HST.161 Molecular Biology and Genetics in Modern Medicine
Fall 2007

Harvard-MIT Division of Health Sciences and Technology
HST.161: Molecular Biology and Genetics in Modern Medicine, Fall 2007
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Chromosomes
(part 2)

FISH

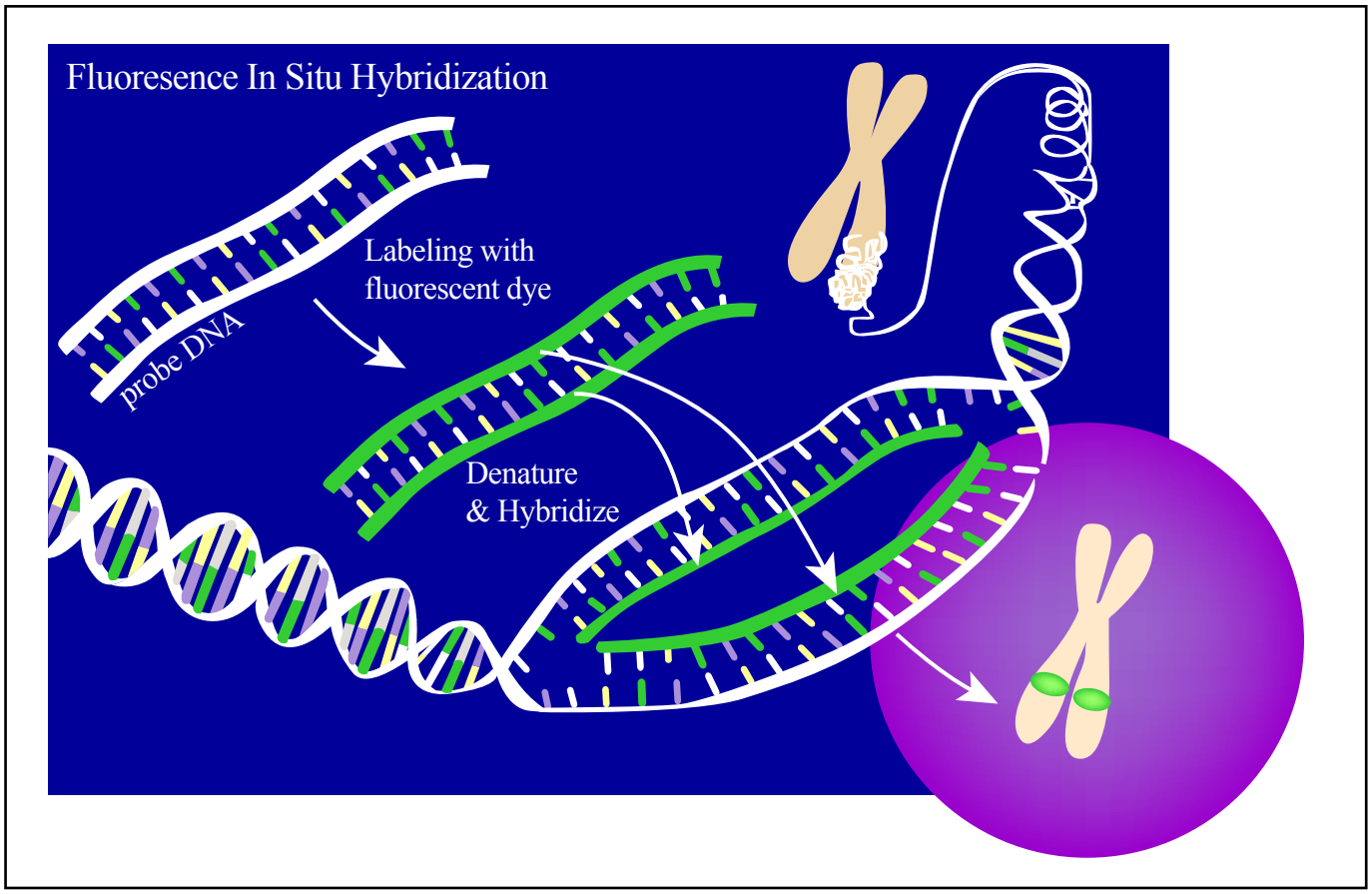

Figure by MIT OpenCourseWare.

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Images of different types of FISH: whole-chromosome paint, multicolor FISH (spectral karyotyping), and rainbow FISH (Rx).

Unbalanced Structural Abnormalities

- Deletions
- Duplications
- Isochromosomes
- Rings
- Markers

Deletions (*a.k.a.*, contiguous gene syndromes, segmental aneusomy syndromes)

- Loss of chromosomal segment; hemizygosity
- Classified as terminal or interstitial
- Phenotype dependent on number, function of genes
- Deletion must be larger than 3 – 5 mb for classical cytogenetic detection
- May be unbalanced result of balanced chromosome rearrangement in parent

Deletion Syndromes

- Classically detectable terminal deletions
  - Wolf-Hirschhorn - 4p-, Cri-du-chat - 5p-, 9p-,18p-,18q-
- Microdeletions (detectable by FISH)
  - Williams syndrome – 7q11.2
  - WAGR syndrome - 11p13
  - Angelman s. / Prader-Willi s. – 15q11-q13
  - Rubinstein-Taybi syndrome – 16p13.3
  - Smith-Magenis s. – 17p11.2
  - Miller-Dieker s. - 17p13.3
  - DiGeorge syndrome / VCFS – 22q11.2
    - » Many more….


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Karyotype of an individual with genotype 46,XX,del(4)(p16).

Wolf Hirschhorn syndrome (4p- syndrome)

- Growth deficiency of prenatal onset
- Microcephaly, skull assymetry
- Prominent forehead (Greek helmet)
- Hypertelorism, Epicanthal folds
- Developmental delay, seizures
- Cleft lip and/or palate, short upper lip
- Low set ears
- Crytorchidism and/or hypospadius
- Heart defects

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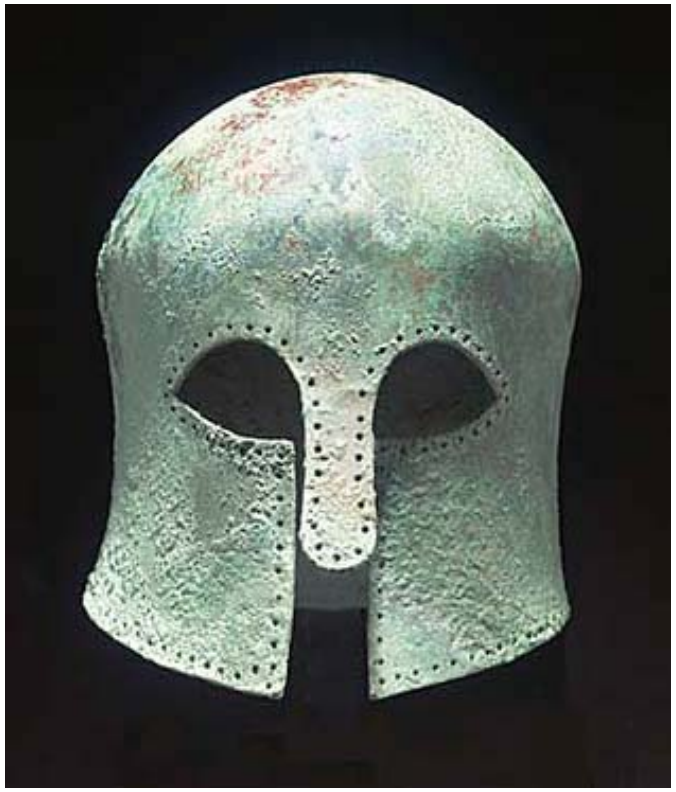
Photographs of children with Wolf Hirschhorn syndrome.



Cri-du-chat (5p- syndrome)

- One of most common deletion syndromes
  del(5)(p15.2) (critical region)
- Characteristic high-pitched cry - diagnostic
- Low birth weight, hypotonia
- Microcephaly, micrognathia
- Round face, low set ears
- Feeding difficulties
- Mental retardation

Cri-du-chat syndrome

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Photographs of children with Cri-du-chat syndrome, from specialchild.com and criduchat.asn.au.

Image from

www.specialchild.com

Image and wav from
www.criduchat.asn.au

DiGeorge syndrome / velo-cardio-facial s. (DGS/VCFS)

high arched or cleft palate
thymus aplasia or hypoplasia
conotruncal cardiac defects
mildly dysmorphic features
developmental delay

VCFS phenotypically milder than DGS


Images removed due to copyright restrictions.
Photographs of young people with DiGeorge syndrome.

ish del(22)(q11.2q11.2)(TUPLE1-)

Image removed due to copyright restrictions.
Image of fluorescent chromosomes; ish del(22)(q11.2q11.2)(TUPLE1-).

Image removed due to copyright restrictions.
Chromosomal map.

• The deletions which cause DGS are most frequently caused by unequal crossover between repeat sequences at positions A and D which are ~ 3 megabases apart

Mechanisms of chromosome rearrangements mediated by low copy repeats

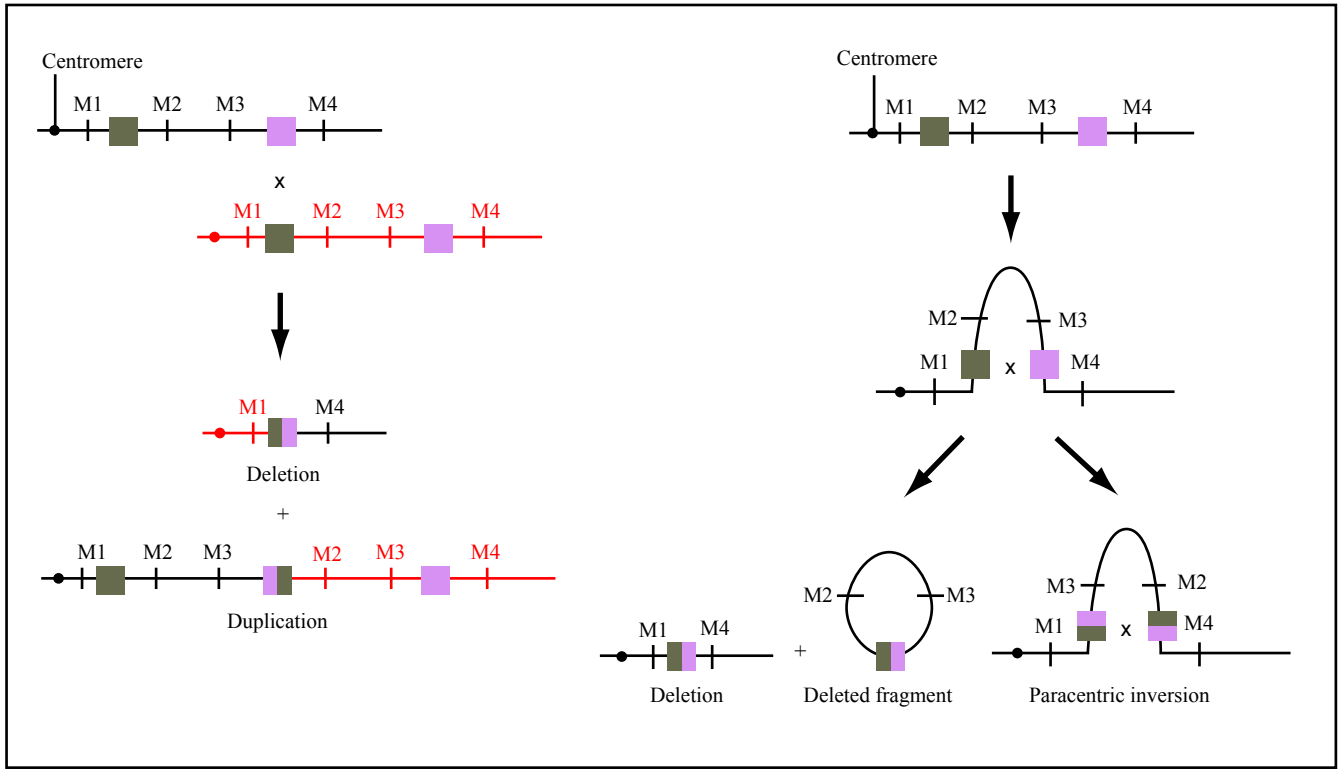

Figure by MIT OpenCourseWare.

Interchromosomal

Intrachromosomal

Genomic disorders mediated by segmental duplications (LCRs)			
Genomic disorder	Chromosomal rearrangement	Chromosomal location	Rearrangement size (Mb)
Charcot-Marie-Tooth disease type 1A (CMT1A)	Interstitial duplication	17p12	1.5
Hereditary neuropathy with pressure palsies (HNPP)	Deletion	17p12	1.5
Smith-Magenis syndrome (SMS)	Deletion	17p11.2	5
Duplication 17p11.2	Interstitial duplication	17p11.2	5
Neurofibromatosis type1 (NF1)	Deletion	17q11.2	1.5
Prader-Willi syndrome (PWS)	Deletion	15q11-15q13	4
Angelman syndrome (AS)	Deletion	15q11-15q13	4
Inverted duplication 15 (inv dup (15))	Supernumerary marker chromosome	15q11-15q14	4
Williams-Beuren syndrome (WBS)	Deletion	7q11.23	1.6
DiGeorge and velocardiofacial syndromes (DGS/VCFS)	Deletion	22q11.2	3
Cat eye syndrome (CES)	Supernumerary marker chromosome	22q11.2	3
X-linked ichthyosis	Deletion	Xp22	1.9
Haemophilia A	Inversion	Xq28	0.5

Markers (a.k.a. ESACs)

- By definition, unknown chromosomal origin
- With FISH, most “markers” can now be described
- Phenotype depends on size, copy number, % cells w/ marker, chromosomal origin
  - X markers can be more severe than supernumerary X chromosome

Ring Chromosomes

- Formation: breakage in both arms followed by fusion at breakpoints with loss of distal fragments (deletion)
- Mitotic Instability (Recombination)
  - –increase in size leads to increased instability
- Small rings can be supernumerary; phenotype can depend on copy number

Ring Chromosomes

- Ring chromosomes are formed when a chromosome undergoes two breaks and the broken ends of the chromosome reunite in a ring structure.
- Have been detected for every human chromosome.

Image removed due to copyright restrictions.
Illustration of a ring chromosome.

Taken from Thompson & Thompson Genetics in Medicine 6th ed.

Fragile sites

- Appear as constriction or unstained region
- Inducible by specific culture conditions
- Only 3 fragile sites assoc. w/ pathology
  - FRAXA Xq27.3 Fragile X syndrome
  - FRAXE Xq28 X-linked mild MR
  - FRA11B 11q23 ??Jacobsen syndrome
- >100 fragile sites exist as normal variants
- May be implicated in cancer


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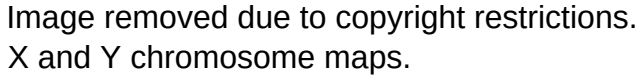
Differentiation of male and female gonads; see http://herkules.oulu.fi/isbn951426844X/html/graphic11.png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X and Y chromosome maps.

Y Chromosome

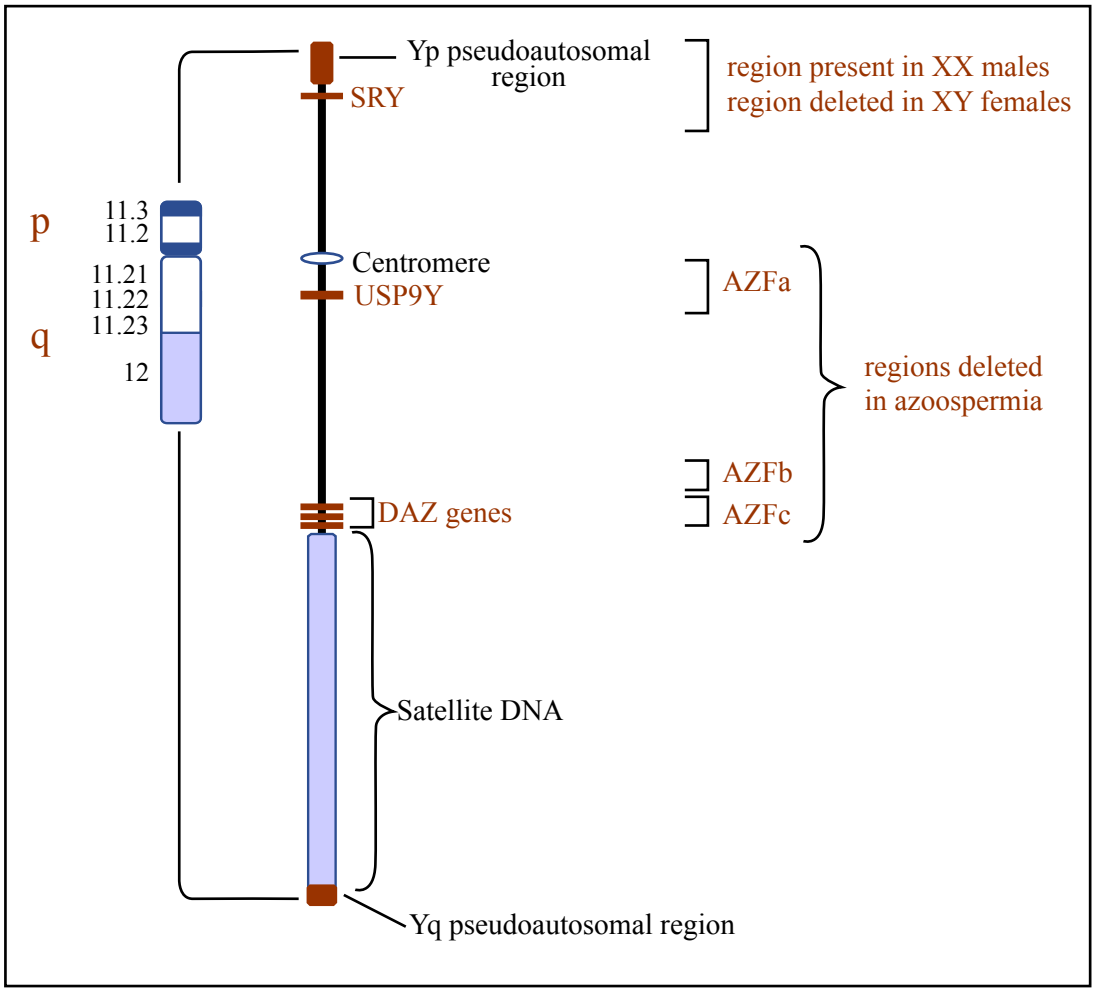

Figure by MIT OpenCourseWare.

Adapted from Thompson and Thompson; Genetics in Medicine

Important Y Chromosome Genes

- *SRY* gene (TDF)
  - Maps just proximal (5 kb) to PAR1; Yp11.3
  - Not sufficient for normal male sexual differentiation
- *AZF* (azoospermia factor) genes on Yq
  - 3 non-overlapping *AZF* regions (e.g., *DAZ*, *USP9Y*)
  - 10% males with idiopathic azoospermia/severe oligospermia deleted in this region
  - Necessary, but not sufficient for spermatogenesis

Dosage Compensation (Mammals)

- Inactivation of all but one one X chromosome per cell
- Lyon Hypothesis (1961)
  - In phenotypically normal females only a single X chromosome is active
  - X-inactivation occurs early in development (blastocyst)
  - Inactivation is random
  - Inactivation is clonal and irreversible in somatic cells

Numerical Abnormalities of the Sex Chromosomes

Frequencies of sex chromosome aneuploidies

- 1/400-1/500 liveborns
- Most common:
  - 47,XXX (~1/1000females)
  - 47,XXY (~1/1000 males)
  - 47,XYY (~1/1000 males)
- Turner syndrome: 45,X (~1/5000 females)
    - »~ 1-2% of all conceptuses
    - »~20% of all SAB

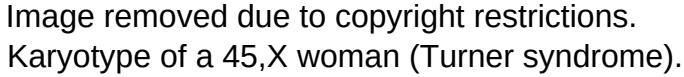
Image removed due to copyright restrictions.
Karyotype of a 45,X woman (Turner syndrome).

Turner Syndrome Phenotype

- **Short stature** (under 5 ft): *SHOX* gene maps in PAR
- **Gonadal dysgenesis** (usually streak)
- Fetal **cystic hygroma** (lymphedema)
  - Post-natal neck webbing
- Low posterior hairline, shield chest with widely spaced nipples, cubitus valgus, **coarctation of aorta** and renal anomalies
- Deficiencies in spatial perception, perceptual motor organization and fine motor skills
- Fully viable, though **99% of 45,X conceptuses are lost**

Turner syndrome

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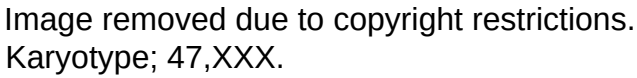
Photographs of a girl with Turner syndrome.

www.endocrineonline.org/ ts.htm

Karyotypes in Turner Syndrome

- ~ 50% show 45,X
- Remaining 50%:
  - 46,X,i(Xq) ~15%
  - 45,X/46,XX ~7%
  - 45,X/46,X,i(Xq) ~5%
  - 45,X/ 46,X,r(X) ~16%
  - 45,X/46,X,del(Xp) ~5%
  - Other ~2%

- 45,X/46,XY ascertained through clinic visits
  - Phenotype ranges from females with classical TS to infants with ambiguous genitalia to normal but infertile males
  - **Risk for gonadal tumors**
- 45,X/46,XY ascertained prenatally
  - Phenotypically male infant 90-95% of the time
  - ? Normal fertility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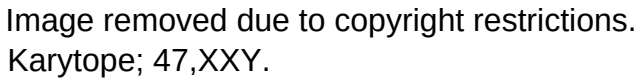
Karyotype; 47,XXX.

47,XXX: Phenotype

- Physically normal with normal sexual development and usually **normal fertility**
- Many taller than average
- IQ 10-15 points lower than siblings
- Language delay, learning disabilities and impaired gross motor skills often exist
- Increased frequency of psychosocial disorders

Sex chromosome abnormalities--males

47 XXY--Klinefelter syndrome	• 1/1,000
48 XXXY--Klinefelter syndrome	• 1/25,000
47 XYY	• 1/1,000
Other X or Y abnormalities	• 1/1,500
XX males	• 1/20,000
Overall incidence Males	**~ 1/400**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Karytope; 47,XXY.

Klinefelter Syndrome: Phenotype

- Hallmark features: hypogonadism, androgen deficiency and **impaired spermatogenesis**
- Variable, but classic features:
  - Tall, thin, long legs
  - Feminine distribution of body fat, gynecomastia
  - Underdeveloped, secondary sexual characteristics with small, firm testes and sparse body hair
- Reduced IQ (particularly verbal), dyslexia, ADD

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Illustration and photographs of people with Klinefelter syndrome.

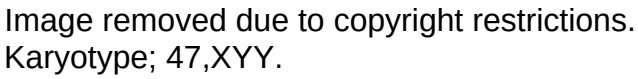
Image removed due to copyright restrictions.
Karyotype; 47,XYY.

47,XYY: Phenotype

- Increased height
- Increased risk of behavioral problems
- Possibly some reduction in IQ
- **Normal fertility**

Sex Chromosome Tetrasomy and Pentasomy

- Rare
  - case reports only (no unbiased ascertainment studies)
- Phenotype more severe with each additional chromosome
  - more severe for X than for Y
- Supernumerary X chromosomes
  - Reduced IQ
  - Skeletal and cardiovascular abnormalities
  - In males, malformed genitalia (and **infertility**)
  - In females, effect on fertility unclear

Y Chromosome Structural Aberrations

- Sterility
  - Most of the euchromatic region must be present for germ cell development
- No phenotype
  - Most of the heterochromatic region can be deleted, rearranged without phenotypic effect

PGD - Preimplantation Genetic Diagnosis

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Take one cell from 8 cell embryo after IVF.
Perform diagnostic test for specific condition or disease.

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Single-cell FISH assays to determine chromosome balance in the blastomere.