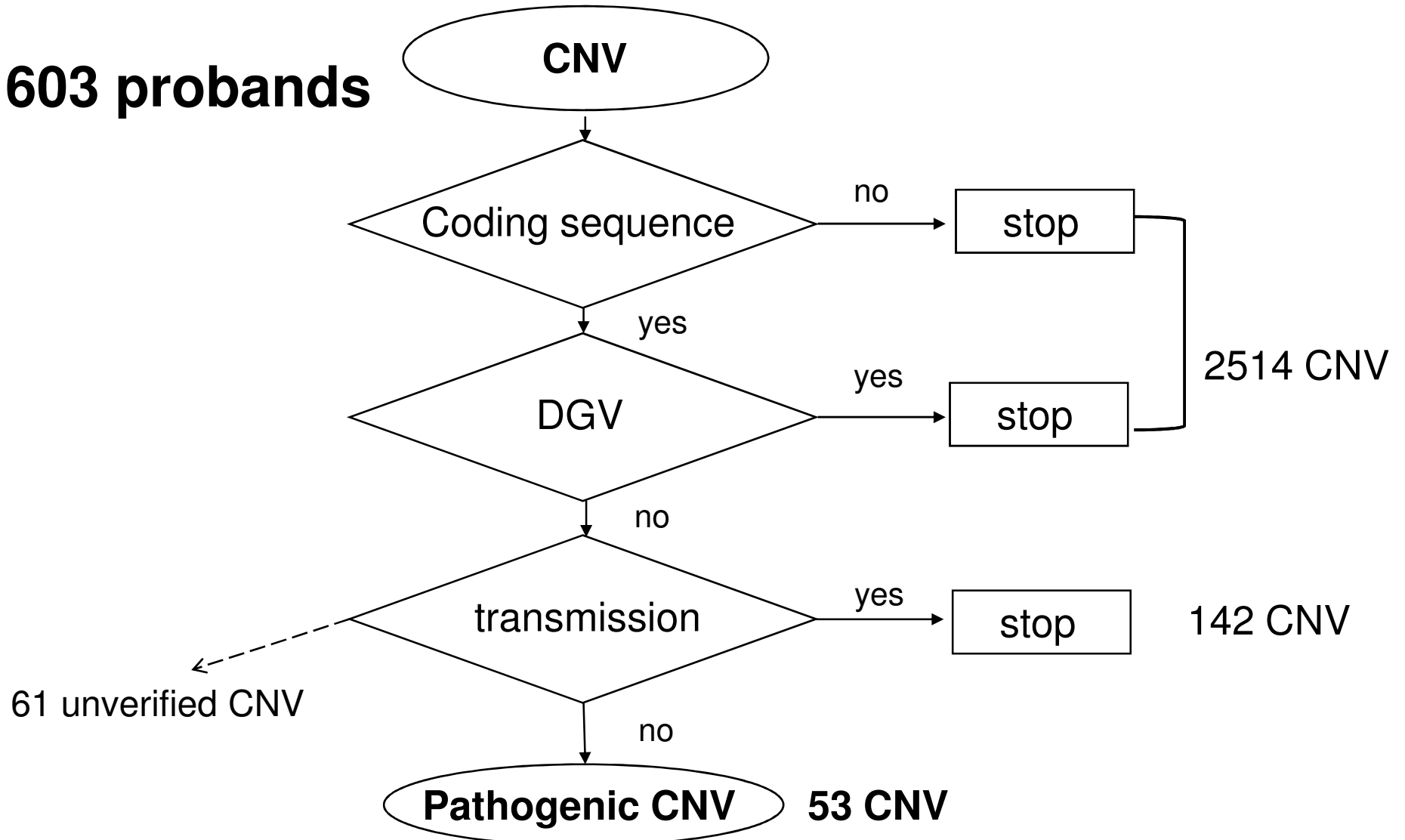
Cytogenetic diagnosis in mental retardation



2007-2008 : HumanCNV370-Duo and HumanCNV370-Quad
2009-2010 : HumanCytoSNP-12

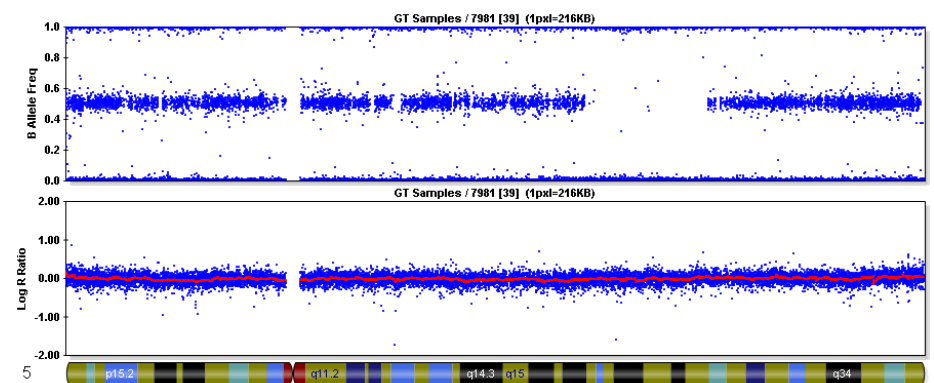
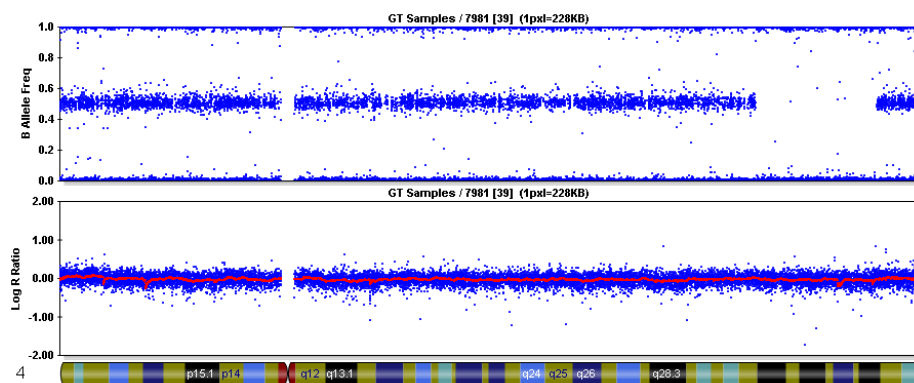
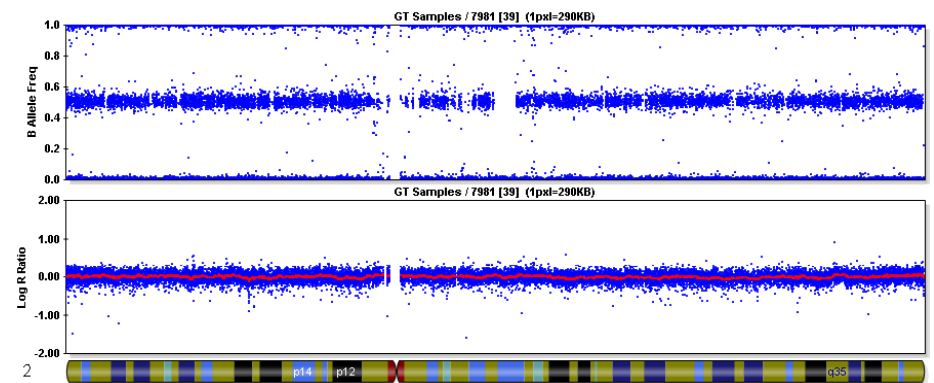
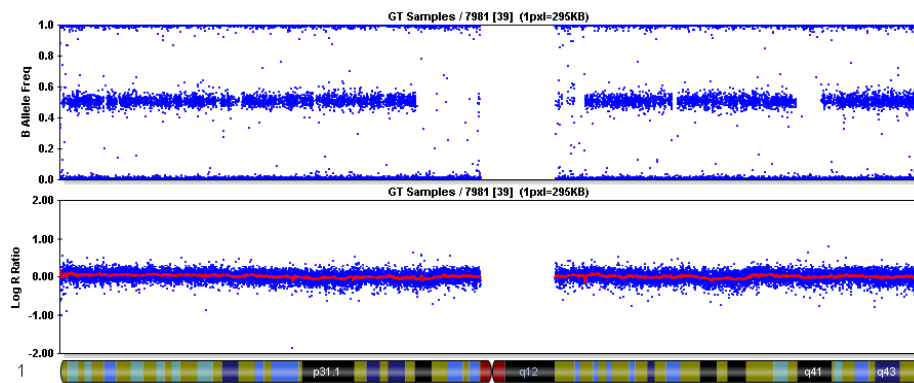
CNV validation

603 probands



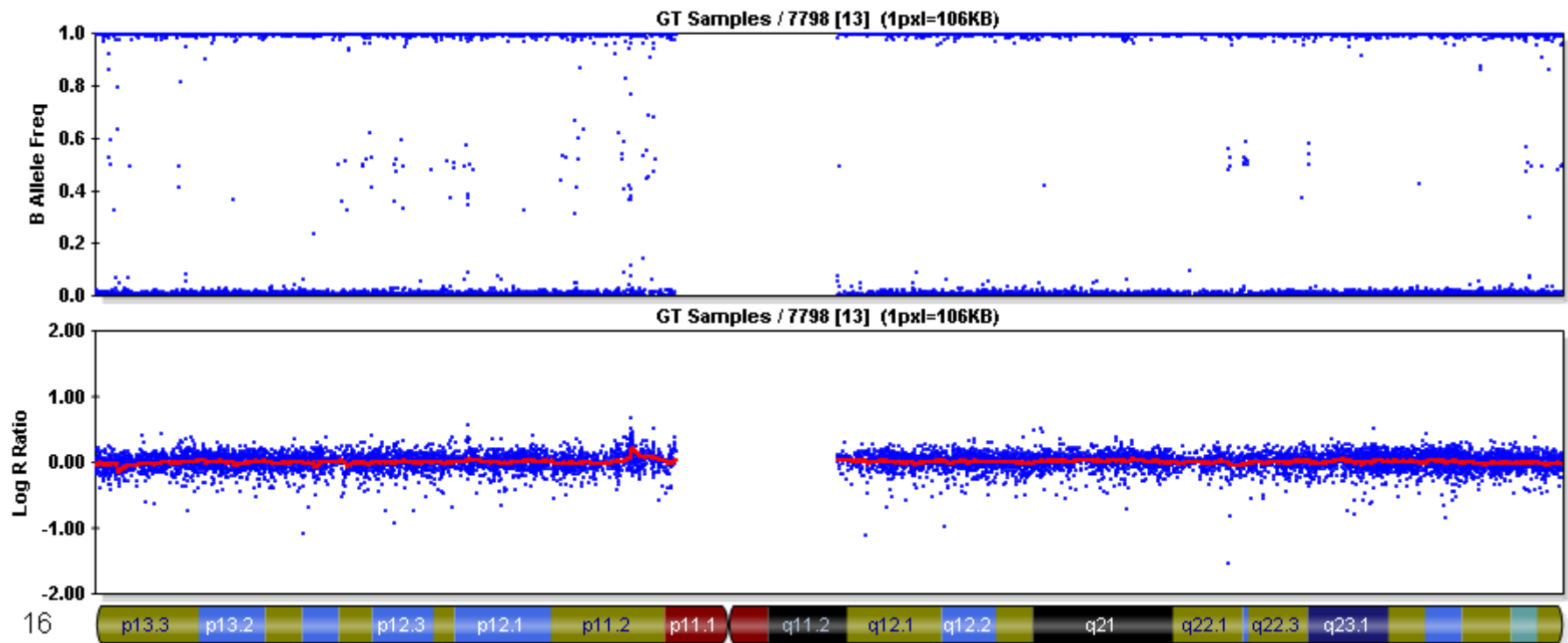
« copy neutral » LOH

consanguinity



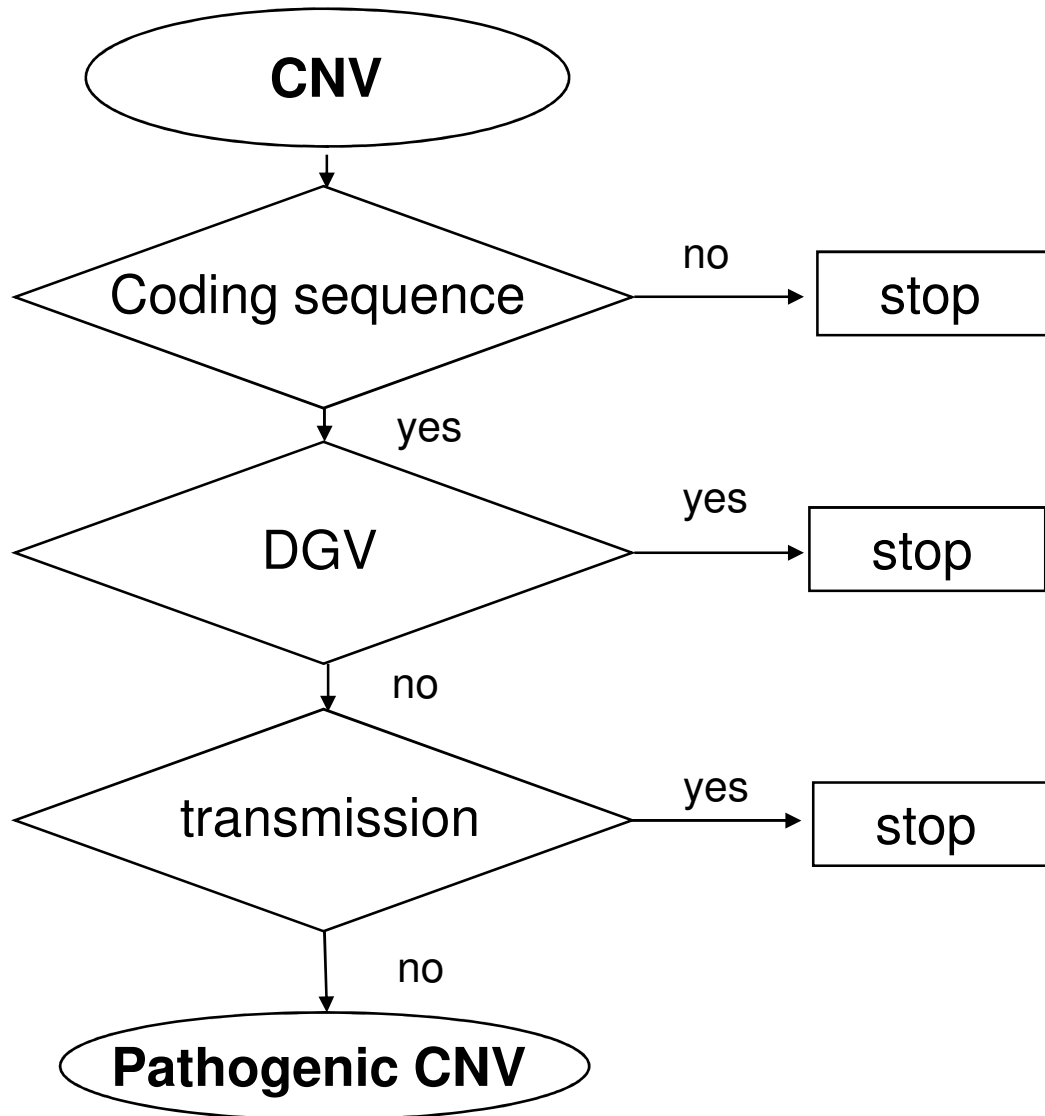
« copy neutral » LOH

Uniparental disomy



603 probands : 5 upd

Interpretation problems



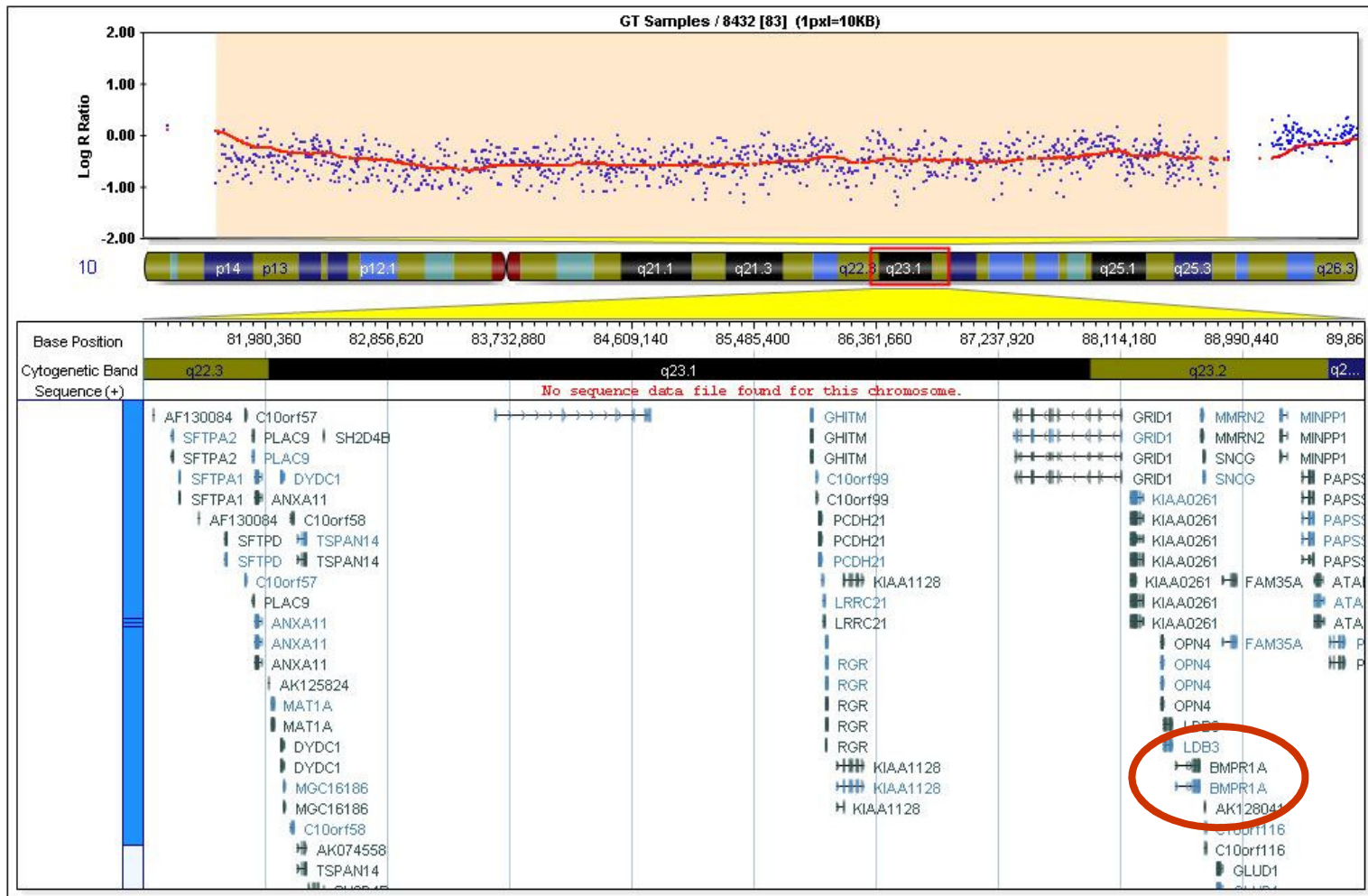
MiR ?
regulation sequence ?

Autosomal recessive
diseases ?
Complex diseases ?

De novo polymorphism

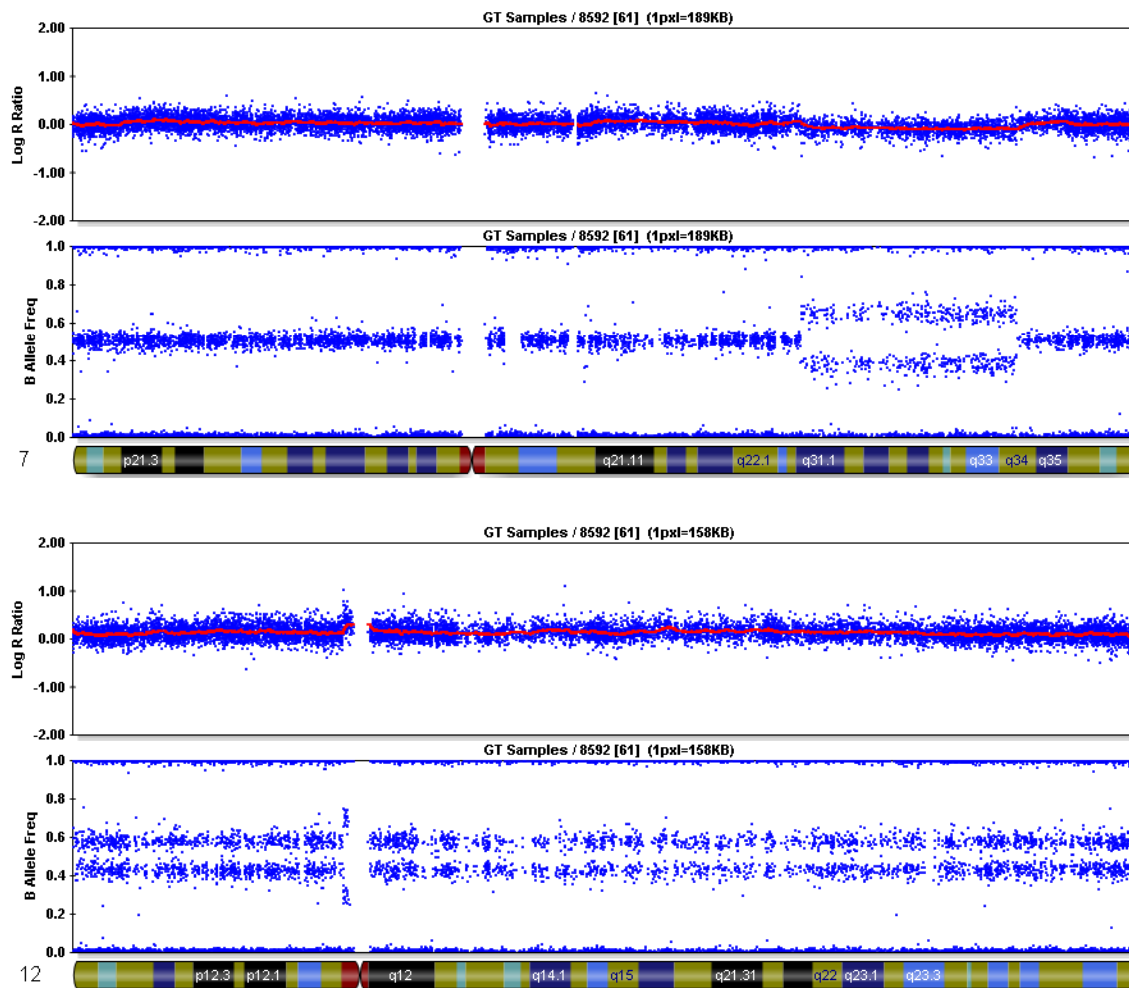
Interpretation problems

Presymptomatic diagnosis of high cancer risk



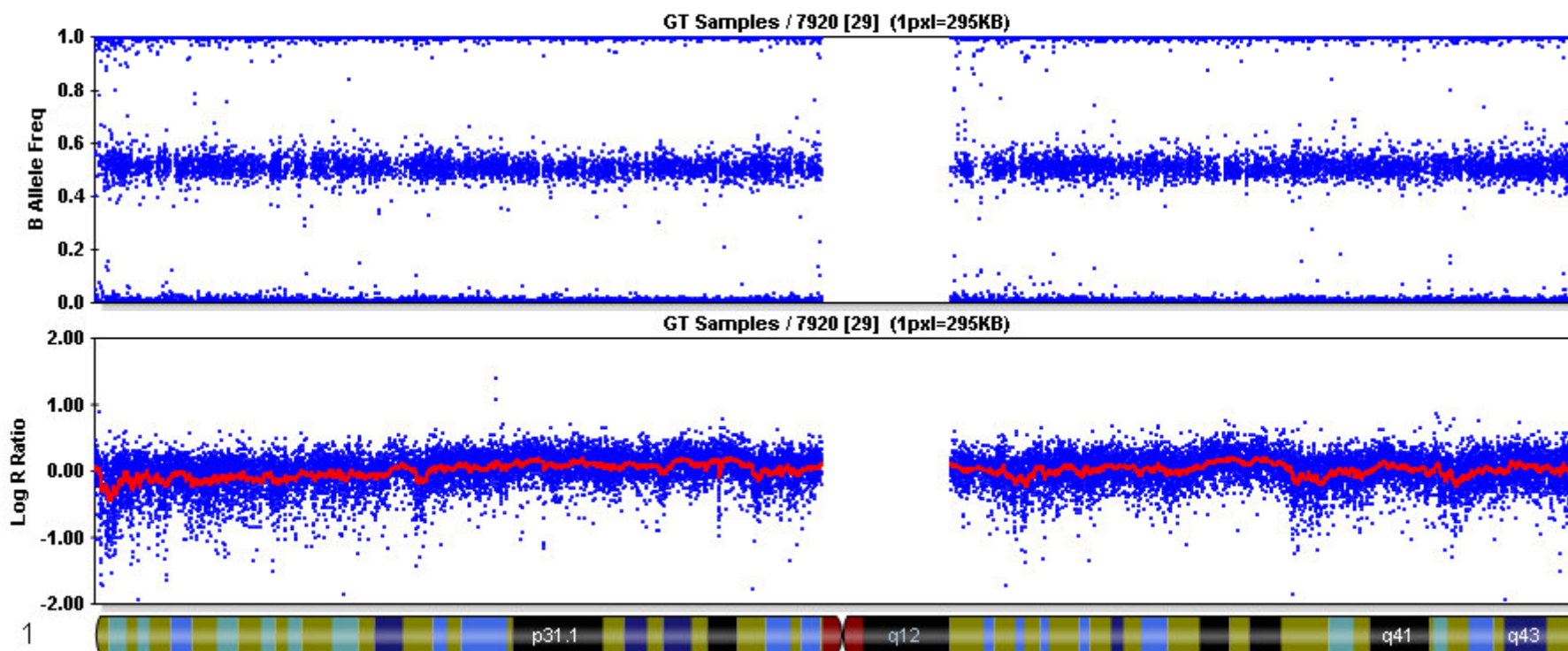
Interpretation problems

Fortuitous diagnosis of a lymphoma



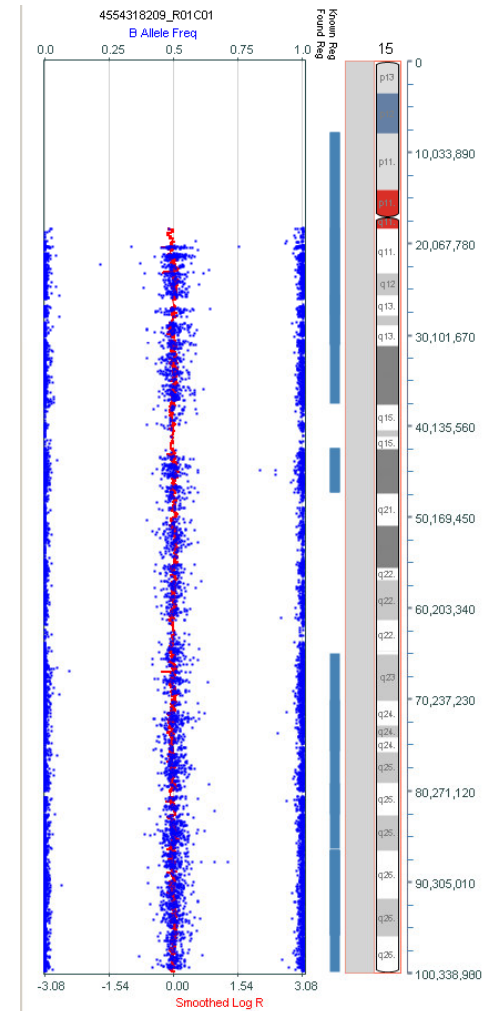
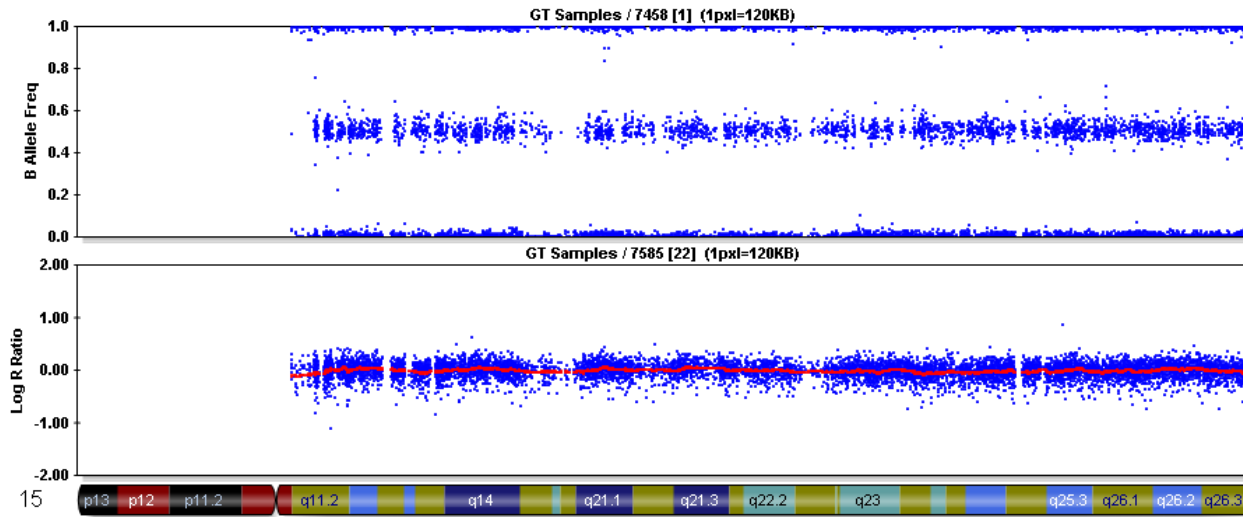
Quality control

- Call rate = 0.998
- p10 GC = 0.69
- Control dashboard ok



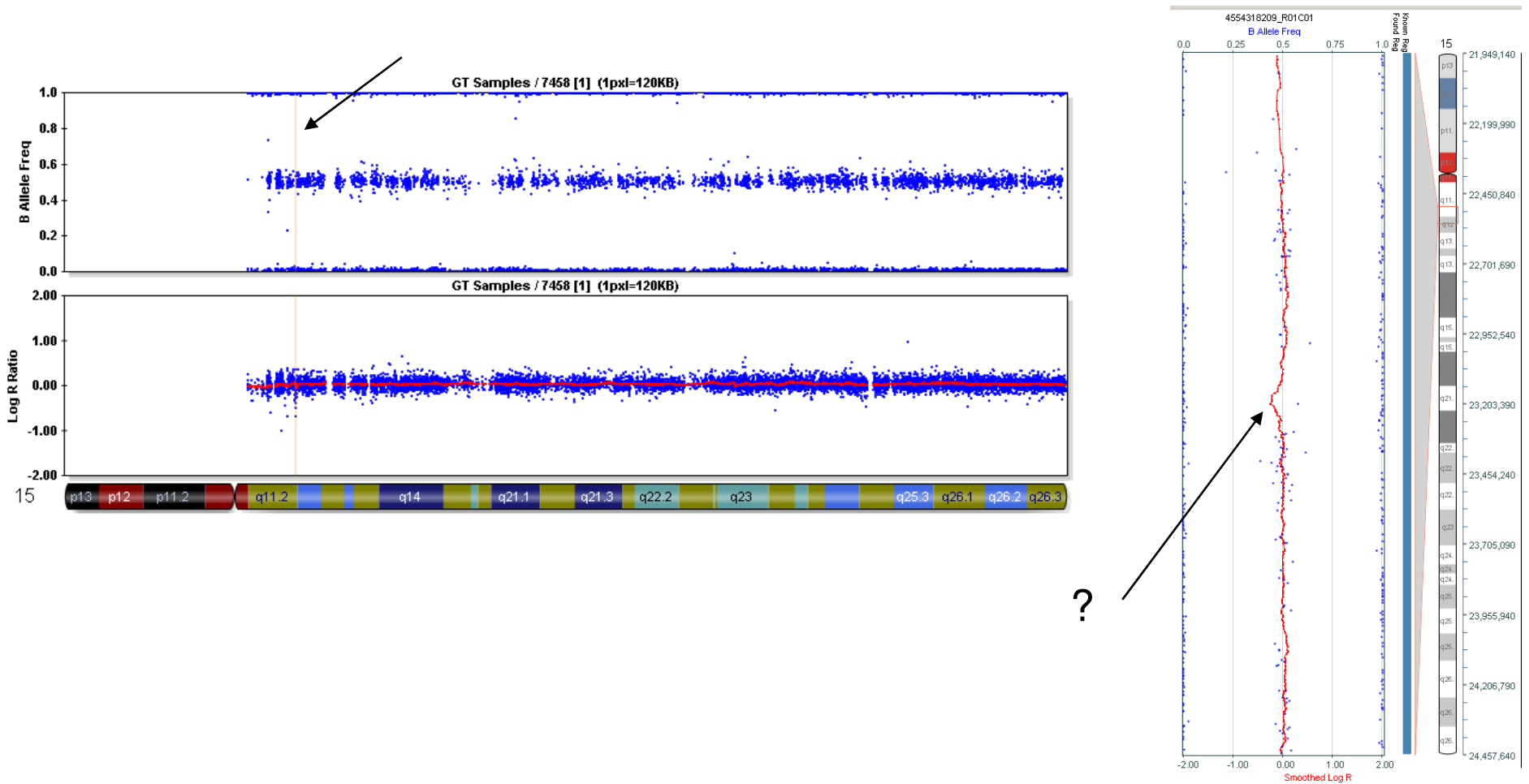
Softwares

Using the Illumina cluster file



Softwares

Clustering SNP with the patients of the same technique



Summary

- CNV analysis on microarray : now used in routine diagnosis for patients with mental retardation

- Difficulties in interpreting CNVs :
 - Pathogenic significance
 - Unexpected anomalies

Illumina chips vs Array CGH in constitutional cytogenetics

- Benefits :
 - No control DNA
 - Diagnosis of uniparental isodisomies
 - High throughput
- Flaws :
 - quality controls
 - Must process many samples at the same time to cluster SNP



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