University Medical Center *Ljubljana*

Indikacije za citogenetsku obradu ženske neplodnosti / Indications for karyotyping of infertile women

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Objectives

- describe observation of chromosomes and indications for karyotyping
- share the Slovenian experience with you

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Karyotype

- complete **set of chromosomes** in a species or an individual organism

- usually **displayed** as a systematized arrangement of chromosome pairs in descending order of size

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How many chromosomes

- Investigation into the human karyotype took many years to settle the most basic question:

normal diploid human cell contain?

Hans von Winiwarter
in 1912 reported
47 *chromosomes in spermatogonia and* ***48*** *in oogonia*

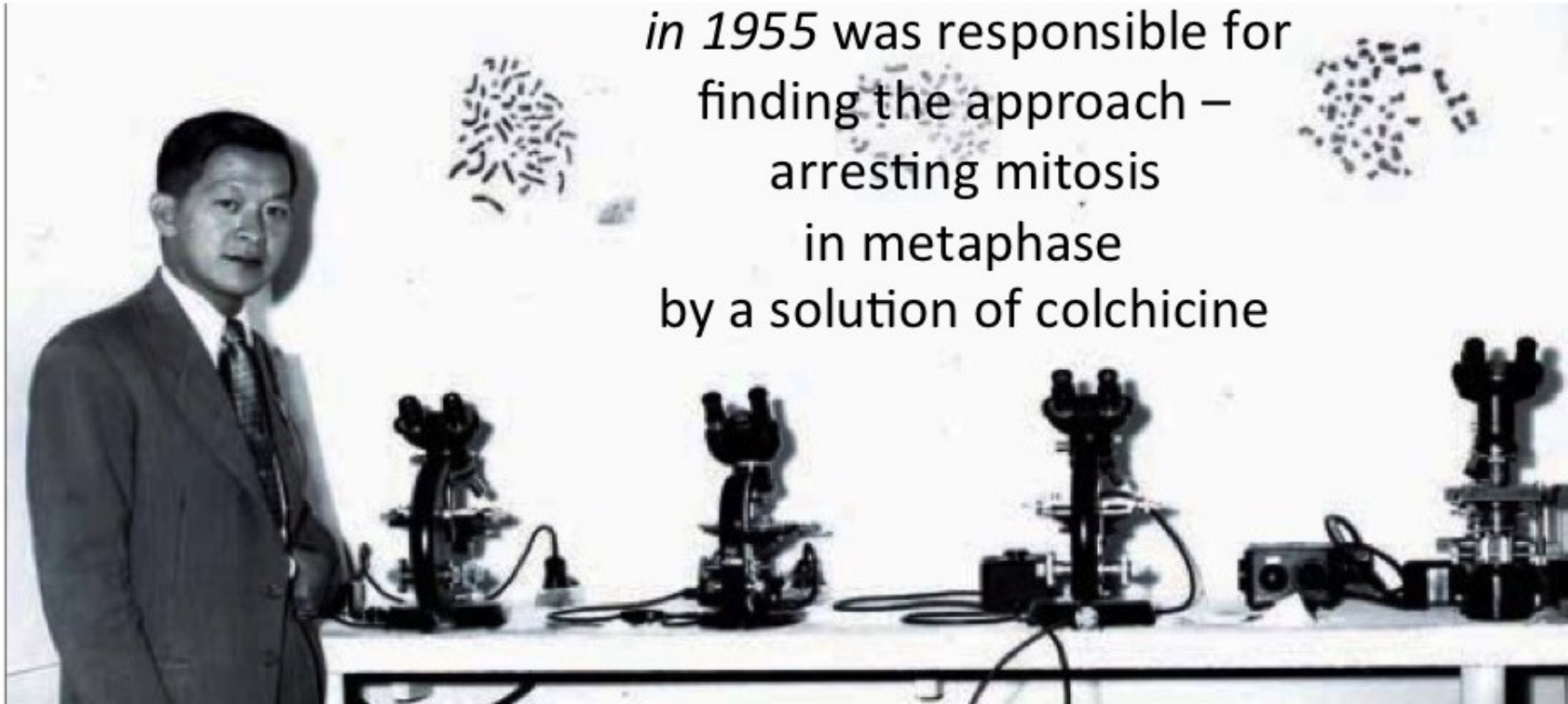
http://culture.ulg.ac.be/jcms/prod_62841/fr/

How many chromosomes

- In textbooks, the **number** of human chromosomes remained at **48** for over 30 years

Joe Hin Tjio

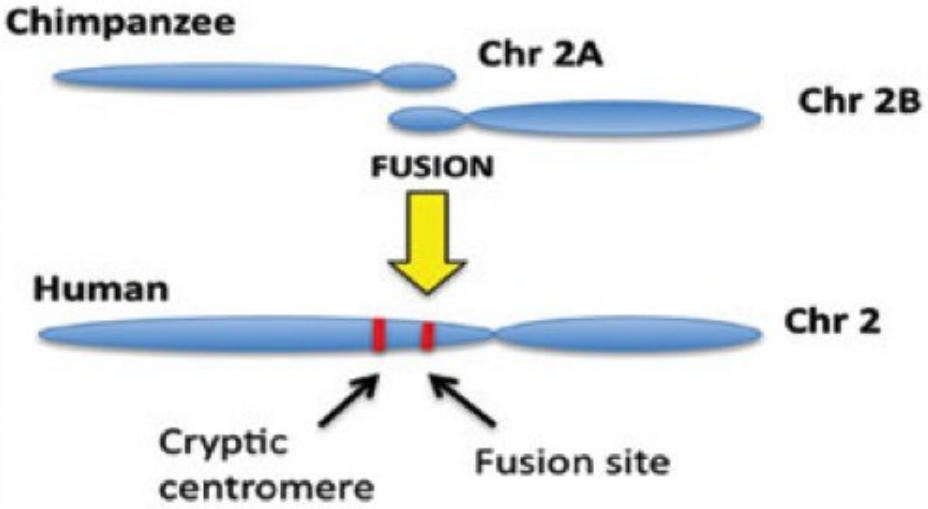
in 1955 was responsible for finding the approach – arresting mitosis in metaphase by a solution of colchicine



http://alchetron.com/Joe-Hin-Tjio

How many chromosomes

- great apes have **48** chromosomes
- human chromosome **2** is now known to be a result of an **end-to-end fusion** of two ancestral ape chromosomes



Observation of chromosomes

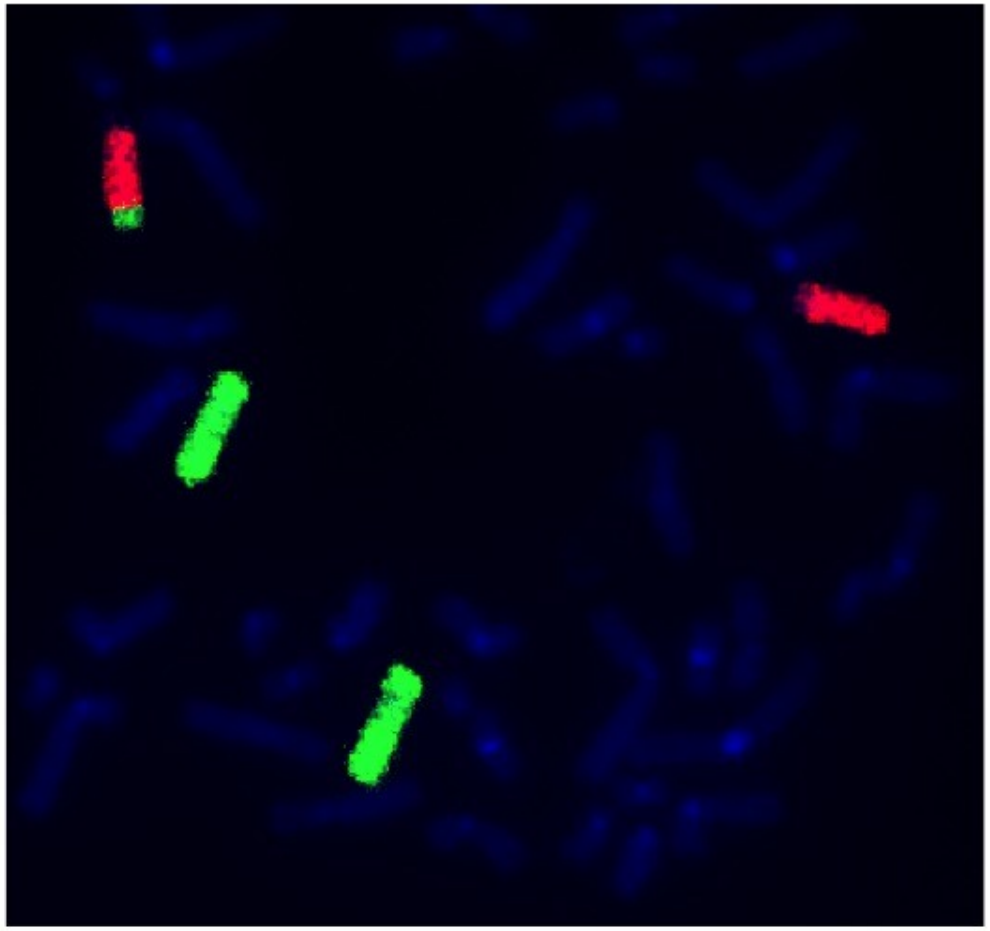
Gersak K. Genetsko svetovanje in prenatalna diagnostika. In: Ginekologija in perinatologija, 2016.

Classic karyotype cytogenetics

often obtained with *Giemsa staining*

produce 300–400 bands in a human genome

Observation of chromosomes

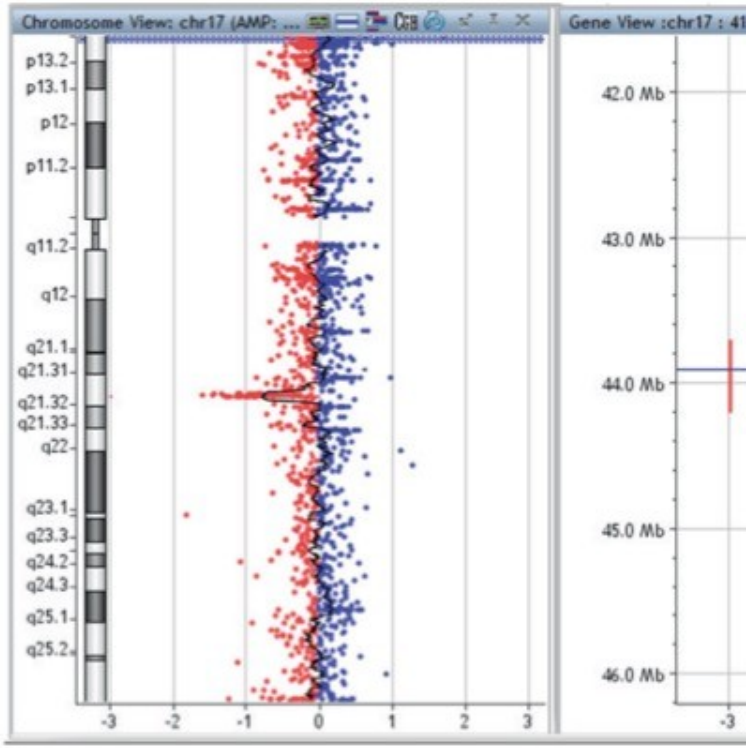


Bregant L, Geršak K, Veble A. Genet Couns. 2005;16:59-63.

Fluorescence
***in situ* hybridization**
cytogenetic technique
uses fluorescent probes
to detect
presence or absence
of specific parts
of the chromosome

Observation of chromosomes

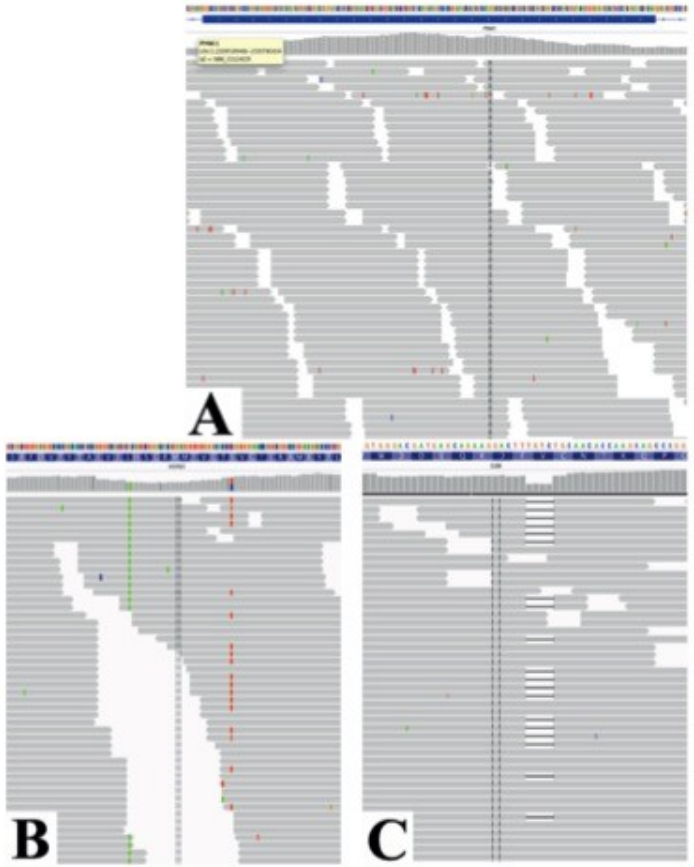
Array comparative genomic hybridization (a-CGH)
molecular cytogenetic technique
for analysing
copy number variations
of DNA in a test sample
compared to
a reference sample



Lovrečić L. Molekularna citogenetika. In: Genetika v ginekologiji, 2015.

Observation of chromosomes

Next-generation sequencing
(NGS or exome)
molecular technique
for determination of
the precise order
of nucleotides
within a DNA molecule;
individual genes,
larger genetic regions,
full chromosomes, entire genome



Maver A. Nova generacija sekvenciranja. In: Genetika v ginekologiji, 2015.

what are the indications for karyotyping?

- during pregnancy
- perinatal period
- during infancy and adolescence
- in adulthood

karyotyping of infertile women

abnormal
menstrual cycle

recurrent
pregnancy loss

prior to assisted
reproduction
techniques

developmental
anomalies

karyotyping of infertile women

associated with
functioning ovaries and
age-appropriate
external genitalia

anomalies of müllerian
duct system range from
agenesis to duplication

developmental anomalies

karyotyping of infertile women

associated with
functioning ovaries and
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external genitalia

anomalies of müllerian duct system range from agenesis to duplication

developmental anomalies

cytogenetics:
translocation t(12;14),
monosomy of 10q26

molecular cytogenetics:
microdeletions at
1q21.1, 16p11.2,
17q12, 22q11.21,
Xq21.31

karyotyping of infertile women

hypogonadotropic
hypergonadotropic

described as anemorhoea
hypogonadism
gonadal dysgenesis

abnormal menstrual cycle

karyotyping of infertile women

hypogonadotropic
hypergonadotropic

described as anemorhoea
hypogonadism
gonadal dysgenesis

abnormal menstrual cycle

cytogenetics:
translocation t(7;8)
8p11 ***KAL 2*** *(FGFR1)*
encoding
fibroblast growth factor receptor-1

molecular cytogenetics:
microdeletions at
8p12-p11,
Xp22.3 ***KAL 1***

karyotyping of infertile women

hypogonadotropic
hypergonadotropic

described as anemorhoea
hypogonadism
gonadal dysgenesis

abnormal menstrual cycle

cytogenetics:
X chromosome
abnormalities

molecular cytogenetics:
deletions at
Xq21.3–Xq27 (***POF1***),
Xq13.3–q21.1 (***POF2***)

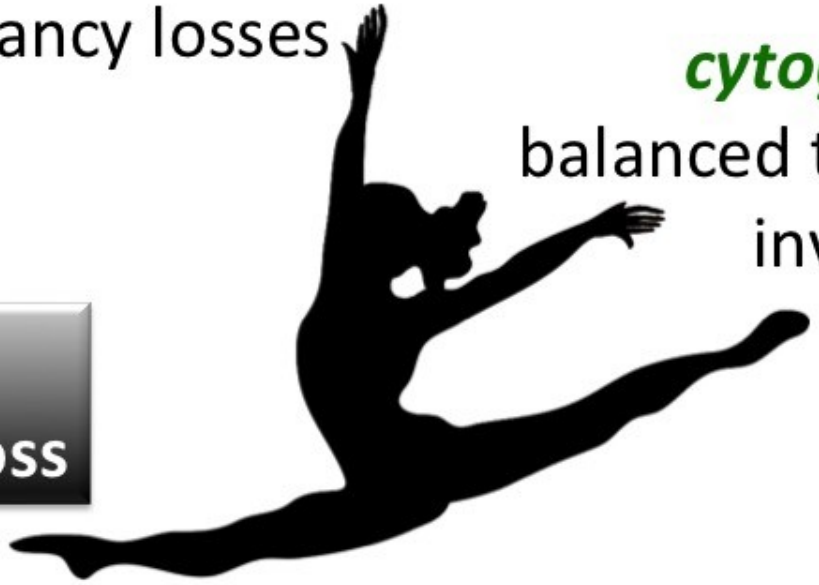
karyotyping of infertile women

associated with
anatomical conditions,
endocrine disorders
and immune factors

defined by three or more
consecutive pregnancy losses

cytogenetics:
balanced translocations,
inversions

recurrent pregnancy loss



karyotyping of infertile women

including
chromosome
aberrations and
single gene mutations

10% of infertile women
show genetic abnormalities

prior to assisted reproduction techniques

cytogenetics:
X chromosome
abnormalities,
inversions

our experience

abnormal
menstrual cycle

recurrent
pregnancy loss

developmental
anomalies

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our experience

developmental anomalies

a-CGH is used during the last 4 years

UMC Ljubljana, Clinical Institute of Medical Genetics

11 women with Mayer-Rokitansky-Kuster-Hauser syndrome

1 microdeletion at 1q21.1

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our experience

abnormal menstrual cycle

10-years period
197 women with at least
6 months of amenorrhoea
referred to
Clinical Institute of Medical Genetics, UMC Ljubljana

65 women 45,X (***33%***),
18 women balanced translocation with X involved (***9%***),
25 women
X mosaicism (***13%***)

Geršak K, Veble A. RBMO 2011;22:399– 403

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our experience

recurrent pregnancy loss

karyotyping
10-years period
UMC Ljubljana, Clinical Institute of Medical Genetics

424 women with regular menstrual cycles

67 translocations (***16%***),
39 X mosaicism (***10%***)

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In summary

- array-comparative genomic hybridization (a-CGH) and next-generation sequencing (NGS or exome) technologies have swiftly spread throughout the medical field

In summary

- array-comparative genomic hybridization (a-CGH) and next-generation sequencing (NGS or exome) technologies have swiftly spread throughout the medical field
- however, they fail to detect chromosomal rearrangements because breakpoints are either located in introns or not associated with a gain or loss of genetic material

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In summary

- **karyotype, this old-fashioned genetic tool**, can still remain powerful, cheap technology and useful within some genetic issues which also involve **female infertility**

Thank you

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