Cytogenetic Molecular Diagnostics in the Constitutional and Oncologic Setting

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Cytogenetics, Genomic Microarray

What is cytogenetics

- The original whole genome analysis
  - Analysis of chromosomes from a tissue of interest to identify large scale genomic alterations
    - G-banded karyotype
  - Molecular cytogenetics analyzes smaller regions for imbalances and rearrangements
    - FISH and **genomic microarray**

Pediatric indications for a cytogenetic analysis

- Growth abnormality
  - Small/large for age
- Neurologic impairment
  - mental retardation / seizures / microcephaly / hypotonia / psycho-emotional dysfunction
- Dysmorphic features
- Cardiovascular malformations
- Other congenital anomalies

Most common tissue studied: peripheral blood

Professional Society Recommendations

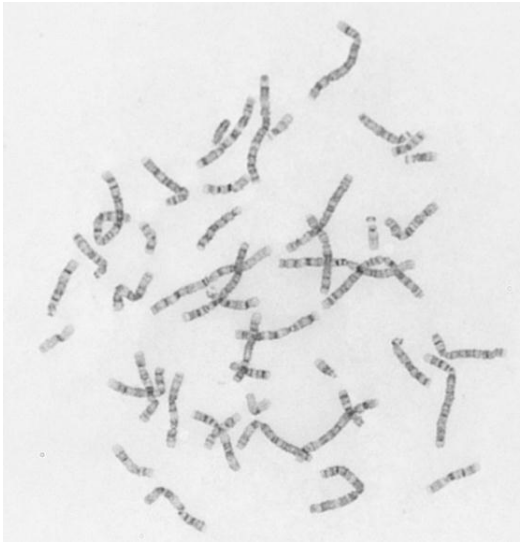
- **Recommending General Cytogenetic Testing for Children with Developmental Delay**
- *American Academy of Pediatrics*
- Pediatrics 2006 118: 405-420 (PMID: 16818591)
- Pediatrics 2006 117: 2304-2316 (PMID: 16740881)
- *American College of Medical Genetics*
- Genet Med. 2005 Nov-Dec;7(9):650-4. (PMID: 16301868)
- *American Academy of Neurology/Child Neurology Society*
- Neurology. 2003 Feb 11;60(3):367-80. (PMID: 12578916)
- **Recommending General Cytogenetic Testing for Children with Autism**
- *American College of Medical Genetics*
- Genet Med. 2008 Apr;10(4):301-5. (PMID: 18414214)
- *American Academy of Neurology/Child Neurology Society*
- Neurology. 2000 Aug 22;55(4):468-79. (PMID: 10953176)
- *American Academy of Pediatrics*
- Pediatrics 2007 120: 1183-1215 (PMID: 17967920)

Indications for a oncology-related chromosome analysis

- Diagnostic chromosome rearrangements
  - CML and t(9;22)
- Prognostic rearrangements
  - ALL and hyperdiploidy (good) vs hypodiploidy (poor)
- Monitoring of secondary changes
  - t(9;22) and +der(22) or i(17q) or +8
- Monitoring effectiveness of therapy
  - Disappearance of previously detected chromosome rearrangement - good
  - Appearance of new chromosome rearrangements – not good
    - Secondary hematologic malignancies

Most common tissue studied: bone marrow/peripheral blood for leukemias/lymphomas; tissue biopsy for solid tumors

Standard Karyotyping



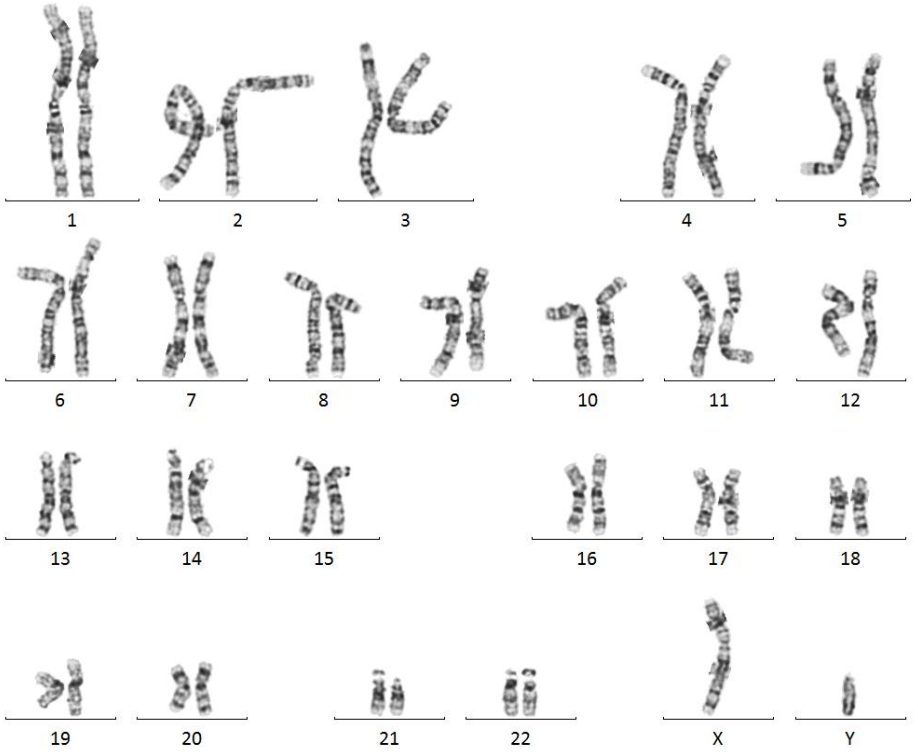
G-banding (Giemsa) chromosomes in metaphase

Benefits:

- Viewing entire genome
- Can visualize individual cells and individual chromosomes

Limits:

- Limit of resolution around 5-10 Mb (depending on region of genome and length of chromosomes)
- Need an actively growing source of cells

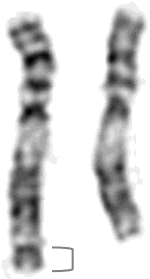


Common types of chromosome abnormalities detected with standard chromosome analysis

aneuploidies

Trisomy 21

deletions, duplications

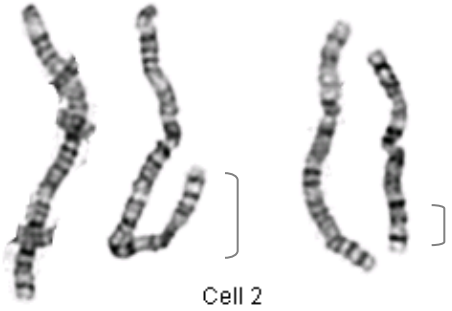


Terminal deletion of 11

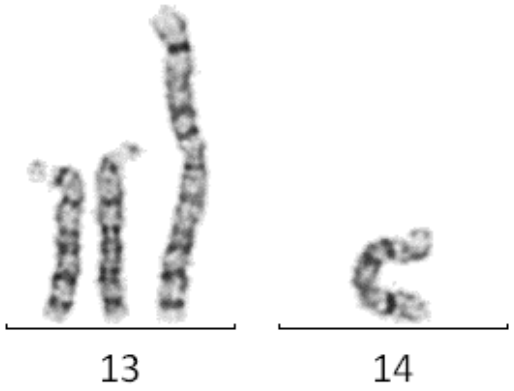
inversions

Pericentric inversion of 16

Balanced and unbalanced translocations



Reciprocal translocation between 3 and 6



Unbalanced translocation between 13 and 14

Fluorescence *in situ* hybridization (FISH)

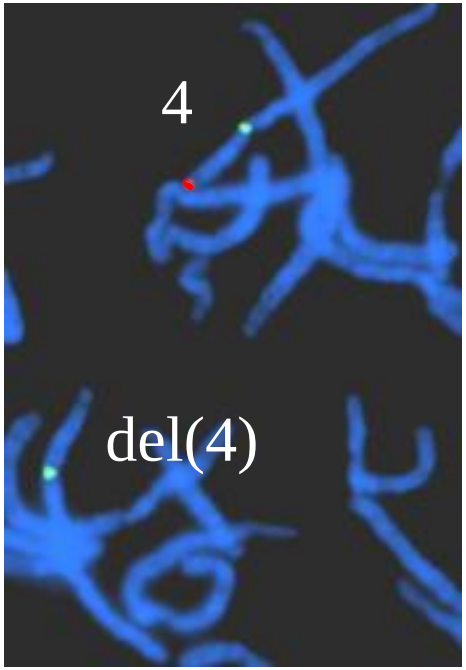
- Label DNA with fluorescent molecule and hybridize to human chromosomes on a slide
- Benefits:
  - Can turn almost any DNA into a probe
  - For clinical use, most probes 100-500 kb
  - Much higher resolution as compared to G-banding for identifying deletions, insertions, and translocation breakpoints
  - Can use cells in any state of the cell cycle as well as archived tissue
  - Can analyze results on a cell-by-cell basis
  - Shorter TAT since tissue does not need to be cultured for metaphase cells
- Limits:
  - Only going to see the region of the genome complementary to your probe

Example of FISH to detect a small deletion

- Microdeletion of 4p detected by FISH using a probe for the Wolf-Hirschhorn syndrome (WHS) critical region (red) and chromosome 4 centromere (green)

4

normal appearing 4s

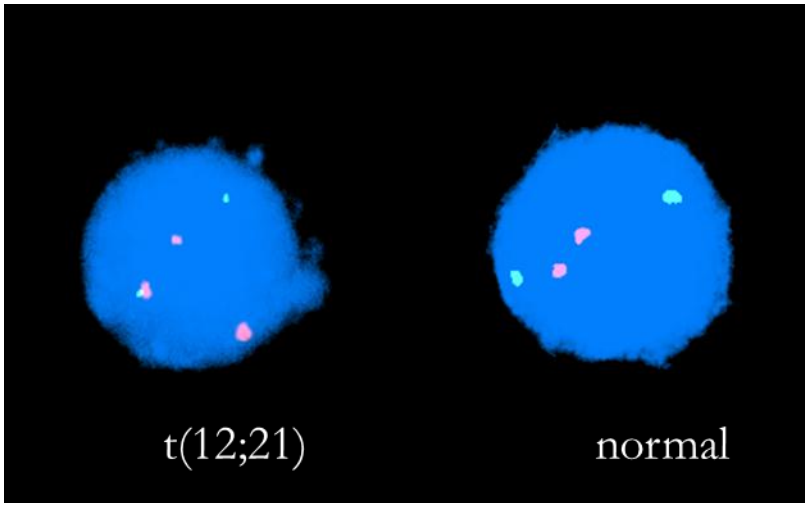


deletion between 2-4 Mb in 25-30% of patients with WHS

Must have suspicion of WHS to run this probe

FISH to identify cryptic rearrangement

- t(12;21)(p13;q22) is a cryptic chromosome alteration (banding pattern is unchanged) but found in ~25% pediatric B-ALL

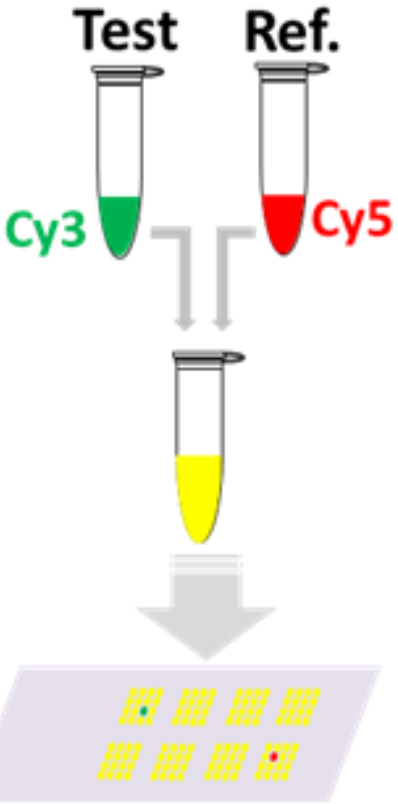


Genomic Microarray

Compare the hybridization of patient DNA and reference DNA on a slide containing oligonucleotides from across the genome

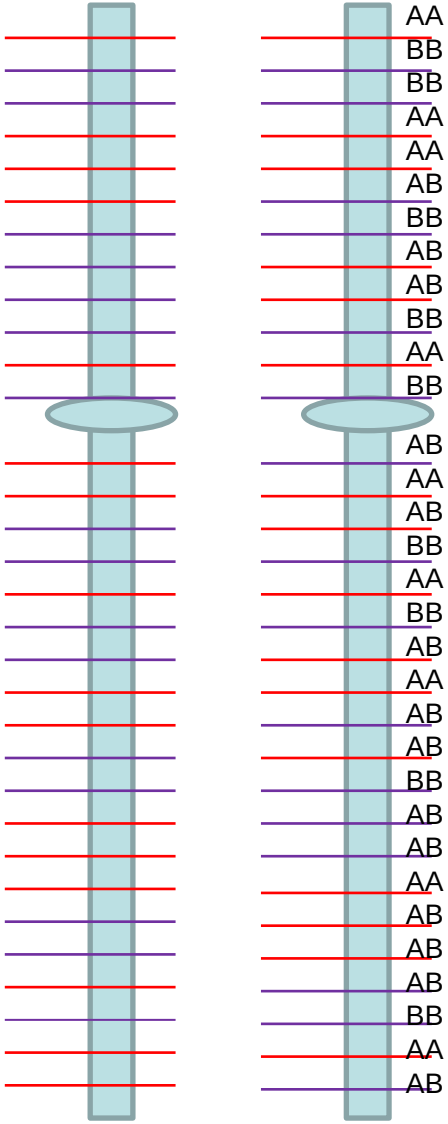
If patient has deletion – more of reference DNA hybs

If patient has duplication – more of patient DNA hybs



Added twist, if oligos have SNP built-in, can determine allele and dosage

Interpreting the Allele track (SNP data)



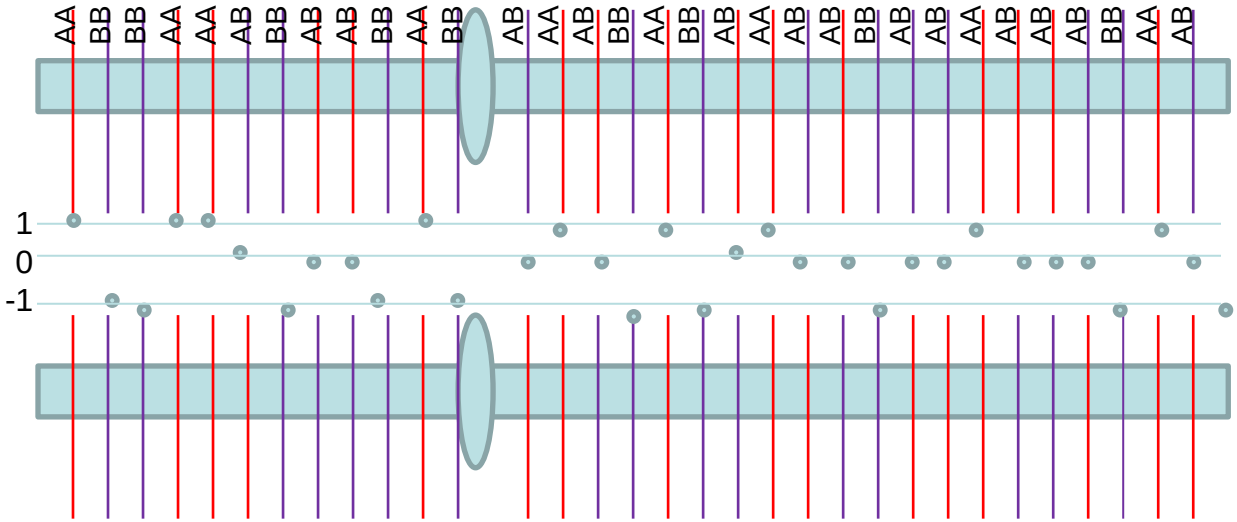
Each allele (A and B) has a value of 0.5 and the Allele Peak plot is simply a difference of A-B

Normal (2N):

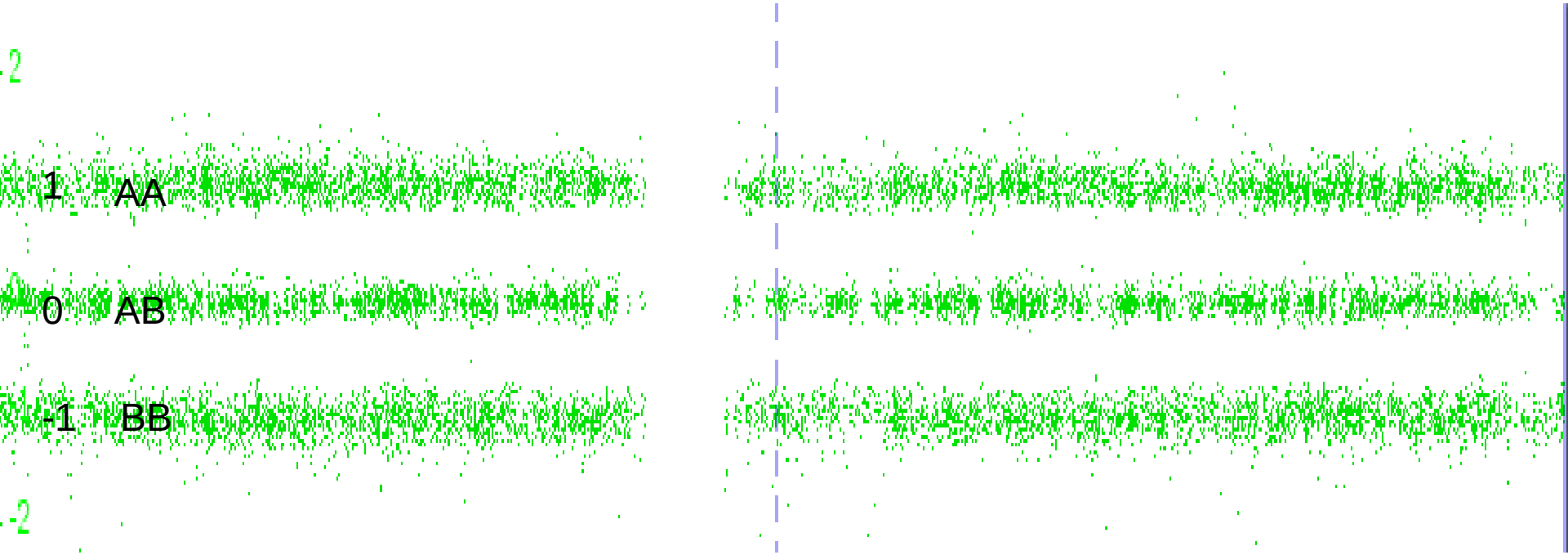
AA: (0.5+ 0.5) -0 = **+1**

AB: 0.5-0.5 = **0**

BB: 0-(0.5+0.5) = **-1**



Allele track for 2N



3N (Hemizygous gain):

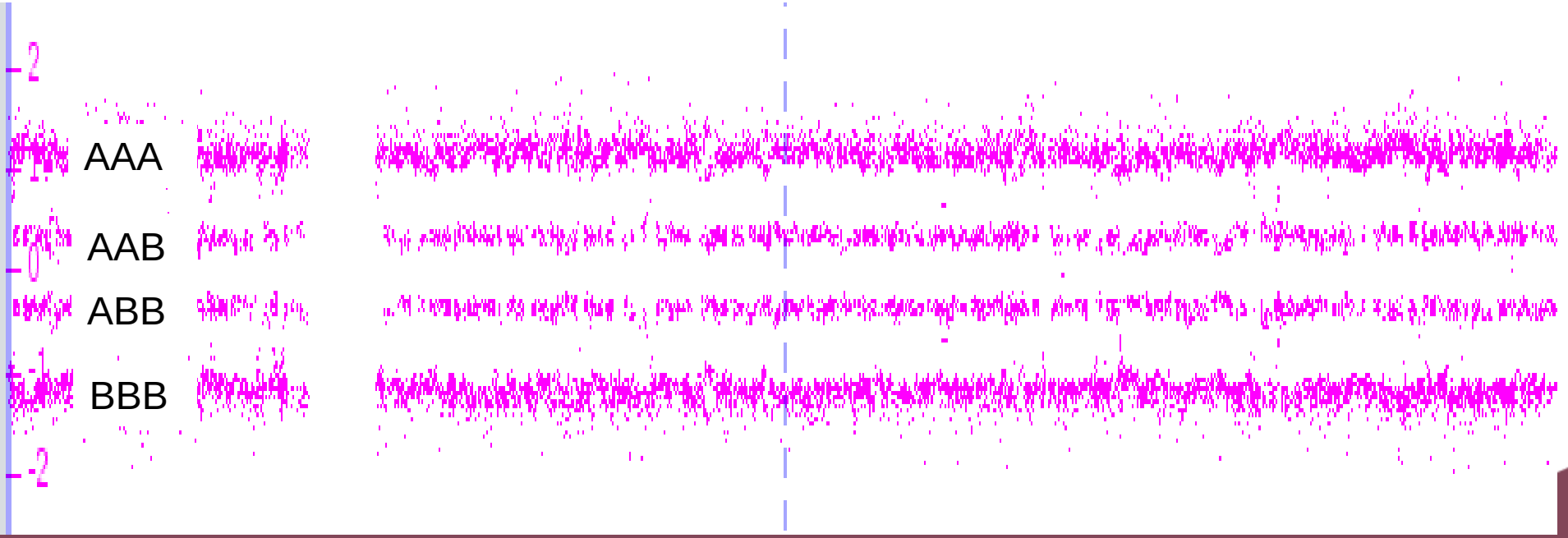
AAA: (0.5 +0.5+0.5)-0 = **+1.5**

AAB: (0.5+0.5)-.05 = **+0.5**

ABB: 0.5-(0.5+0.5) = **-0.5**

BBB: 0-(0.5+0.5+0.5) = **-1.5**

Example of Hemizygous Gain Allele Track:

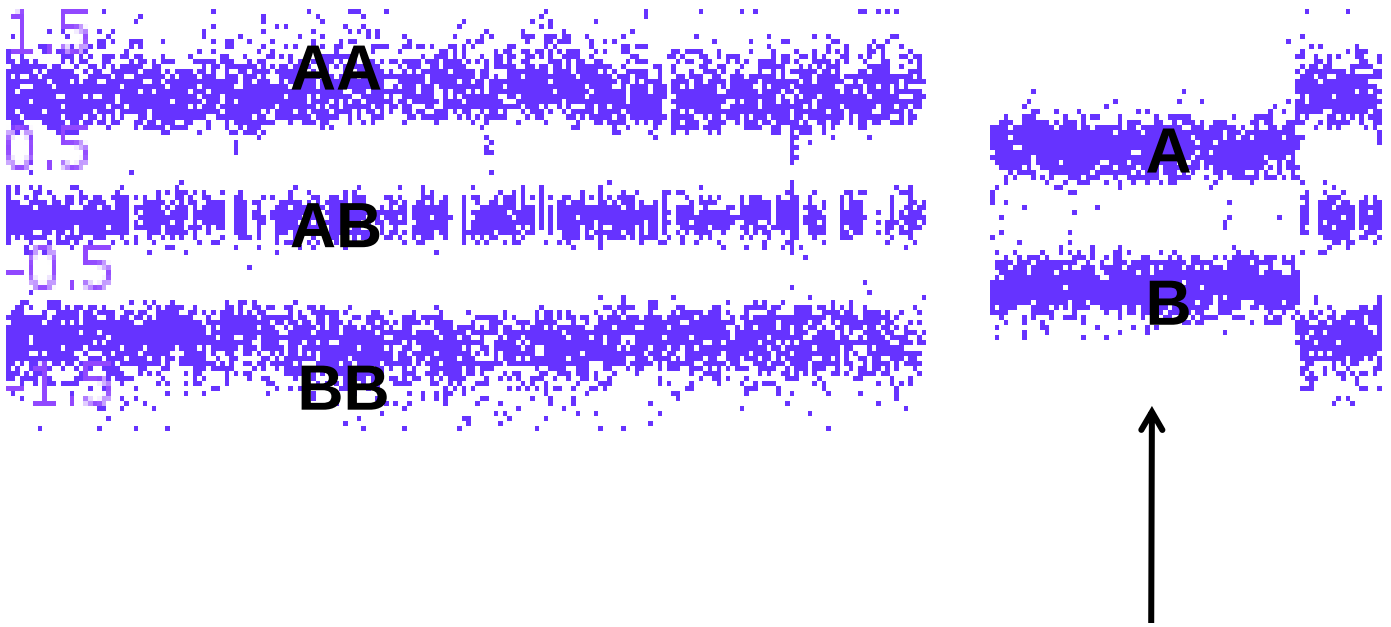


1N (Hemizygous loss):

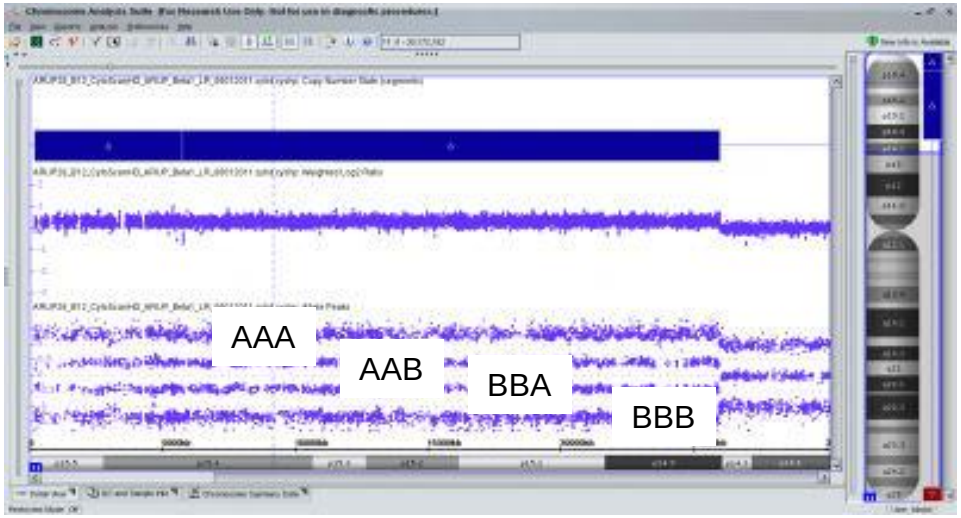
A: 0.5-0 = **+0.5**

B: 0-0.5 = **-0.5**

Example of Hemizygous Loss Allele Track:

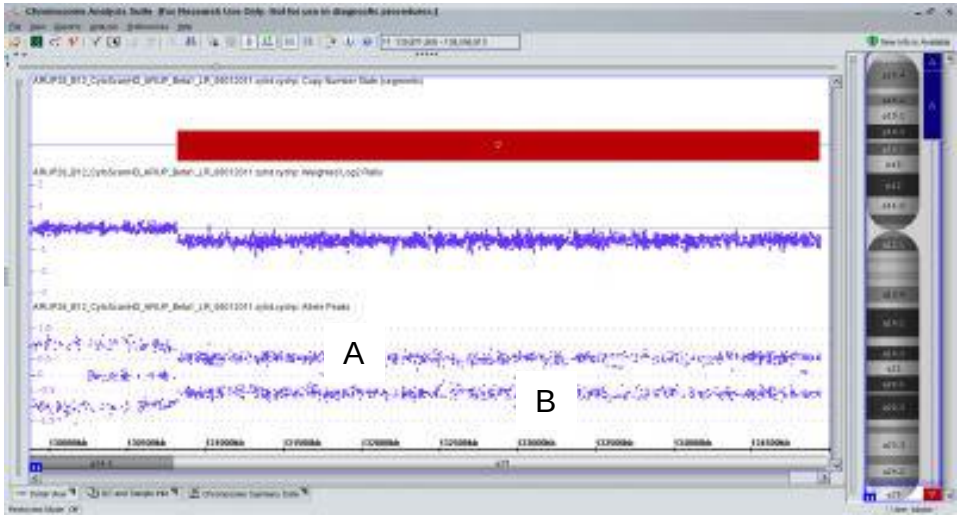


Example: losses and gains with precise breakpoints and allelic information from genomic microarray



Log2ratio elevated (~0.4) showing gain in patient compare to reference DNA

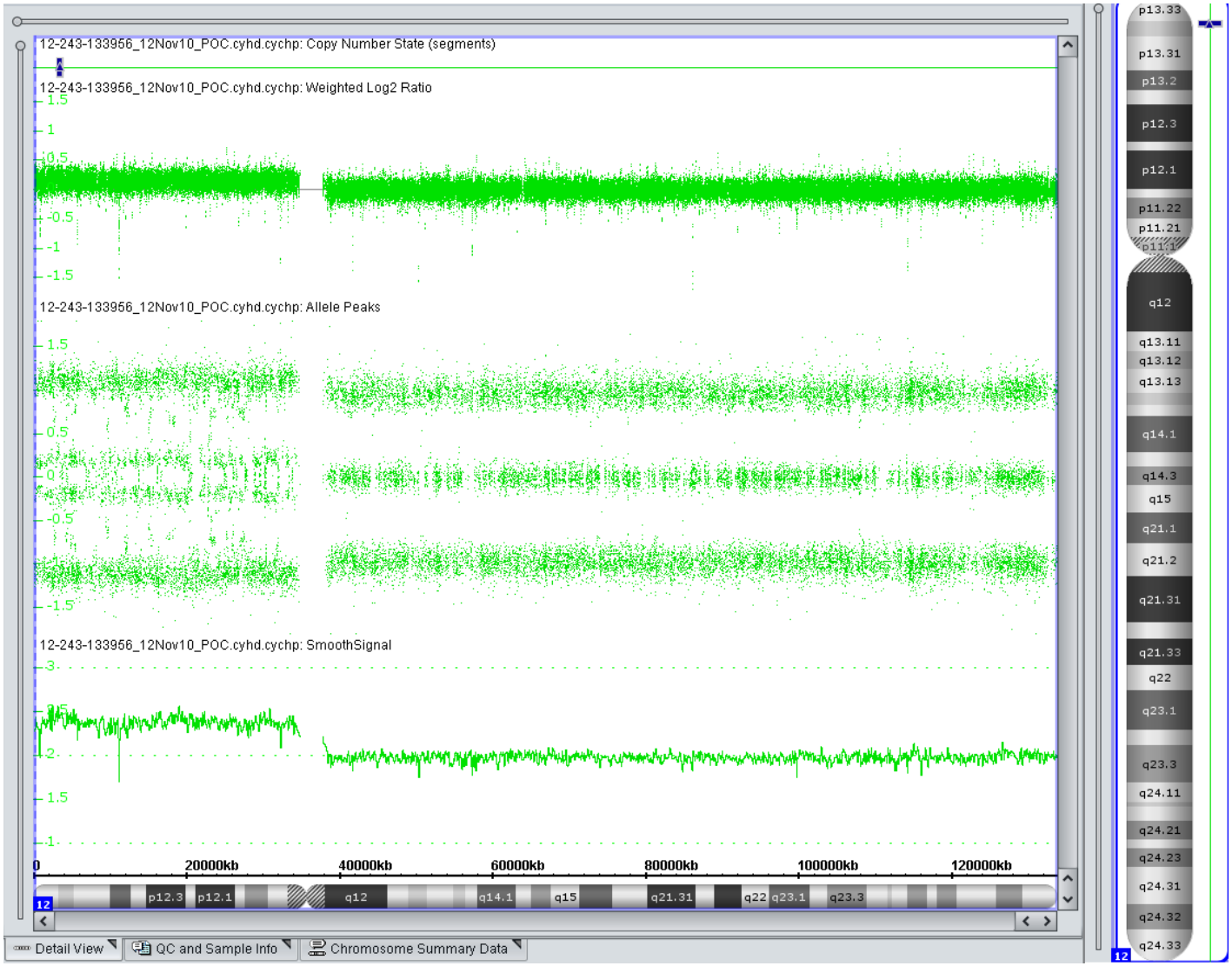
Allele pattern consistent with 3 alleles



Log2ratio lowered (~ -0.7) showing deletion in patient compare to reference DNA

Allele pattern consistent with single allele

Example of Mosaic Gain of 12p

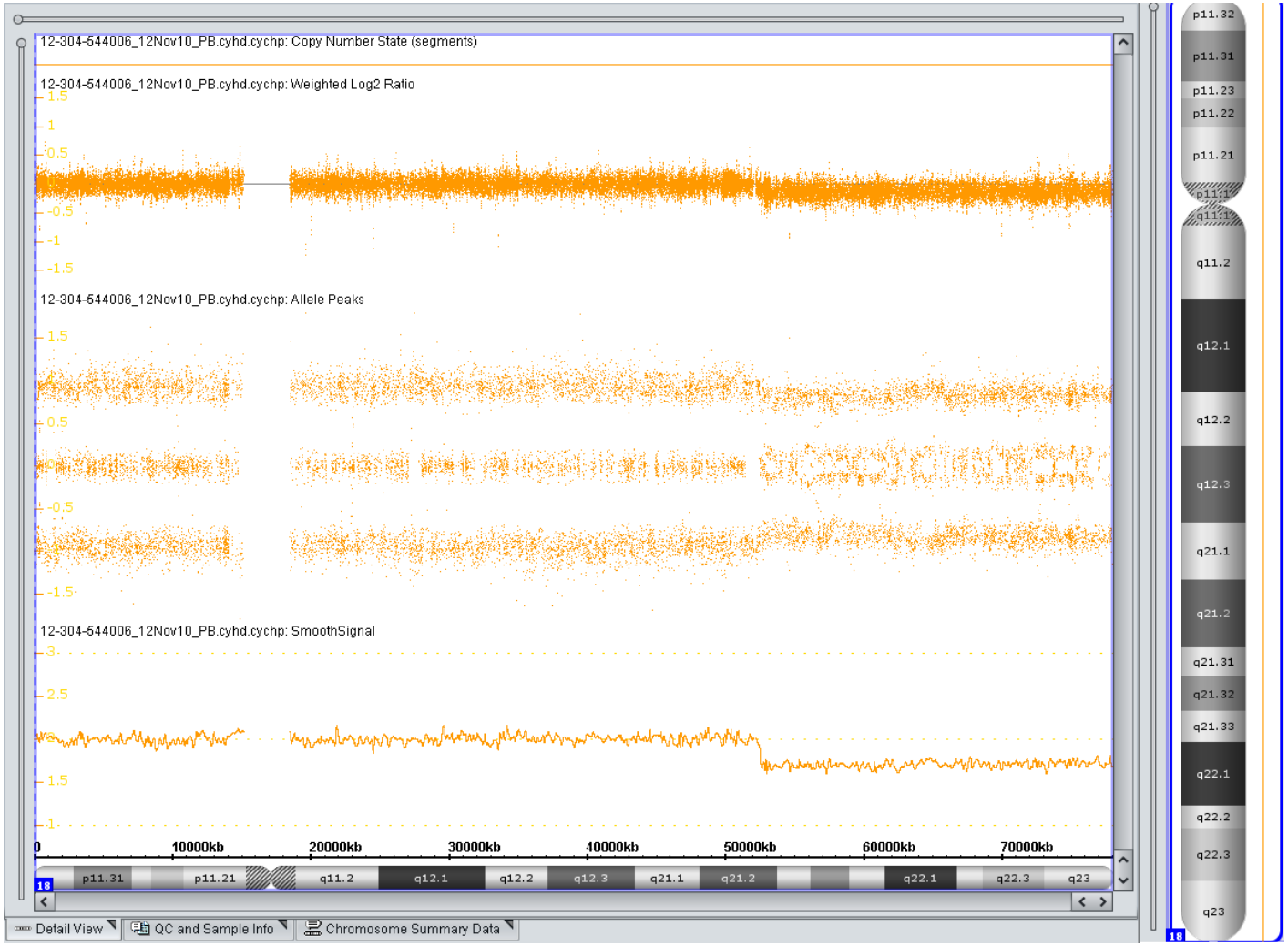


Log2ratio elevated

Allele track showing pattern in between 2N and 3N

Smooth signal (running average of log2 ratio) showing CN state of 2.4

Example of Mosaic Loss of part of 18q

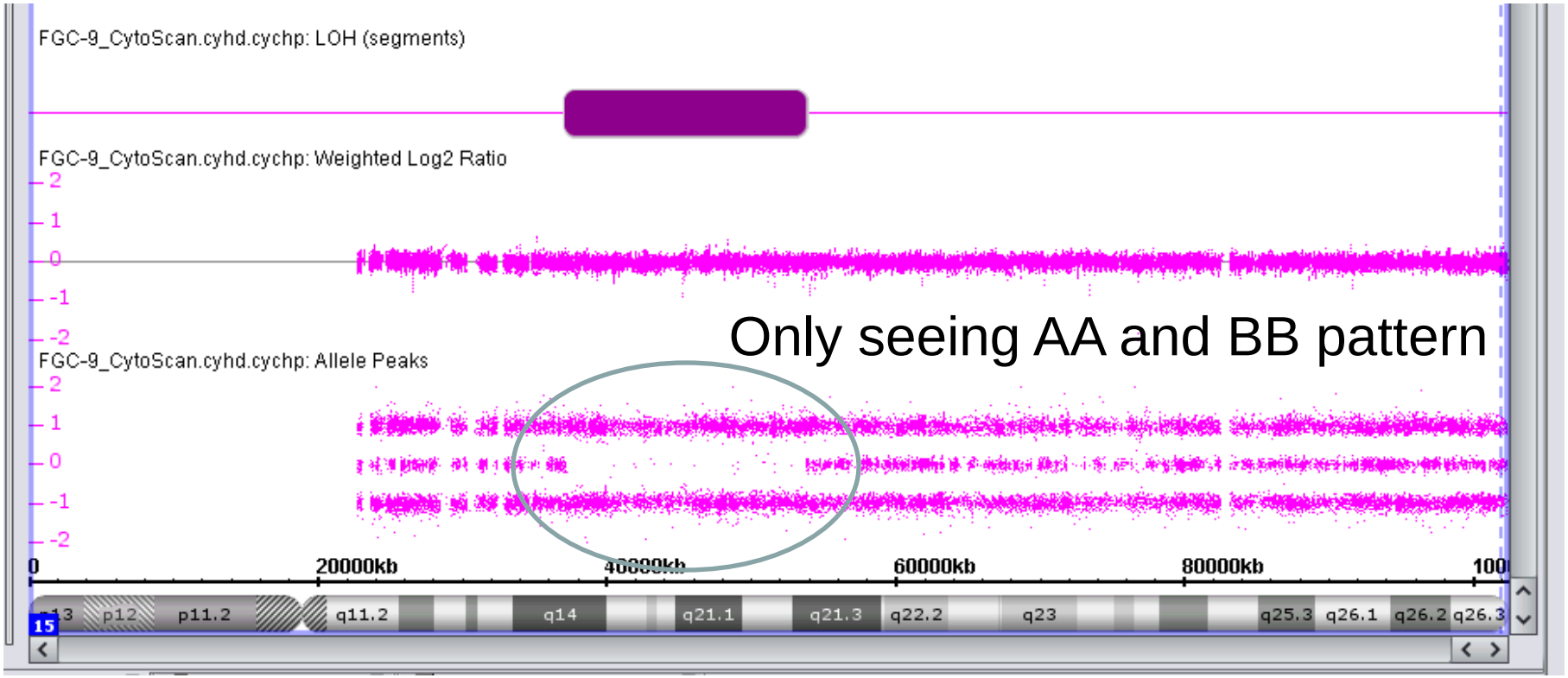


Log2ratio lowered

Allele track showing pattern in between 2N and 1N

Smooth signal (running average of log2 ratio) showing CN state of 1.7

Copy-Neutral Absence of Heterozygosity (AOH)



Mosaic AOH (or acquired loss of heterozygosity)

red circle ~ 16 Mb of mosaic loss of heterozygosity

Genomic Microarray with SNP-based array

- Benefits
  - Can customize array to concentrate clones in areas of interest (targeted regions) and/or spread clones throughout genome (backbone)
  - Resolution will depend on density of clones in region of interest, but can be as good as less than 10 kb
  - Detection of smaller abnormalities
  - Detection of cryptic abnormalities
  - Better definition of cytogenetic abnormalities
  - Interpretation usually less subjective than standard chromosome analysis
  - Can use on archived or non-growing tissue
  - Can detect copy neutral absence of heterozygosity
  - Alelle track results in better detection of mosaicism

- Limits
  - Will not detect balanced rearrangements
  - May uncover copy number changes of unclear clinical significance
  - Will not detect copy number changes in regions of the genome that are not on the array platform
  - Not all regions of the genome are clearly measured for copy number by this technology
    - Regions that are normally highly variable don’t easily show clear clinical variation when patient compared to reference pool

Detection rate for each technology for postnatal constitutional

- Routine G-banded chromosome analysis
  - 5-8% (depending on severity of MR and MCA)
- Genomic microarray *after* normal chromosomes
  - 10-12%
- Genomic microarray as a first-tier test
  - 12-15%
  - Miller *et al.* (2010). Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* 86: 749-764. PMID: 20466091

Professional Society Statements Recommending Genomic Microarray as First-tier Test for ID, Autism and MCA

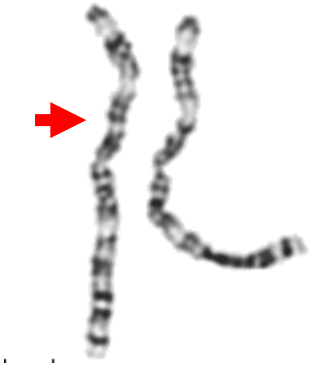
- *American College of Medical Genetics*
  - Genet Med. 2010 Nov;12(11):742-5. (PMID: 20962661)
- *Canadian College of Medical Geneticists*
  - CCMG Position Statement (Clinical) (http://www.ccmg-ccgm.org/policy.html#position)

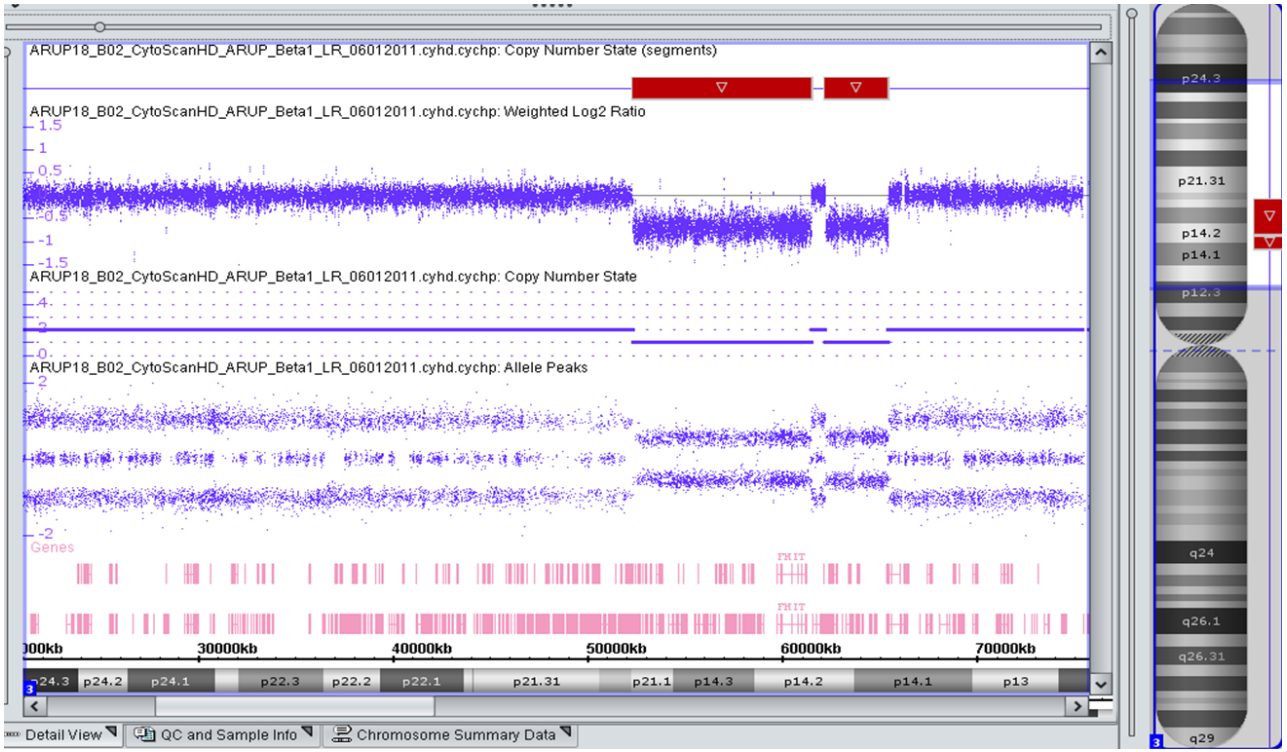
Better definition of cytogenetic abnormalities

G-band designation **vs.** **Genomic microarray**

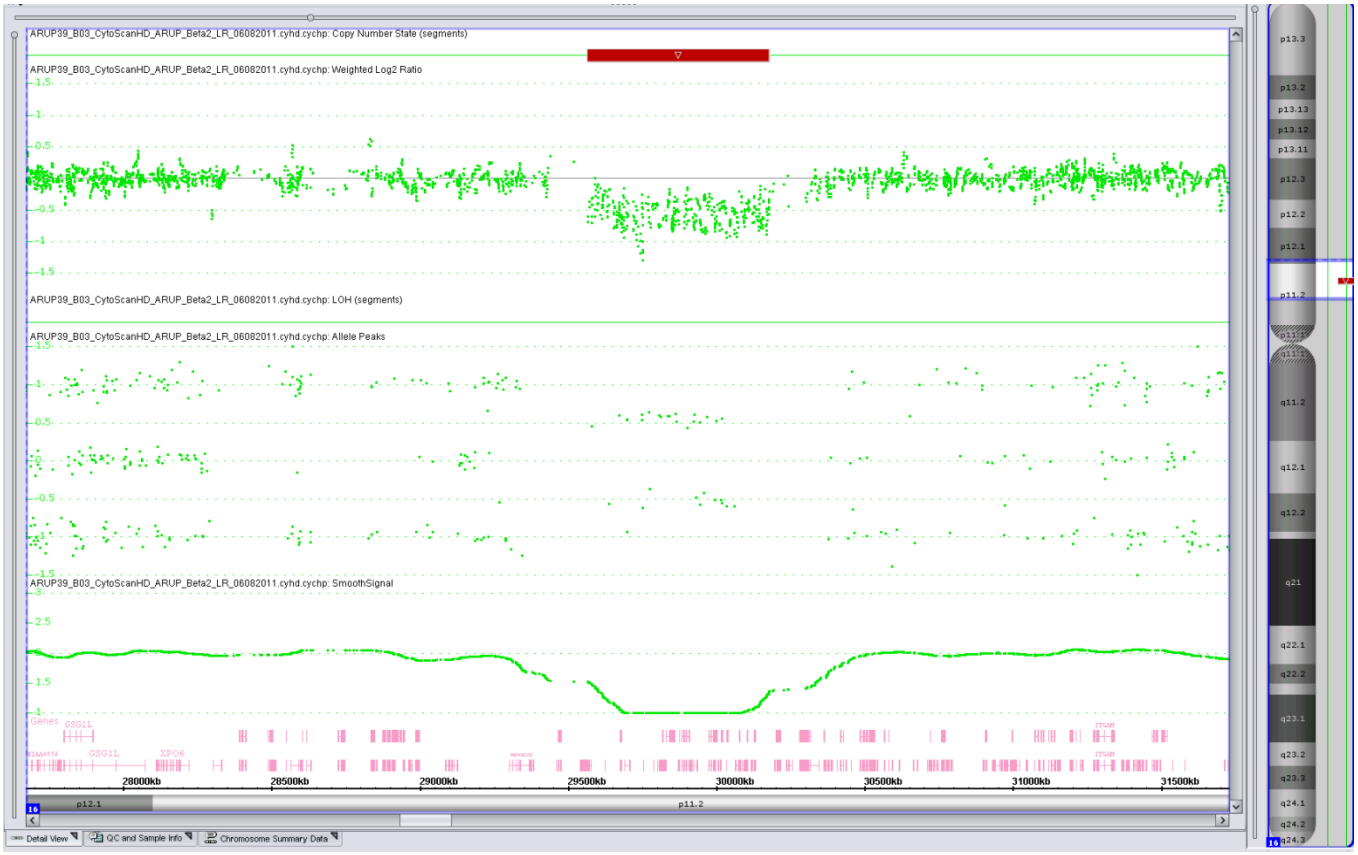
Del 3p14.2p21.3 (+/- a band = +/- ~3 Mb)

Two deletions in 3p, defined breakpoints within 25kb





Common microdeletion/microduplication syndromes

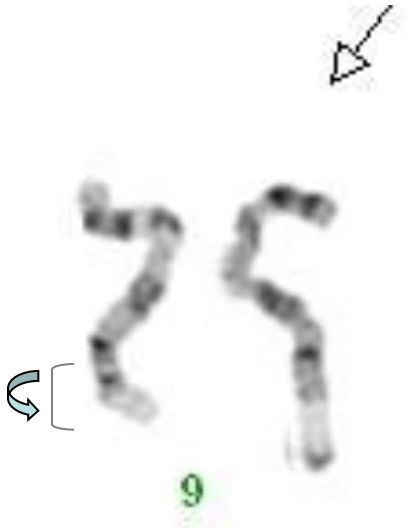


16p11.2 “autism region”

Currently greater than 50 recurrent microdeletion/microduplication syndromes easily detected by microarray and missed by chromosomes

Less subjective analysis of chromosome rearrangements

Proband's 9s



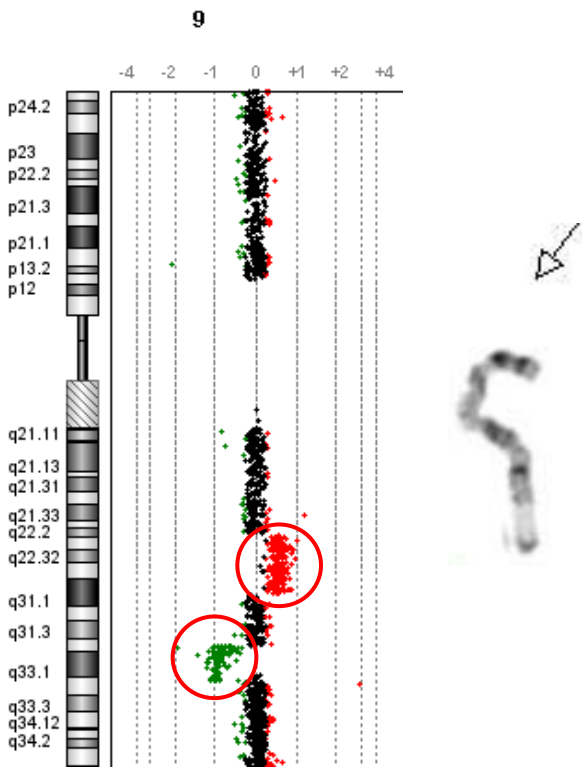
Mother's 9s

Interpretation:

Both proband and mother have a paracentric inversion in the long arm of 9: inv(9)(q32q34.3)

But this does not explain differing phenotypes (proband has DD + MCA, mother normal)

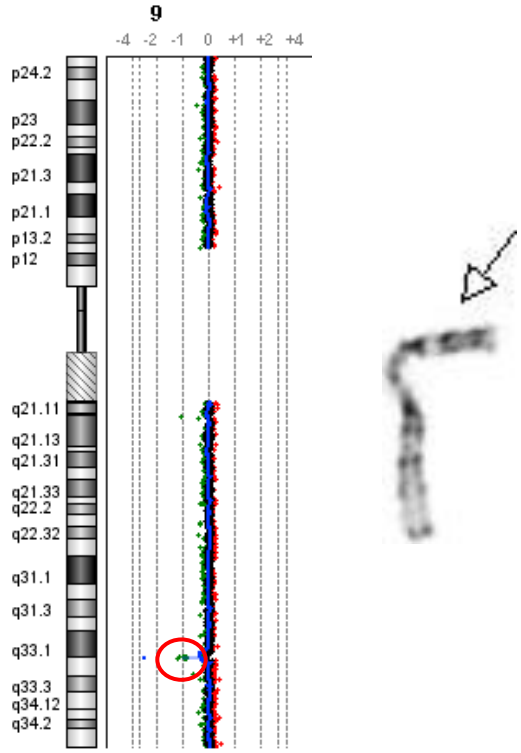
Differing microarray results despite identical banding patterns



proband's complex unbalanced 9

10.8 Mb duplication within 9q22-31.1

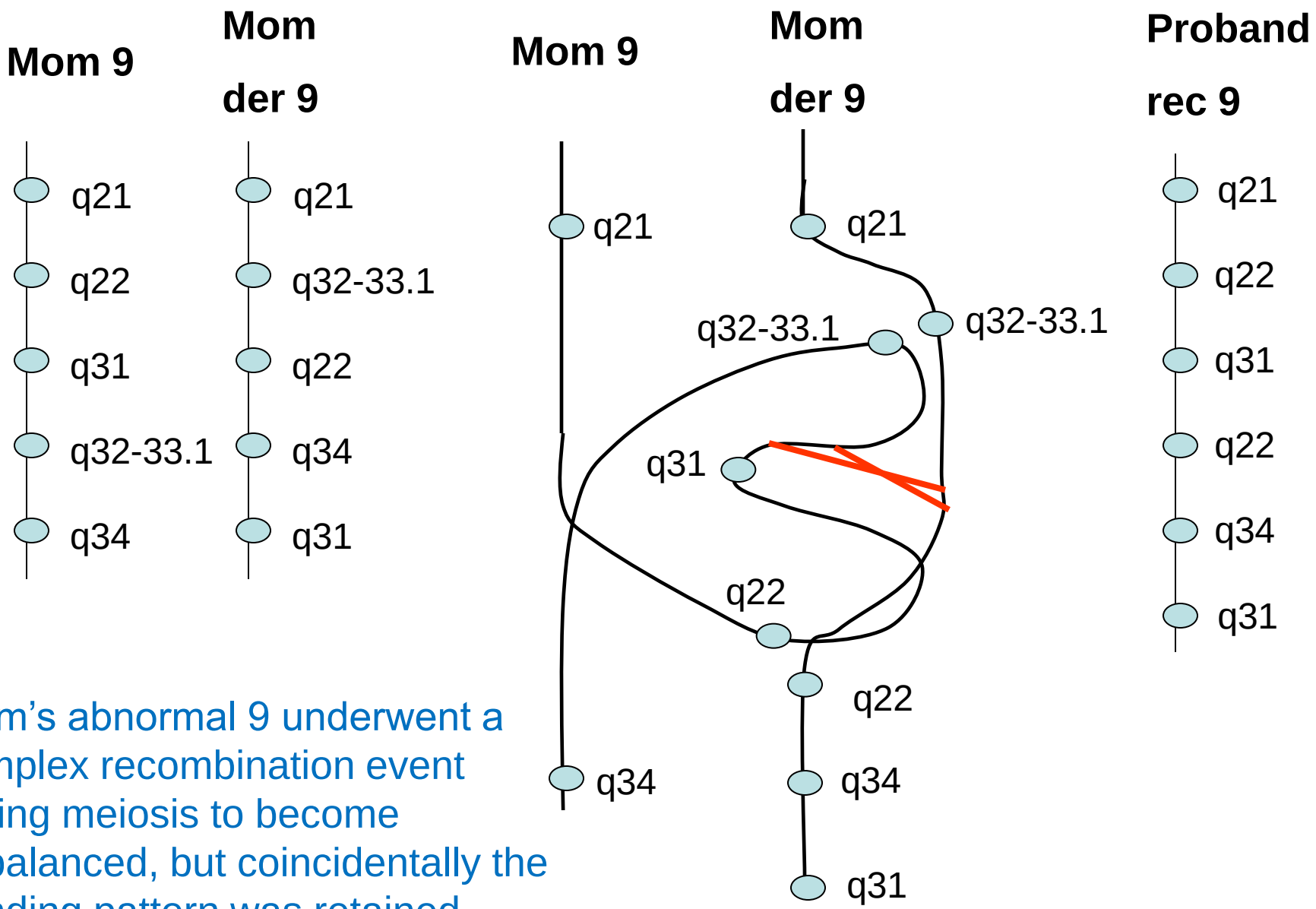
9.0 Mb deletion within 9q32-33.1



mother's 9

"clinically" balanced

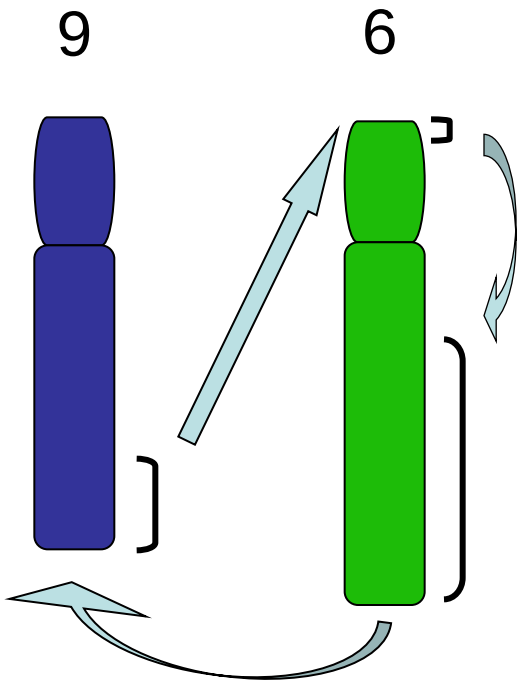
550 kb deletion in 9q33.1 no genes involved

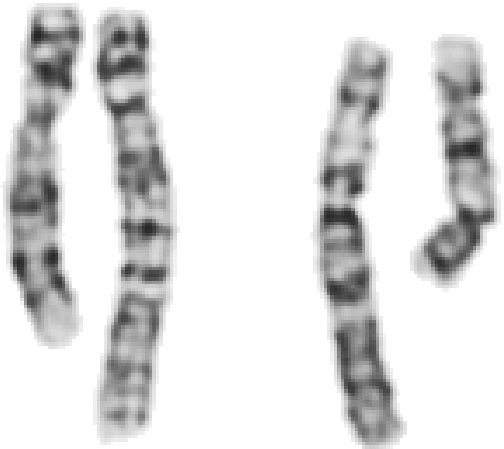


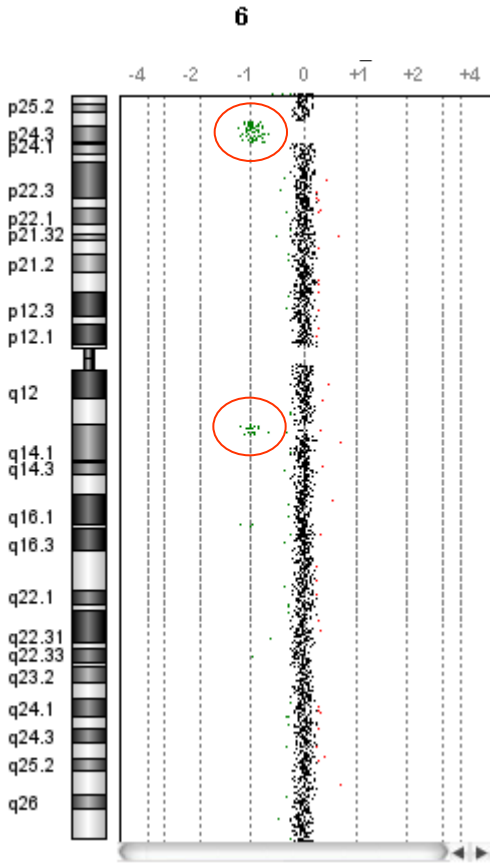
Mom's abnormal 9 underwent a complex recombination event during meiosis to become unbalanced, but coincidentally the banding pattern was retained

South et al, *Journal of Molecular Diagnostics, Vol. 12, No. 5, September 2010*

Example of loss at breakpoints in an apparently balanced rearrangement



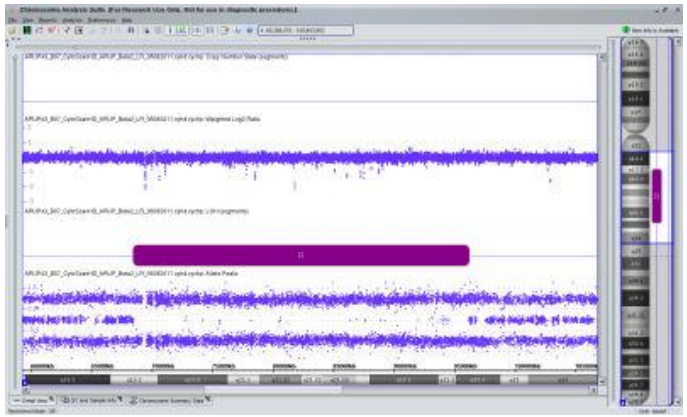


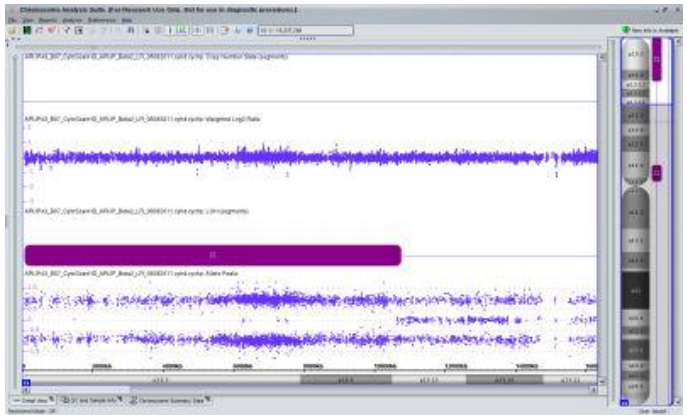


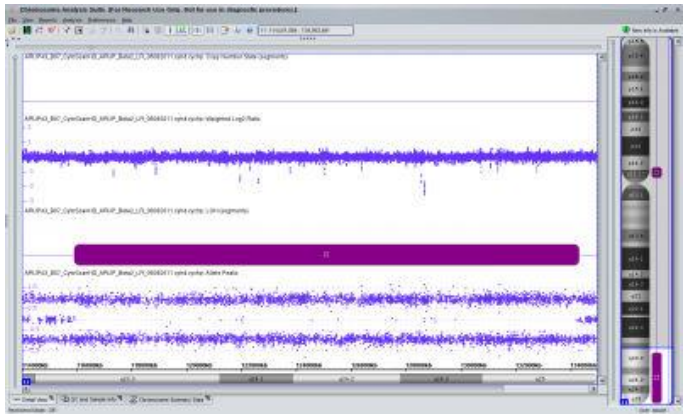
three way translocation: t(9q32;6p25;6q13)
4.9 Mb deletion at 6p25.1-24.1
2.1 Mb deletion at 6q13-q14.1

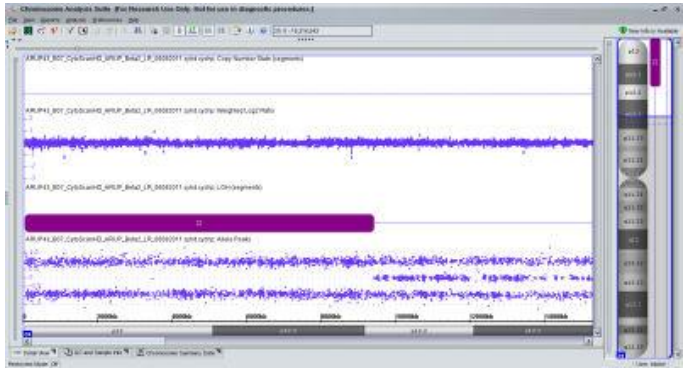
South ST. Clin Lab Med. 2011 Dec;31(4):513-24,

Multiple regions of absence of heterozygosity – increased AR risk









Notable Called LOH Events (ordered by size)						
Data file name	**Called CN**	**Gain/Loss**	**Chromosome**	**Start**	**Stop**	**Size (kb)**
ARUP43_B07_CytoScanHD_ARUP_Beta2_LR_06082011.cyhd.cychp		LOH	4	68470454	96237271	27766.817
ARUP43_B07_CytoScanHD_ARUP_Beta2_LR_06082011.cyhd.cychp		LOH	11	115912443	134311979	18399.536
ARUP43_B07_CytoScanHD_ARUP_Beta2_LR_06082011.cyhd.cychp		LOH	16	89560	10753600	10664.04
ARUP43_B07_CytoScanHD_ARUP_Beta2_LR_06082011.cyhd.cychp		LOH	20	61794	9439488	9377.694

Tool to assist with autozygosity mapping for AR genes

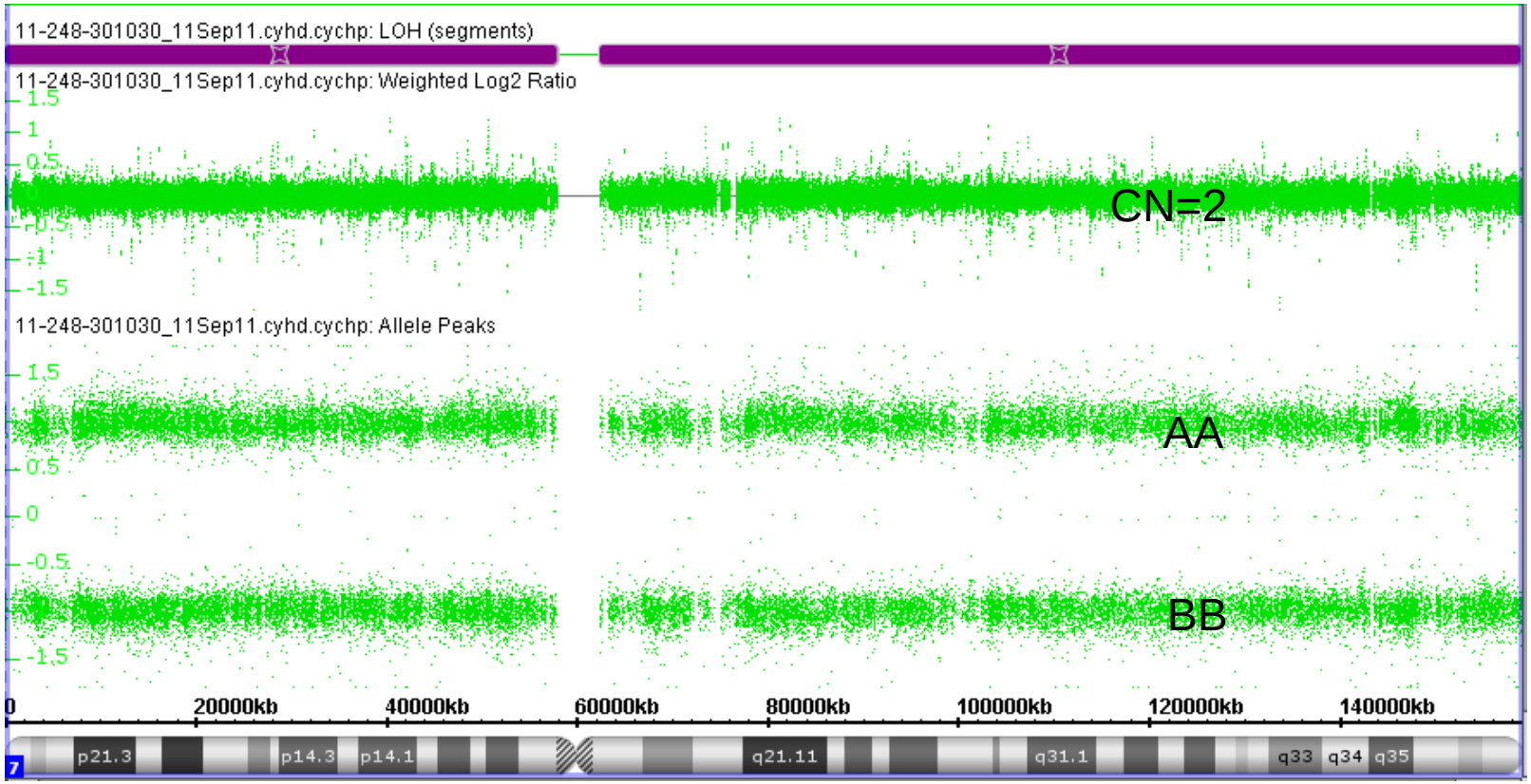
http://ccs.miami.edu/cgi-bin/ROH/ROH_analysis_tool.cgi

A clinical evaluation tool for SNP arrays, especially for autosomal recessive conditions in offspring of consanguineous parents.
Wierenga KJ, Jiang Z, Yang AC, Mulvihill JJ, Tsinoremas NF.
Genet Med. 2012 Oct 25

Chromo-some	Approximate Linear Position	# of genes[a]	# of genes[b]	# of genes[c]	# of genes[d]
2	171-199 Mb	12	5	1	0
2	216 - 221 Mb	6	1	2	0
3	3 - 7 Mb	2	0	1	0
3	153 - 171 Mb	4	1	0	0
6	109 - 118 Mb	3	0	0	0
7	144 - 148 Mb	0	0	0	0
7	151 - 155 Mb	0	0	0	0
8	60 - 63 Mb	1	0	0	0
9	14 - 27 Mb	0	0	0	0
12	99 - 113 Mb	10	3	3	0
12	113 - 130 Mb	6	4	2	0
14	76 - 89 Mb	3	1	2	1[e]
15	59 - 65 Mb	2	0	1	0
16	57 - 64.5 Mb	0	0	0	0
16	64.7 - 77 Mb	8	1	1	0
18	7 - 15 Mb	2	1	1	0
18	17 - 10 Mb	2	1	1	0

a- Number of genes with autosomal recessive inheritance within this LCSH
b- Number of genes with autosomal recessive inheritance that, when mutated, may be characterized by hypotonia within this LCSH
c- Number of genes with autosomal recessive inheritance that, when mutated, may be characterized by developmental delay within this LCSH
d- Number of genes with autosomal recessive inheritance that, when mutated, may be characterized by obesity within this LCSH
e- *TTC8/BBS8* Associated with Bardet-Biedl syndrome

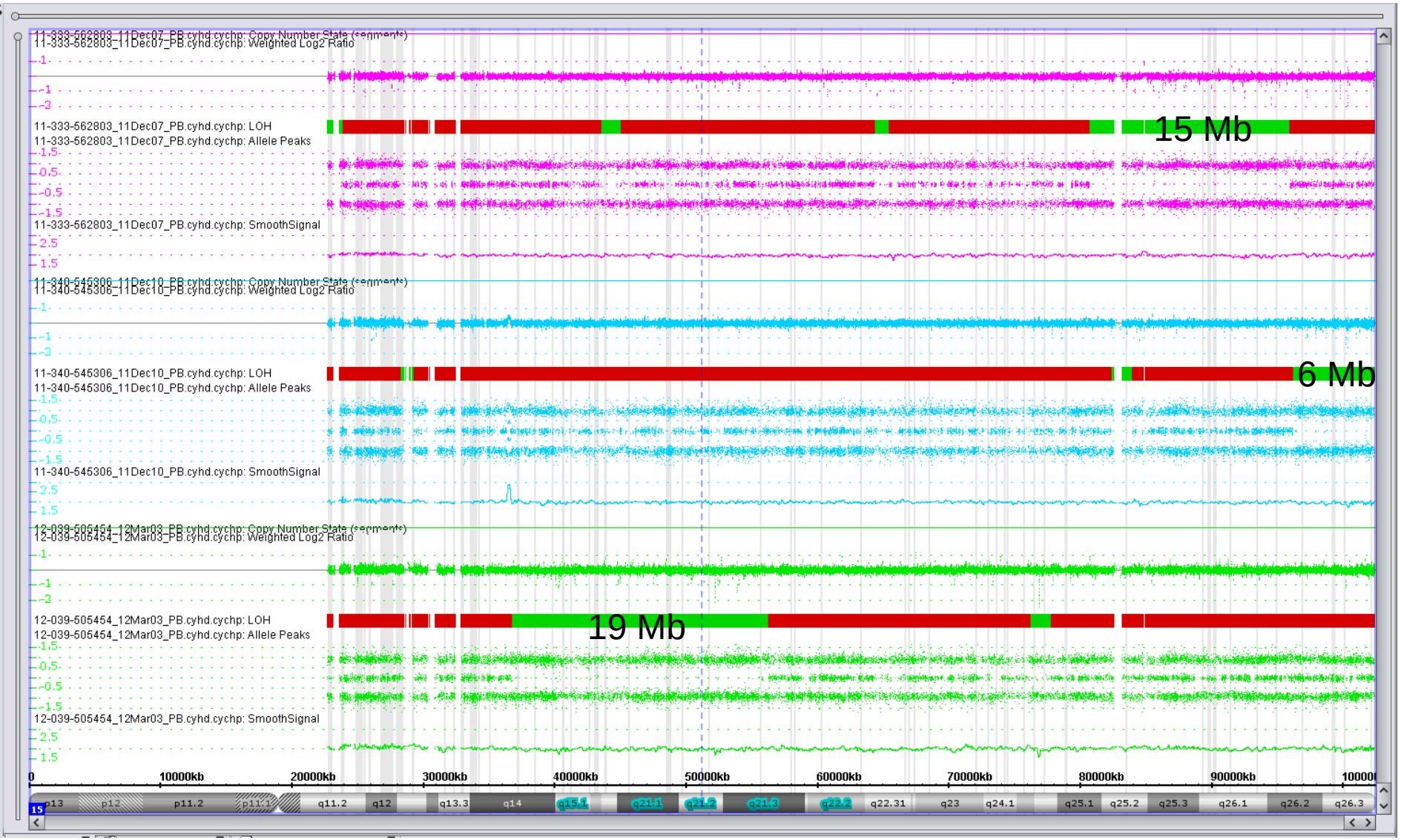
Microarray easily detects whole chromosome isodisomy



3 m.o male. Failure to thrive
Finding consistent with uniparental isodisomy of chromosome 7.

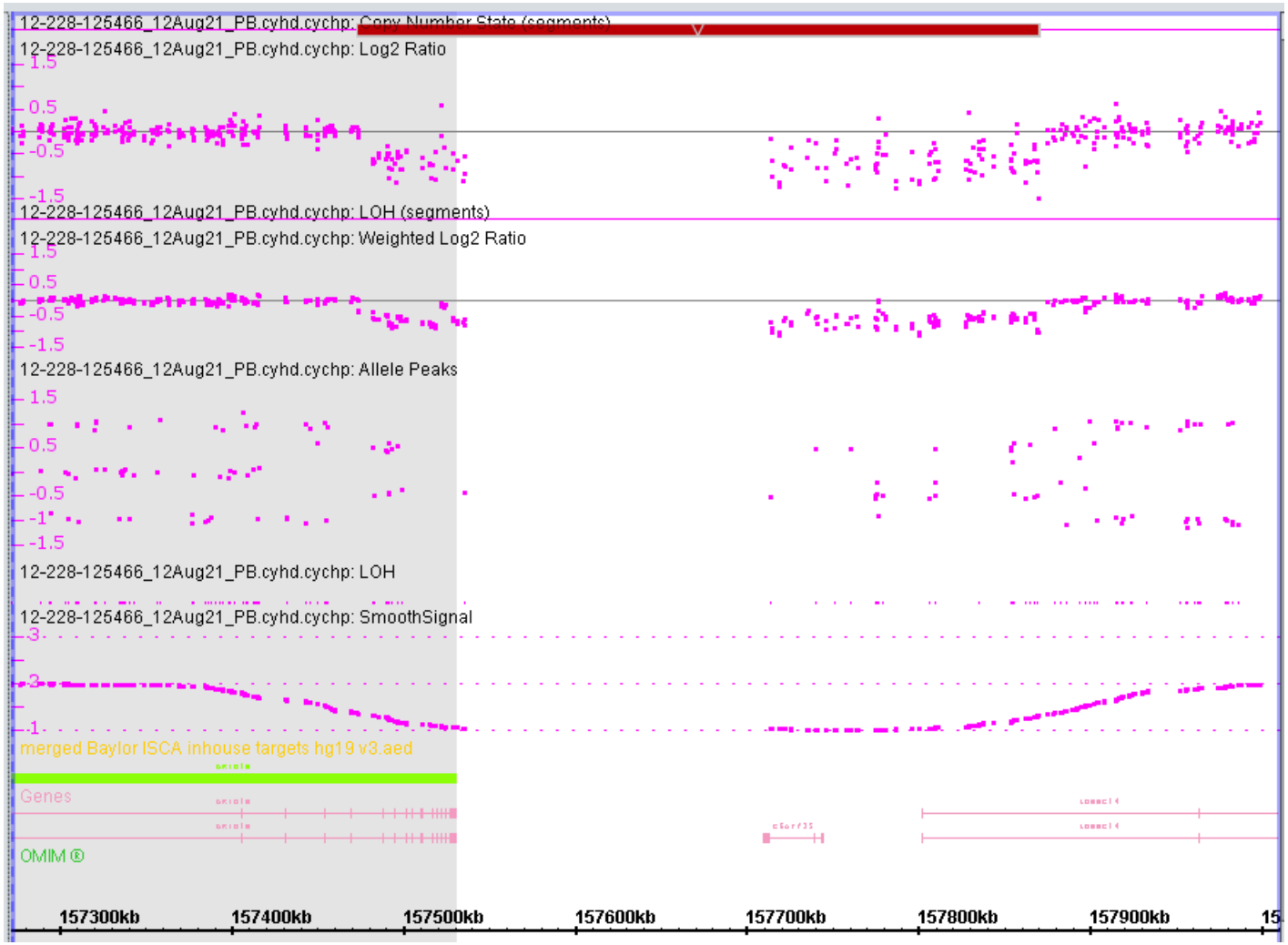
Maternal UPD7 is associated with Russell-Silver syndrome; whereas paternal UPD7 has not been associated with a specific clinical consequence. Additionally, recessive disorders such as cystic fibrosis mapping to chromosome 7 should be considered

For hetero UPD, the AOH can be anywhere on chromosome, or absent

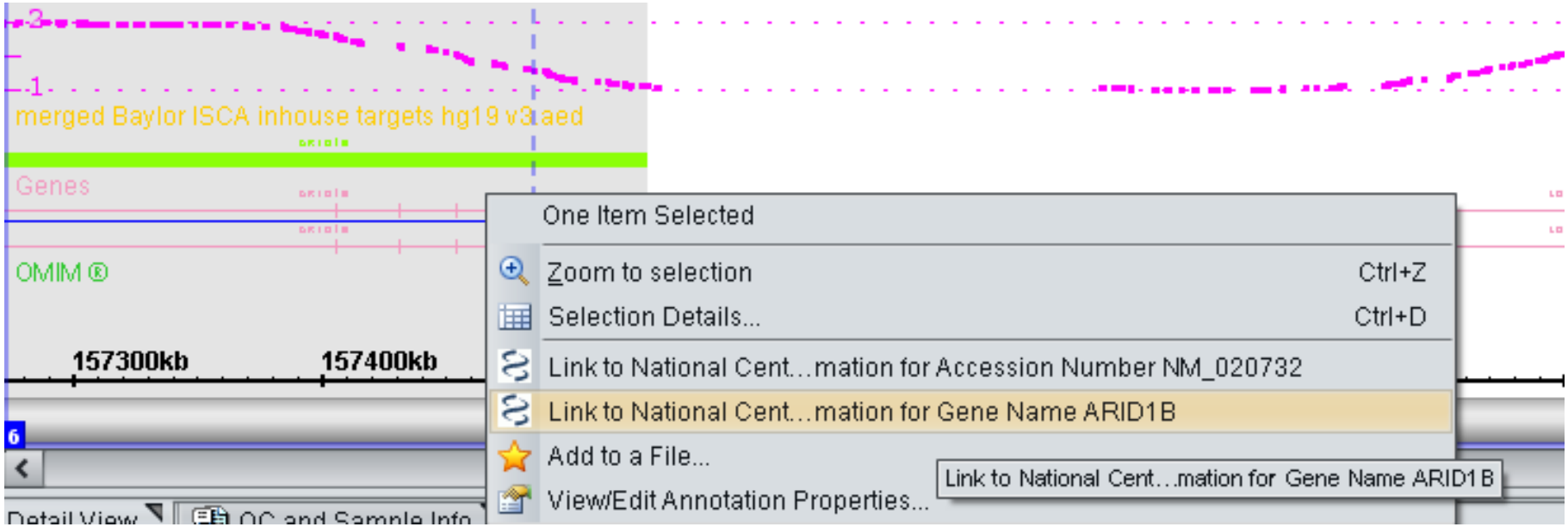


All three cases were confirmed UPD 15 by methylation – Prader Willi

Today's variant of unknown significance may later be more easily classified



Link out to most recent literature important



Related articles in PubMed

1. Mutations in SWI/SNF chromatin remodeling complex gene ARID1B cause Coffin-Siris syndrome. Santen GW, *et al*. Nat Genet, 2012 Mar 18. PMID 22426309.
2. Haploinsufficiency of ARID1B, a member of the SWI/SNF-a chromatin-remodeling complex, is a frequent cause of intellectual disability. Hoyer J, *et al*. Am J Hum Genet, 2012 Mar 9. PMID 22405089.

Very recent identification of haploinsufficiency

Molecular Genetics

Hoyer et al. (2012) performed Sanger sequencing of candidate genes, including ARID1B, in a region on chromosome 6q25 that was deleted in a patient with mental retardation (see 612863). A total of 8 mutations in the ARID1B gene (see, e.g., 614556.0001-614556.0005) were found in 8 (0.9%) of 887 individuals with mental retardation. All mutations were in the heterozygous state, occurred de novo, and resulted in haploinsufficiency of the ARID1B gene. Given the known function of ARID1B, the findings indicated that chromatin-remodeling defects are an important contributor to neurodevelopmental disorders.

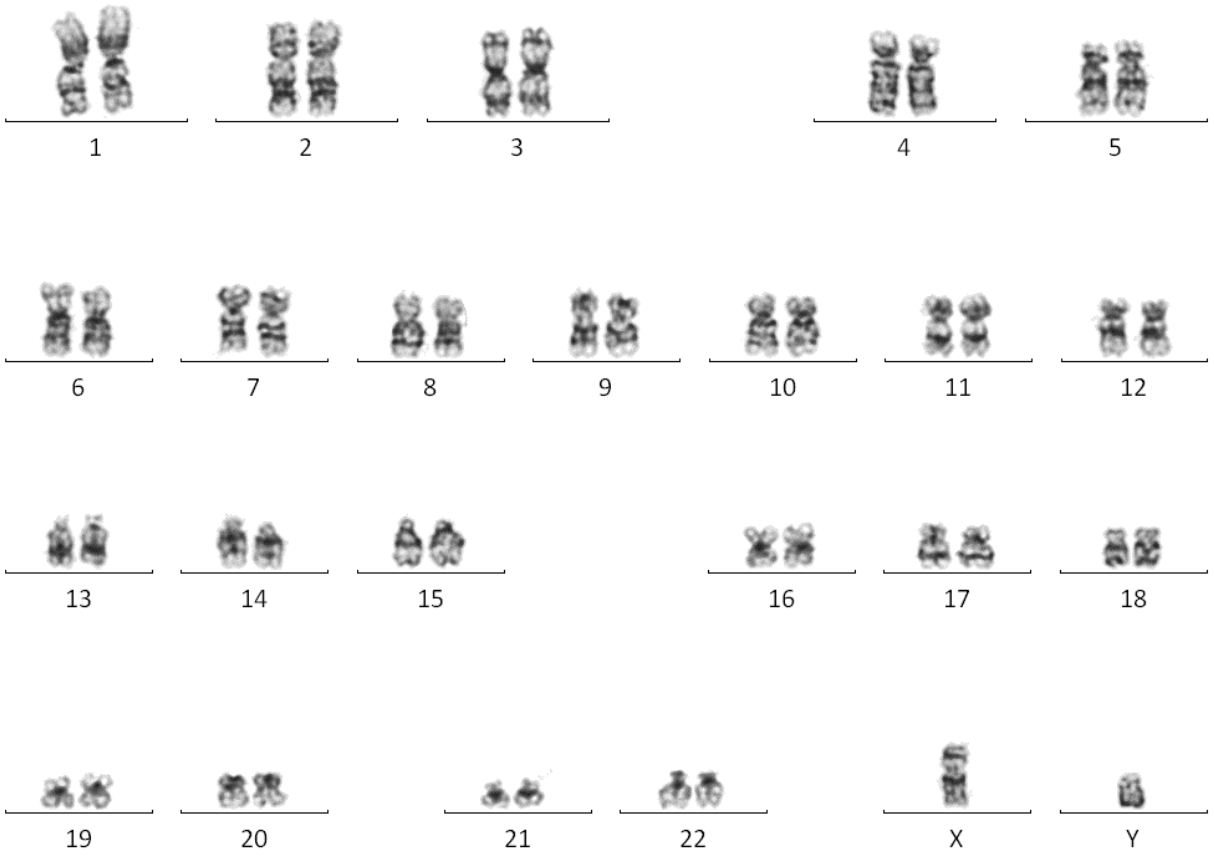
In 5 patients with multiple congenital anomalies and mental retardation, Tsurusaki et al. (2012) identified 4 nonsense or frameshift mutations in ARID1B (e.g., 614556.0006, 614556.0007), which encodes a subunit of the SWI/SNF complex. Three of these mutations occurred de novo. One of the patients carried a microdeletion involving ARID1B. In a total of 20 affected individuals with a similar constellation of clinical features, Tsurusaki et al. (2012) identified germline mutations in one of 6 SWI/SNF subunit genes.

By exome sequencing, Santen et al. (2012) identified 3 de novo truncating mutations in the ARID1B gene (614556.0008-614556.0010) in individuals with syndromic mental retardation. Array-based copy number variation analysis in 2,000 individuals with intellectual disability revealed an additional 3 subjects with a deletion affecting ARID1B.

Contributors:	Ada Hamosh - updated : 4/30/2012
Creation Date:	Cassandra L. Kniffin : 3/29/2012
▸ Edit History:	alopez : 05/02/2012

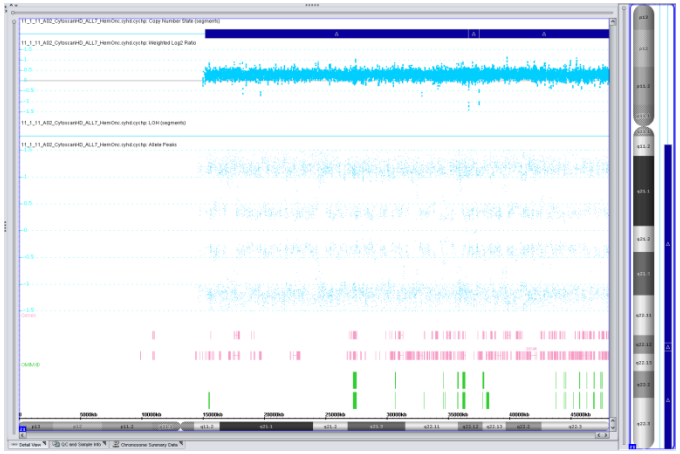
Case also supports value of reporting variants of unknown significance: What if the array had been ordered in 2011 – should this deletion have NOT been identified or reported?????

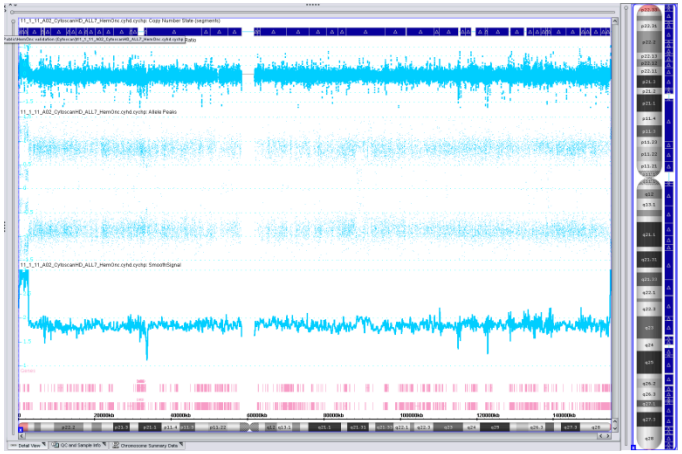
Overcome the preferential growth of nonmalignant cells



Normal karyotype in all metaphase cells from a patient with acute lymphoblastic leukemia

Microarray shows +21, +X and a small deletion of IKZF1





High resolution analysis shows IKZF1 deletion

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Deletion of *IKZF1* and Prognosis in Acute Lymphoblastic Leukemia

CONCLUSIONS

Genetic alteration of *IKZF1* is associated with a very poor outcome in B-cell–progenitor ALL.

N ENGL J MED 360;5 NEJM.ORG JANUARY 29, 2009

Leukemia (2010) 24, 1258–1264

www.nature.com/leu

ORIGINAL ARTICLE

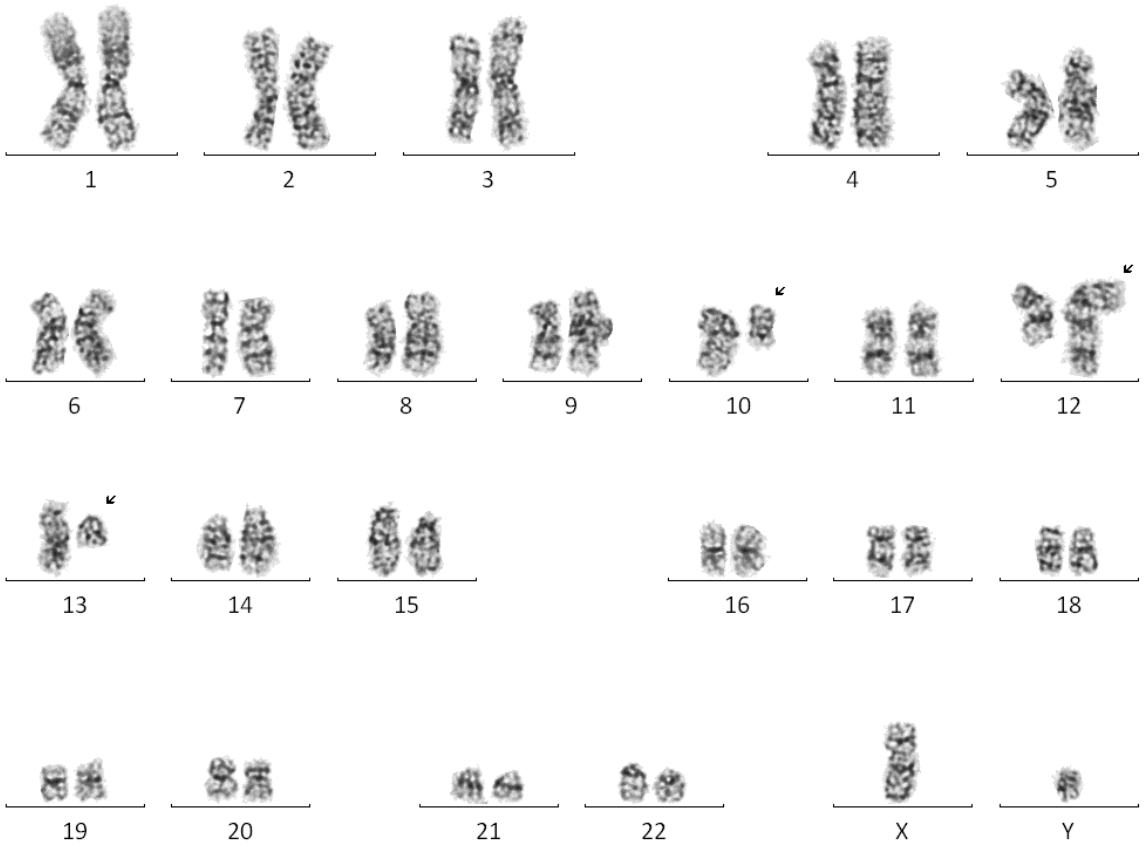
IKZF1 deletions predict relapse in uniformly treated pediatric precursor B-ALL

RP Kuiper[1,6], E Waanders[1,6], VHJ van der Velden[2], SV van Reijmersdal[1], R Venkatachalam[1], B Scheijen[3], E Sonneveld[4], JJM van Dongen[2], AJP Veerman[4,5], FN van Leeuwen[3], A Geurts van Kessel[1] and PM Hoogerbrugge[3,4]

[1]Department of Human Genetics, Radboud University Nijmegen Medical Centre and Nijmegen Centre for Molecular Life Sciences, Nijmegen, The Netherlands; [2]Department of Immunology, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands; [3]Department of Pediatric Hemato-Oncology, Radboud University Nijmegen Medical Centre and Nijmegen Centre for Molecular Life Sciences, Nijmegen, The Netherlands; [4]Dutch Childhood Oncology Group, The Hague, The Netherlands and [5]Department of Paediatric Oncology, VU University Medical Centre, Amsterdam, The Netherlands

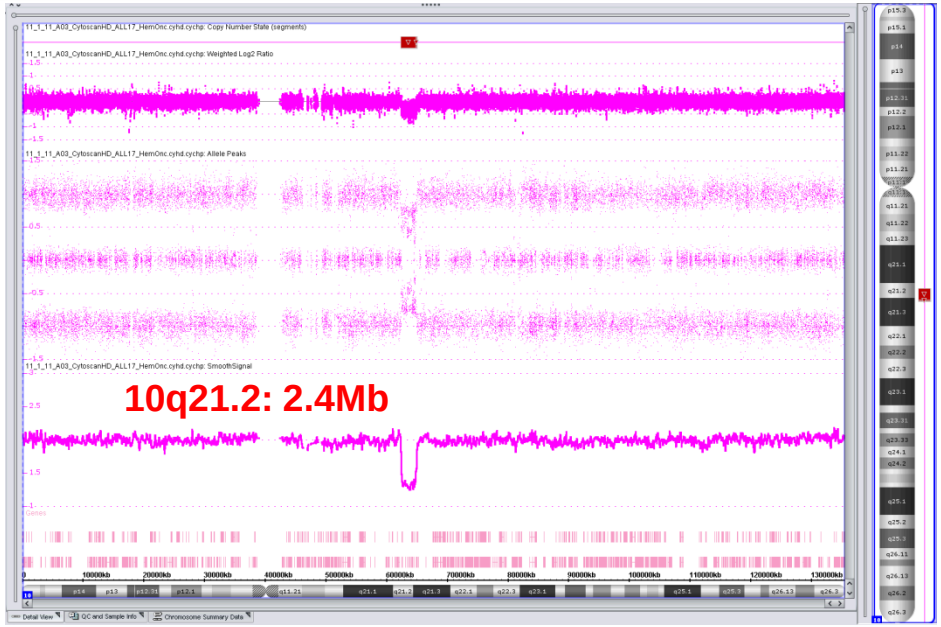
Better breakpoint characterization

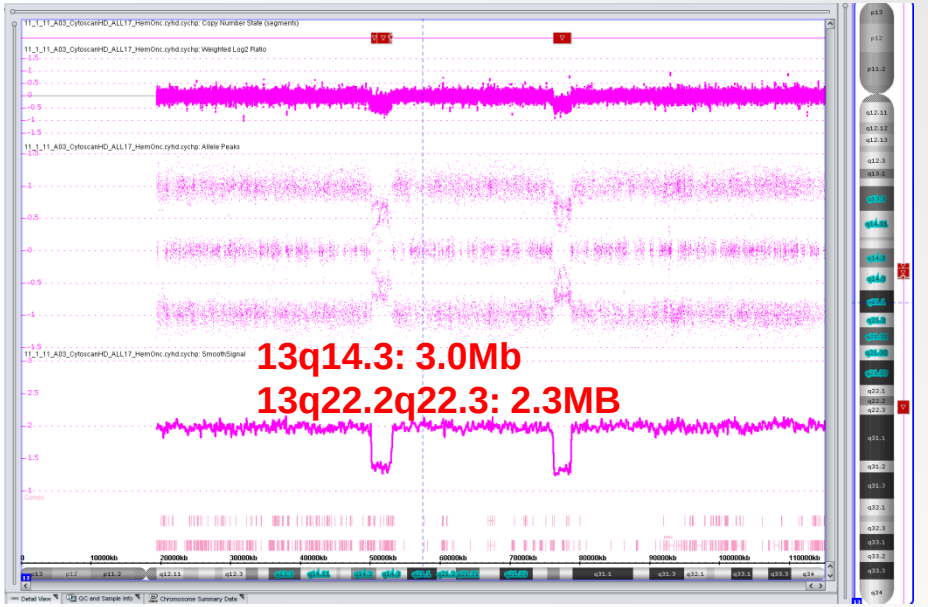
ALL with apparently balanced rearrangements

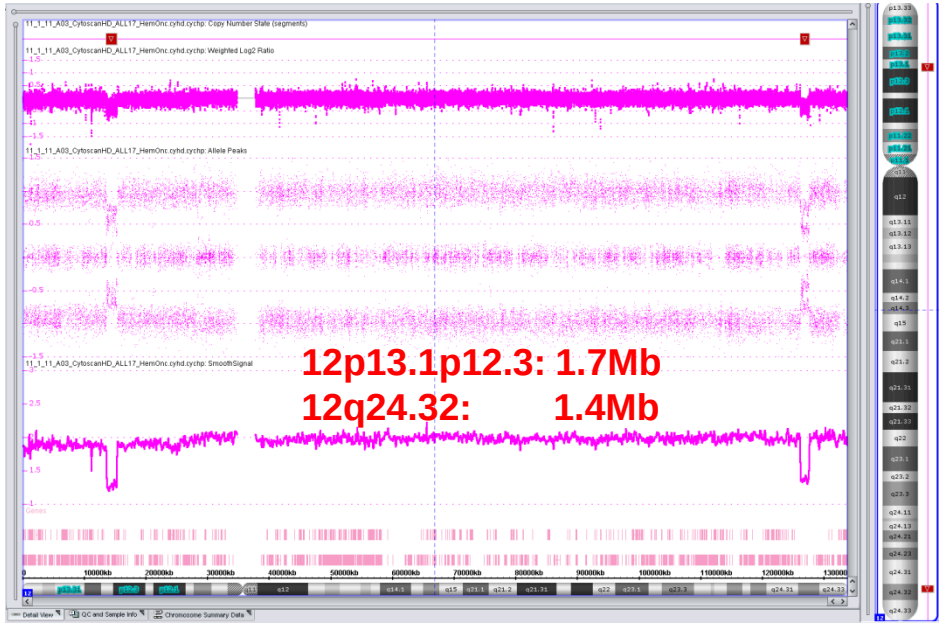


46,XY,der(10)t(10;12)(q22.1;p13),der(12)t(10;12)(q22.1;p13)t(12;13)(q24.3;q14),der(13)t(12;13)(q24.3;q14)[5]/46,XY[15]

With Cytoscan HD, multiple deletions were detected around the breakpoints

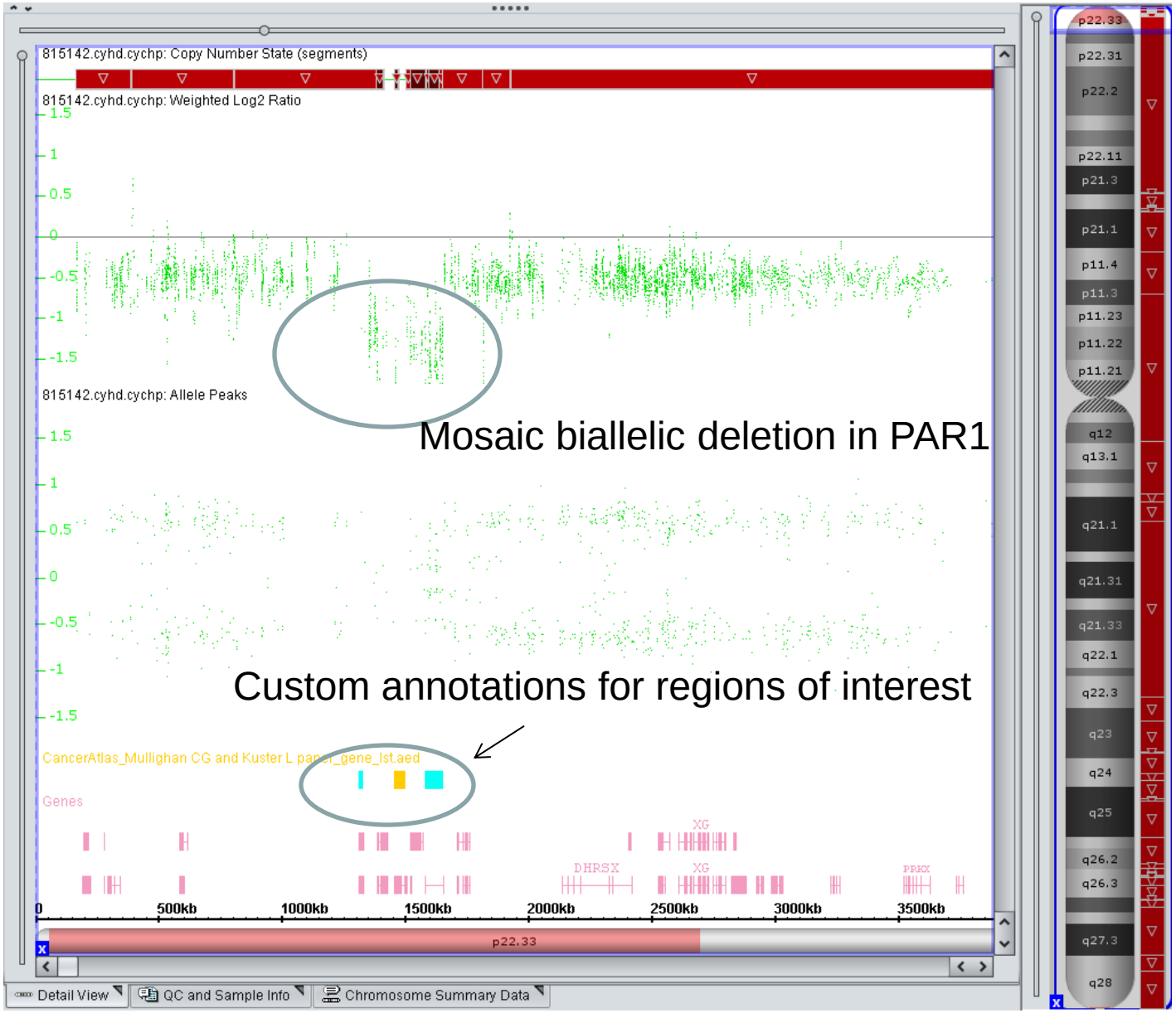






Can evaluate genes in intervals for known roles as either fusion or deletion products in ALL

Some deletions may delete important genes, others may result in fusions



CRLF2 overexpression

- Involved in B-cell precursor proliferation and survival

- 3 alterations identified in ALL

▫*IGH@/CRLF2* translocation

▫*P2RY8-CRLF2* fusion

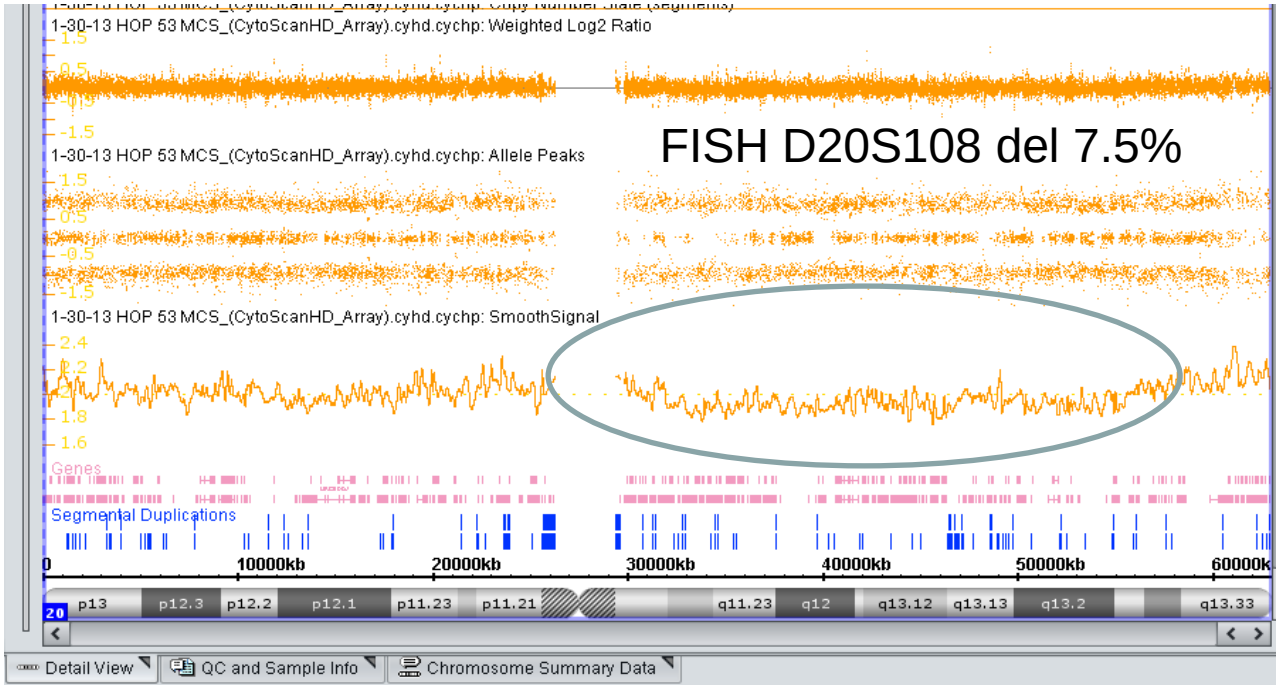
▫Phe232Cys activating mutation

Frequently associated with JAK2 mutations

Inferior outcome

J Clin Oncol. 2012 Sep 1;30(25):3100-8

How low can we go? Likely dependent on percentage of clone and size of aberration - smaller (bp wise) alterations likely missed at lower percentages



Whole genome more informative than targeted FISH

No chromosome analysis, ALL FISH Panel only

ABNORMAL FISH RESULTS

nuc ish 8q24(MYCx3)[112/200]

9q34(ABL1x3)[124/200]

NORMAL FISH RESULTS

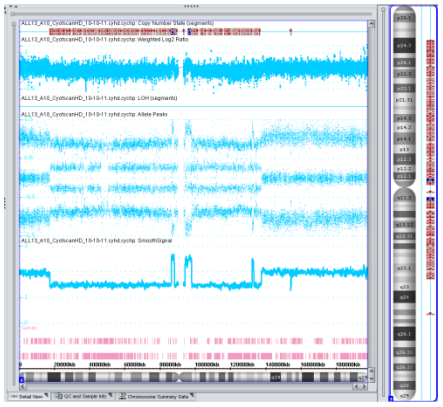
nuc ish 11q23(MLLx2)

14q32(IGH@x2)

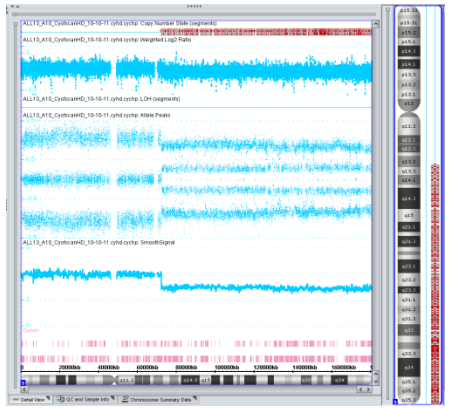
19p13.3(TCF3x2)

22q11.2(BCRx2)

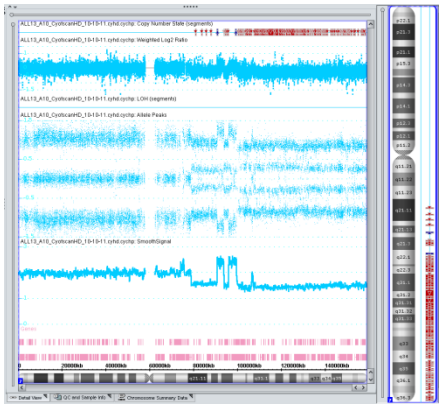
Whole genome array results suggestive of diagnosis of MDS/MPD.



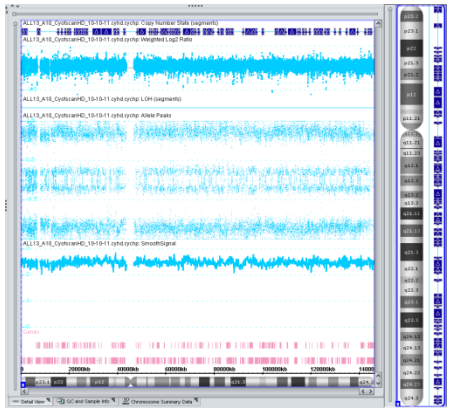
Chr 3: complex loss/gain



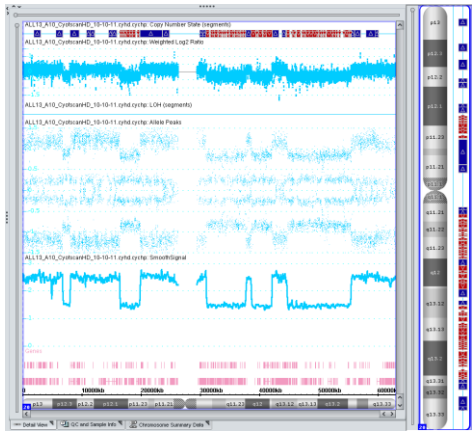
Chr 5: deletion of 5q



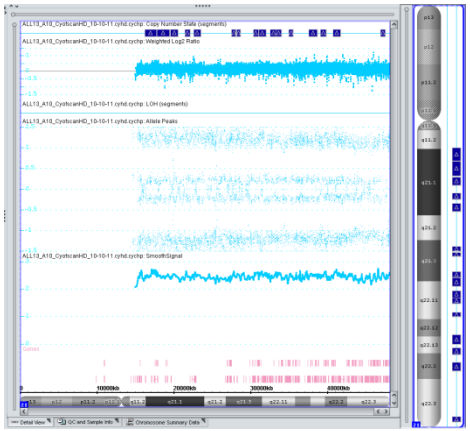
Chr 7: complex 7q loss/gain



Chr 8: trisomy



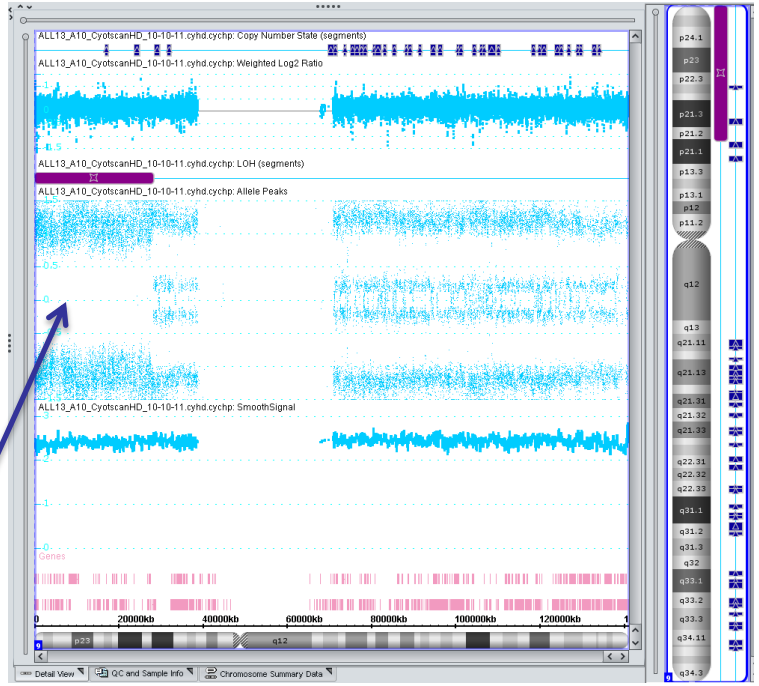
Chr 20: complex loss/gain



Chr 21: trisomy

Homozygous JAK2 (9p24.1) mutation associated with aLOH 9p observed in ~37% of MPDs.

Klampfl T et al., Blood, 2011.



Chr 9: trisomy plus LOH of 9p

ORIGINAL ARTICLE

Chromosomal Microarray versus Karyotyping for Prenatal Diagnosis

Ronald J. Wapner, M.D., Christa Lese Martin, Ph.D., Brynn Levy, M.Sc.(Med.), Ph.D., Blake C. Ballif, Ph.D., Christine M. Eng, M.D., Julia M. Zachary, Melissa Savage, M.S., Lawrence D. Platt, M.D., Daniel Saltzman, M.D., William A. Grobman, M.D., M.B.A., Susan Klugman, M.D., Thomas Scholl, Ph.D., Joe Leigh Simpson, M.D., Kimberly McCall, B.S., Vimla S. Aggarwal, M.B., B.S., Brian Bunke, B.S., Odelia Nahum, M.Sc., Ankita Patel, Ph.D., Allen N. Lamb, Ph.D., Elizabeth A. Thom, Ph.D., Arthur L. Beaudet, M.D., David H. Ledbetter, Ph.D., Lisa G. Shaffer, Ph.D., and Laird Jackson, M.D.

N Engl J Med 2012; 367:2175-2184 | December 6, 2012 | DOI: 10.1056/NEJMoa1203382

Primary Aim:

Evaluate The Performance Of Chromosomal Microarray Analysis (CMA) As An Independent Clinical Method For Prenatal Cytogenetic Diagnosis:

- Determine The Accuracy Of CMA In The Detection Of The Common Autosomal And Sex Chromosomal Aneuploidies
- Determine The Ability of CMA To Diagnose Less Common, But Clinically Significant, Cytogenetic Deletions and Duplications Currently Not Detected By Karyotype
- Evaluate The Utility Of CMA In Specific Clinical Scenarios Such As Ultrasound Detection Of Congenital Anomalies

CMA Result When Karyotype Shows Non-Mosaic Common Autosomal and Sex Chromosome Aneuploidy

N = 4282

Common Aneuploidy = 374 (8.7%)

Karyotype	N	N (% correct by CMA)	Mosaic Array
Trisomy 21	188	188 (100)	3
Trisomy 18	93	93 (100)	2
Trisomy 13	36	36 (100)	0
45, X	39	39 (100)	3
Other Sex Aneuploidy	18	18 (100)	0

Accuracy of CMA in Identifying Common Aneuploidy

100% (CI: 99-100)

CMA Result When Karyotype Shows "Other" Chromosome Abnormalities

Karyotype	N	N (% correct by CMA)	Mosaic Array
Balanced Structural Rearrangement	40	0 (0)	-
Unbalanced Structural Rearrangement	22	21 (100)	1
Marker	3	2 (66.7)*	0
Triploidy	17	0 (0.0%) **	-

- Missed Marker Consisted Of Only Heterochromatin On Further Evaluation

** 15/17 (88.2%) Cases Identified By Maternal Cell Contamination Studies, Array did not utilize SNP data

Clinically Relevant Information Seen by CMA and Reported to Patients in Cases with **Normal Karyotype**

By Indications for Testing

Indication	Total Clinically Relevant	95% CI
AMA N=1966	34 (1.7%)	1.2 – 2.4
Positive Screen N=729	12 (1.6%)	0.9 – 2.9
US Anomaly N=755	45 (6.0%)	4.5 – 7.9

Utility of Genomic Microarray for Stillbirths

N Engl J Med. 2012 Dec 6;367(23):2185-93. doi: 10.1056/NEJMoa1201569.

Karyotype versus microarray testing for genetic abnormalities after stillbirth.

Reddy UM, Page GP, Saade GR, Silver RM, Thorsten VR, Parker CB, Pinar H, Willinger M, Stoll BJ, Heim-Hall J, Varner MW, Goldenberg RL, Bukowski R, Wapner RJ, Drews-Botsch CD, O'Brien BM, Dudley DJ, Levy B; NICHD Stillbirth Collaborative Research Network.

⊕ **Collaborators (40)**

Pregnancy and Perinatology Branch, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health, Bethesda, MD 20892-7510, USA.

Ability to obtain results:

karyotype: 70.5%

microarray: 87.4%

Detection of pathogenic abnormality:

karyotype: 5.8%

microarray: 8.3%

Relative increase in diagnosis of genetic abnormality:

all stillbirths: 41.9%

antepartum stillbirths: 34.5%

stillbirths with anomalies: 53.8%

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society for Maternal-Fetal Medicine

COMMITTEE OPINION

Number 581 • December 2013

(Replaces No. 446, November 2009)
(See also Practice Bulletin No. 88)

The American College of Obstetricians and Gynecologists Committee on Genetics
Society for Maternal-Fetal Medicine

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

The Use of Chromosomal Microarray Analysis in Prenatal Diagnosis

- Microarray recommended in cases undergoing invasive testing with at least one ultrasound abnormality - can replace karyotype
- Not restricted to advanced maternal age
- Microarray recommended in cases of IUFD or stillbirths

Conclusions

- Microarray provides a more detailed and less subjective analysis of abnormal DNA copy number compared to standard chromosome analysis, and detect AOH
- AOH detection can allow for homozygosity mapping and suspicion of UPD in constitutional – additional testing for follow-up often required
- aLOH in cancer is usually selecting mutation in region to result in 2 copies of mutation
- Most microarray platforms do not detect balanced rearrangements
  - Clinically relevant in ~1% ID/MCA/autism
  - Very clinically relevant for adult with history of reproductive losses
  - Variably important in hematologic malignancies, can supplement with FISH and PCR according to indication

Conclusions

- For ID/MCA/autism, the detection rate for genetic etiology using microarray alone is ~15%
- For hematologic malignancies, detection rates improve over standard chromosomes ~20-40%
  - Approximately half of this gain is detection of clinically relevant aLOH
- For prenatal, detection rates improve over standard chromosomes in 6.0% with a structural anomaly and in 1.7% of those whose indications were advanced maternal age or positive screening results.
- For stillbirths, improved detection over standard chromosomes: from 5.8% (karyotype) to 8.3% (microarray) and increased ability to obtain results