Prä- und postnatale diagnostische und prädiktive genetische Testung

Öffentliche Anhörung des Deutschen Ethikrates

22.03.2012

K.R. Held

genteQ

Reprogenetics

genetische Basisrisiken

- A.Manifestation beim Neugeborenen
- Chromosomenstörungen 0,4%
- monogene Störungen 1,0%
- multifaktorielle Störungen 3,0%
- B.Manifestation beim Erwachsenen
- monogene Störungen 4,0%
- multifaktorielle Störungen 100 %

Schmidtke, 2001

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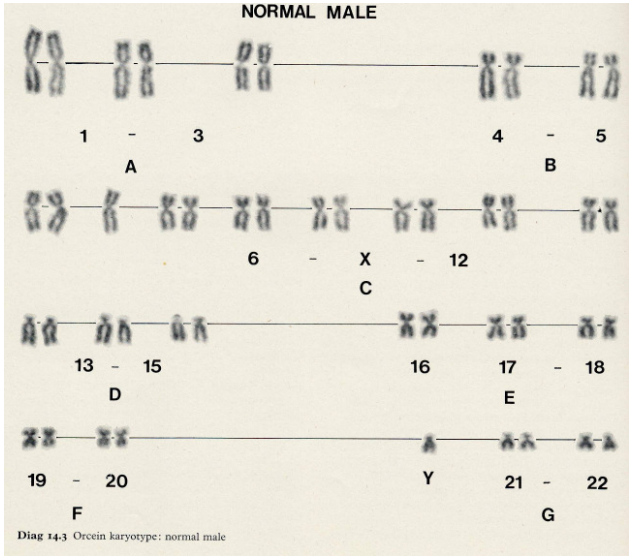
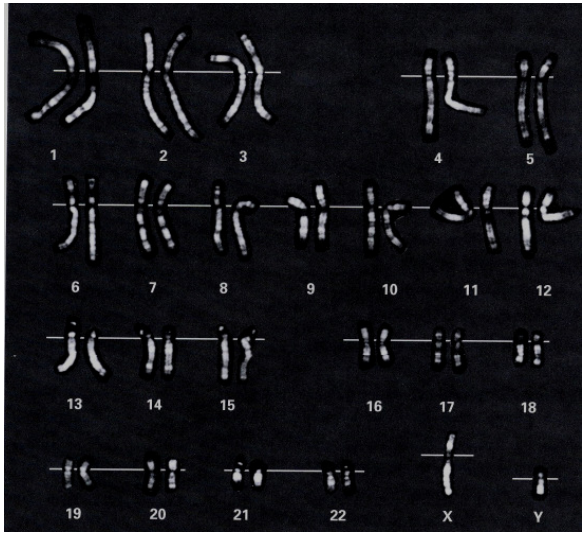
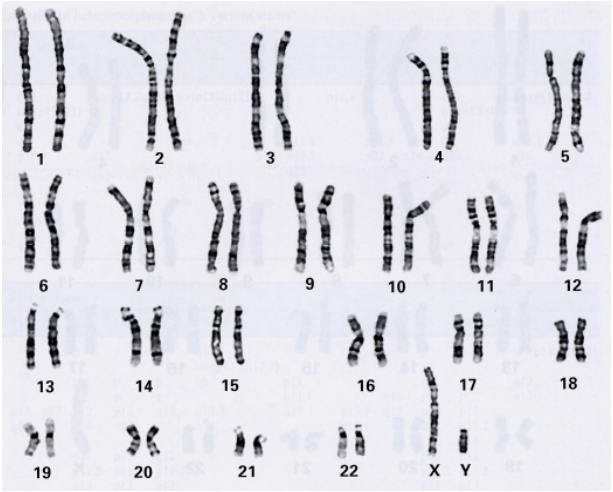
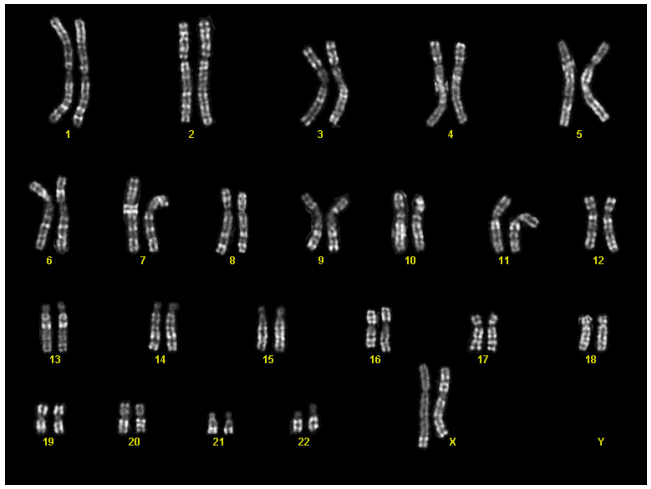
Entwicklung der zytogenetischen Bänderungstechniken



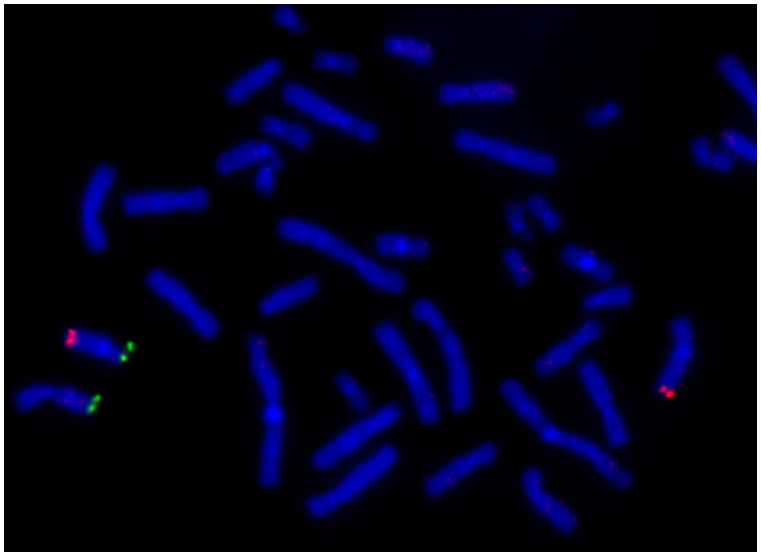
Diag 14.3 Orcein karyotype: normal male

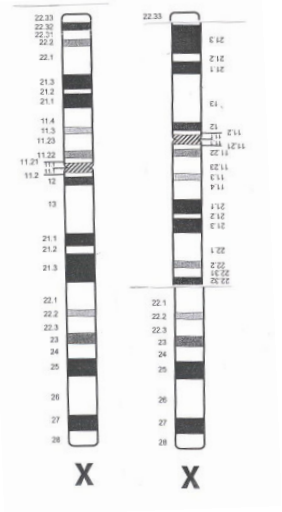


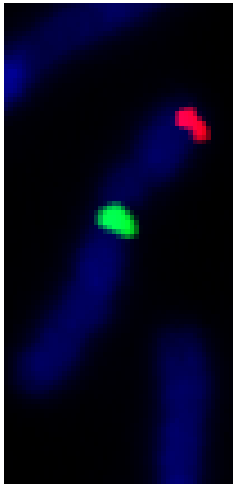


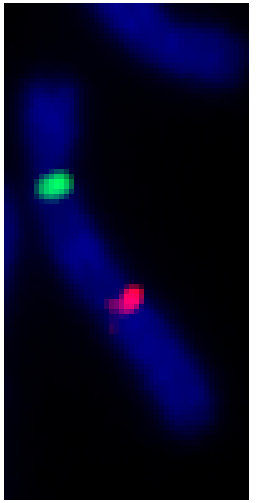


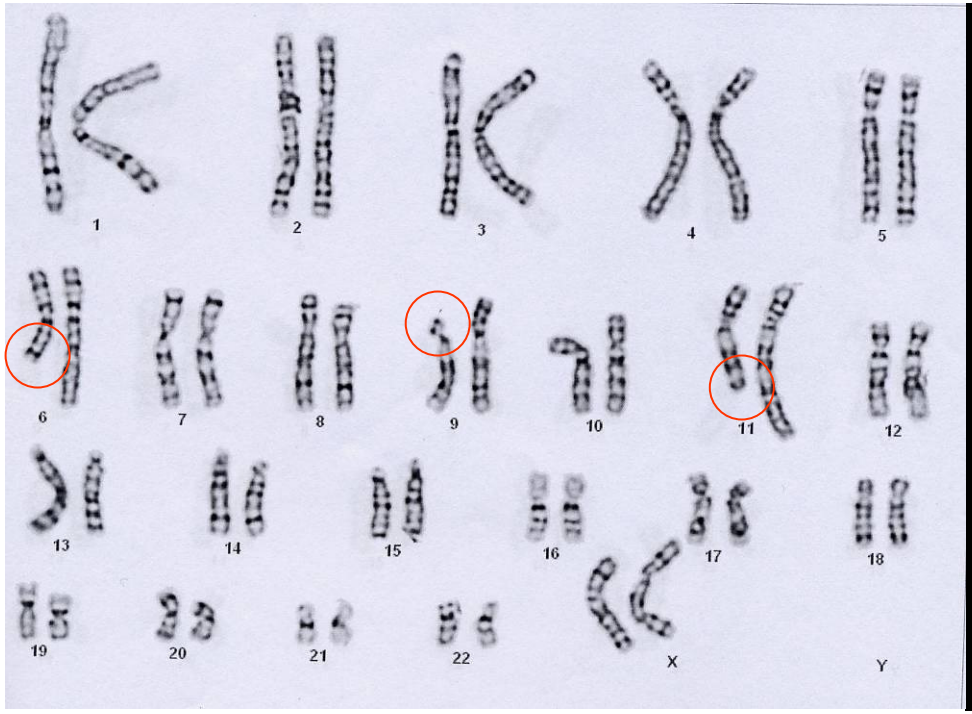
Moderne FISH Techniken

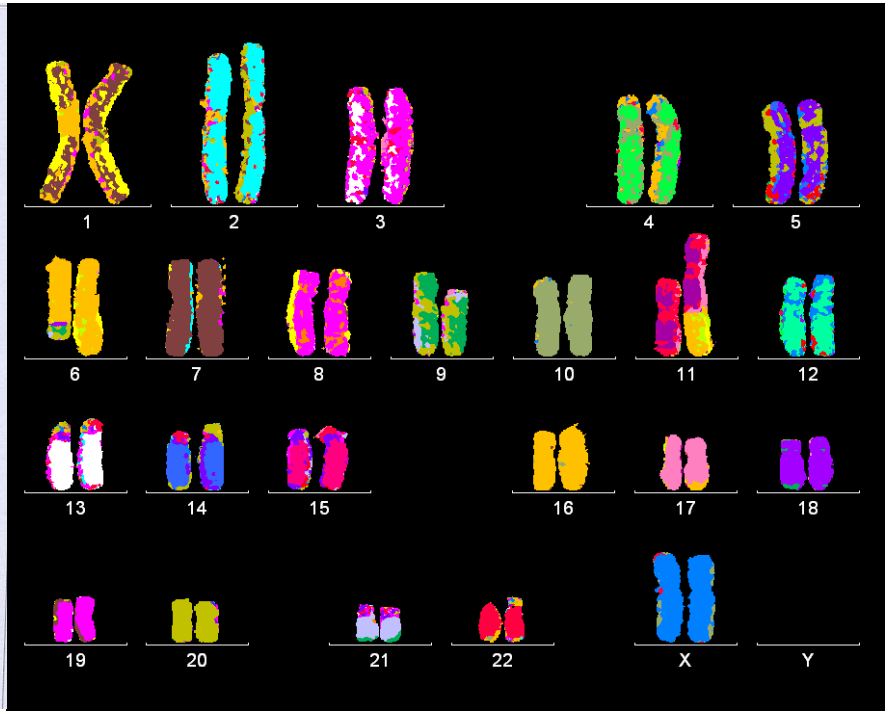






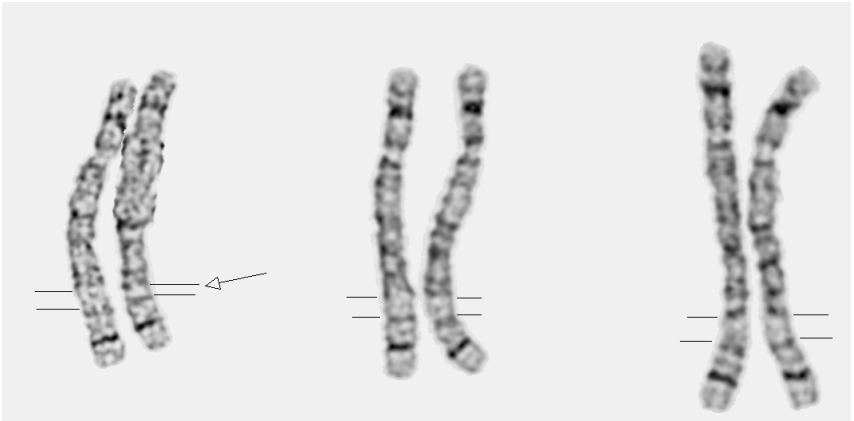


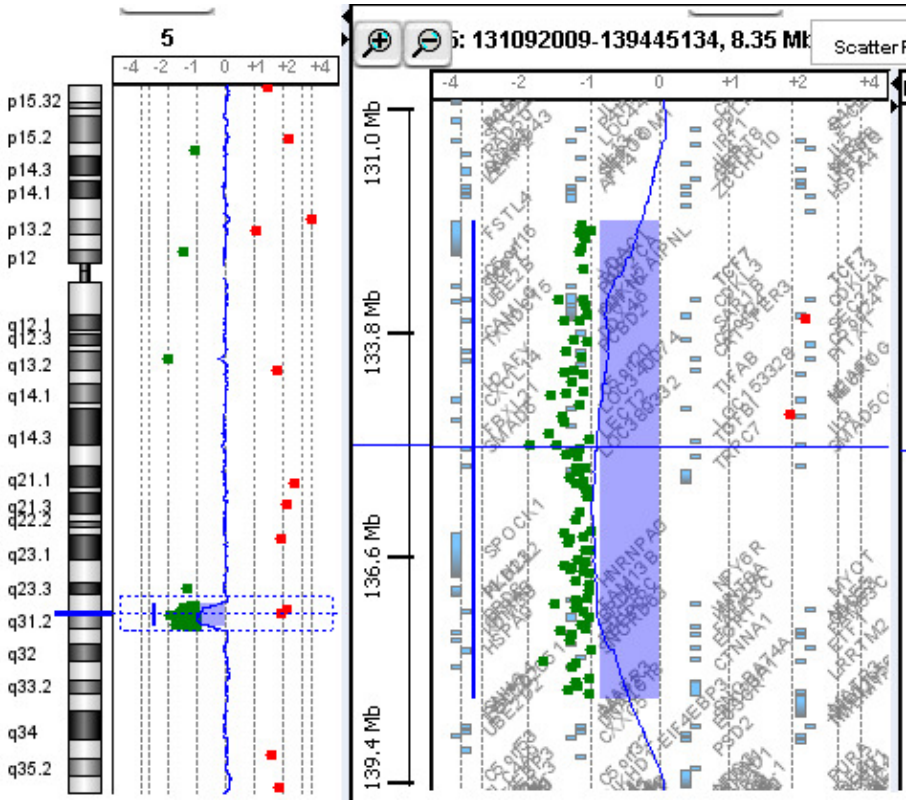




Deletion 5q

Ultraschallbefund: IUGR, Corpus cal-losum Agenesie, Hypotelorismus, Polydactylie, VSD





Deletion 5q schließt das Gen *PITX1 ein*. (Gurnett et al. 2008)

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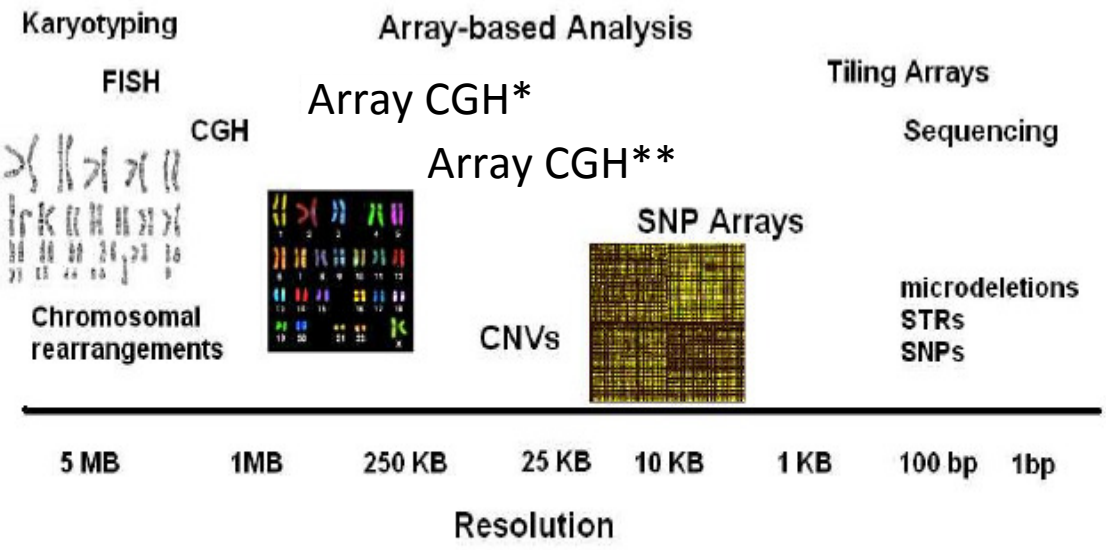
aCGH vs. SNP arrays: Resolution

Reprogenetics

More resolution, more counseling nightmares:

Abnormalities smaller than 5MB are not well understood and difficult to counsel

- **At 150 Kb resolution 50% of people have CNVs: it is difficult to differentiate a new polymorphism from an abnormality**

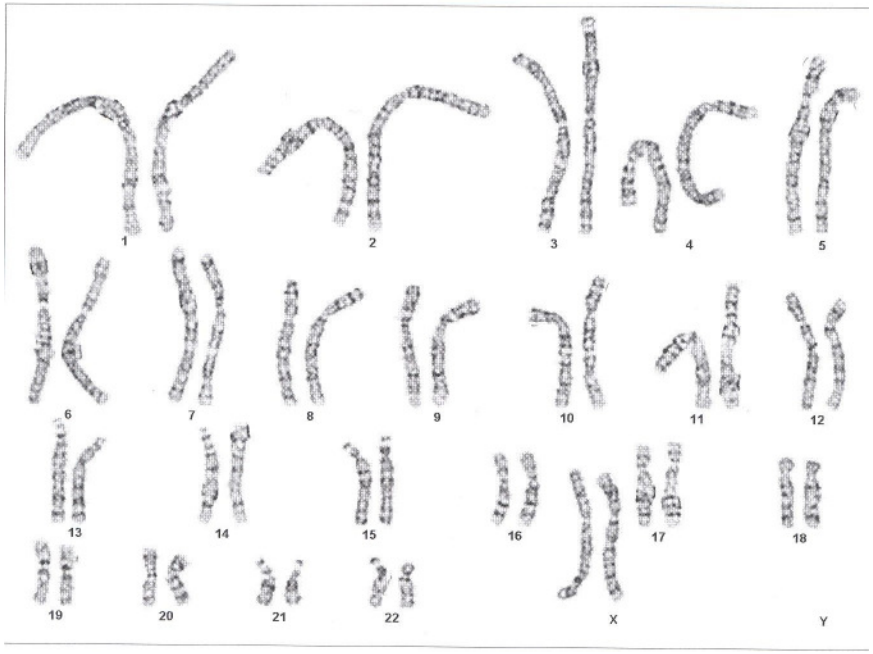


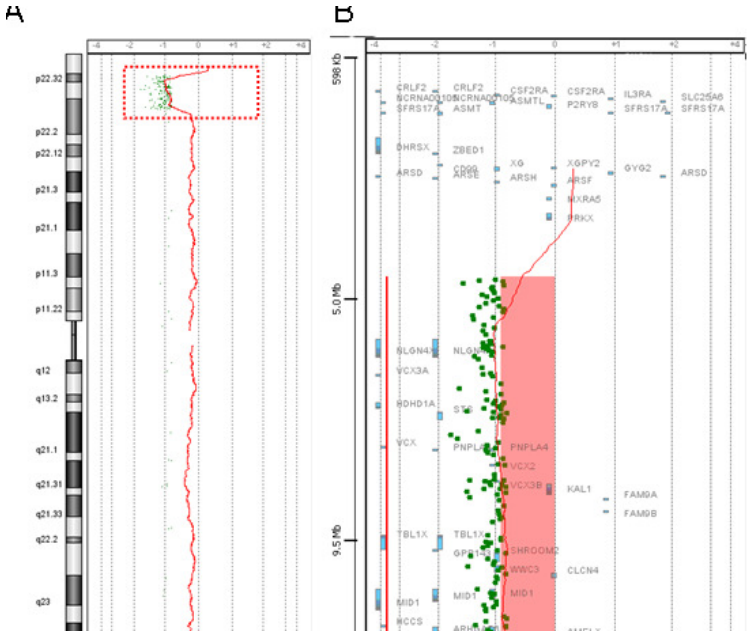
illumina

* Bac array, ** oligo array

Deletion Xp22.2p22.3

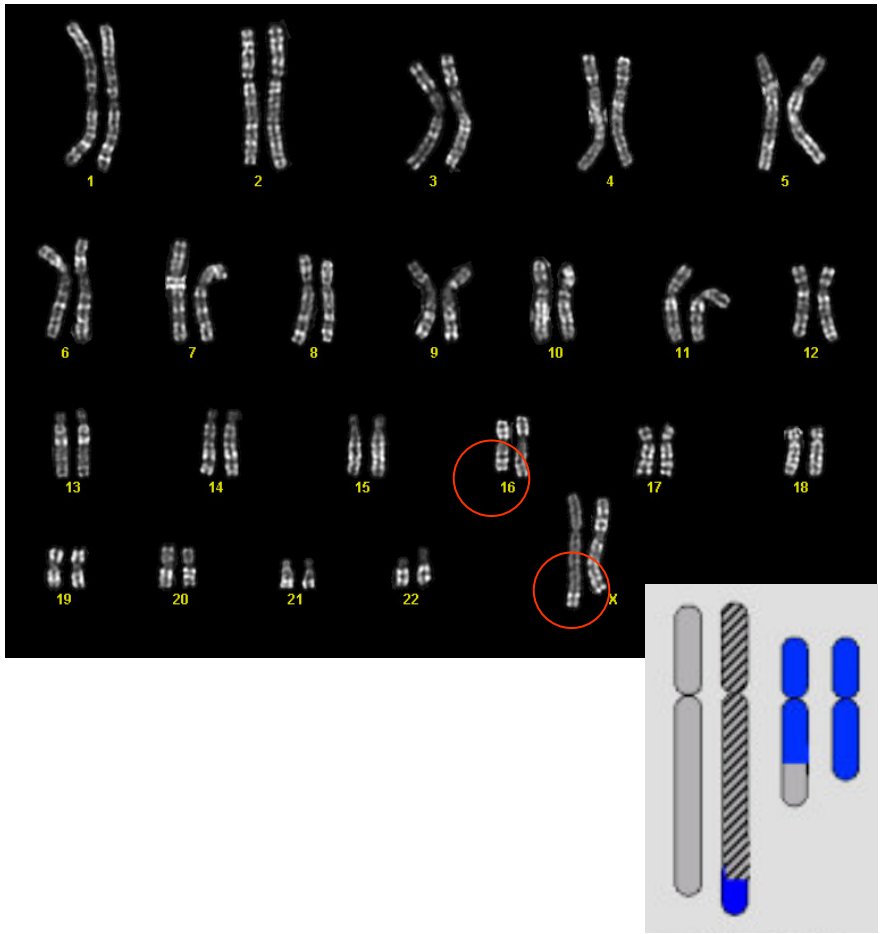
Ultraschallbefund: Mikrophthalmie, Hydrozephalus, Corpus callosum Agenesie

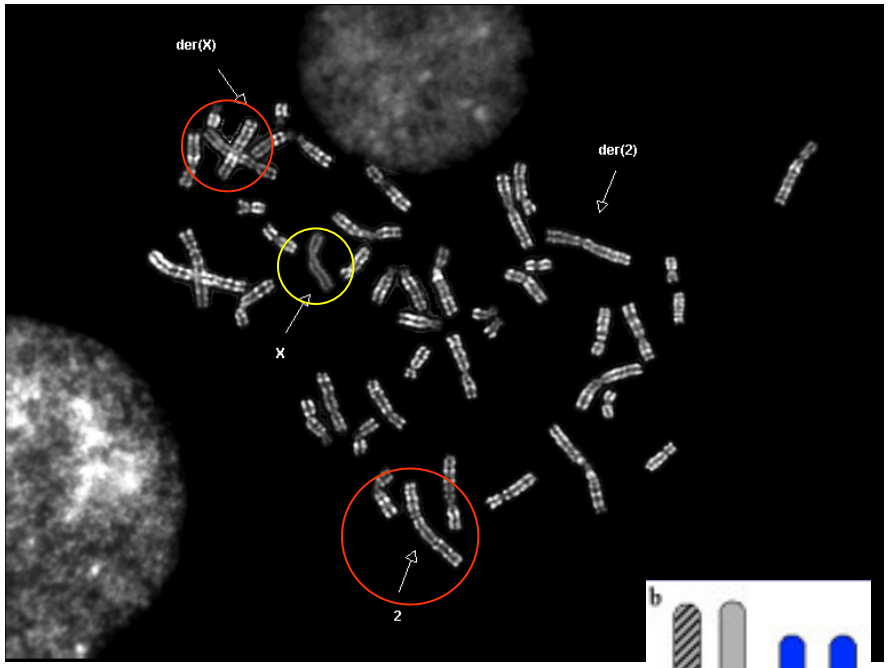




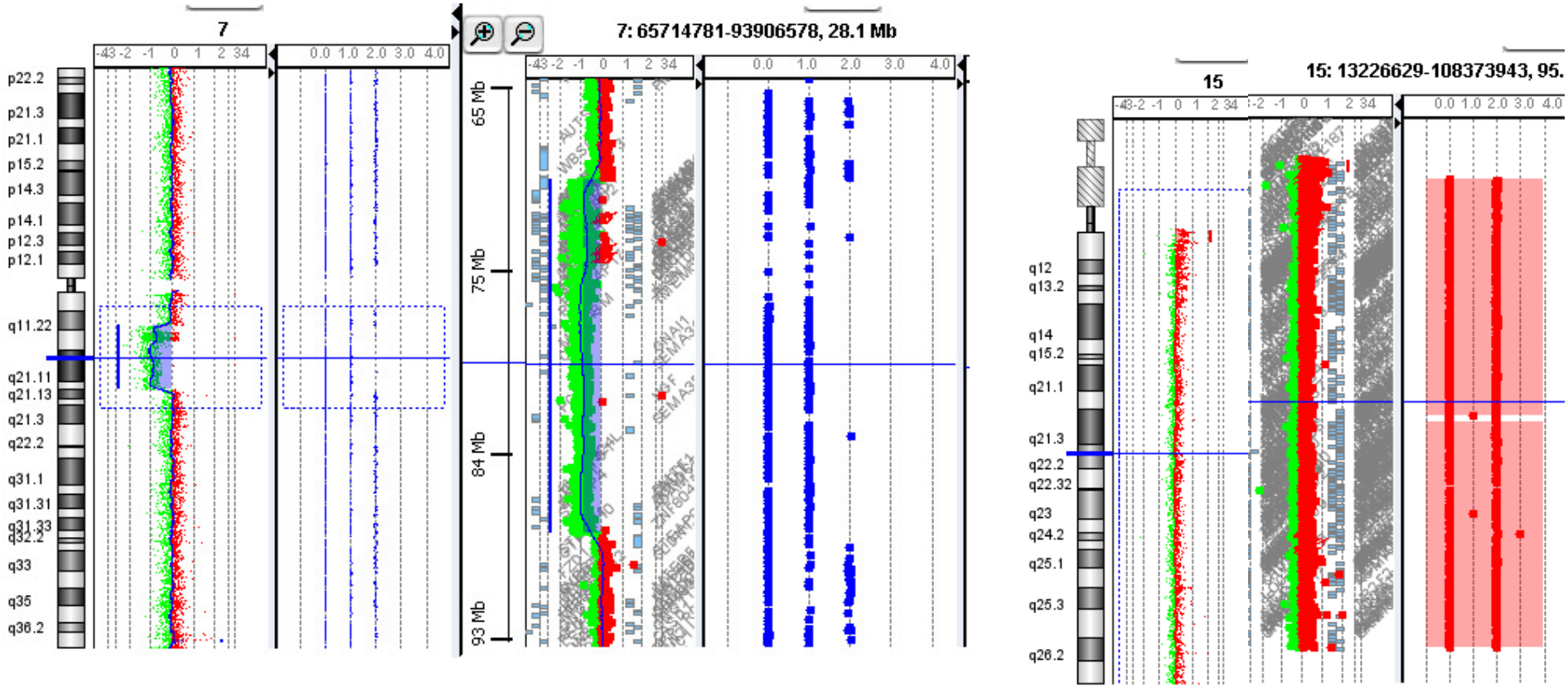
(Die Deletion schließt u. a. die Gene HCCS, AMELX, KAL1 und NLGN4X ein)

46,X,t(X;16)(q27;q21) de novo
46,X,t(X;2)(p11.21;q11.2) de novo





Oligo/SNP Array:
Deletion 7q11.22-q21.13 (ca. 17,5 Mb)
Uniparentale Isodisomie 15



Hochdurchsatzsequenzierung oder „new-generation-sequencing“ (NGS)

- Kosten/humanes Genom 2007: **ca. 1 Mio. US$**
- Kosten/humanes Genom 2009: **100.000 US$**
- Kosten/humanes Genom **heute: 7.500 US$**
-
- Kosten/humanes Genom 2012: **1.000 US$**
- **????? Wenn wir nur „krankheitsrelevante“ Gene sequenzieren würden?????**

DTC Direct to consumer testing

WHAT IS RECOMBINE?

Recombine is a genetic test for couples. Our service can help to ensure that you bring a happy, healthy child into this world.

Recombine tests for over 200 monogenic diseases and conditions which may affect your child by analyzing DNA from you and your partner. Along with molecular diagnostics, the Recombine. Us service also includes a genetic counseling session with a Recombine certified genetic counselor to help you interpret your results and understand what decisions can give your child the best chance at a healthy life.

The Recombine Genetic Test for couples has the largest disease coverage of any commercially available genetic test. Each mutation was hand picked by our team of bioinformaticians, molecular geneticists and genetic counselors.

GENETIC TEST

ILLUMINA ISELECT CUSTOM ARRAY PLATFORM
- Blood or Saliva samples can be analyzed

CHIP DESIGN IS PROPRIETARY

NEARLY 200 DISEASES AND 1250 MUTATIONS

BLOOD TYPE AND HISTOCOMPATIBILITY

ALMOST EVERY MAJOR, COMMON GENETIC DISEASE
- Cystic Fibrosis
- Tay Sachs
- Alpha Thalassemia*
- Beta Thalassemia
- Sickle-Cell Anemia
- Spinal Muscular Atrophy*
- Fragile X Syndrome

GENETIC COUNSELING

COST PER TEST 400 € PROX

Recombine, 2012

FSHR Gen Polymorphismus und „ovarian response“

Variable	Asn/Asn ($n = 22$)	Asn/Ser ($n = 71$)	Ser/Ser ($n = 15$)	*P* value
Poor responder	0	15 (21.1)	7 (46.7)	0.008[a]
Normal responder	22 (100)	46 (64.8)	0	0.004[a]
Hyper responder	0	10 (14.1)	8 (53.3)	0.037[a]

[a]Using Chi-square test , FSHR - Follicle-stimulating hormone receptor; Asn - Asparagines, Ser - Serine; Figures in parenthesis are in percentage

Sheikhha et al., 2011

Häufigkeit von venösen Thromboembolien bei Verwandten bei Vorliegen/Fehlen der *FV Leiden* oder Prothrombin *G20210A* Mutation

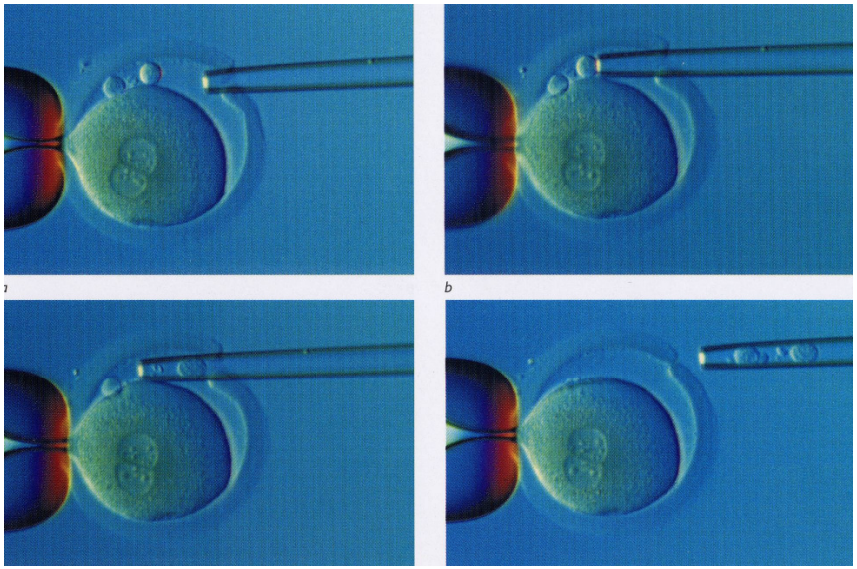
Inzidenz von VTE bei Verwandten,Eintritt pro 100 Personenjahre

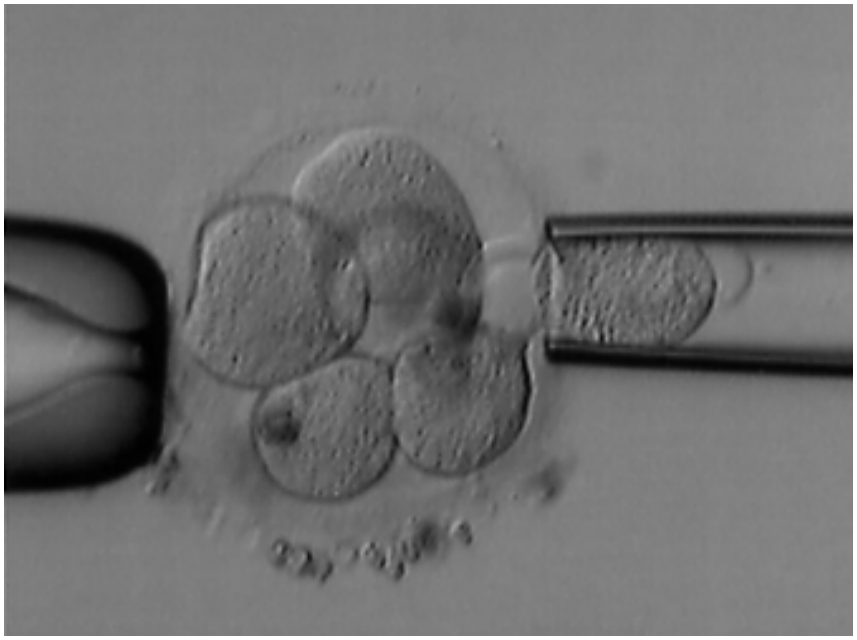
Manifestationsalter	Index-Fall FVL / PGM positiv	Index-Fall FVL / PGM negativ	VTE (Verw.) Manifestationsalter
< 45 Jahre	0,28	0,27	42,8
45 – 60 Jahre	0,22	0,13	53,1
61 – 70 Jahre	0,26	0,11	54,0
> 71 Jahre	0,09	0,08	56,9

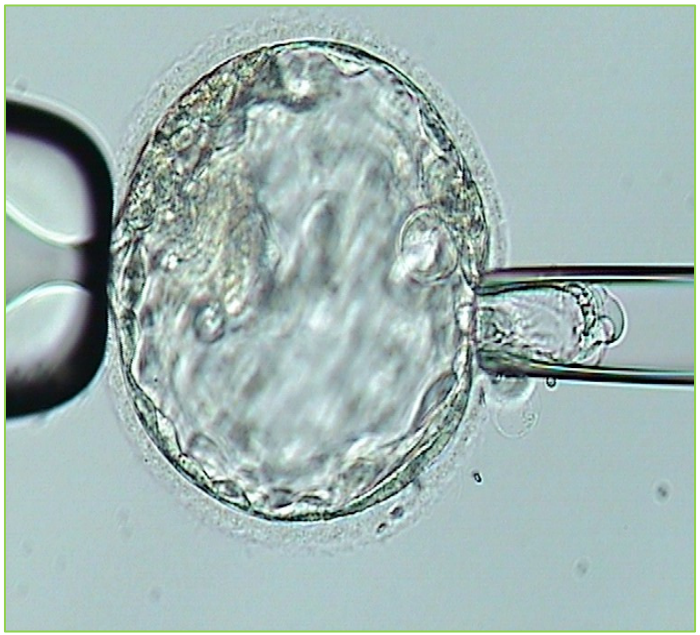
Couturaud et al., 2009

Reprogenetics

Polkörperbiopsie
Embryobiopsie
Blastozystenbiopsie

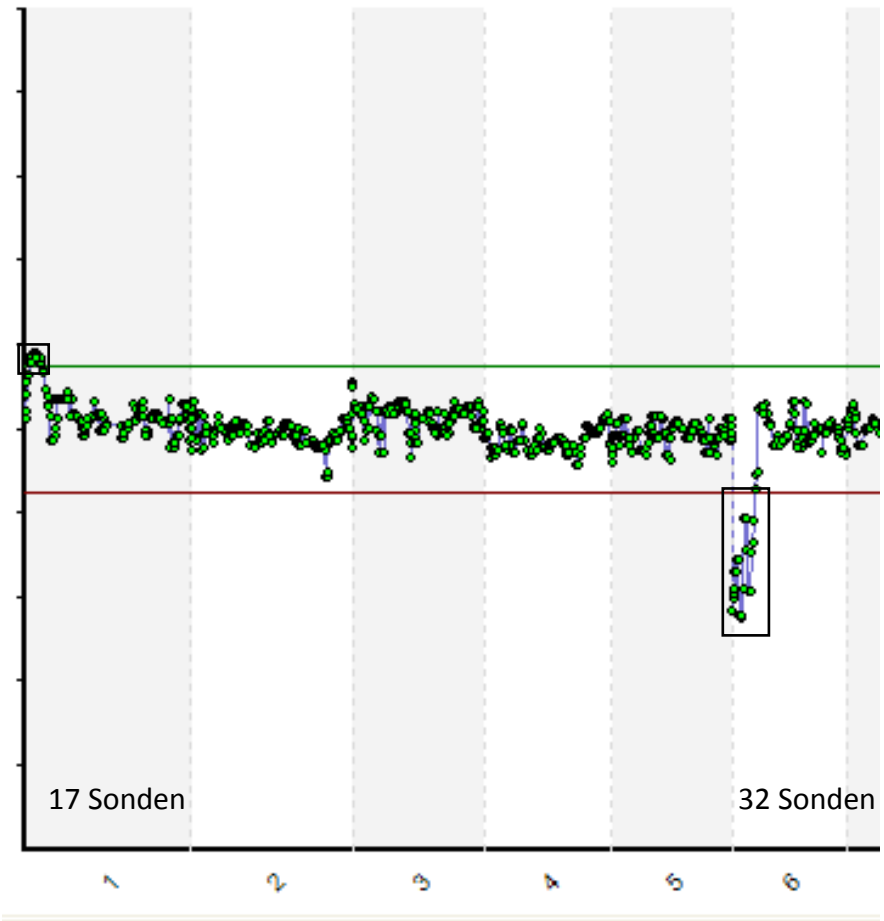




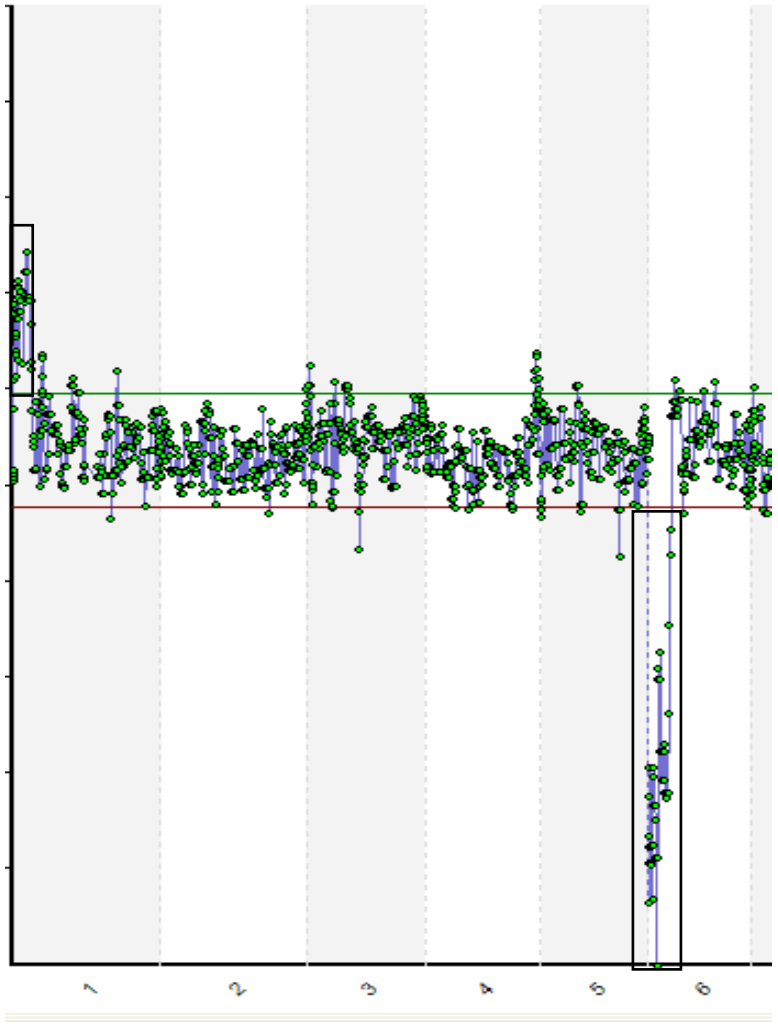


PB: Verlinsky & Kuliev, 2005

PB 1b
V3



PB 1b
24sure+



63 Sonden

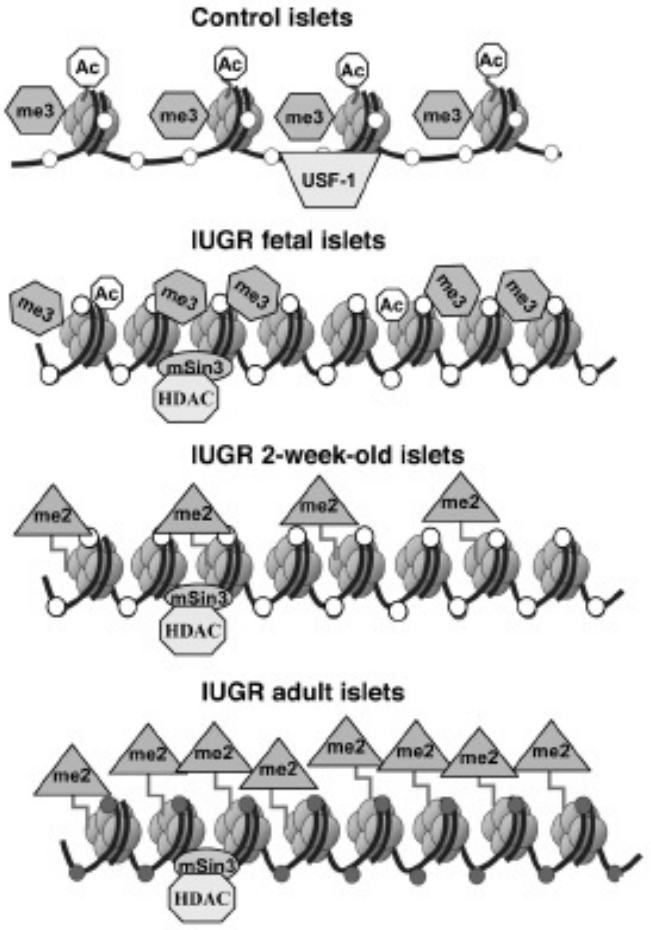
61 Sonden

Sample vs. Male
Ref

Reprogenetics

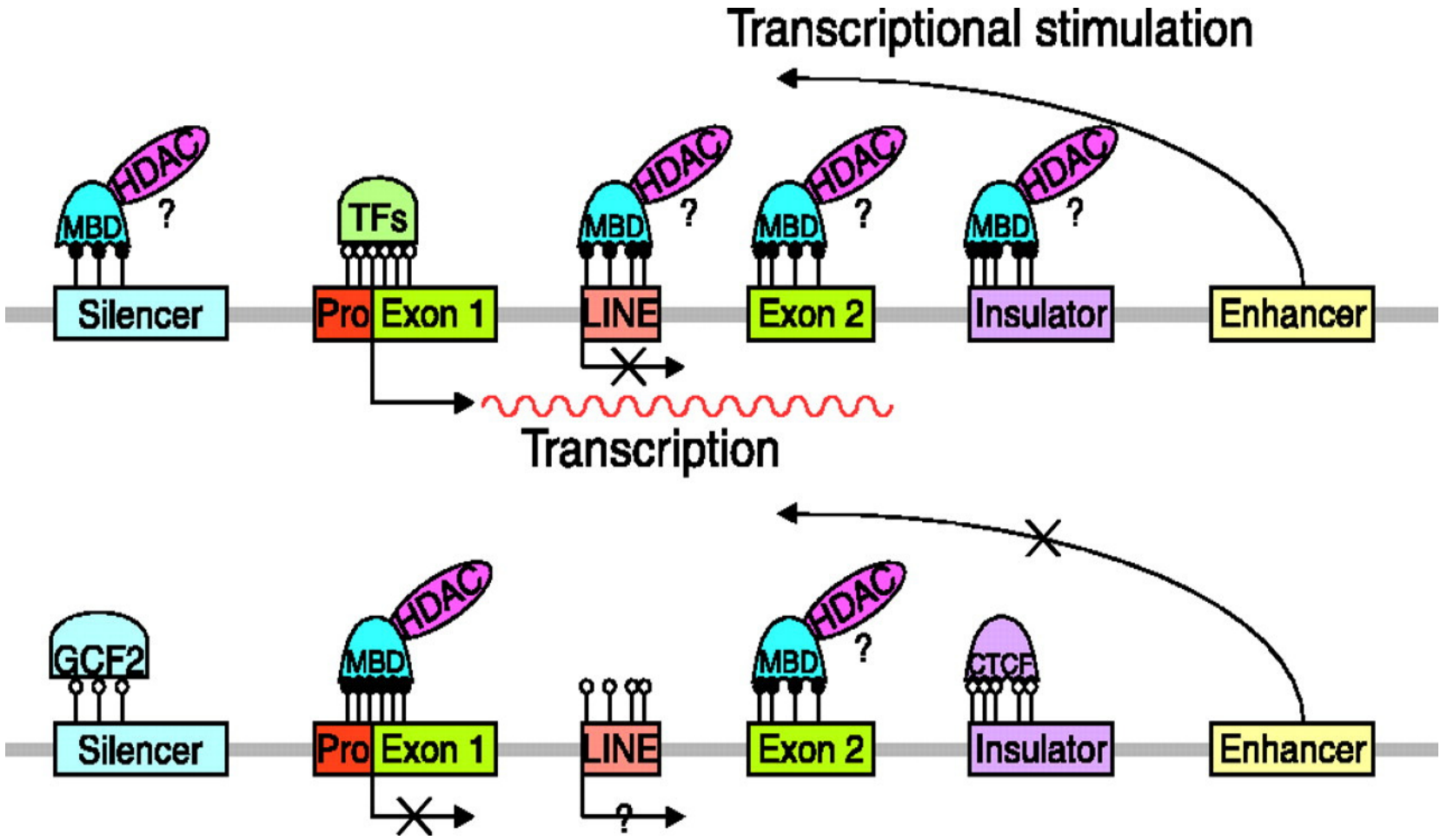
EPIGENETIK

vererbare oder reversible Modifikation der Chromosomen, die die Genexpression beeinflussen bei unveränderter Nucleotidabfolge der Gene



Park et al., 2008

Transcription



HDAC histone deacetylases Tfs transcription factors
GCF2 GC binding factor 2 CTFC CTC binding factor
MBD methyl CpG binding domain proteins

Jones and Takai, 2001

Blockage rate of embryos following ICSI of mouse embryos obtained from IVM, freshly ovulated and 13hr aged oocytes Lacham-Kaplan and Trounson (2008)

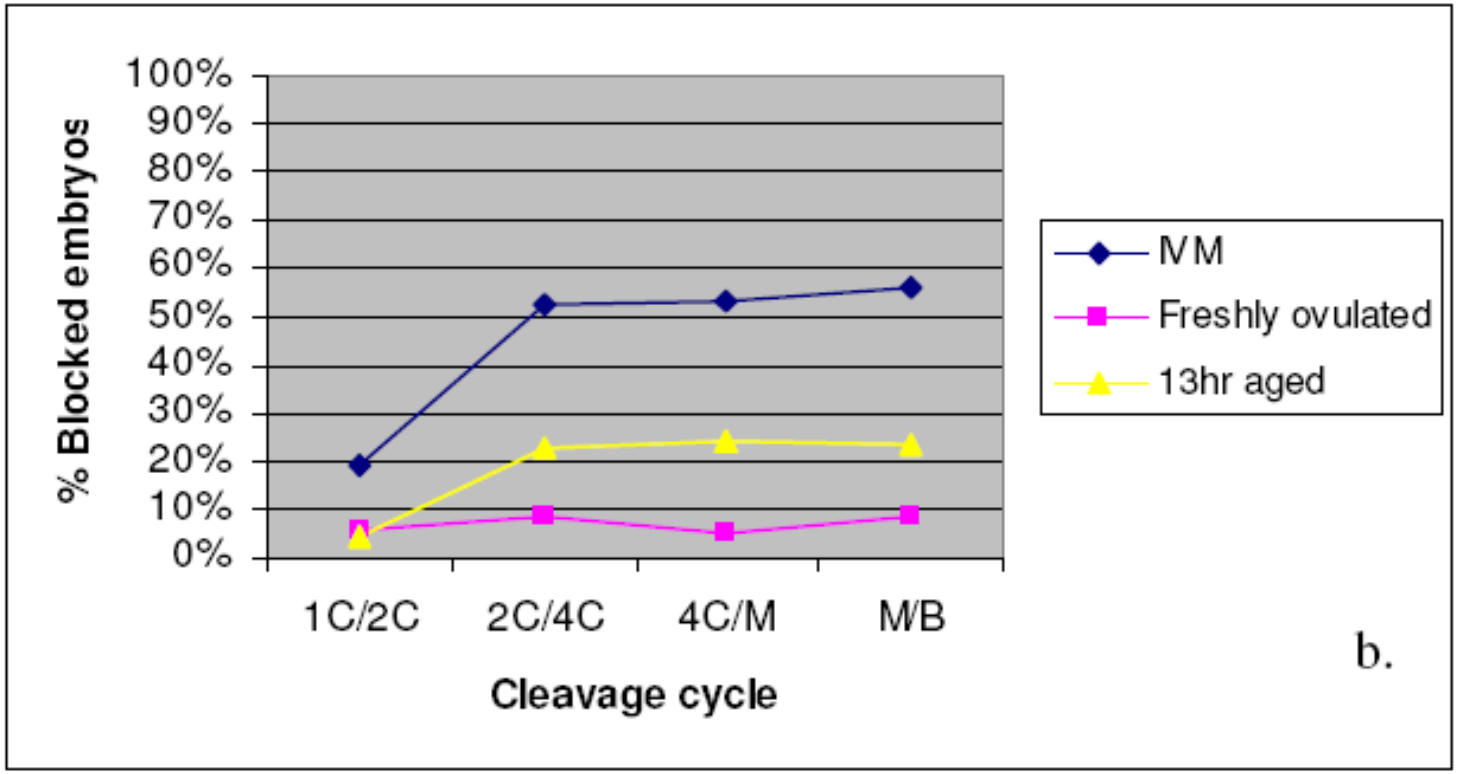


Figure 1
Blockage rate of embryos following IVF (a) and ICSI (b) of embryos obtained from IVM, freshly ovula
13 hr aged oocytes.

Reprogenetics

Gene Expression Profiling of Single Bovine Embryos Uncovers Significant Effects of In Vitro Maturation, Fertilization and Culture

SADIE L. SMITH,[1†] ROBIN E. EVERTS,[2‡] LI-YING SUNG,[1§] FULIANG DU,[3] RAYMOND L. PAGE,[4] BOYD HENDERSON,[5] SANDRA L. RODRIGUEZ-ZAS,[2] TSHIMANGADZO L. NEDAMBALE,[1#] JEAN-PAUL RENARD,[6] HARRIS A. LEWIN,[2,7] XIANGZHONG YANG,[1#] AND X. CINDY TIAN[1*]

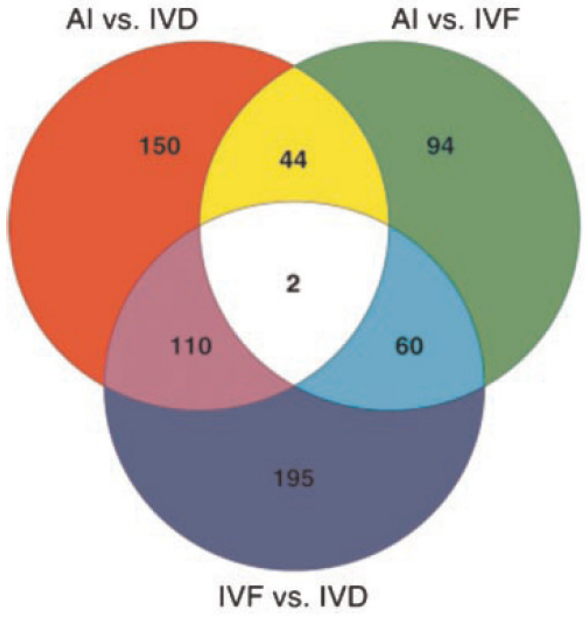


Figure 2. Venn diagram characterizing differential gene expression between and specific to individual embryo types. Each circle represents the differential expression between two embryo types out of 5,296 genes. The upper-right-hand circle shows the 200 genes that are differentially expressed between AI and IVF embryos; 94 genes (green) are uniquely expressed in AI versus IVF only, 44 genes (yellow) are specific to AI embryos (LOS candidates) and 60 genes (aqua) are IVF specific. The two genes in the middle are expressed at a different level in each of the three embryo types. [See color version online at www.interscience.wiley.com.]

AI in vivo fertilized and matured

IVD in vivo fertilized, in vitro matured

IVF in vitro fertilized and matured

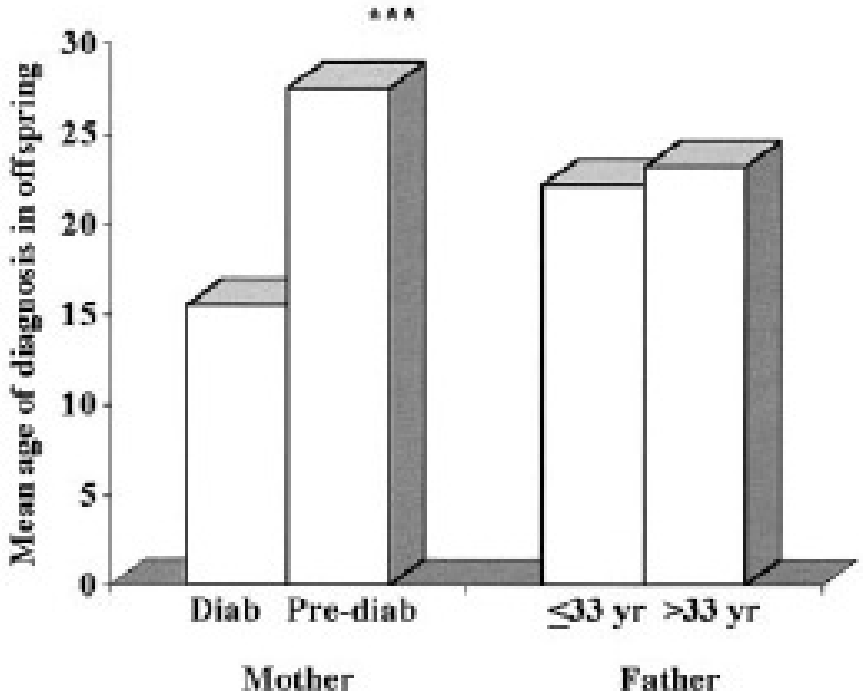
We found that genes responsible for and regulated by epigenetic mechanisms were differentially expressed in the IVF and IVD embryos. Previous research has indicated that these genes are most likely involved in the LOS phenotype. Many are important for, or affected by, the early epigenetic events that establish subsequent gene expression and differentiation during development. The IVF embryos were in vitro matured and fertilized; thus, the early significant remodeling of their genomes could have been aberrant, and this might be responsible for the variable gene expression among the individual IVF embryos. The great inconsistency in the appearance of LOS in IVF fetuses, even when the same culture conditions are implemented, indicates that there is variability in the embryo's susceptibility to perturbations. The IVD embryos were fertilized in vivo and their paternal genome reorganized under normal conditions. These embryos had more homogenous expression patterns and presumably responded to the culture system in a similar manner. Thus, the possibility exists for a greater incidence of LOS in embryos that are only subjected to in vitro culture.

Smith et al., Mol. Reprod. Dev. 76: 38-47, 2009

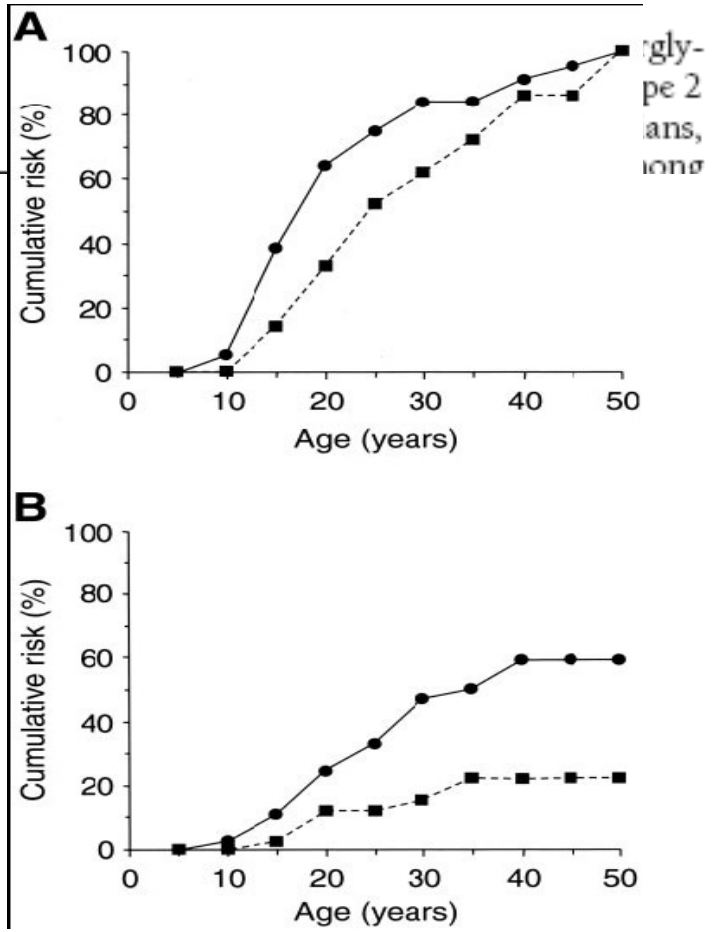
Reprogenetics

Intrauterine Hyperglycemia Is Associated With an Earlier Diagnosis of Diabetes in HNF-1α Gene Mutation Carriers

AMANDA STRIDE, MRCP
MAGGIE SHEPHERD, PHD
TIMOTHY M. FRAYLING, PHD
MIKE P. BULMAN, PHD
SIAN ELLARD, PHD
ANDREW T. HATTERSLEY, DM



Diabetes care, 2002



HNF-1alpha carrier.
Klupa et al 2002

Research article

Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of *Pdx1*

Jun H. Park,[1] Doris A. Stoffers,[2,3] Robert D. Nicholls,[4] and Rebecca A. Simmons[1,3]

[1]Department of Pediatrics, Children's Hospital of Philadelphia, [2]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, and [3]Institute for Diabetes, Obesity, and Metabolism, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA. [4]Birth Defects Laboratories, Division of Medical Genetics, Department of Pediatrics, Children's Hospital of Pittsburgh, and Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

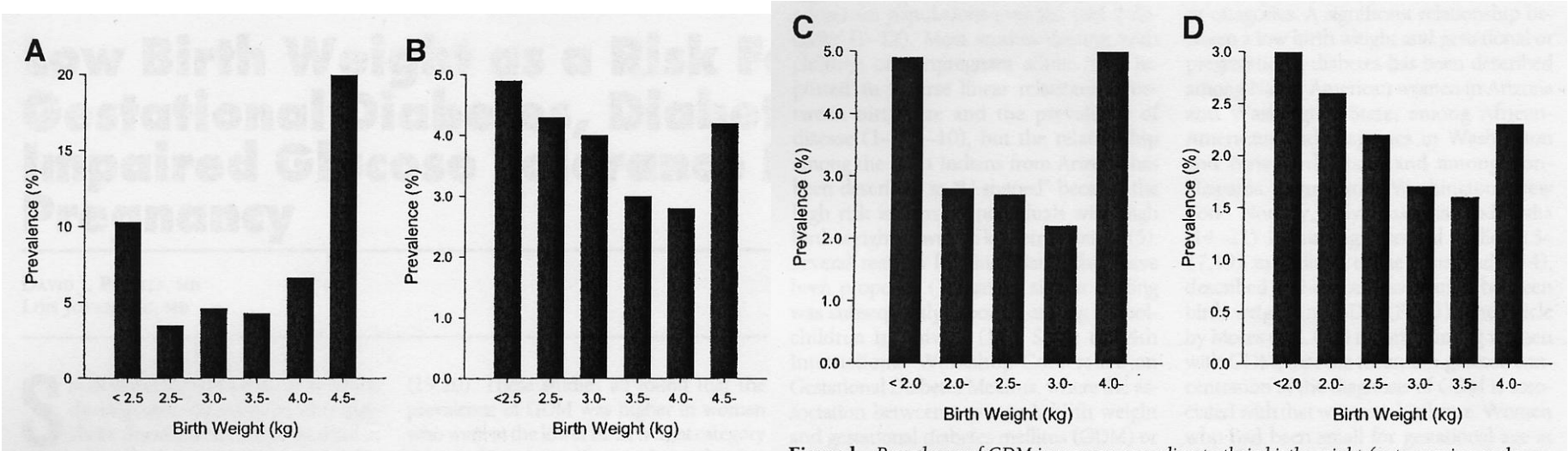
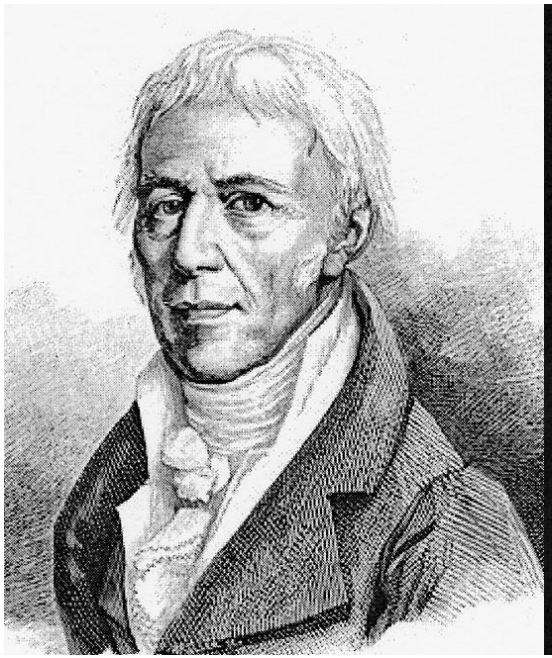
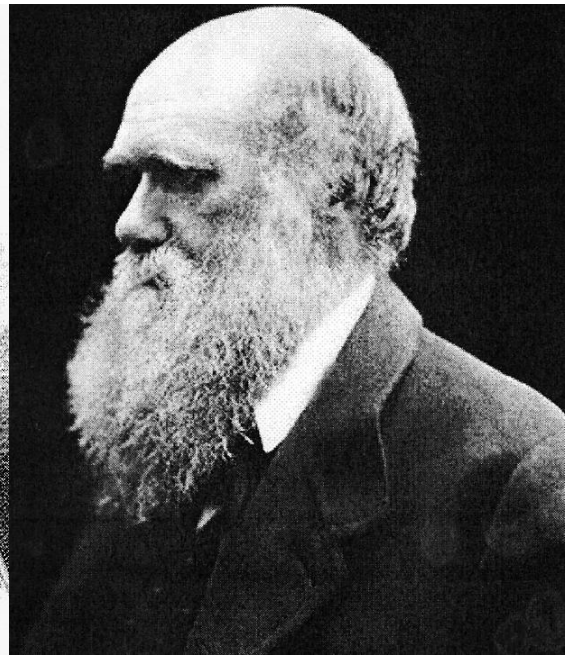


Figure 1—*Prevalence of GDM in women according to their birth weight (note varying scales on both axes). A: Pima Indians (data from Pettitt and Knowler [14]); B: Norwegian women (data from Egeland et al. [16]); C: African-American women (data from Williams et al. [15]); D: women from New York State (data from Innes et al. [17]).*

Vielen Dank fürs Zuhören!



Jean Baptiste de Lamarck
1744 - 1829



Charles Darwin
1809 - 1892

Gregor Mendel
1822 - 1884