Clinical Cytogenetic Testing: Applications in Constitutional and Oncology Settings

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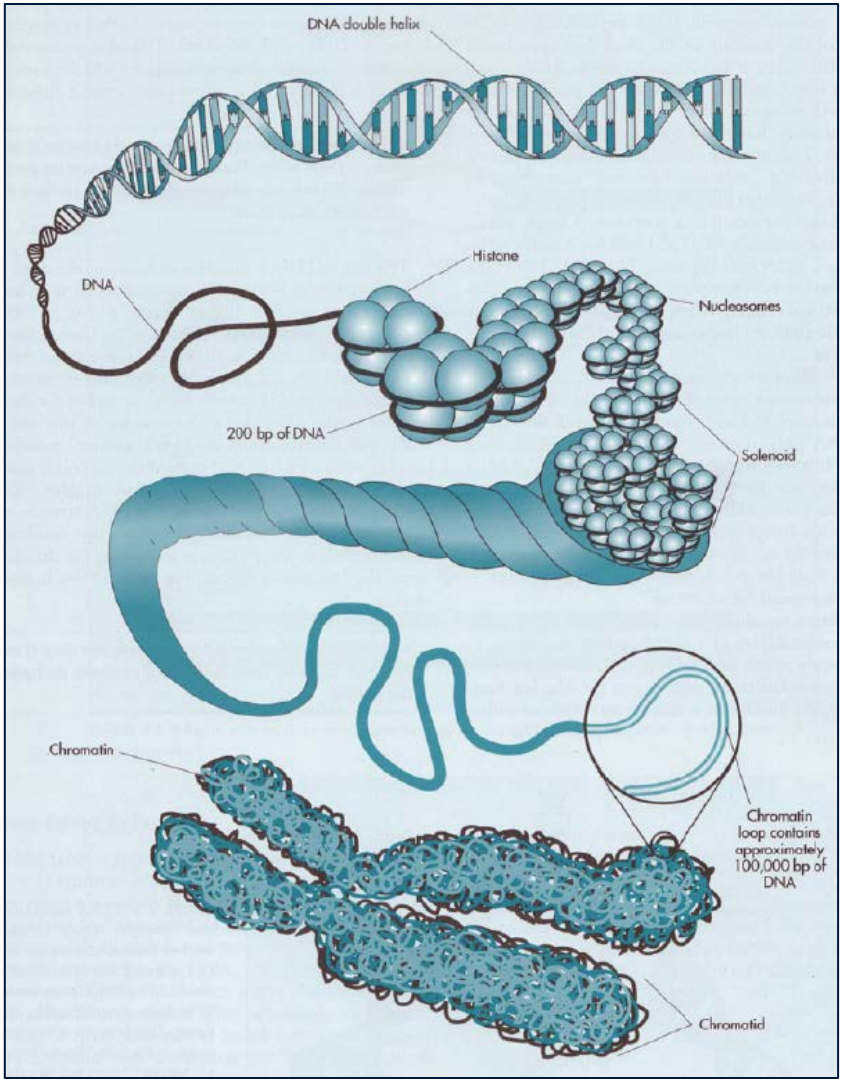
Learning Objectives

- List the areas of medicine that overlap with clinical cytogenetics and common indications for testing across these disciplines
- Explain the basic methodologies, technical capabilities and limitations of chromosome analysis, FISH and genomic microarray
- List common cytogenetic abnormalities encountered across different clinical contexts, including childhood developmental phenotypes, prenatal and perinatal diagnosis, pregnancy loss and in cancer

What is Cytogenetics?

- The study of chromosomes and genomic structure, function, and variation and their role in human disease and heredity
- Clinical cytogenetics overlaps with several areas of medicine: pathology, pediatrics, neurology, endocrinology, psychiatry, obstetrics and gynecology, hematologic oncology, other areas of medical oncology



Gersen and Keagle, Principles of Cytogenetics, 3rd Ed 2013
reprinted from Jorde et al. Medical Genetics 3rd Ed 2006

Constitutional versus cancer cytogenetics

- Constitutional cytogenetics: diagnosis of heritable genetic abnormalities in children, adults, pregnancy, and fetal loss
  - Abnormalities may be inherited or *de novo*
- Cancer cytogenetics: detection of acquired or somatic (versus germline/constitutional) genetic abnormalities for the diagnosis, prognosis, therapy, and/or monitoring of many types of cancer (especially leukemia and lymphoma)

Indications for Constitutional Cytogenetic Testing

- Postnatal, childhood growth and development
  - Perinatal: Birth defects, malformations, dysmorphisms, ambiguous genitalia
  - Growth: failure to thrive, growth delay, short stature
  - Developmental delay (fine and gross motor, speech)
  - Cognitive: intellectual disability, learning disability
  - Neurological: hypotonia, seizures, ataxia
  - Behavioral: autism, OCD, psychiatric illness

Tissues studied: Peripheral blood, buccal swab, skin biopsy

Indications for Constitutional Cytogenetic Testing

- Adolescent, adult sexual development and fertility
  - Amenorrhea, primary or secondary ovarian failure, premature menopause
  - Azoospermia, oligospermia, hypogonadism
  - History of infertility or spontaneous abortions
  - Birth of a child with a chromosomal abnormality

Tissues studied: Peripheral blood

Indications for Constitutional Cytogenetic Testing

- Prenatal
  - Abnormal maternal serum screening (first or second trimester)
  - Abnormal cell-free DNA testing (cfDNA), non-invasive prenatal testing (NIPT)/screening (NIPS)
  - Abnormal ultrasound findings: cystic hygromas/hydrops, cardiac defects, other malformations, IUGR, etc.
  - Advanced maternal age (AMA), generally ≥ 35 yrs
  - Parental or familial chromosome abnormality
- Fetal or neonatal demise (products of conception, POC)

Tissues studied: Amniotic fluid, chorionic villus sampling, fetal tissues

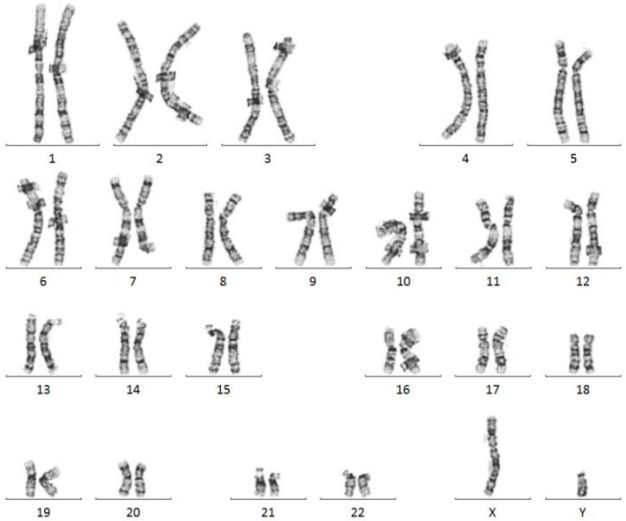
Indications for Cancer Cytogenetic Testing

- Hematologic oncology
  - Myeloid: Acute myeloid leukemia (AML), Chronic myeloid leukemia (CML), Myelodysplastic syndromes (MDS), Myeloproliferative neoplasms (MPN)
  - Lymphoid: Acute lymphoblastic leukemia/lymphoma (ALL), Chronic lymphocytic leukemia (CLL), Non-Hodgkin lymphoma (NHL), Plasma cell neoplasms (Multiple Myeloma, MM)
- Bone marrow transplant
- Other areas of oncology (solid tumors)

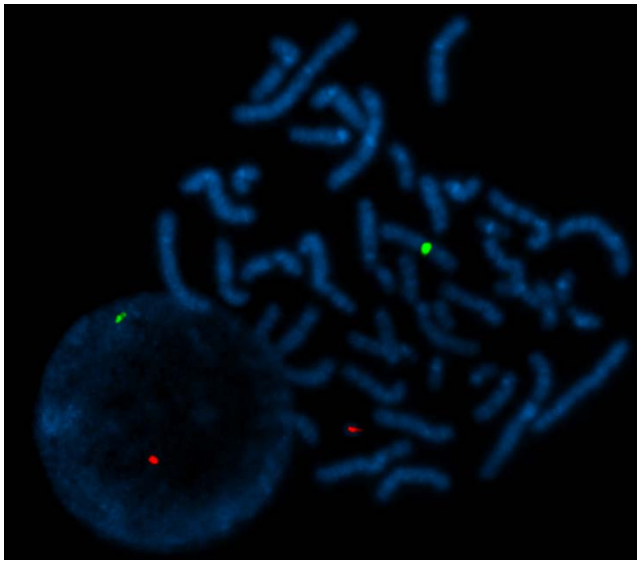
Tissues studied: bone marrow, peripheral blood, lymph nodes, solid tumor, pleural fluid, spinal fluid

Techniques for Cytogenetic Studies

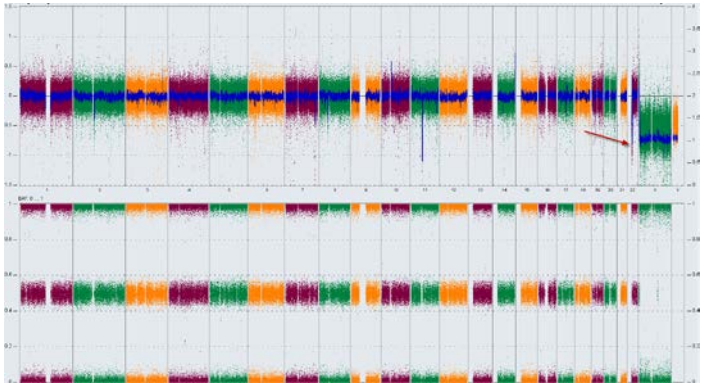
Chromosome analysis/karyotyping

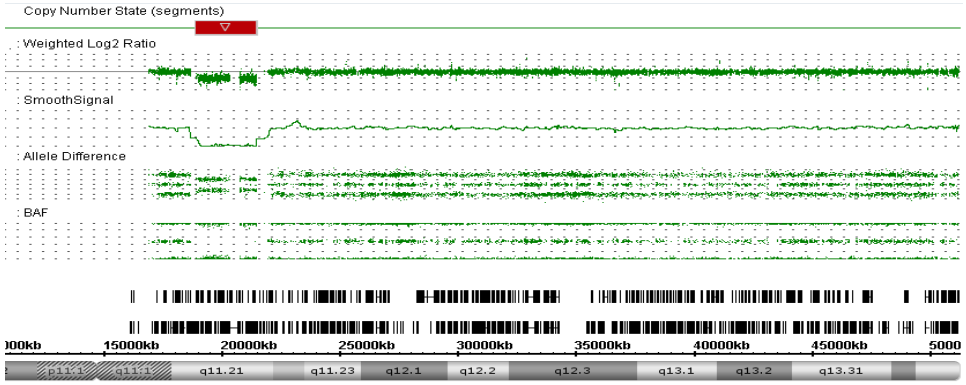


Fluorescence in situ hybridization (FISH)

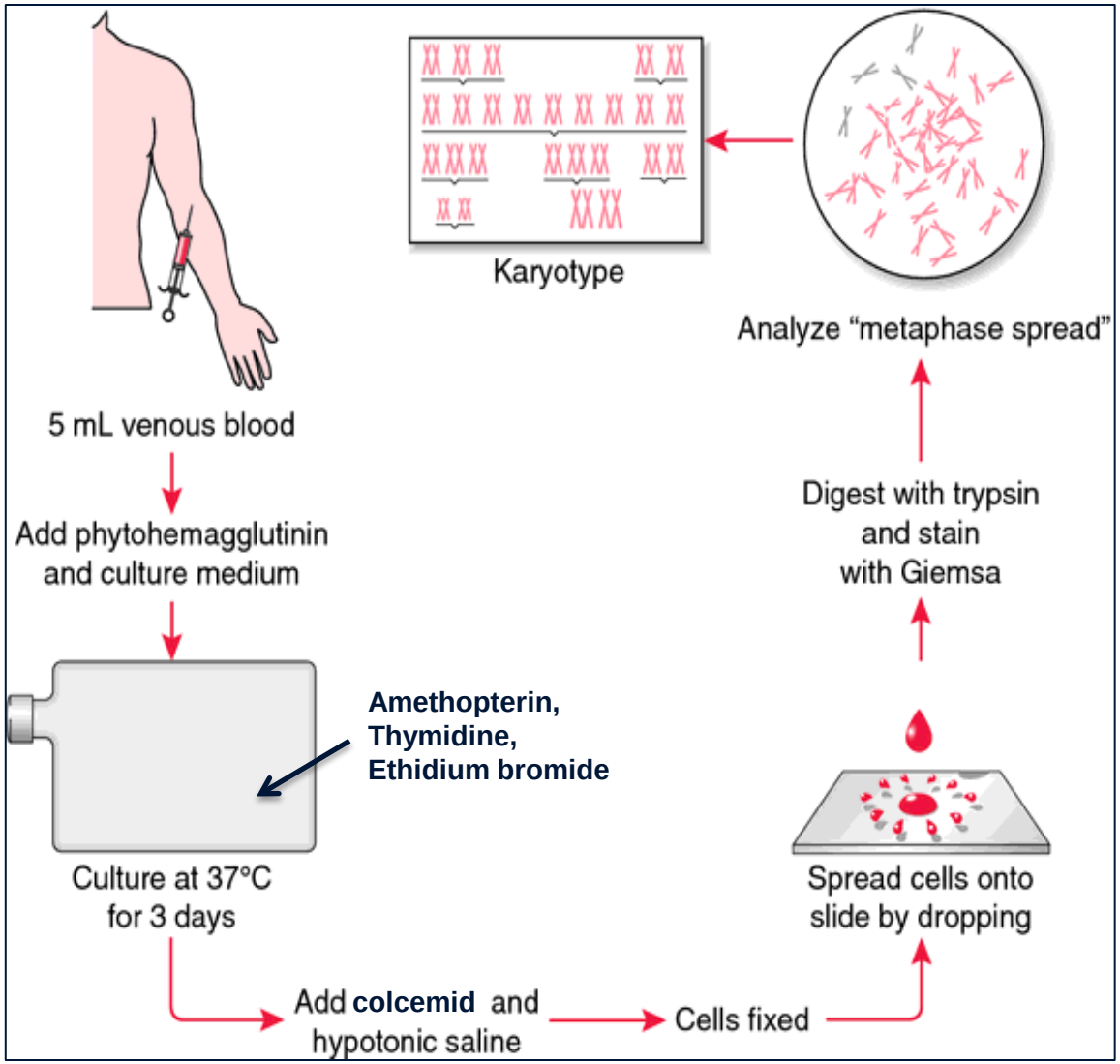


Genomic microarray analysis (GMA)





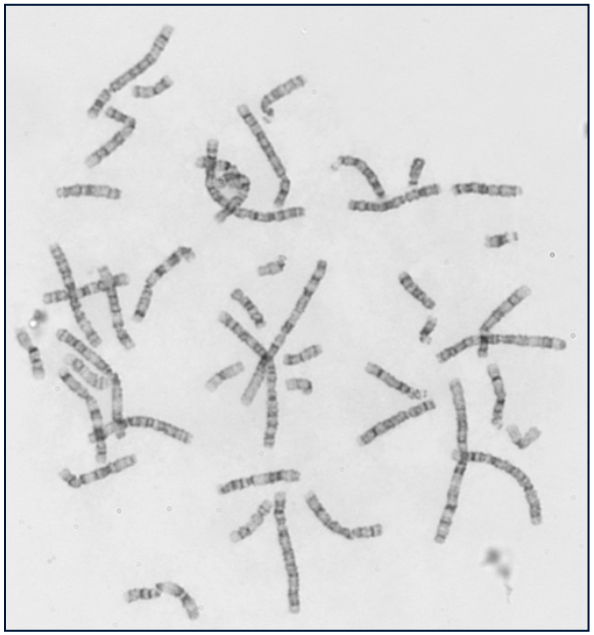
Preparation of metaphase chromosomes



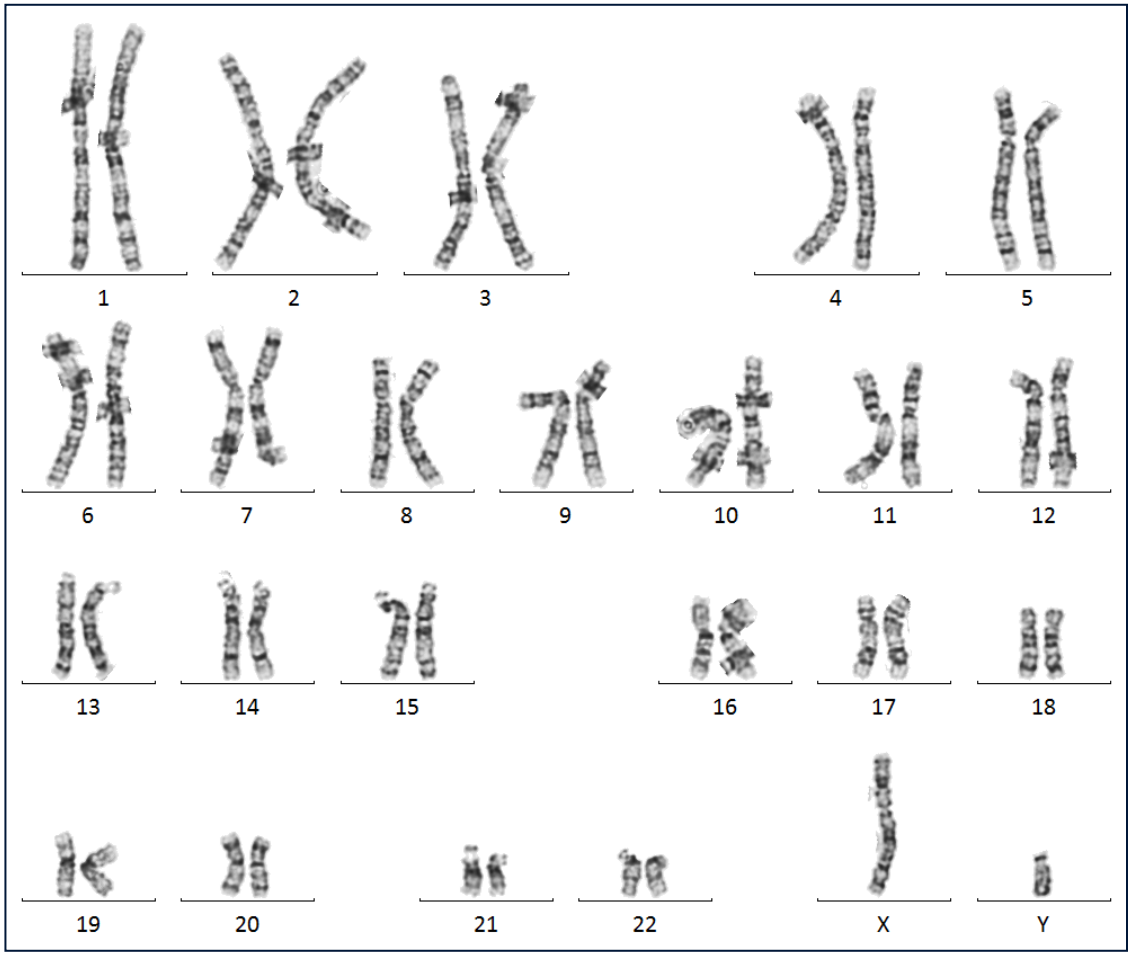
Modified from Preparation of a karyotype. From Mueller and Young, 2001

Karyotyping

Metaphase spread



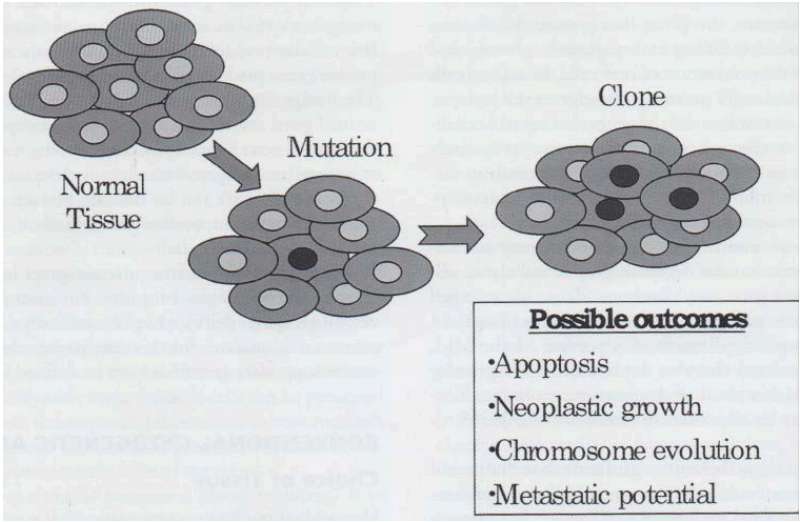
Karyogram



- Karyotype: 46,XY

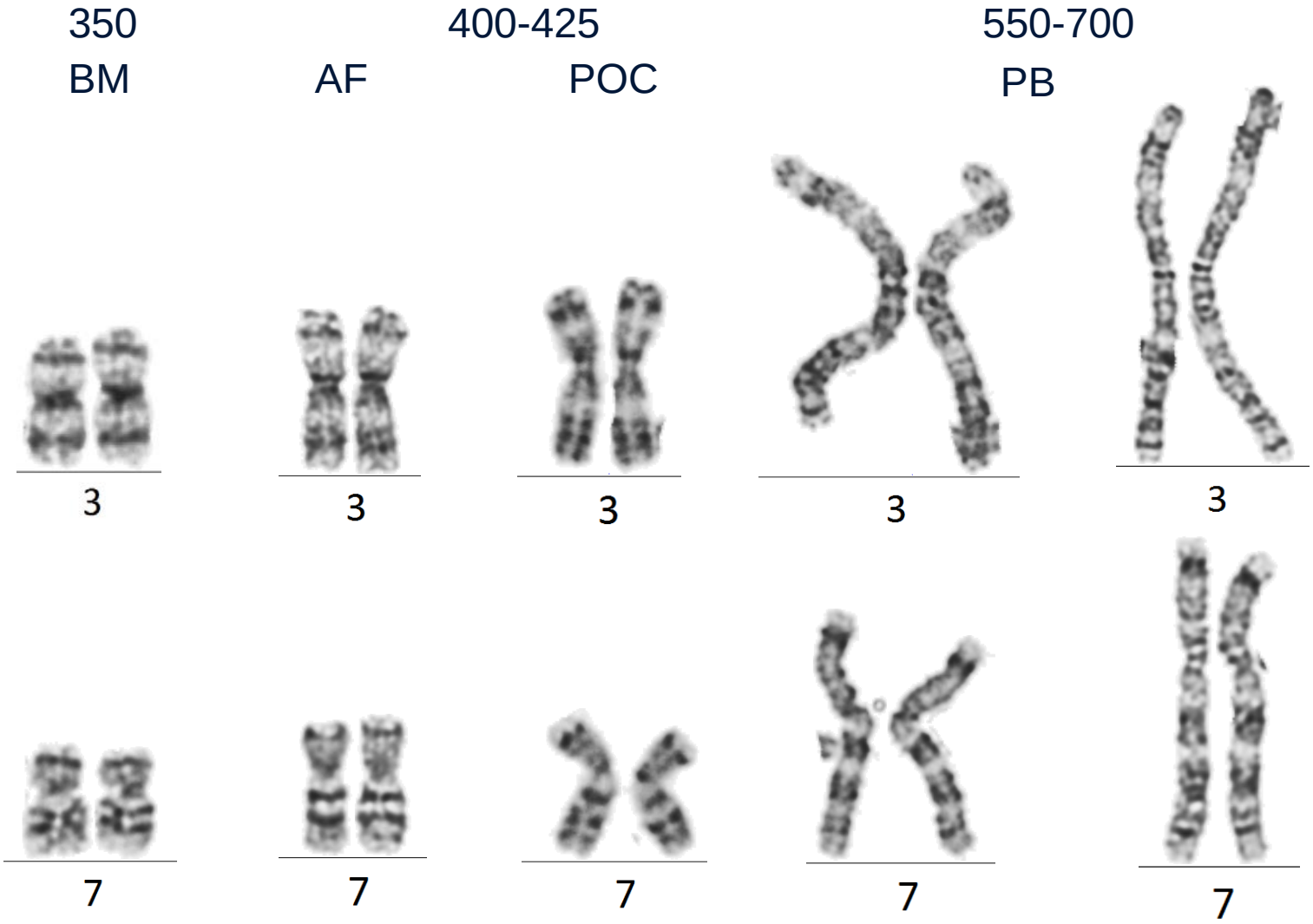
Overview of chromosome analysis

- Generally, 20 cells are analyzed from multiple cultures
- Definition of a clone:
  - At least two metaphase cells with the same extra chromosome or structural abnormality
  - At least three metaphase cells with the same chromosome loss



Dewald *et al*., Cytogenetic Studies in Neoplastic Hematologic Disorders 2nd Ed.

Differences in level of resolution by sample type



Pros and Cons of Chromosome Analysis

Advantages

- Genome-wide approach
- Detects both numerical and structural abnormalities
- Gold standard: well-established technology

Disadvantages

- Resolution is limited
- Requires culturing
  - Some tissues/cell types do not grow well in culture
  - Potential for *in vitro* artifacts
- Analysis is subjective

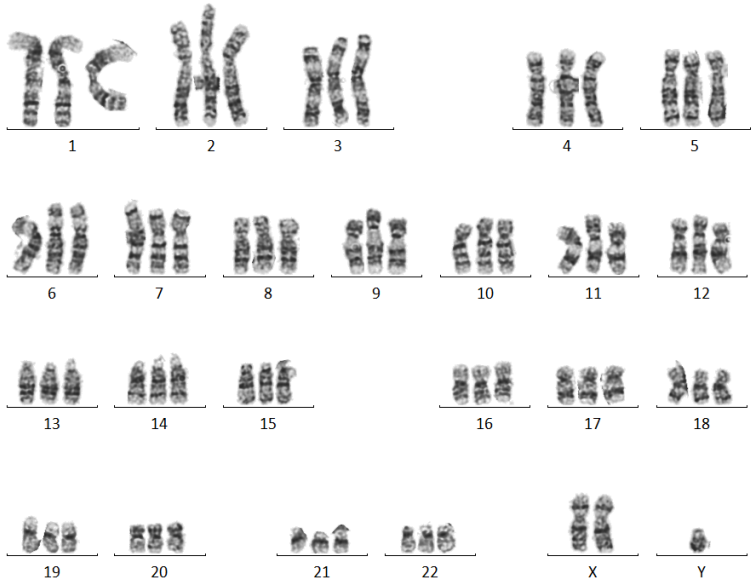
Common Constitutional Numerical Abnormalities

Aneuploidy

- 47,XXY (Klinefelter syndrome)
- 45,X (Turner syndrome)
- 47,XX,+21 (Down syndrome)
- 47,XY,+18 (Edwards syndrome)
- 47,XY,+13 (Patau syndrome)
- 47,XX,+16

Polyploidy

- Triploidy (e.g. 69,XXY)



- Tetraploidy (e.g. 92,XXYY)

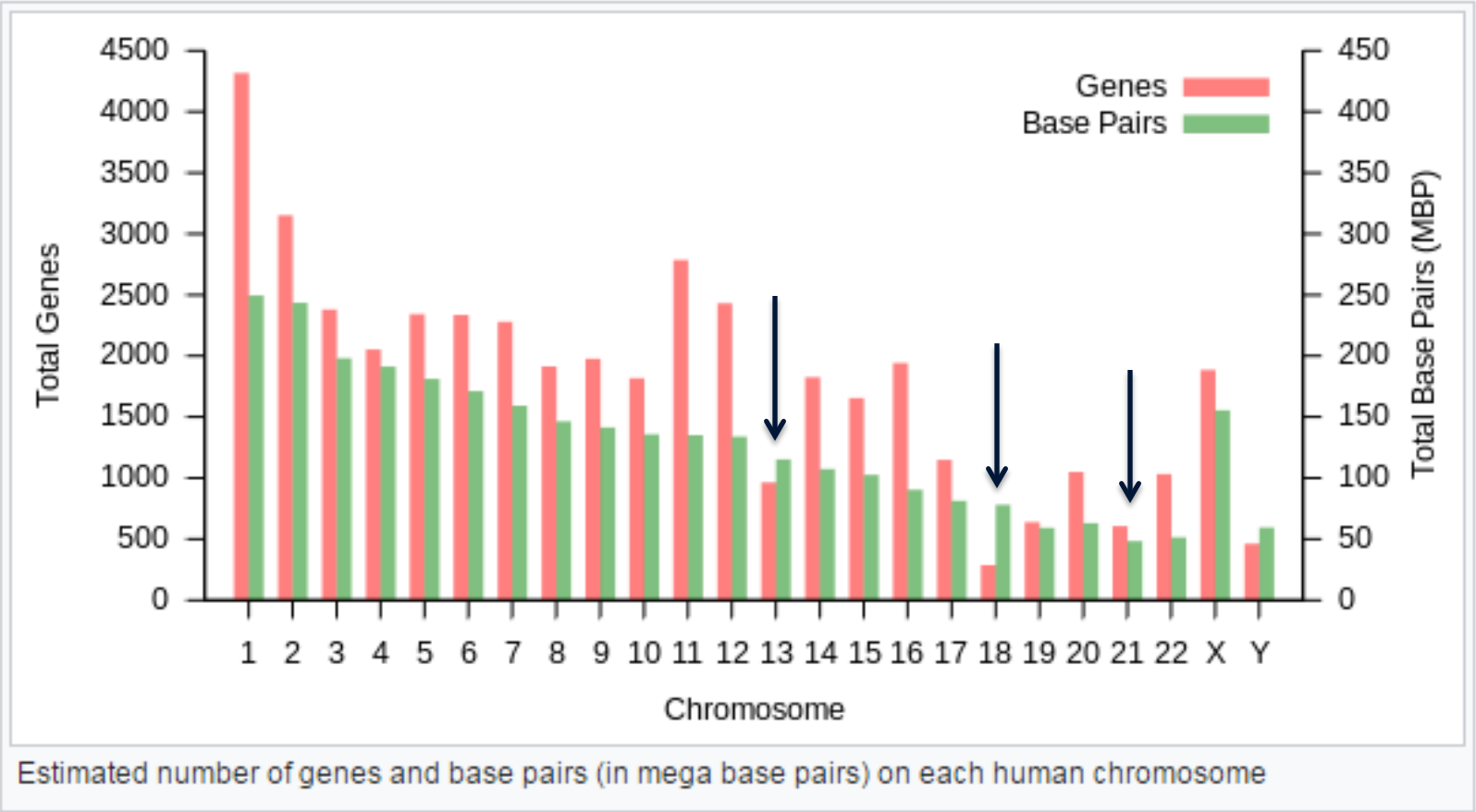
Observed frequencies of chromosomal abnormalities in gametes and pregnancy

Incidence of aneuploidy during development

Gestation (weeks)			0	6-8	20	40
Stage	Sperm	Oocytes	Pre-implantation embryos	Spontaneous abortions	Stillbirths	Livebirths
Incidence of aneuploidy	1-2%	~20%	~20%	35-50%	4%	0.3%
Most common aneuploidies	Various	Various	Various	45,X, +16, +21, +22, Triploidy	+13, +18, +21	+13, +18, +21, XXX, XXY, XYY

Table modified from Hassold and Hunt, 2001, Nat Rev Genet

Chromosome size and gene content correlates with incidence of *postnatal* trisomy



Estimated number of genes and base pairs (in mega base pairs) on each human chromosome

Image source: wiki commons

Incidence of aneuploidy detected in newborns

Abnormality	Rate/1000	Rate (1/n)
Autosomal Trisomies (All)	1.62	617
13	0.04	24,058
18	0.21	4,812
21	1.37	730
Sex Chromosome Aneuploidies (All)	2.70	375
45,X and variants	0.29	3,509
47,XXX and 47,XXX/46,XX	0.50	2,000
47,XXY and variants	0.72	1,400
47,XYY and 46,XY/47,XYY	0.53	1,887

Data from: Milunsky and Milunsky, Genetic Disorders of the Fetus, 6th Ed. (2010). Benn, Chp. 6

- Incidence of sex chromosome aneuploidy is higher

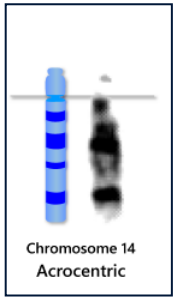
- True rates are underestimated, especially for sex chromosome aneuploidies, which may be unrecognized at birth

Parental Origins of Aneuploidy

Table 1. Summary of studies of the origin of human trisomies[a]

Trisomy	*n*	Maternal		Paternal		PZM (%)
		MI (%)	MII (%)	MI (%)	MII (%)	
Acrocentrics						
13	74	56.6	33.9	2.7	5.4	1.4
14	26	36.5	36.5	0.0	19.2	7.7
15	34	76.3	9.0	0.0	14.7	0.0
21	782	69.6	23.6	1.7	2.3	2.7
22	130	86.4	10.0	1.8	0.0	1.8
Non-acrocentrics						
2	18	53.4	13.3	27.8	0.0	5.6
7	14	17.2	25.7	0.0	0.0	57.1
8	12	50.0	50.0	0.0	0.0	50.0
16	104	100	0.0	0.0	0.0	0.0
18	150	33.3	58.7	0.0	0.0	8.0
XXX	46	63.0	17.4	0.0	0.0	19.6
XXY	224	25.4	15.2	50.9	0.0	8.5
X		~30		~70		

[a]Adapted from Hall *et al*. (6). MI, meiosis I; MII, meiosis II; PZM, post-zygotic mitotic.



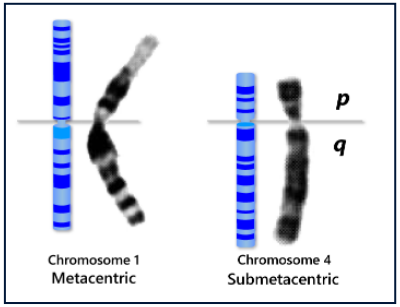
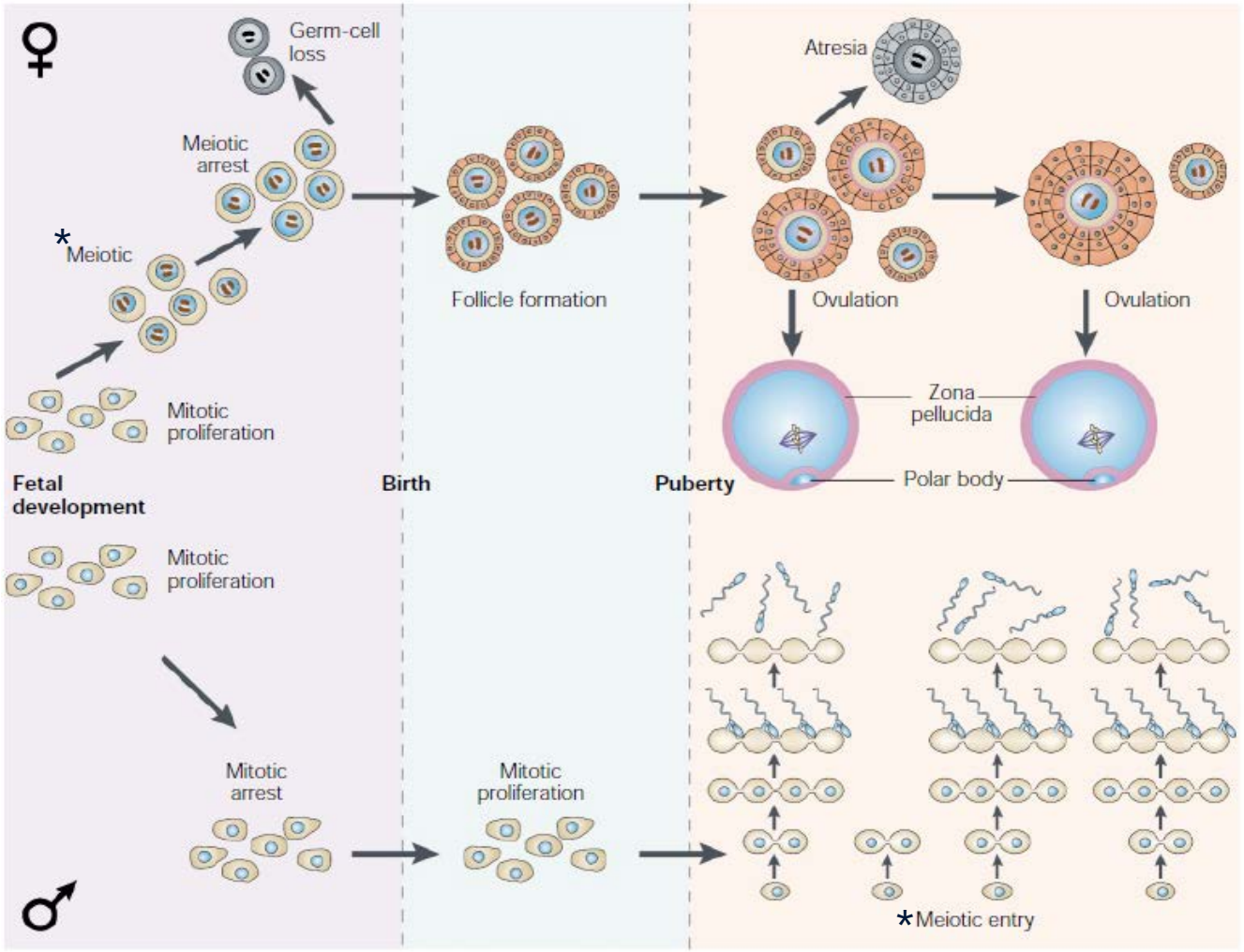


Table: Hassold, Hall and Hunt, 2007, Hum Mol Genet

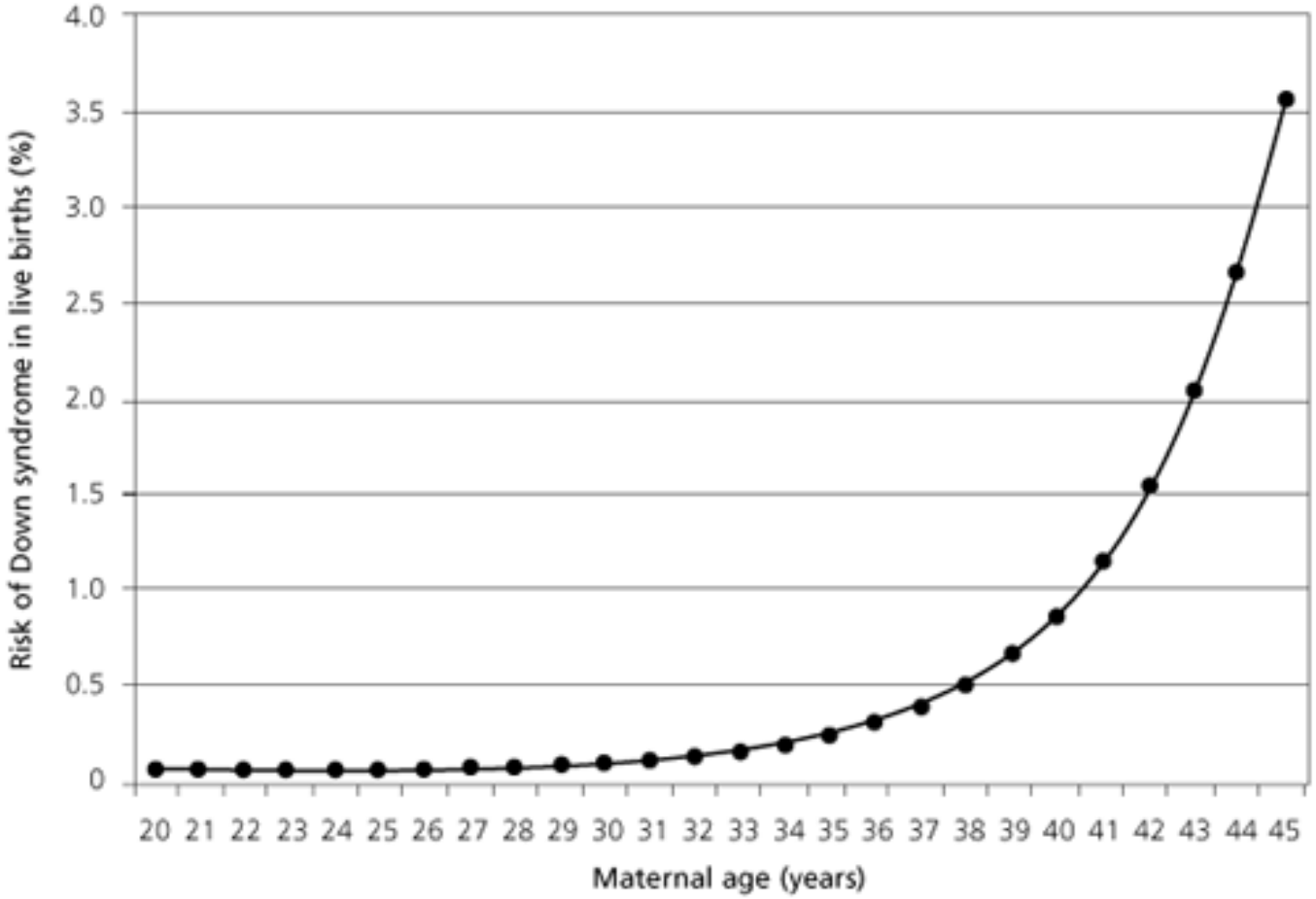
Images modified, source: http://learn.genetics.utah.edu/content/chromosomes/readchromosomes/

Oogenesis vs Spermatogenesis



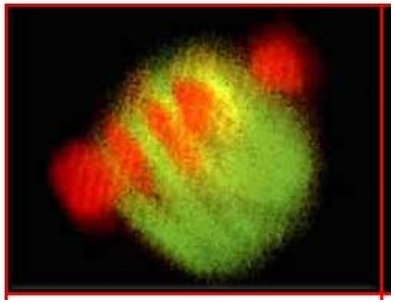
Hassold and Hunt (2001) Nat Rev Genet

Down Syndrome and Maternal Age

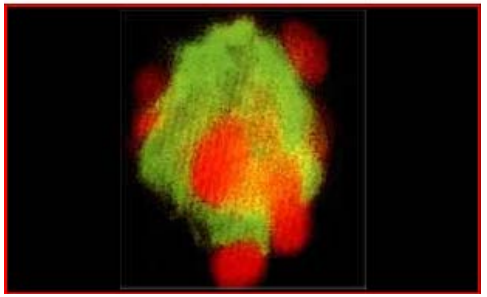


Newberger (2000) Am Fam Physician

Ovum from a woman in her 20's



Ovum from a woman in her 40's



Battaglia et al., 1996

Incidence of aneuploidy detected prenatally with various ultrasound findings

Table 6.11 Ultrasound abnormalities and frequency of fetal aneuploidy

Defect	*Nicolaides et al. 1992*[131]		*Halliday et al. 1994*[132]	*Hanna et al. 1996*[133]	*Rizzo et al. 1996*[134]	*Overall frequency*[a]
	Isolated No. Aneupl/ Total (%)	*Multiple No. Aneupl/ Total (%)*	*Isolated No. Aneupl/ Total (%)*	*Primary U/S Abn. No. Aneupl/ Total (%)*	*Primary U/S Abn. No. Aneupl/ Total (%)*	*No. Aneupl/ Total (%)*
Abdominal wall defect	1/30	41/86 (48)	3/45 (7)	38/196 (19)	7/16l (44)	90/373 (24)
Agenesis of corpus callosum	–	–	–	0/2 (0)	8/19 (42)	8/21 (38)
Choroid plexus cyst	1/49	33/72 (46)	0/21 (–)	21/514 (4)	–	55/656 (8)
Congenital heart disease						166/339 (49)
Unspecified	0/4	101/152 (66)	8/42 (19)	10/60 (17)	20/34 (59)	
Ventricular septal defect	–	–	–	8/21 (38)	9/13 (69)	
Atrioventricular canal	–	–	–	2/2 (100)	8/11 (82)	
Cystic hygroma	0/4	35/45 (73)	11/21 (52)	65/108 (60)	22/33 (67)	133/211 (63)
Diaphragmatic hernia	0/38	17/41 (41)	2/17 (12)	8/72 (11)	2/5 (40)	29/173 (17)
Duodenal atresia	1/6	9/17 (53)	3/10 (30)	10/45 (22)	8/15 (53)	31/93 (33)
Echogenic bowel	–	–	–	5/34 (15)	–	5/34 (15)
Facial cleft	0/8	31/56 (55)	1/7 (14)	–	3/11 (28)	35/82 (43)
Holoprosencephaly	0/7	15/51 (29)	3/9 (33)	9/19 (47)	6/12 (50)	33/98 (34)
Hydrocephaly	2/42	40/144 (28)	7/30 (23)	25/256 (9)	–	74/472 (16)
Hydronephrosis	–	–	–	8/110 (7)	–	8/110 (7)
Hydrops (nonimmune)	7/104	18/106 (17)	23/57 (40)	37/116 (32)	6/17 (35)	91/400 (22)
IUGR	4/251	133/424 (31)	8/37 (22)	71/389 (18)	–	216/1101 (20)
Limb anomalies	0/18	195/457 (43)	4/29 (14)	3/39 (8)	3/6 (50)[b]	205/549 (37)
Microcephaly	0/1	8/51 (16)	0/1 (0)	5/28 (18)	–	13/81 (16)
NTD[c]	–	–	1/33 (3)	4/57 (7)	2/6 (33)	7/96 (7)
Nuchal fold/thickness/ edema	0/12	53/132 (40)	5/21 (24)	15/75 (20)	–	73/240 (30)
Oligohydramnios	–	–	1/14 (7)	14/97 (14)	–	15/111 (14)
Polyhydramnios	–	–	2/9 (22)	23/194 (12)	–	25/203 (12)
Renal anomalies	9/482	87/360 (24)	3/29 (10)	7/107 (7)	–	106/978 (11)
TF/EA	0/1	18/23 (78)	–	4/10 (40)	3/6 (50)	25/40 (63)
Two-vessel cord	–	–	–	5/72 (6)	–	5/72 (7)

Defect	Overall frequency
Cystic hygroma	133/211 (63%)
Tracheo -esophageal atresia	25/40 (63%)
Congenital heart defect	166/339 (49%)
Agenesis of corpus collosum	8/21 (38%)
Limb anomalies	205/549 (37%)
Neural tube defect	7/96 (7%)
Choroid plexus cyst	55/656 (8%)

Benn P. 2010. Prenatal Diagnosis of Chromosomal Abnormalities through Amniocentesis. In: Milunsky and Milunsky, eds. Genetic Disorders of the Fetus. 6th Edition.

Structural Abnormalities

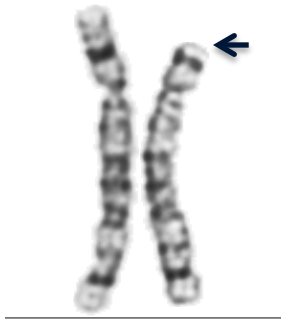
- Definition: Breakage and rejoining of chromosomes or chromosome segments
- May be either balanced or unbalanced
- Breakpoints can disrupt gene expression (within a gene or regulatory element)
- Can create gene fusions or affect gene expression (↑↓) by position effect
  - Common in cancer

Structural Chromosome Abnormalities

(Abnormal chromosome is on the right)

Deletions

Terminal



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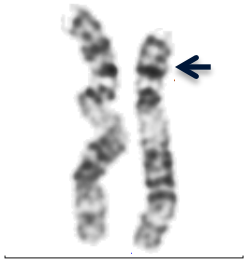
Interstitial



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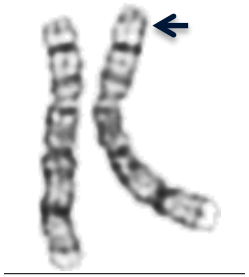
Duplications



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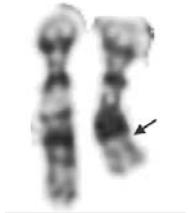
Insertions



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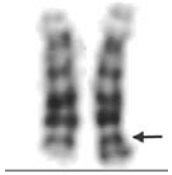

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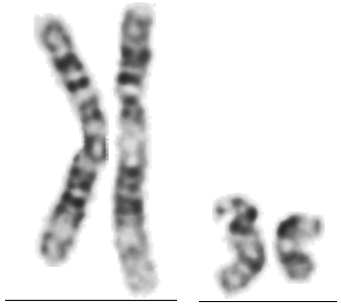
Reciprocal Translocations

Balanced



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22

Unbalanced

11

22

Robertsonian Translocations

13

14

13

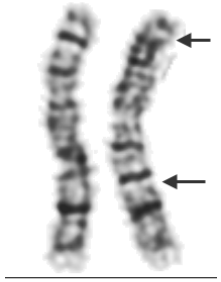
14

Structural Chromosome Abnormalities

(Abnormal chromosome is on the right)

Inversions

Pericentric



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Paracentric

7

Ring chromosomes

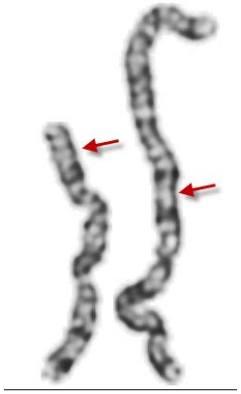
X

13

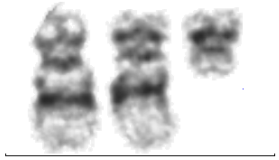
Recombinant chromosomes

8

Isochromosomes



X



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15

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Incidence of chromosome abnormalities detected in newborns

Abnormality	Rate/1000	Rate (1/n)
Autosomal Trisomies	1.62	617
Sex Chromosome Aneuploidies	2.70	375
Balanced Structural Rearrangements	2.04	490
Translocations, insertions	0.97	1,028
Inversions	0.16	6,331
Robertsonians	0.91	1,099
Unbalanced Structural Rearrangements	0.63	1,587
Translocations, insertions, inversions	0.09	10,935
Robertsonians	0.07	13,366
Deletions, rings	0.06	17,184
+Markers (e.g. isochromosomes)	0.41	2,455

Data from: Milunsky and Milunsky, Genetic Disorders of the Fetus, 6th Ed. (2010). Benn, Chp. 6

- ~1/500 is a carrier of a balanced rearrangement

Some syndromic microdeletion and duplication regions

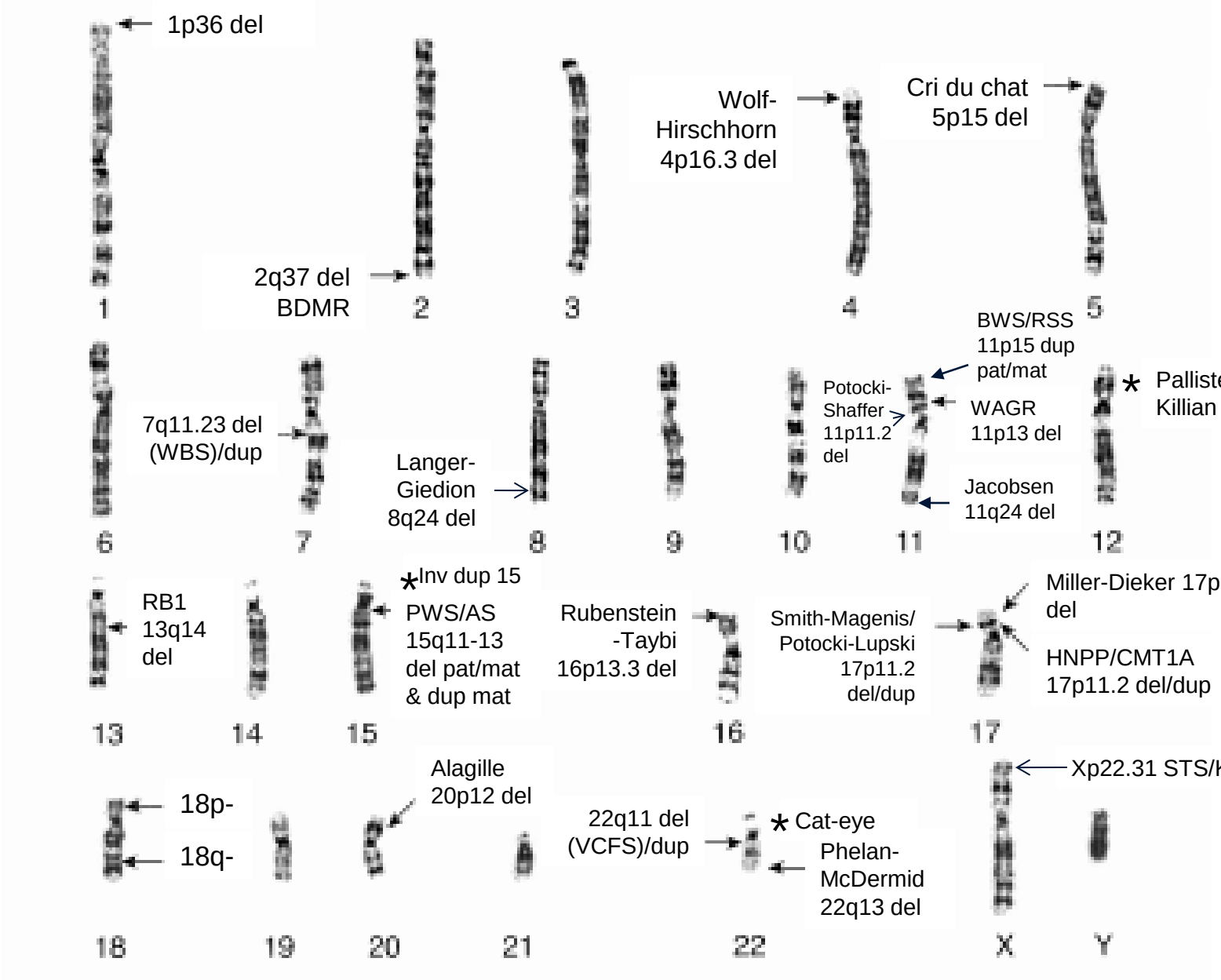


Image modified from Gardner, Sutherland and Shaffer Chromosome Abnormalities and Genetic Counseling 4th ed (2011)

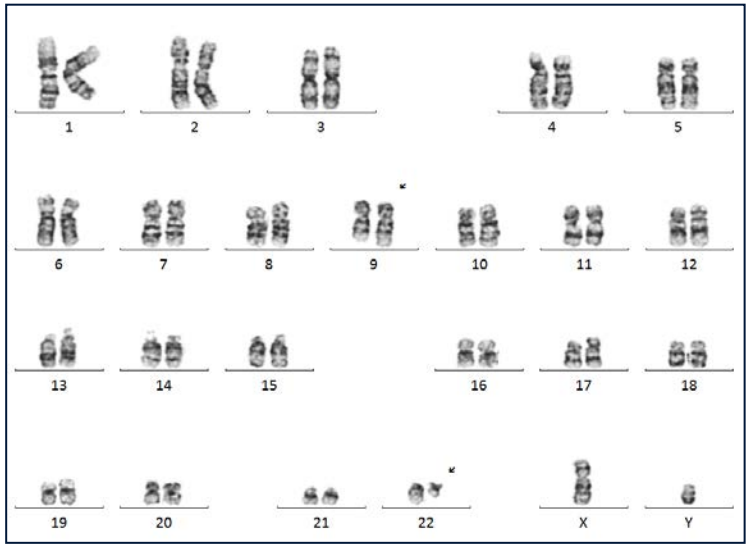
Incidence of Microdeletion and Duplication Syndromes

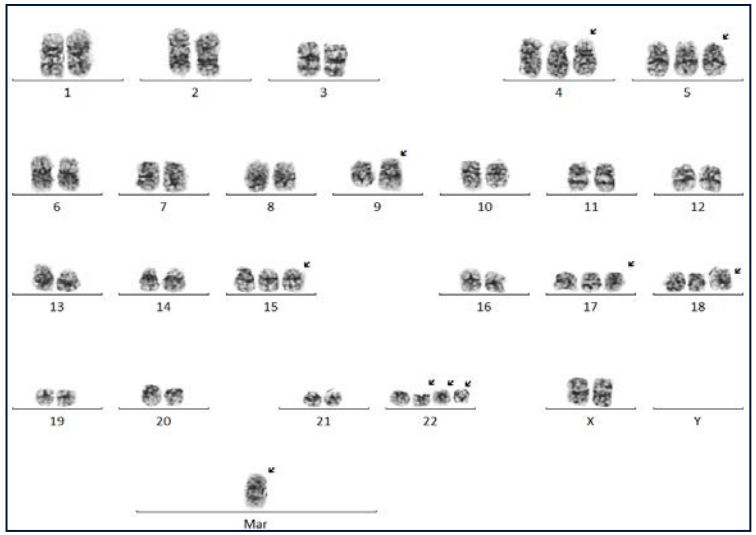
Syndrome	Incidence	Cause
1p36 deletion	1:7500	Terminal deletion
1q21.1 deletion (distal)	1:500	Interstitial deletion (SD)
4p-/Wolf-Hirschhorn	1:50,000	Terminal deletion
5p-/Cri du chat	1:50,000	Terminal deletion
7q11.23/Williams	1:7500	Interstitial deletion (SD)
15q11q13/Prader-Willi	1:20,000	Interstitial deletion (pat)/ mUPD/methylation defect/mutation
22q11.2/DiGeorge/VCFS	1:5000	Interstitial deletion (SD)

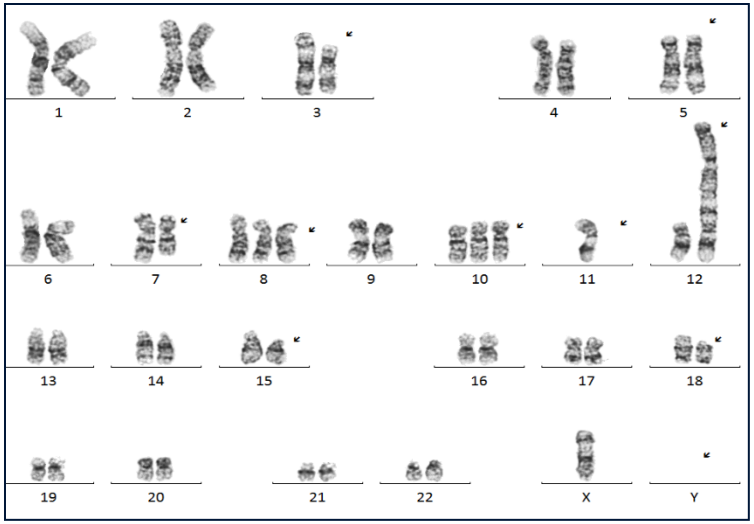
Chromosome Abnormalities in Cancer

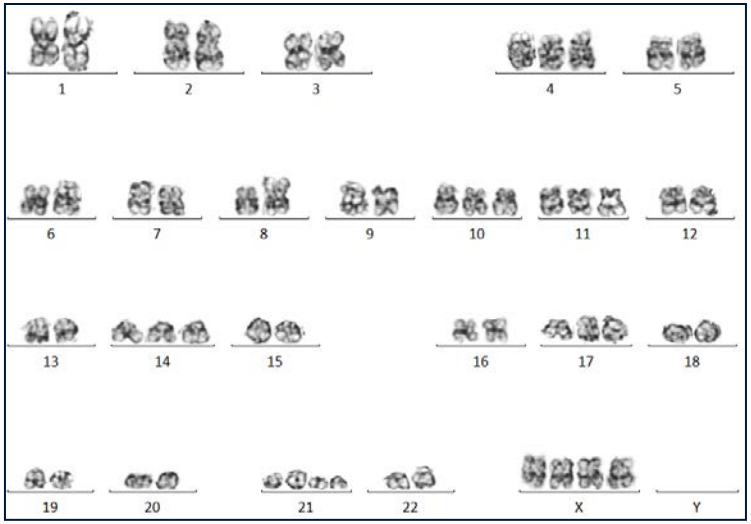
- Numerical
  - Aneuploid: 2n - or + chromosomes
    - Monosomy or trisomy
  - Polyploid: 1n, 2n, 3n, 4n, etc. where n=23 chr.
- Structural
  - Deletions
  - Duplications/amplifications
  - Translocations: balanced or unbalanced
  - Inversions
- Copy-neutral loss of heterozygosity (LOH)
  - Mitotic recombination
  - Mitotic malsegregation: uniparental disomy

Karyotyping in Cancer



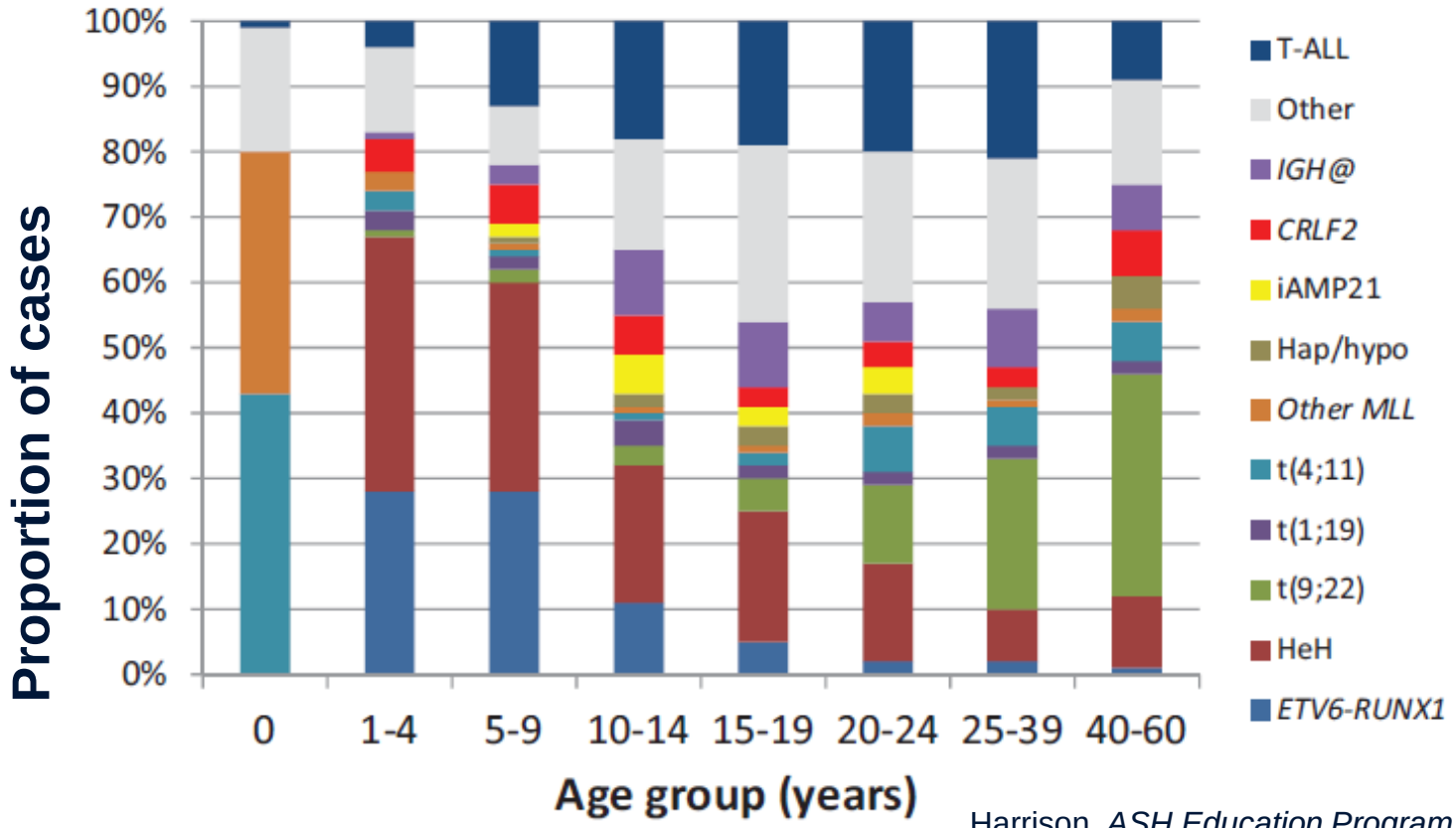






e.g. Clinical Utility of Karyotype in ALL

Cytogenetic subtype distribution by age



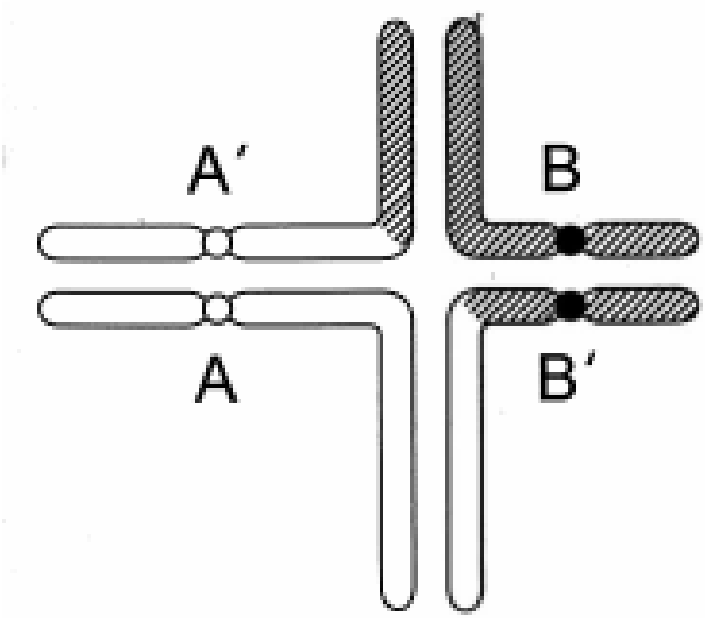
Harrison. *ASH Education Program* (2013) 118-125

Effects of Translocations

- Constitutional carriers are at risk for infertility, recurrent miscarriage and/or birth of a child with a congenital anomaly syndrome
  - Most risk figures fall into the range of 0-30% for a liveborn child with an abnormality (higher end if previous child)
- May disrupt gene expression (breakpoint within a gene or regulatory element by position effect)
  - In the prenatal setting and if *de novo*, risk=~6% (Warburton '91)
- Create gene fusions and affect gene expression by position effect, especially in cancer
  - e.g. Translocation 9;22 BCR-ABL1 chimeric transcript in CML and ALL
  - e.g. Translocation 11;14 CCND1 upregulation by translocation near the IGH locus regulatory region in MCL and MM

Meiosis in the Balanced Translocation Carrier

A, B: Normal chromosomes
A', B': Derivative chromosomes

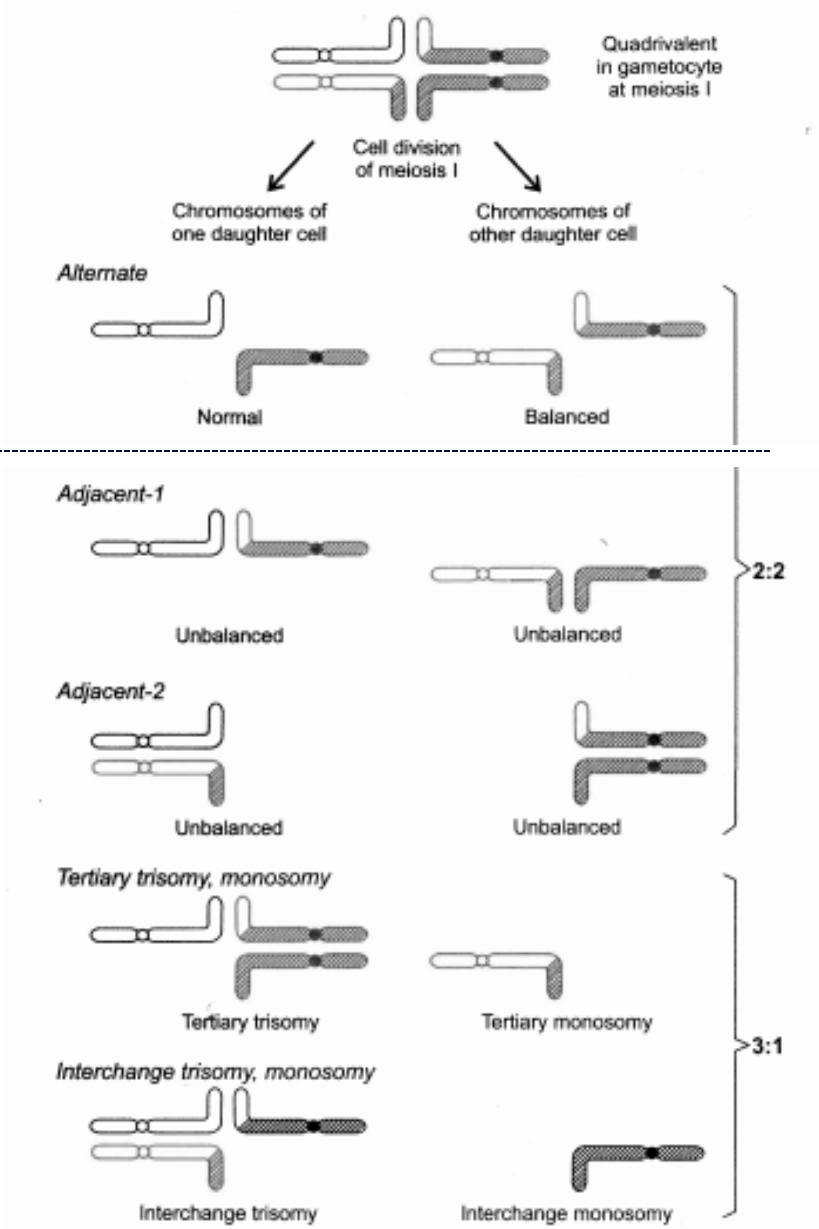


Gardner, Sutherland and Shaffer. 2012

Meiosis in the Balanced Translocation Carrier

Only alternate segregation will result in normal/balanced gametes

All other modes of segregation result in unbalanced gametes

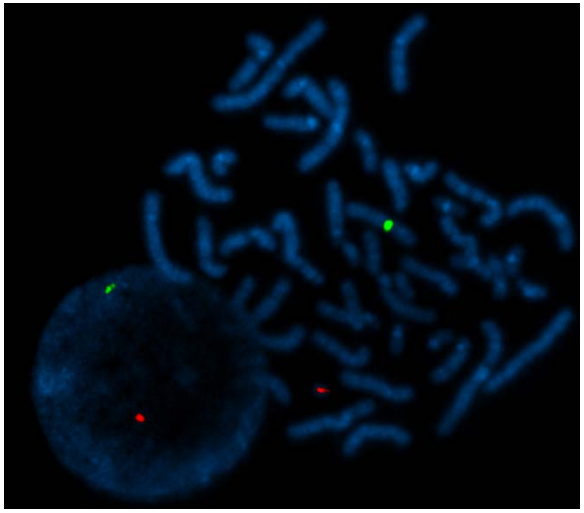


Chromosome Abnormalities and Genetic Counseling. 4th ed. Gardner, Sutherland and Shaffer. 2012

Fluorescence *in situ* hybridization (FISH)

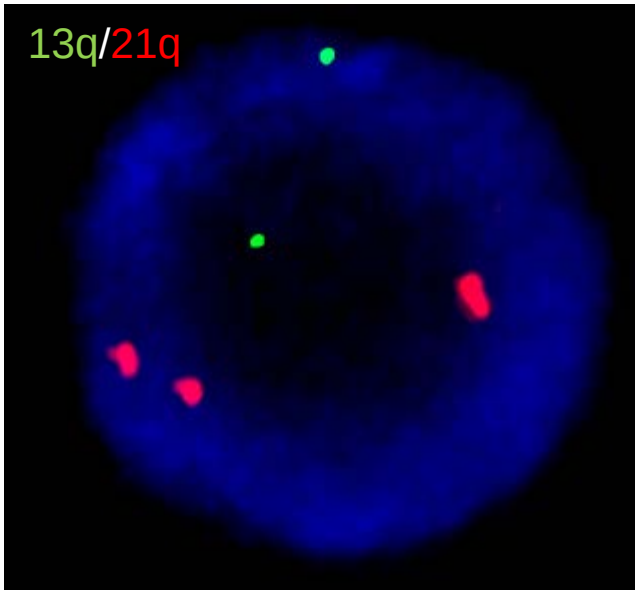
- A fluorescently labeled DNA fragment is used to detect a chromosome, region or gene *in situ*
- Advantages:
  - Much higher resolution compared to karyotyping for identifying deletions, duplications, insertions, and translocation breakpoints (down to the 100's of kb range)
  - Can use cells in any state of the cell cycle (interphase or metaphase), as well as archived tissue
  - Does not require culturing = shorter TAT
  - Greater sensitivity for low-level mosaicism compared to chromosomes (1-5% by interphase FISH)
- Limitation:
  - Targeted approach: only analyzing the region of the genome that is complementary to the FISH probe

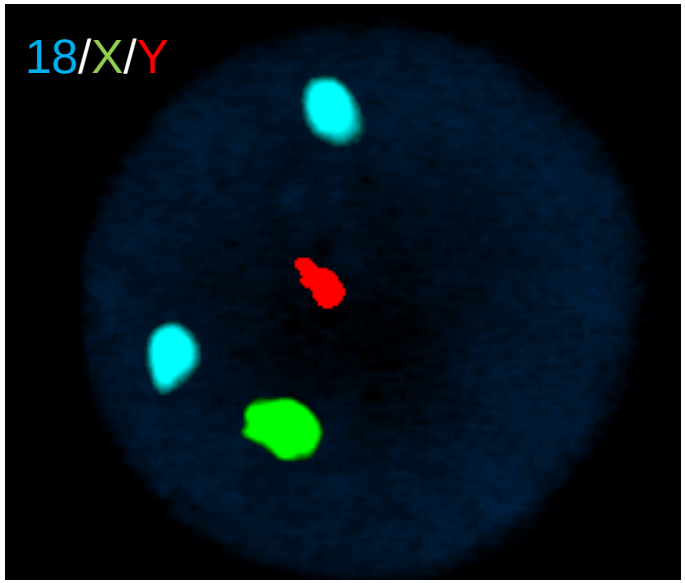
FISH for X and Y centromeres on an interphase and metaphase cell



FISH Applications in Constitutional Studies

- Detecting aneuploidy with rapid TAT
- Characterizing structural abnormalities (e.g. translocations)
- Detecting microdeletions/microduplications
  - For undiagnosed patients, genomic microarray is recommended

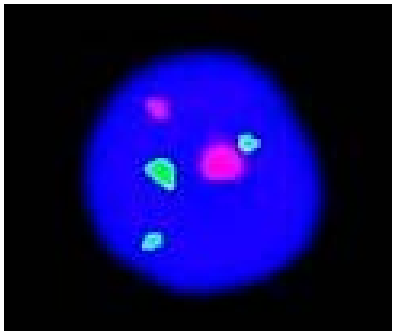




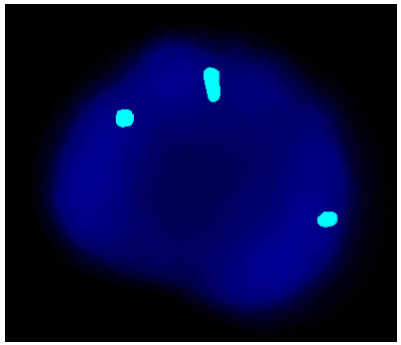
FISH Applications in Oncology Studies

- Diagnosis: often using panels targeting recurrent and/or prognostic/therapeutic alterations, some cytogenetically cryptic
- Monitoring: using FISH probe(s) specific to the abnormal clone or panels to simultaneously monitor for residual disease and disease progression

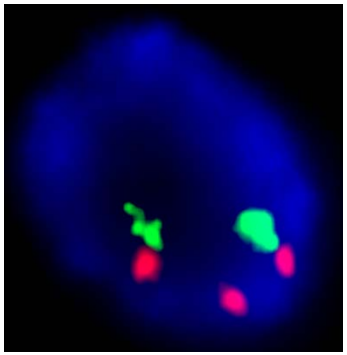
1q21/17p13.1



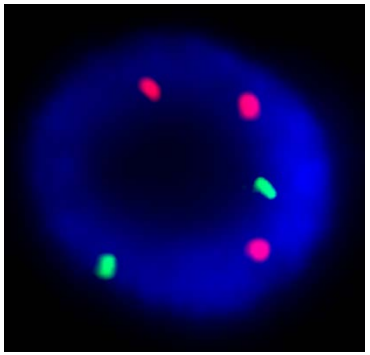
9q34



11q13/14q32



15q22/17q21.2



FISH Applications in Oncology Studies

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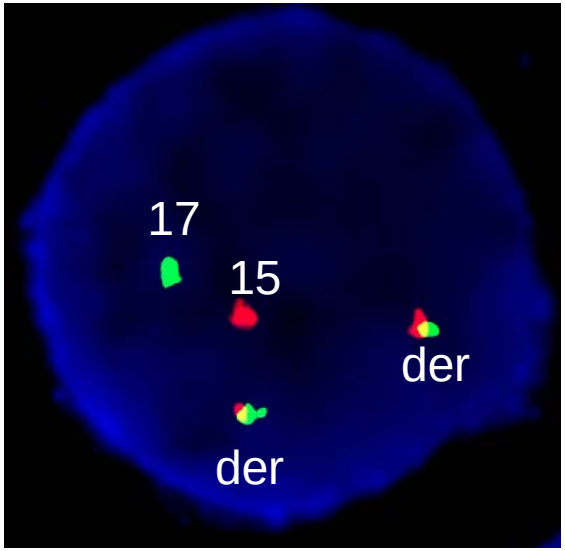
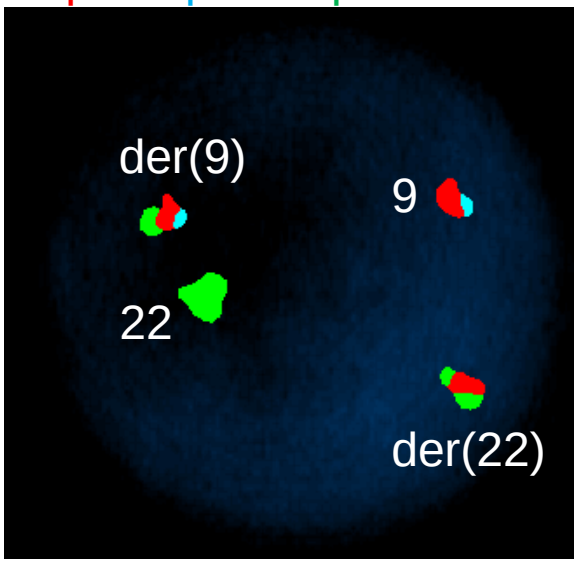
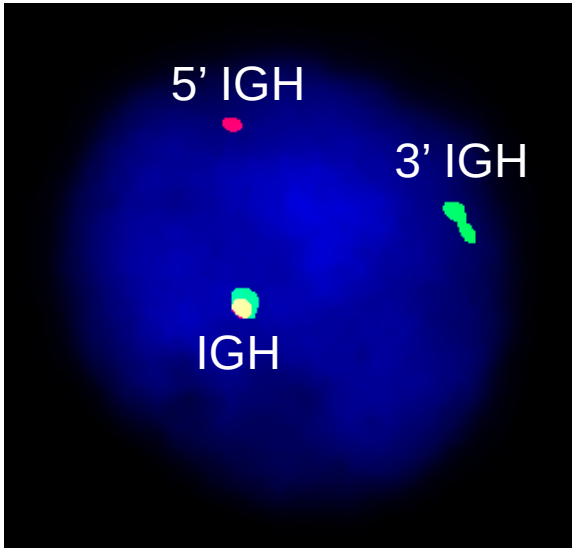
15q22/17q21



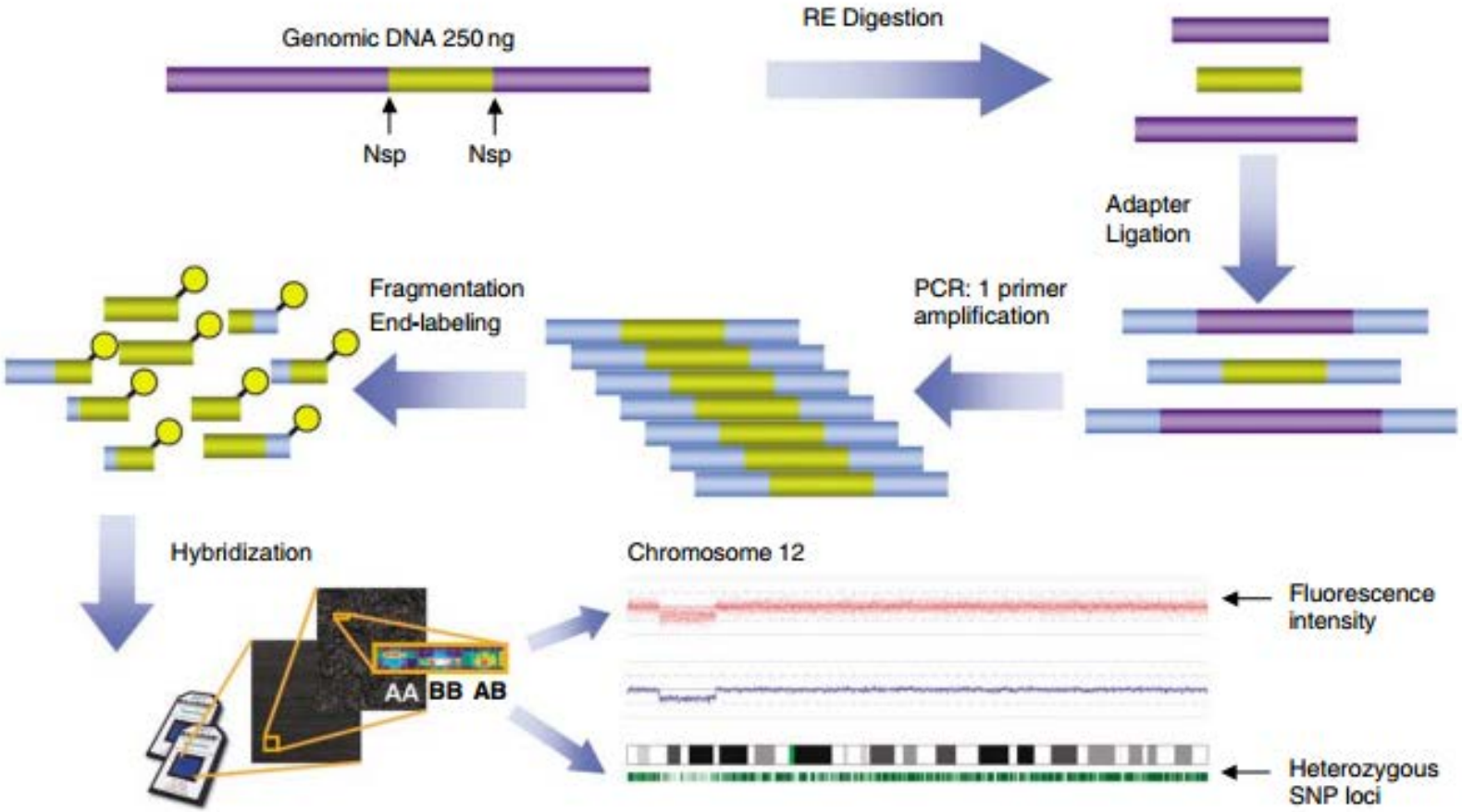
9q34/9q34/22q11



14q32



Genomic SNP Microarray (SNP-A)



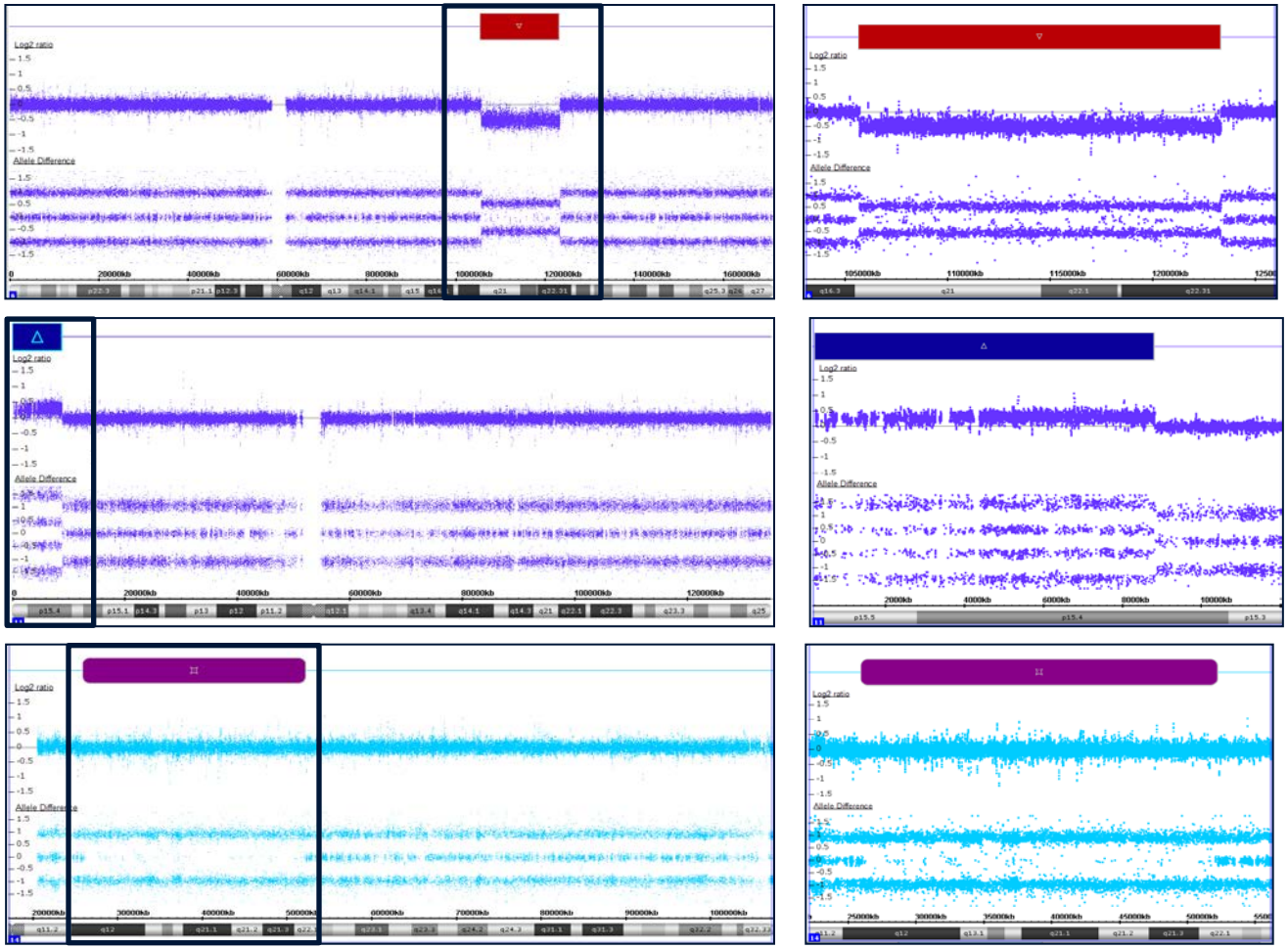
Tiu et al., Leukemia, 2007

Genomic Alterations Detected by SNP-A

Deletion

Duplication

Region of Homozygosity (ROH)



Pros and Cons of Genomic Microarray (GMA)

Advantages

- High resolution technology
  - Down to 10's of kb range (compared to 3-5 Mb by 550-band chromosomes, 100's kb by FISH)
- No cell culturing or cell preparation required
  - Can use on archived tissues: frozen or formalin-fixed paraffin-embedded (FFPE)
- Objective analysis
- Detection of absence or loss of heterozygosity (AOH/LOH) if SNP genotyping is incorporated

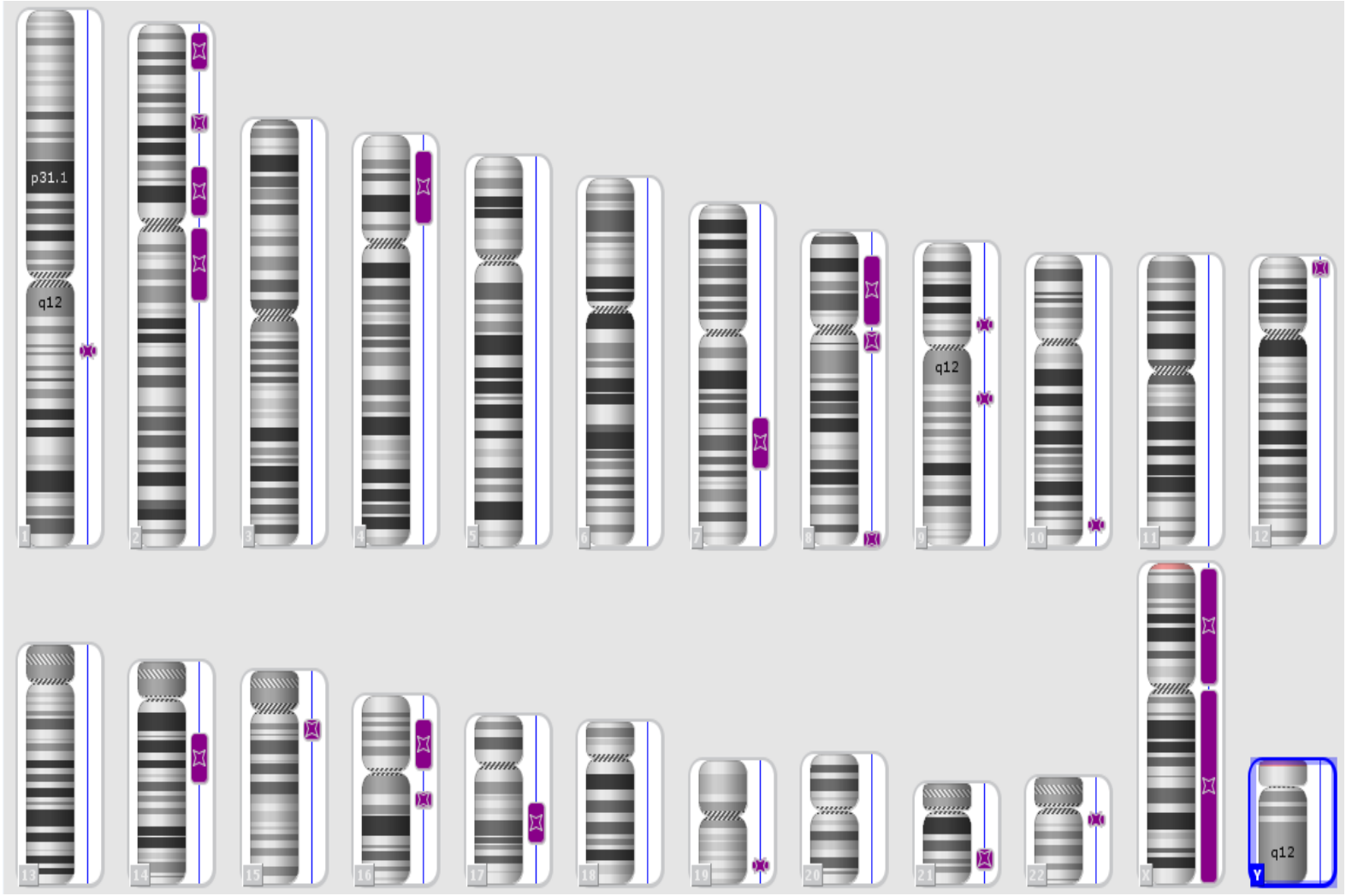
Limitations

- Cannot detect balanced structural abnormalities (i.e. translocations, inversions)
- Cannot interrogate repetitive DNA sequence

Considerations

- May uncover findings unrelated to the indication for testing (incidental findings)

Increased Genome-Wide Absence of Heterozygosity (AOH)



Genetics in Medicine | ACMG STANDARDS AND GUIDELINES

American College of Medical Genetics and Genomics: standards and guidelines for documenting suspected consanguinity as an incidental finding of genomic testing

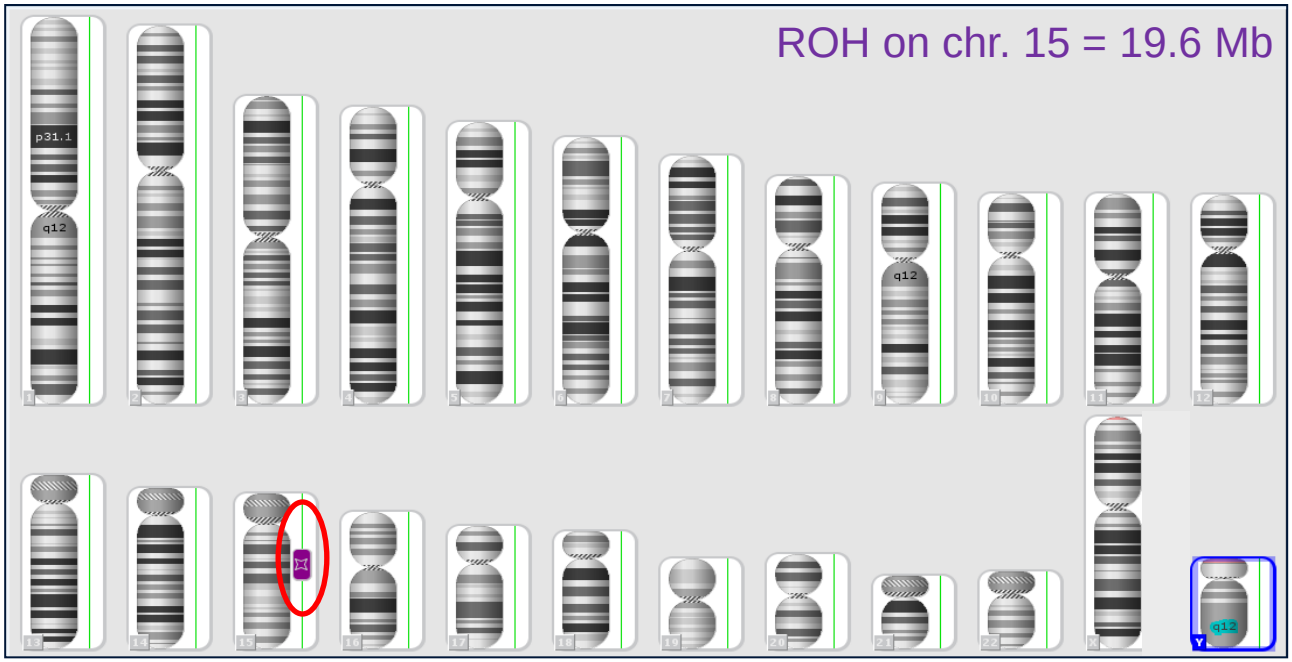
Catherine W. Rehder, PhD[1], Karen L. David, MD, MS[2,3], Betsy Hirsch, PhD[4], Helga V. Toriello, PhD[5], Carolyn M. Wilson, MS[6] and Hutton M. Kearney, PhD[6]

2013

- There is clinical utility in the detection of genomic AOH, even when the % is quite low (<3%)
  - Risk for autosomal recessive disease
- Cases with >10% genomic AOH have the potential of uncovering a situation of familial abuse
- Laboratories are encouraged to develop a reporting policy in conjunction with their ethics review committee and legal counsel

Single large region of homozygosity (ROH) …

…may indicate inheritance of both chromosomes from the same parent (i.e. uniparental disomy, UPD)



- Usual observation is ROH on a single chromosome
- Results from an error during meiosis or mitosis

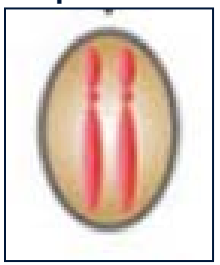
Uniparental disomy (UPD)

- Biparental inheritance: the normal situation; one chromosome is inherited from each parent

Biparental

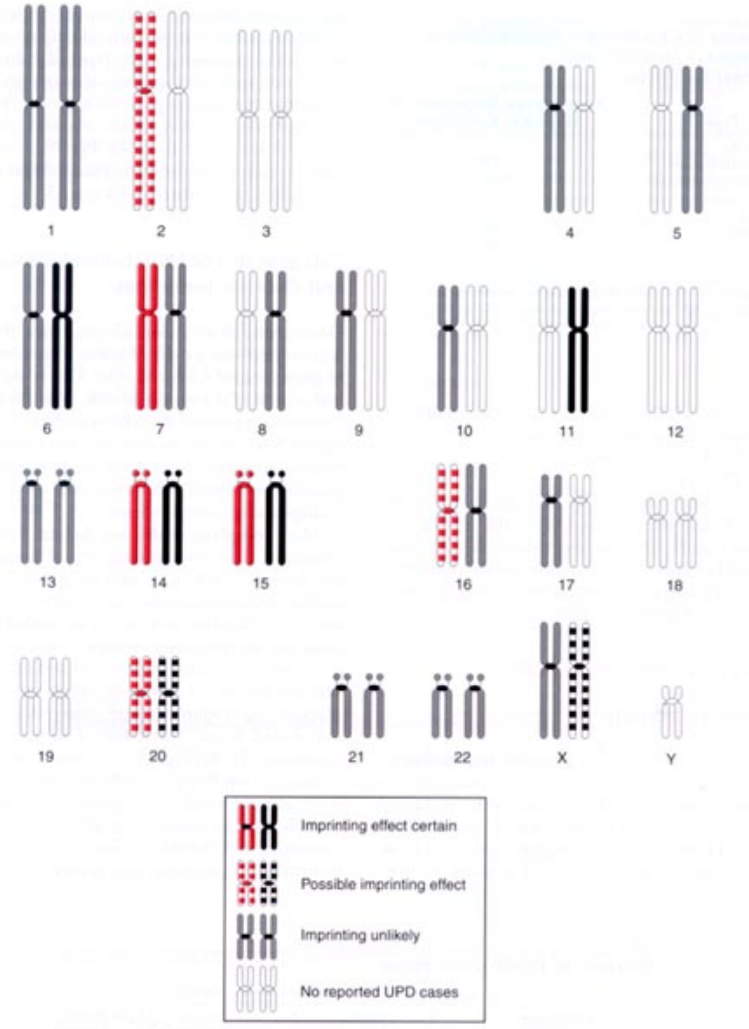
- Uniparental disomy: both chromosome copies come from a single parent
  - Risk for recessive disease for genes in the homozygous chromosome segment
  - Risk for imprinting disorder if involving chromosomes that contain imprinted genes, differentially expressed dependent on parent of origin

Uniparental



Images modified from Yamazawa et al., 2010, Am J Med Gen C

Imprinted chromosomes and human disease due to uniparental disomy (UPD)



Chromosome UPD and Inheritance	Associated Genetic Disease or Abnormalities
Paternal UPD 6	Transient neonatal diabetes mellitus
Maternal UPD 7	Silver-Russell syndrome
Paternal UPD 11	Beckwith-Wiedemann syndrome
Maternal UPD 14	Hypotonia, motor development delay, mild dysmorphic facial features, low birth weight, growth abnormalities
Paternal UPD 14	Severe mental and muscoskeletal abnormalities
Maternal UPD 15	Prader-Willi syndrome
Paternal UPD 15	Angelman syndrome
Maternal UPD 16	Intrauterine growth retardation
Maternal UPD 20	Intrauterine growth retardation and/or postnatal growth retardation

Image from: http://carolguze.com/text/442-10-nontraditional_inheritance.shtml

Velissariou, Balkan J Med Gen

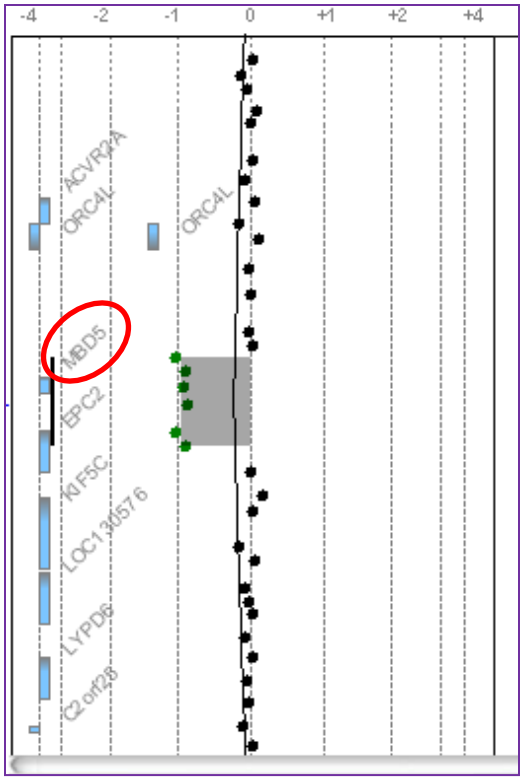
Clinical Utility of GMA in Postnatal Studies

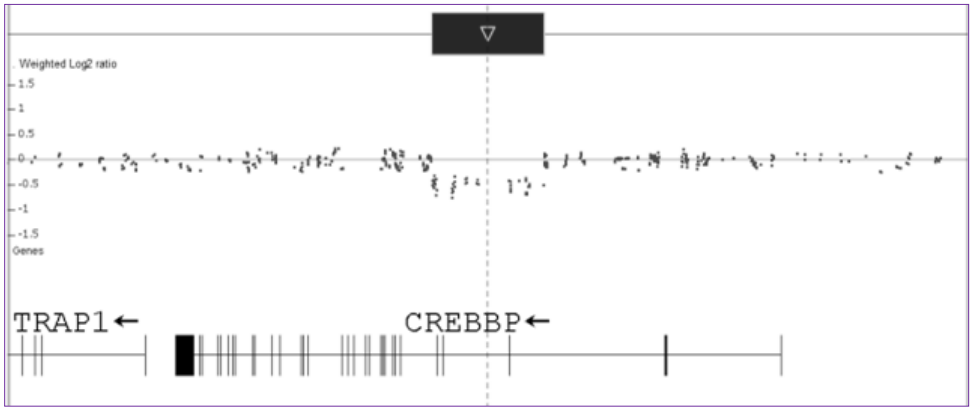
Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies

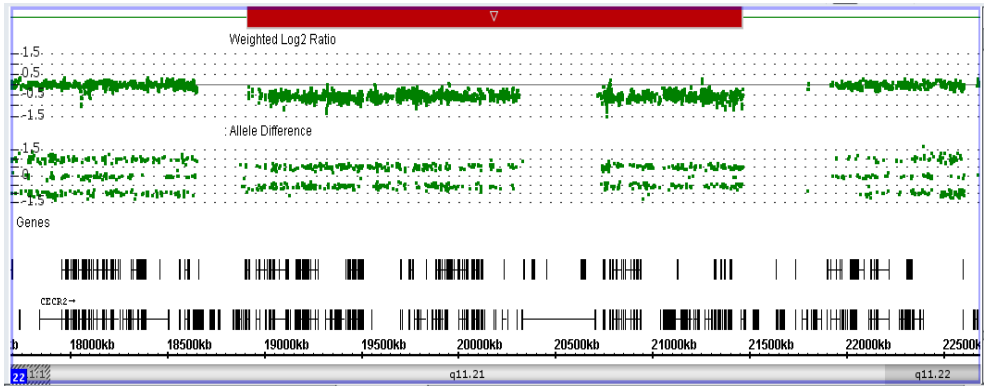
Miller et al., *The American Journal of Human Genetics* 86, 749–764, May 14, 2010

- International standards for cytogenomic arrays (ISCA) consortium: reviewed evidence from 33 studies, including >21,000 patients tested by GMA
- ➢ For genetic testing of individuals with unexplained developmental delay, intellectual disability, autism or multiple congenital anomalies, this technology offers a much higher dx yield (between 15-20%) compared to ~3% by karyotype and excluding other recognizable chromosome syndromes

Detection of submicroscopic, small pathogenic CNVs







Clinical Utility of GMA in Prenatal Studies

Clinically relevant findings in cases with normal karyotype:

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

Wapner et al., NEJM 2012

Clinical Utility of GMA in Prenatal Studies and in Pregnancy Loss

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. Reaffirmed 2015)*

(See also Practice Bulletin No. 88)

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

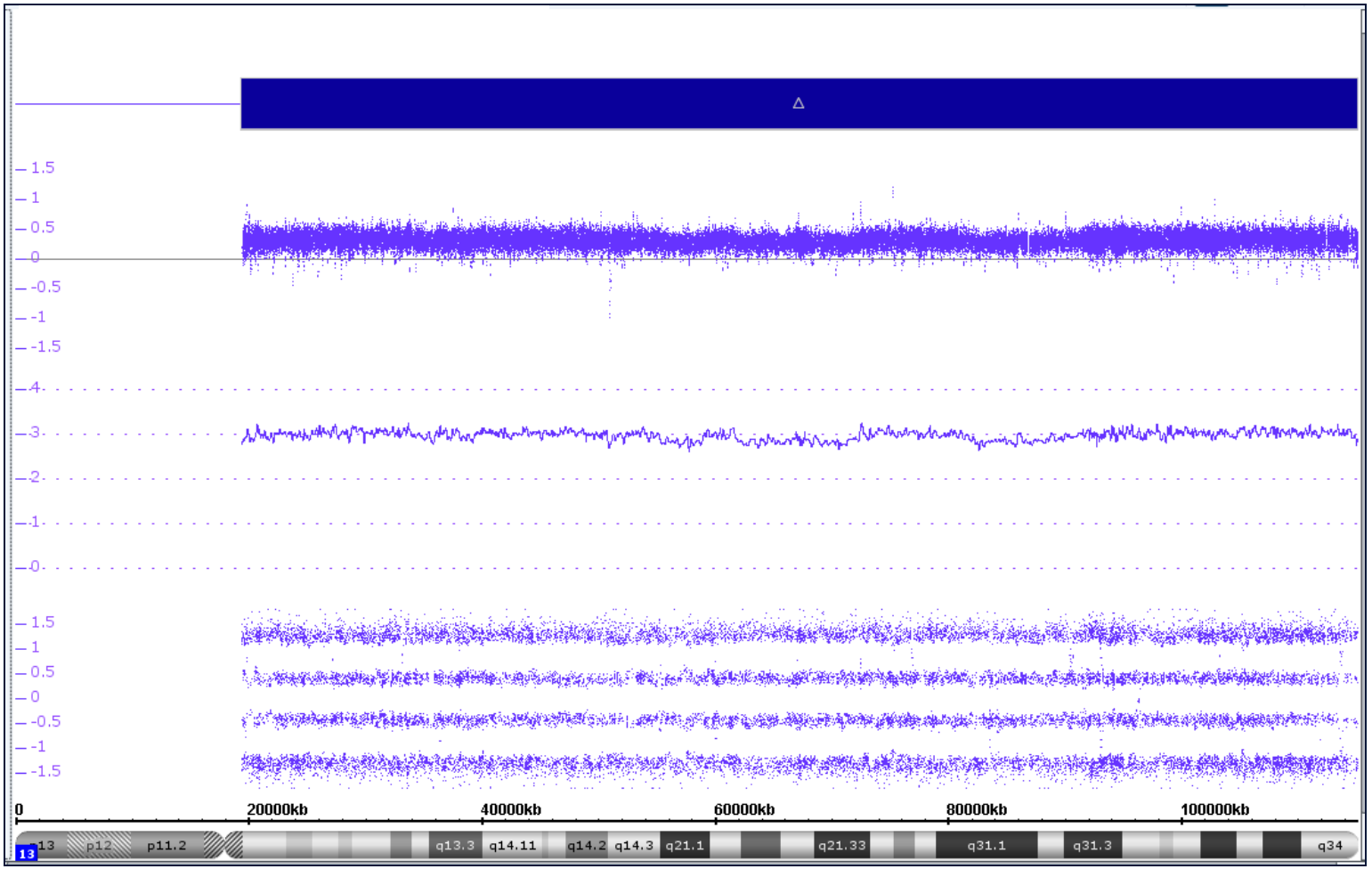
This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

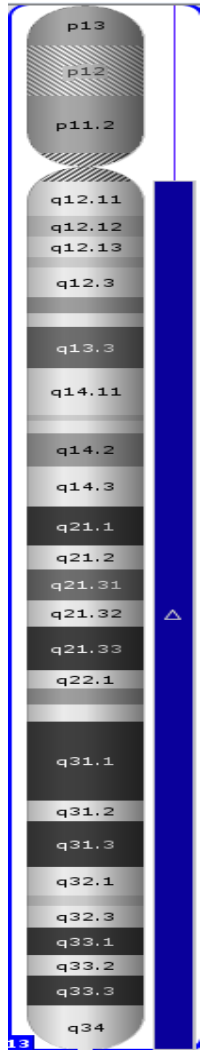
The Use of Chromosomal Microarray Analysis in Prenatal Diagnosis

- Use in prenatal diagnosis: in patients with a fetus with one or more structural abnormalities identified on ultrasound, patients undergoing invasive prenatal diagnostic testing, not restricted to women aged 35+
- Use in intrauterine fetal demise or stillbirth: when further cytogenetic analysis is desired, not recommended for first or second trimester losses due to limited data on utility

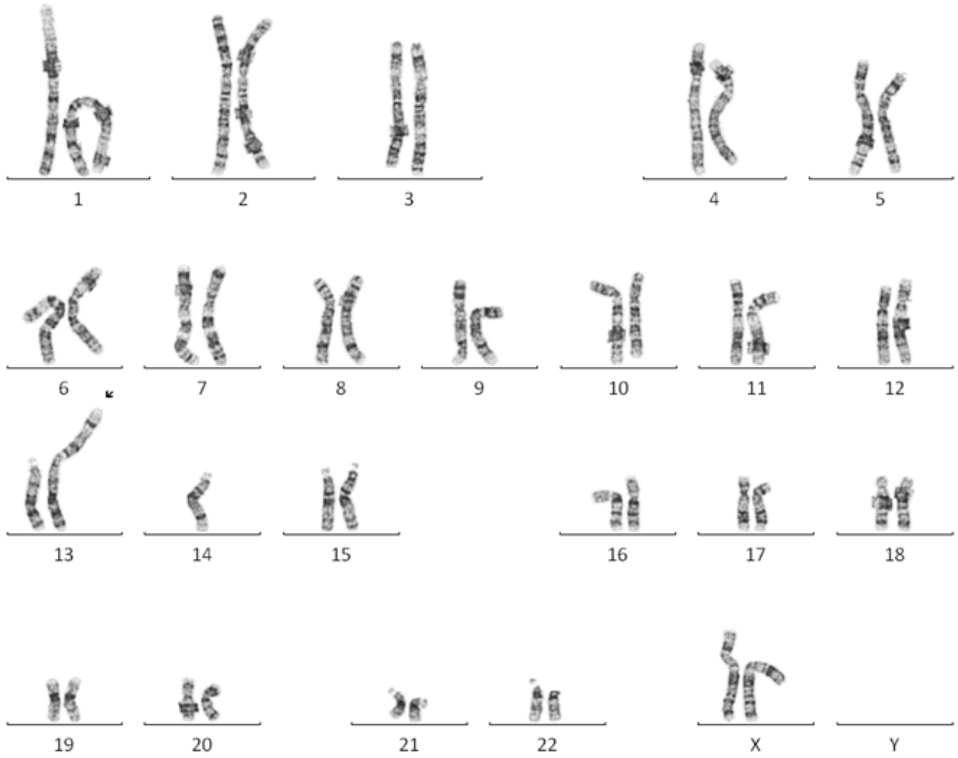
Case: IUFD 24 weeks, fetal tissue, CHR: no grow

Chromosome 13





Maternal chromosome analysis: 45,XX,der(13;14)(q10;q10)



- GMA cannot characterize the structure of copy number changes
- Consideration for recurrence risk should be incorporated into interpretation

Which types of cancers should be studied by GMA?

- Those characterized by recurrent copy number changes
- Those that typically have a normal karyotype (do not grow well in culture or have poor mitotic activity compared to nonmalignant cells)

Examples: ALL, CLL, MDS, MM

Recurrent cytogenetic findings in MDS

Schanz et al., 2012 J Clin Oncol (Table 2)

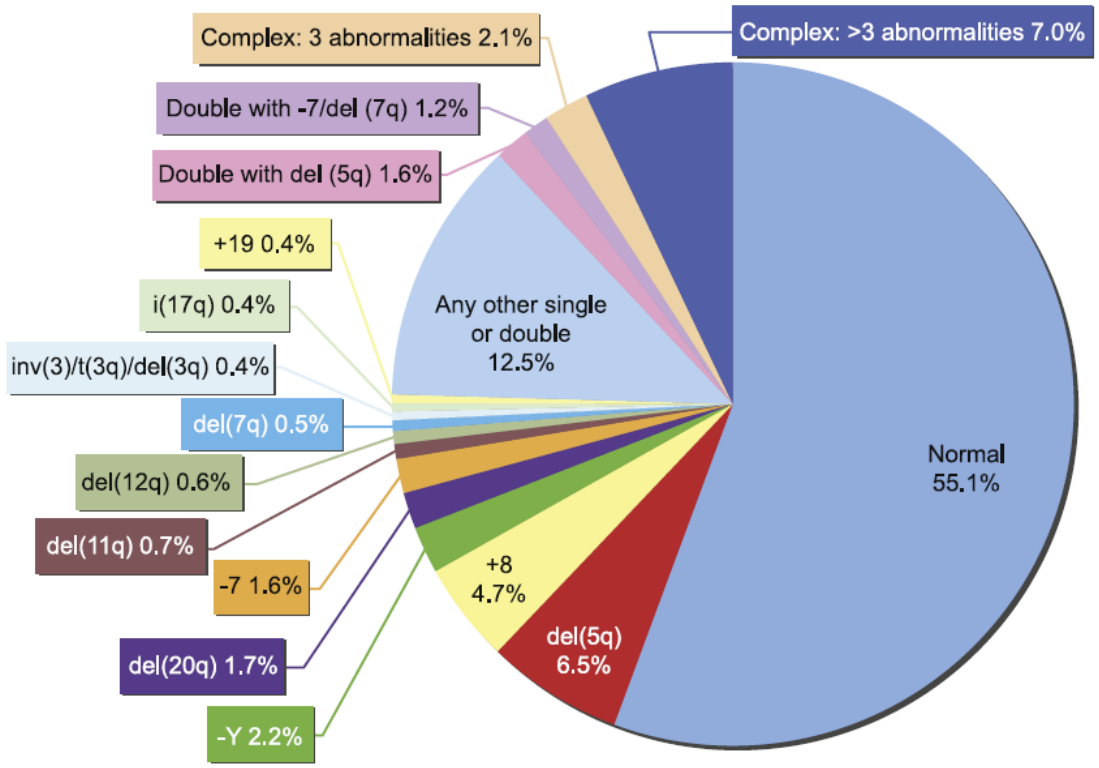


Image source: Nybakken and Bagg, JMD 2014

SNP-A increases the diagnostic yield in MDS from 50% to 70-80%

Normal karyotype (n=296, composite of multiple studies)

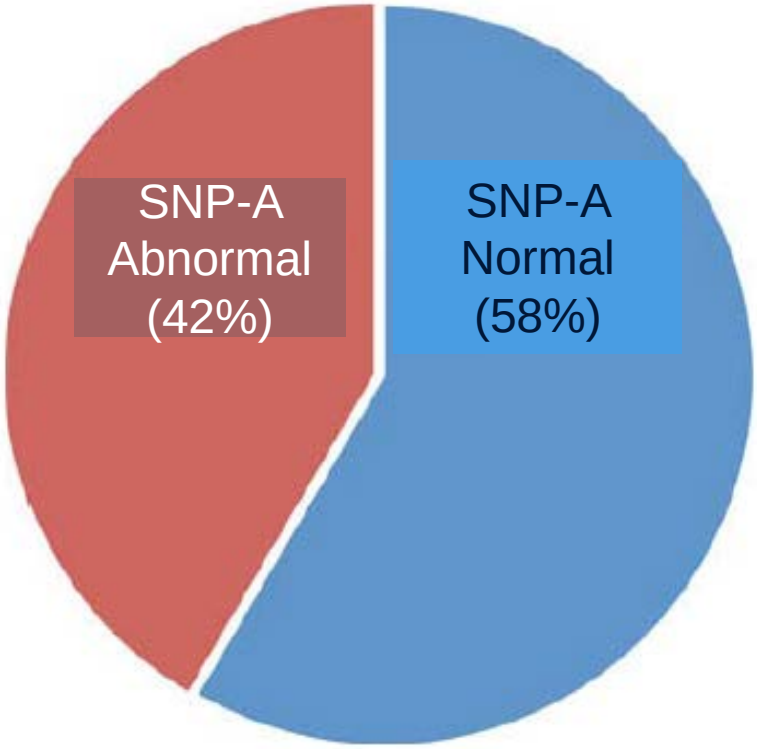
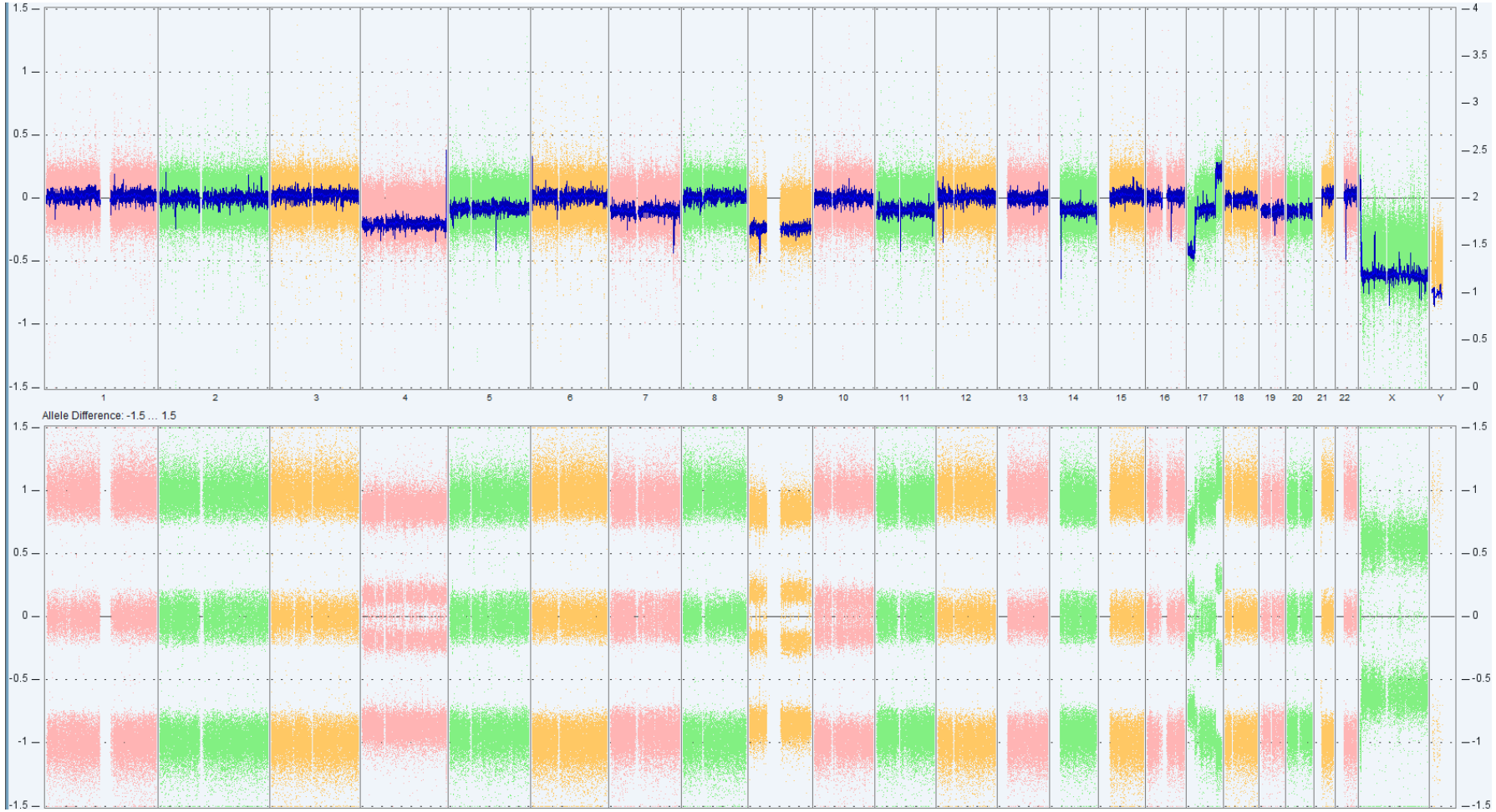


Image source: modified from Kulasekararaj, Br J Haematol 2013

See references: Gondek et al., 2008; Heinrichs et al., 2009; Tiu et al., 2011; others

Example: ALL with no karyotype results due to poor growth in culture, SNP-A shows hypodiploidy



Multiple techniques are employed for the detection of different cytogenetic abnormalities

Technique	Resolution	Sensitivity (mosaicism)	Culturing required?	Global?	Unbalanced abs?	Balanced abs? Structural info?
Chromosome analysis	3-5 Mb (550 bands)	10-15%	Yes	Yes	Yes	Yes
Metaphase FISH	100's kb	n/a	Yes	No	Yes	Yes
Interphase FISH	100's kb	1-5%	No	No	Yes	Yes
Genomic microarray analysis	10-100's kb	10-20%	No	Yes	Yes	No

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Department of Pathology