Genetic factors and poor ovarian response to stimulation

Prof. Bart CJM Fauser, MD, PhD

Fauser, conflict of interest statement

Universitair Medisch Centrum Utrecht

Received fees and grant support from the following companies (in alphabetic order);

Andromed, Ardana, Ferring, Genovum, Glycotope, Merck Serono, Organon, Pantharei Bioscience, Philips, PregLem, Schering, Schering Plough, Serono, and Wyeth.

Lecture learning objectives

Universitair Medisch Centrum Utrecht

- *Ovarian aging and potential relevance for low response*
- *Menopausal age, and relevance*
- *Genetics of (premature) menopause*
- *New genomic technologies and potential relevance for low response*

Universitair Medisch Centrum Utrecht

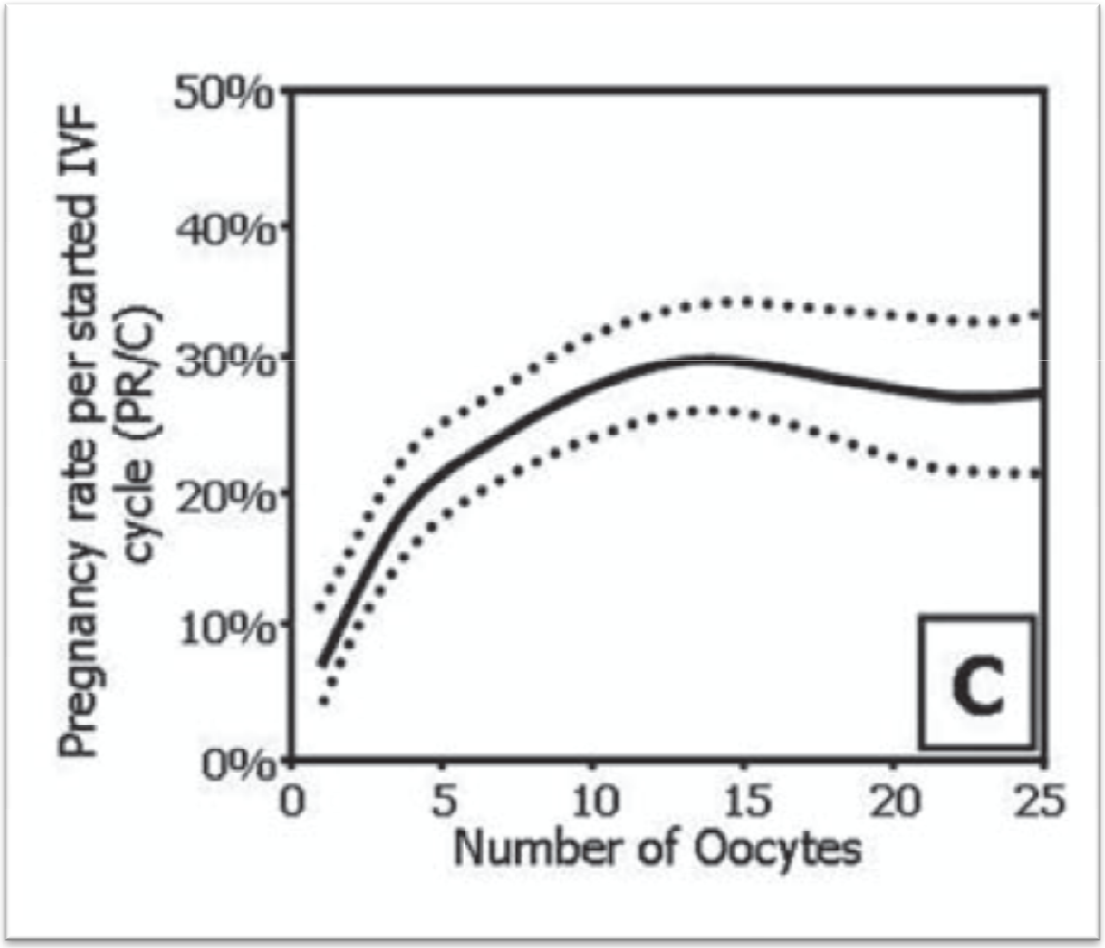
Optimum number of oocytes for a successful first IVF treatment cycle

Mark van der Gaast is a PhD student at the Division of Reproductive Medicine, Department of Obstetrics and Gynaecology of the Erasmus Medical Centre in Rotterdam (The Netherlands). His thesis focuses on endometrial receptivity in human reproduction. He started his Obstetrics and Gynaecology residency in September 2003.

Dr Mark van der Gaast

MH van der Gaast[1], MJC Eijkemans[2], JB van der Net[2], EJ de Boer[3], CW Burger[4], FE van Leeuwen[5], BCJM Fauser[1,6], NS Macklon[1,6,7]

RBM 2006



National Dutch registry

- 7.422 women
- GnRH a, long protocol

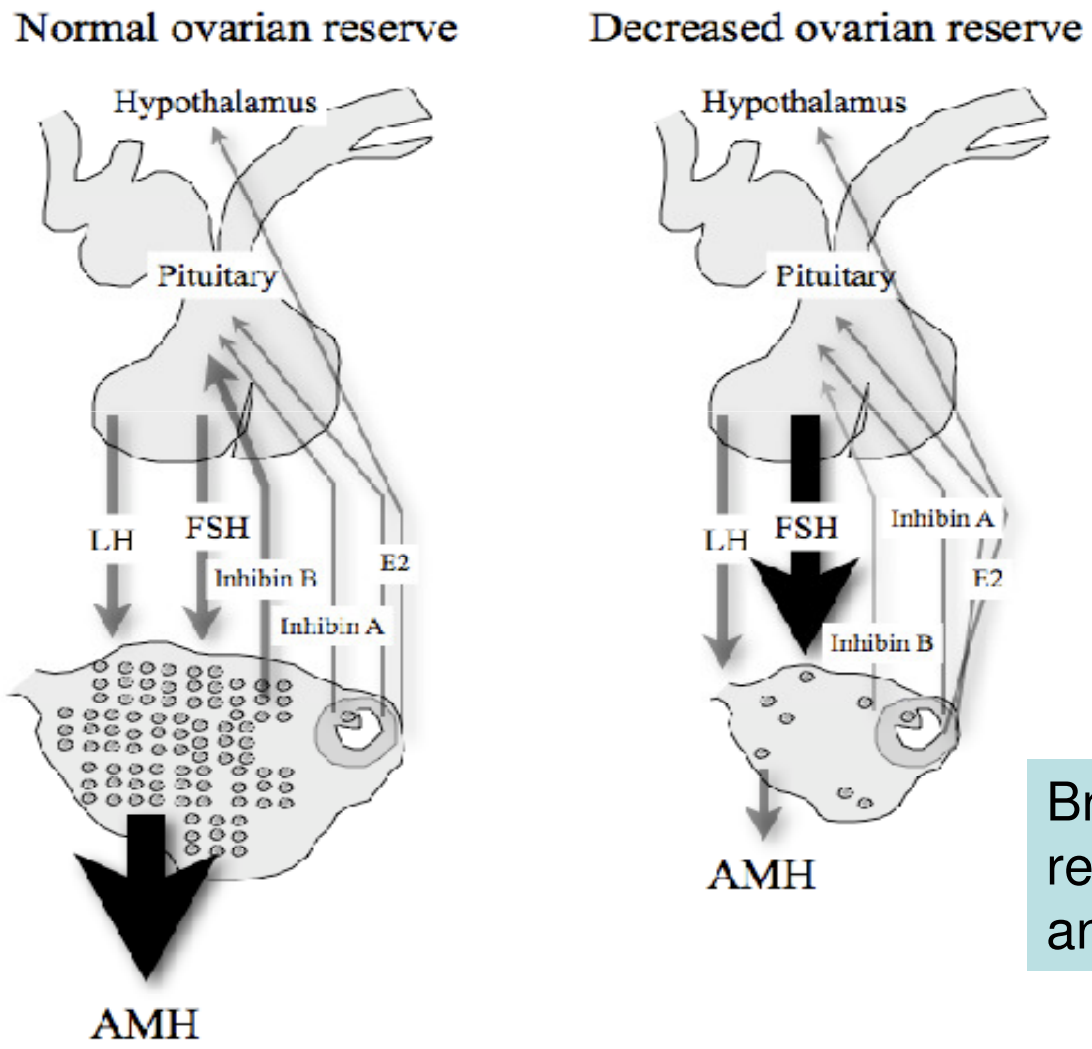
TABLE 1. Evidence fr… esponse to ovarian stimulation for IVF in wo… ransition or menopause

Association between poor response and early menopause

	Study group (IVF poor responders)				Control group (IVF normal responders)			
Study	n	Median follow-up time	Cases entered menopause or menopausal transition (%)	FSH (IU/liter)	n	Median follow-up time	Cases entered menopause or menopausal transition (%)	Adjusted odds or hazard ratio[a]
Farhi, 1997 (326), case report	12	9 months	100	23–85	—	—	—	—
De Boer, 2003/2002 (62, 92), retrospective cohort	636	6 yr	22		3675	5 yr	7%	~3.1 (odds)
Lawson, 2003 (63), retrospective cohort	118	5 yr	50		265	5 yr	16%	~3.1 (hazard)
Nikolaou, 2002 (64), case control	12	7 yr	92		24	7 yr	17%	~5.3 (odds)

Endocrine changes associated with ovarian aging

Universitair Medisch Centrum Utrecht



Broere, direct relationship AMH and menopause

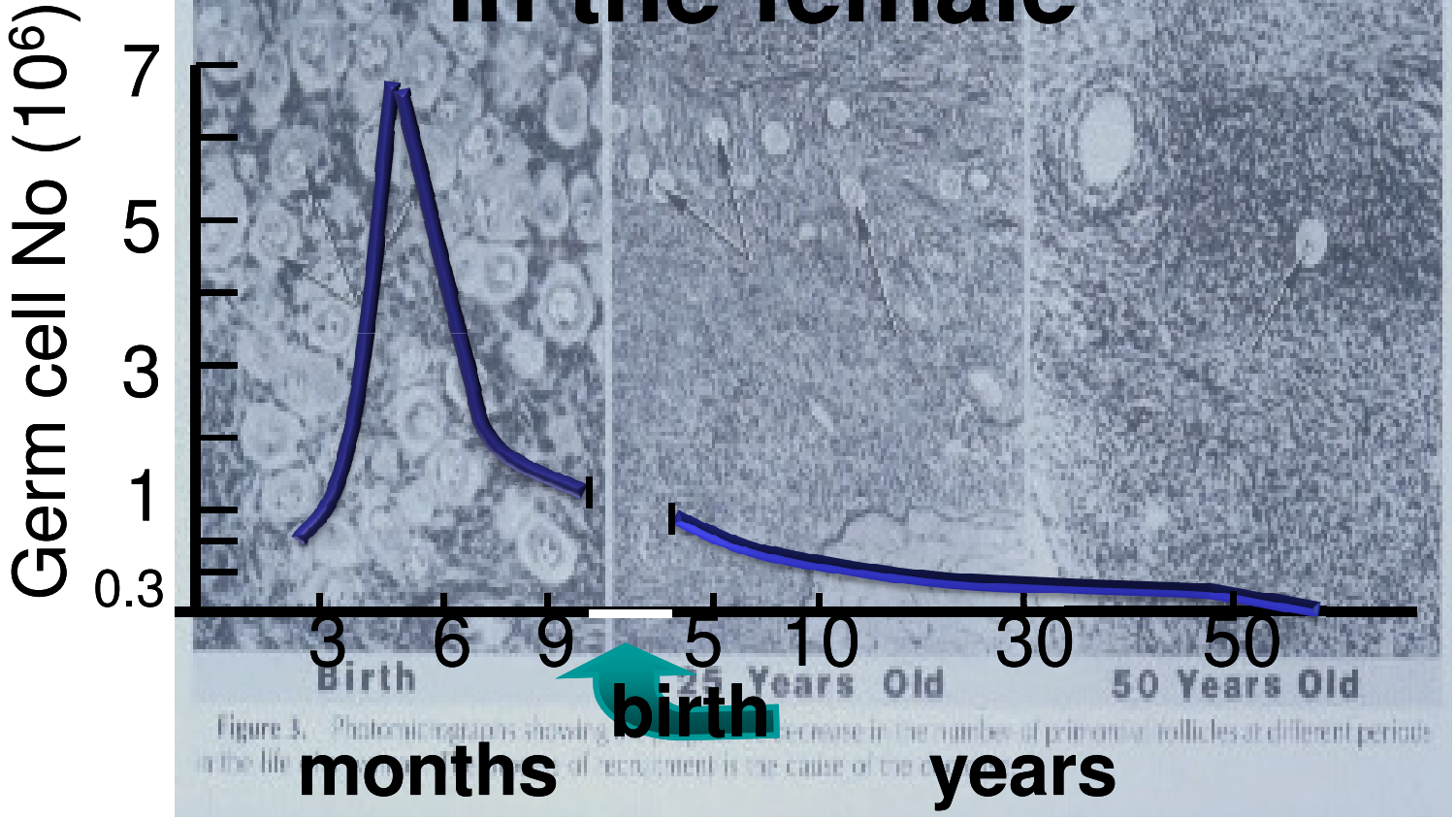
AMH levels and prediction of menopause 12 yrs later

Universitair Medisch Centrum Utrecht

Study design	results
inclusion	130 fertile women 25-46 yrs (t_1) Assessment 12 yrs later (t_2)
Results t_2	35 regular, 31 menopausal transition, 44 postmenopausal
Predictors initial screening for reaching menopause t_2	Age, ROC AUC 0.91 AMH, ROC 0.90 AFC, ROC 0.85
Multi-variate model	

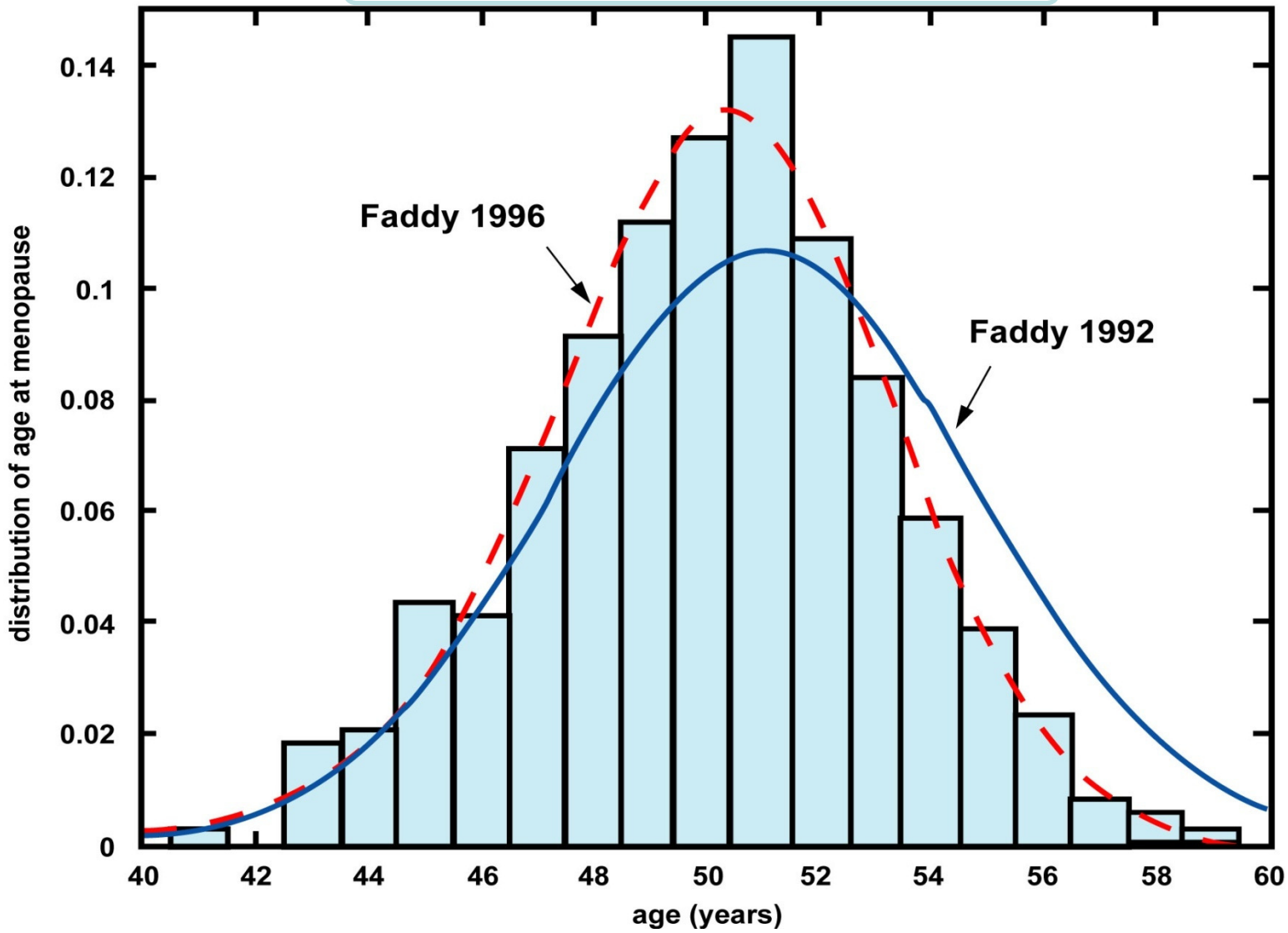
Broer, Florence 2010

Germ cell depletion in the female



Distribution of age at menopause

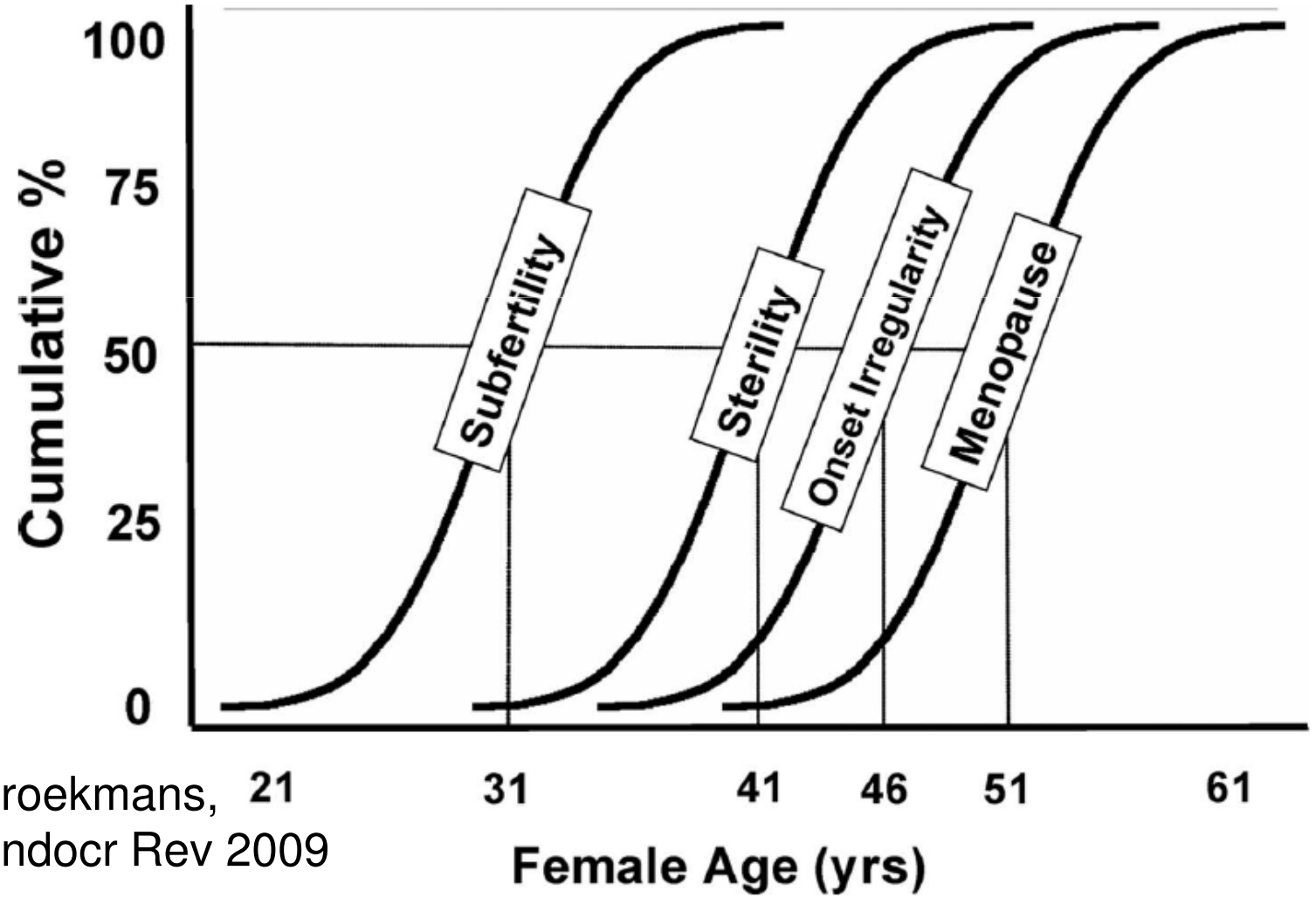
Universitair Medisch Centrum Utrecht



Individual variability in menopausal age is related to preceeding decreased fertility

Universitair Medisch Centrum Utrecht

Low response ➔ early menopause



Broekmans, Endocr Rev 2009

Human Reproduction Update, Vol.14, No.5 pp. 459–484, 2008
Advance Access publication July 4, 2008
doi:10.1093/humupd/dmn024

Functional genetic polymorphisms and female reproductive disorders: Part I: polycystic ovary syndrome and ovarian response

M. Simoni[1,5], C.B. Tempfer[2], B. Destenaves[3] and B.C.J.M. Fauser[4]

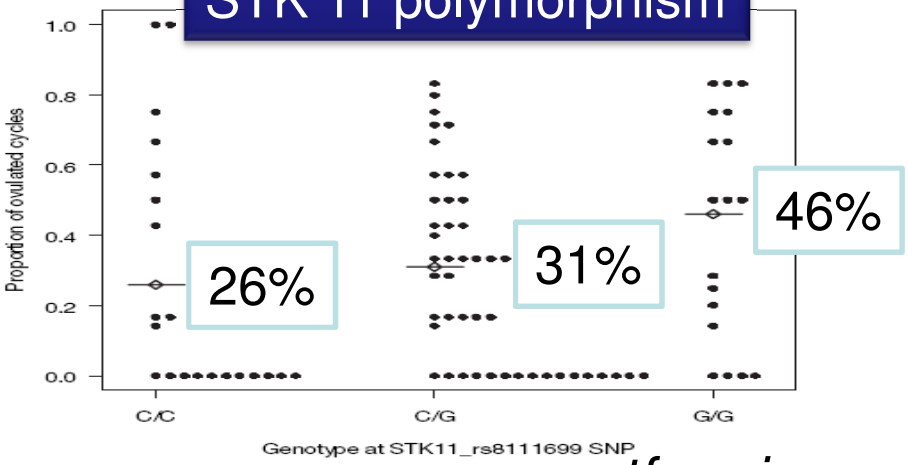
Table V. Polymorphisms in genes encoding sex hormones and hormone regulators, enzymes involved in metabolism and biosynthesis, or paracrine factors.

Gene	Locus	Protein name	Protein function	Variant		Association with ovarian response		Phenotype (cases, *controls*)
				Name	dbSNP ID	Positive (cases, *controls*)	Negative (cases, *controls*)	
Sex hormones and hormone regulators								
AMH	19p13.3	Anti-Müllerian hormone	Hormone	p.I49S	rs10407022			Caucasian women—E_2 levels (53, 45) (Kevenaar *et al.*, 2007)
AMHR2	12q13	Anti-Müllerian hormone type II receptor	Hormone receptor	−482A/G	rs2002555			Caucasian women—E_2 levels levels (53, 45) (Kevenaar *et al.*, 2007)
ESR1	6q25.1	Oestrogen receptor α	Hormone receptor	PvuII RFLP (−397T/C) (g.938T/C)	rs2234693		Spanish women (170) (Mao *et al.*, 2000; de Castro *et al.*, 2004) Chinese women (200, 200) (Sundarrajan *et al.*, 1999)	Caucasian women—follicule/oocyte ratio, pregnancy rate (100, 100) (Georgiou *et al.*, 1997) Chinese women—serum oestradiol levels, follicule/oocyte ratio, pregnancy rate (200, 200) (Sundarrajan *et al.*, 1999)
ESR2	14q23.2	Oestrogen receptor β	Hormone receptor	AluI RFLP (1730A/G) (39A/G)	rs4986938		Spanish women (170) (Mao *et al.*, 2000; de Castro *et al.*, 2004)	
FSHR	2p21-p16	Follicle-stimulating hormone receptor	Hormone receptor	p.N680S (in complete LD with p.A307T, rs6165)	rs6166	German women (93) (Perez Mayorga *et al.*, 2000; Behre *et al.*, 2005) Japanese women (58) (Sudo *et al.*, 2002) Spanish women (102) (de Castro *et al.*, 2003; de Castro *et al.*, 2004) Korean women (263) (Jun *et al.*, 2006) Greek women (125 (Loutradis *et al.*, 2006)	Dutch women (105) (Klinkert *et al.*, 2006)	German women—peak oestradiol levels (93) (Behre *et al.*, 2005) German women—circulating FSH, levels, number of follicules, lutheal phase and menstrual cycle length (23) (Perez Mayorga *et al.*, 2000; Greb *et al.*, 2005) Japanese women (58)—basal FSH (Sudo *et al.*, 2002) Dutch women (148) (Laven *et al.*, 2003) Swedish women (68) (Falconer *et al.*, 2005) Korean women—basal FSH, pregnancy rate (263) (Jun *et al.*, 2006) Greek women (125)—FSH levels, follicule and oocyte number (Loutradis *et al.*, 2006) Dutch women—pregnancy rate (105) (Klinkert *et al.*, 2006)
Enzymes involved in metabolism and biosynthesis								
CYP19A1	15q21.1	Aromatase	Steroid biosynthesis	1672C/T	rs10046		Spanish women (170) (de Castro *et al.*, 2004)	
Paracrine factors								

Pharmacogenomics in Ovulation Induction

Universitair Medisch Centrum Utrecht

312 PCOS
STK 11 polymorphism



metformin

Ovulatory Response to Treatment of Polycystic Ovary Syndrome Is Associated with a Polymorphism in the *STK11* Gene

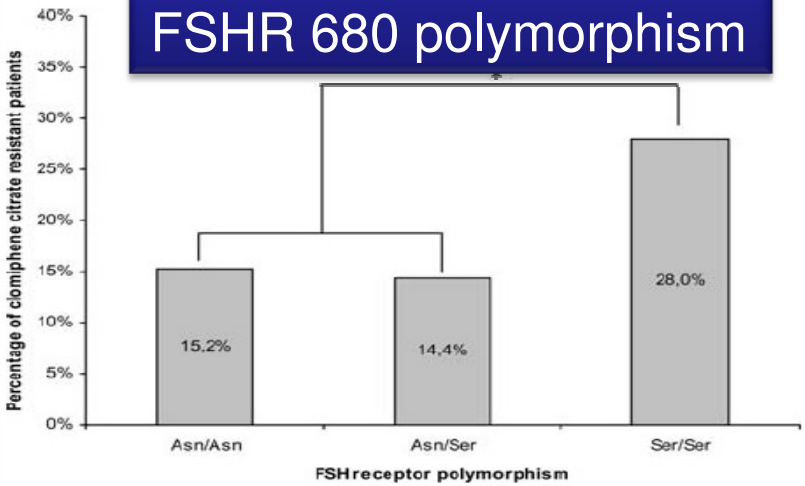
Richard S. Legro, Huiman X. Barnhart, William D. Schlaff, Bruce R. Carr, Michael P. Diamond, Sandra A. Carson, Michael P. Steinkampf, Christos Coutifaris, Peter G. McGovern, Nicholas A. Cataldo, Gabriella G. Gosman, John E. Nestler, Linda C. Giudice, Kathryn G. Ewens, Richard S. Spielman, Phyllis C. Leppert, and Evan R. Myers for the Reproductive Medicine Network*

JCEM 2008

Clomiphene citrate resistance in relation to follicle-stimulating hormone receptor Ser680Ser-polymorphism in polycystic ovary syndrome HR 2009

A. Overbeek[1,4], E.A.M. Kuijper[1], M.L. Hendriks[1], M.A. Blankenstein[2], I.J.G. Ketel[1], J.W.R. Twisk[3], P.G.A. Hompes[1], R. Homburg[1], and C.B. Lambalk[1]

193 PCOS, CRA
FSHR 680 polymorphism

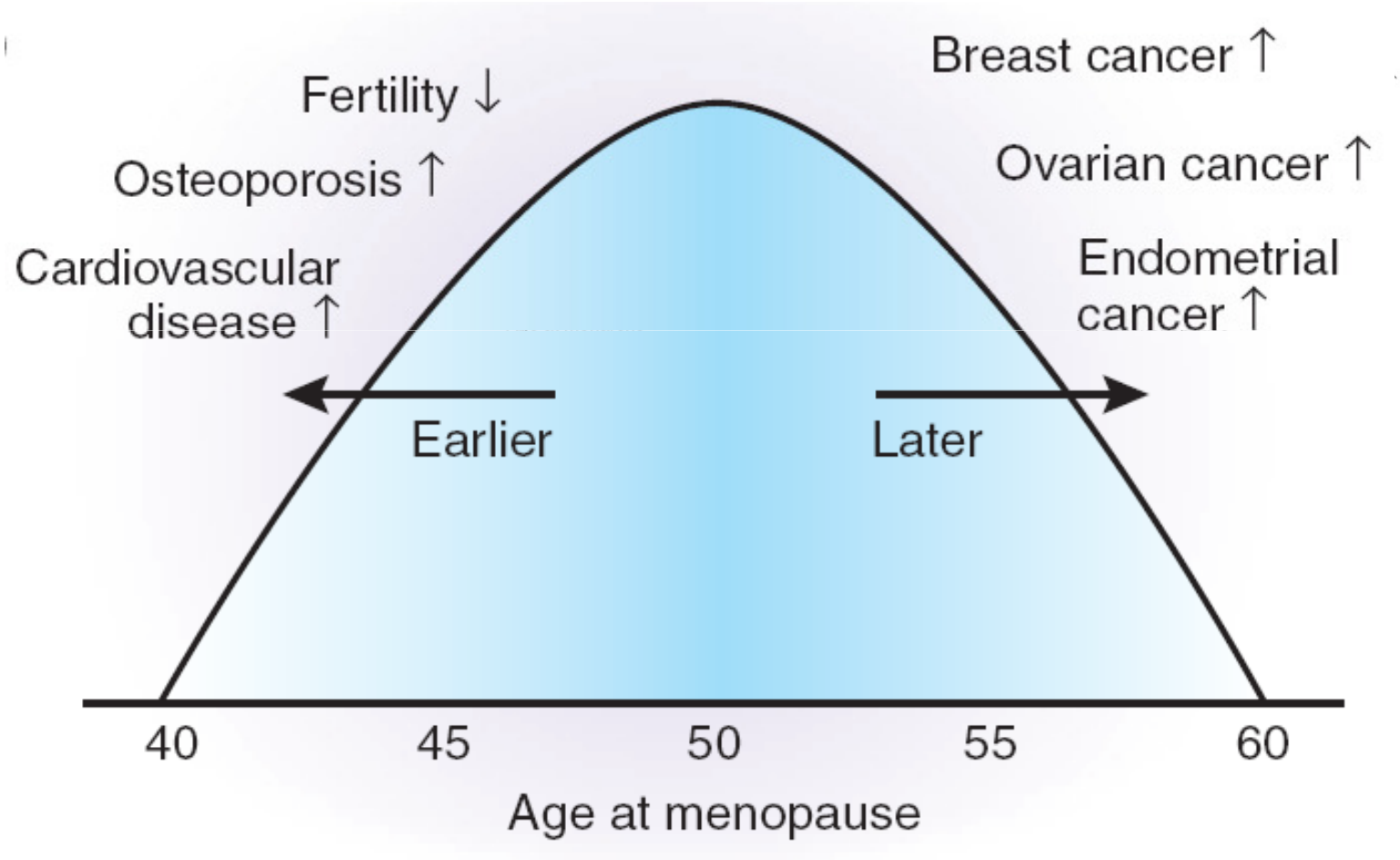


Genetics of reproductive lifespan

Patricia Hartge

NATURE GENETICS | VOLUME 41 | NUMBER 6 | JUNE 2009

ersitair Medisch Centrum
Utrecht



Genetics of age at natural menopause

Universitair Medisch Centrum Utrecht

Table I Genome-wide linkage analyses; regions with (suggestive) linkage with ANM.

Study	Linkage region	LOD score	N[a]	N markers[b]
van Asselt *et al.*, 2004	9q21.3 Xp21.3	2.6 3.1	579[χ] (165 families)	417
Murabito *et al.*, 2005b	Chrom 8 at 26 cM	2.6	861[ψ] (291 families)	401
	Chrom 16 at 11 cM	2.4		
	Chrom 11 at 113 cM	2.1[ω]		

Human genes associated with ovarian insufficiency

Universitair Medisch Centrum Utrecht

X chromosome genes	*References*
BHLHB9 (basic helix-loop-helix)	*Hees et al. 2004*
BMP15 (bone morphogenetic protein)	*Di Pasquale et al. 2004*
DACH2 (drosophila dachsund)	*Prueitt et al. 2002*
DIAPH2 (homologue drosophila diaph)	*Bione et al. 1998*
FMR1 (fragile X mental retardation)	*Allingham et al. 1999*
FMR2	*Murray et al. 1999*
POF1B (POF 1B gene)	*Lamcombe et al. 2006*
XIST (x inactivation transcript)	*Sato et al. 2004*
XPNPEP2 (propyl aminopeptidase)	*Prueitt et al. 2000*

De Vos, Lancet 2010

Human genes associated with ovarian insufficiency

Universitair Medisch Centrum Utrecht

Selected autosomal genes	*References*
DAZL (deleted azzospermia)	*Tung et al. 2006*
EIF5B (eukaryotic translation initiation)	*Fogli et al. 2004*
ESR1 (estrogen receptor)	*Bretherick et al. 2008*
FIGLA (murine factor germline alpha)	*Zhao et al. 2008*
FOXL2 (forkhead transcription factor)	*Crisponi et al. 2001*
FOXO1A / 3A (forkhead box)	*Watkins et al. 2006*
FSHR (FSH receptor)	*Aittomaki et al. 1995*
GALT (galactose-phosphate transferase)	*Leslie et al. 1992*
GDF9 (growth differantiation factor)	*Dixit et al. 2005*
GPR3 (G protein coupled receptor)	*Kovanci et al. 2008*
INHA (inhibin A)	*Dixit et al. 2004*
LHB (LH beta)	*Takahashi et al. 1999*
NOBOX (murine newborn ovary box)	*Zhao et al. 2005*
PGRMC1 (Prog receptor membrane)	*V Dooren et al. 2009*
TGFBR3 (TGF receptor)	*Dixit et al. 2006*

Transgenic mouse models and ovarian insufficiency

Universitair Medisch Centrum Utrecht

system	Study design	Proposed mechanism
GDF9	Knock-out	Early follicle arrest
Bax	Knock-out	Increased ovarian reserve
AMH	Knock-out	Premature foll pool exhaustion
FSHR	Knock-out	Accelerated follicle death
FOXO3a (forkhead transcription)	Knock-out	Early follicle exhaustion
Foxl2 (forkhead/winged helix transcription)	Knock-out	Early follicle exhaustion
Nobox (newborn ovary homeobox)	Knock-out	Accelerated oocyte loss
Sohlhl (spermatogenesis/oogenesis specific helix-loop-helix)	Targeted deletion	Disturbed early follicle transition
Pten (phosphate and tensin homolog deleted chrom 10)	Oocyte specific knock-out	Premature exhaustion

De Vos, Lancet 2010

Possible relevance of POF genetics for ovarian reserve

Universitair Medisch Centrum Utrecht

RBM Online - Vol 19 No 3. 2009 385-390 Reproductive BioMedicine Online; www.rbmonline.com/Article/3871 on web 4 August 2009

Article

Relevance of triple CGG repeats in the *FMR1* gene to ovarian reserve

Dr Norbert Gleicher founded the Centre for Human Reproduction (CHR) in 1981. He is a graduate of Tel Aviv Medical School in Israel and completed his residency at Mount Sinai School of Medicine in New York. Dr Gleicher has published hundreds of scientific papers and book chapters in the areas of reproductive endocrinology and infertility, and high-risk obstetrics. He has edited some of the most prestigious textbooks in these specialties and has also been editor-in-chief of two scientific journals. Dr Gleicher now practices exclusively in New York as Medical Director of CHR-NY.

..... and now it is time for something completely different

Universitair Medisch Centrum Utrecht

A genomics view to complex traits

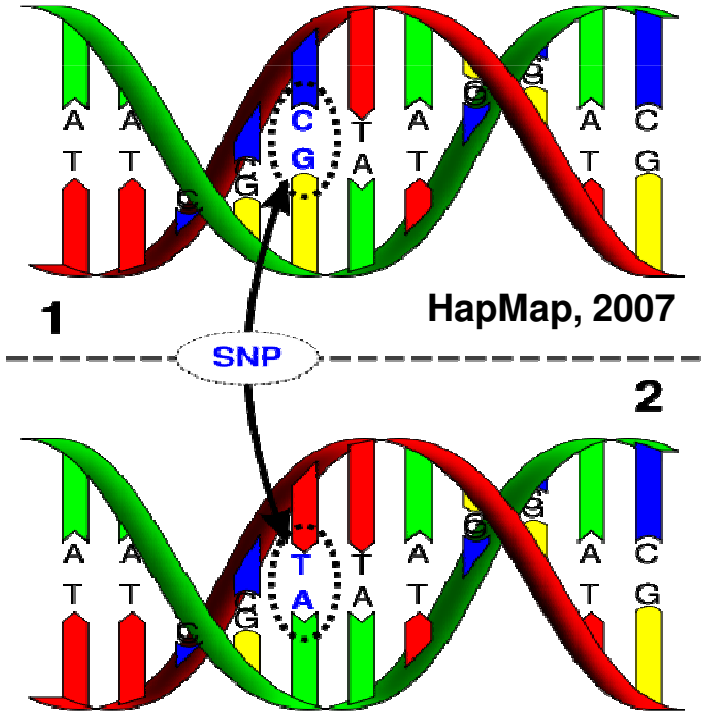
~11,000,000 DNA variants
Genetic association studies

~22,000 genes
Gene expression studies

What is a SNP?

Single Nucleotide Polymorphism (SNP)

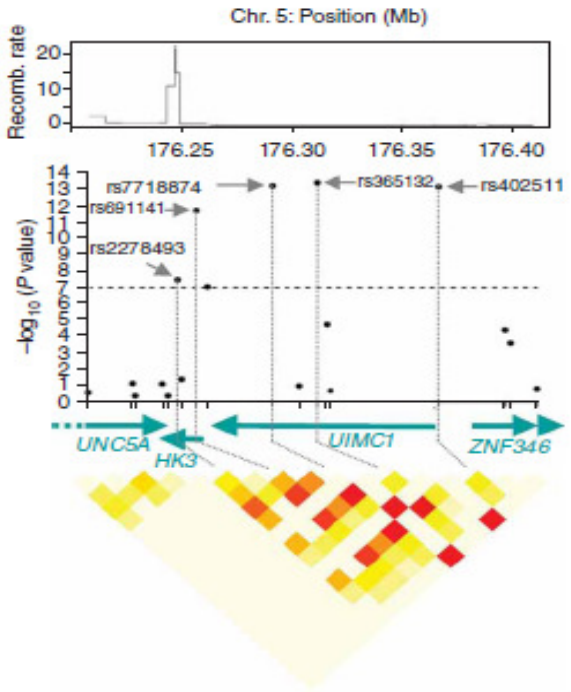
- DNA sequence variation where one nucleotide (A,T,C,G) is changed
- Frequency: 1 in ±235 bp
- C ⇔ T and A ⇔ G most common
- Around 10 million SNPs in the human genome

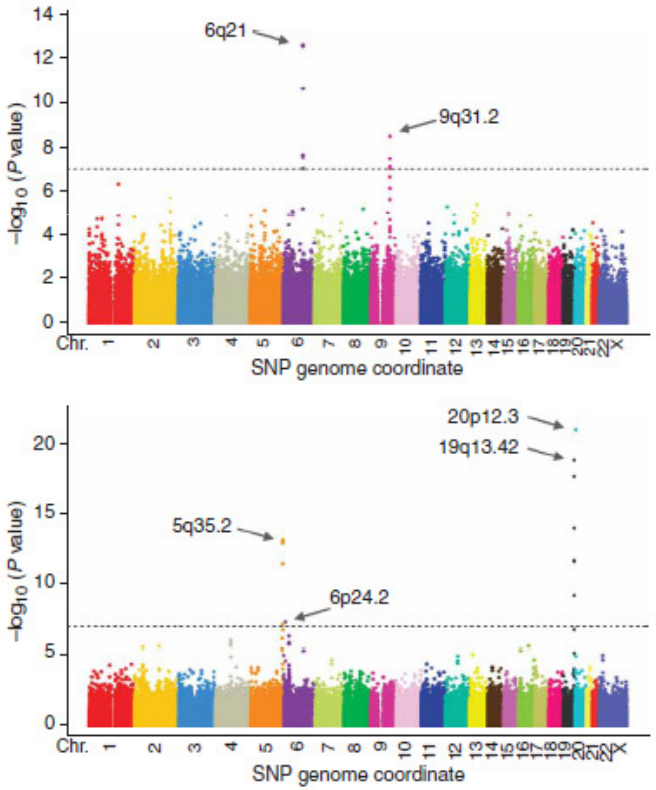


Genome-wide association study (GWAS)

Universitair Medisch Centrum Utrecht

- Made possible by HapMap project 2005
- Around 500.000 SNPs tested
- Mostly tagSNPs
  (covering the whole genome)
- Hypothesis-free





He, 2009

Nature

ITPR2 as a susceptibility gene in sporadic amyotrophic lateral sclerosis: a genome-wide association

Michael A van Es, Paul W Van Vught, Hylke M Blauw, Lude Franke, Christiaan G Saris, Peter M Andersen, I
Sonja W de Jong, Robert van 't Slot, Anna Birve, Robin Lemmens, Vianney de Jong, Frank Baas, Helenius J S
Christine Van Broeckhoven, John H J Wokke, Cisca Wijmenga, Wim Robberecht, Jan H Veldink, Roel A Opho

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

Nature

The Wellcome Trust Case Control Consortium*

PNAS

Genome-wide association study for Crohn's disease in the Quebec Founder Population identifies multiple validated disease loci

John V. Raelson*†, Randall D. Little*, Andreas Ruether‡, Hé
W. E. C. Bradley§, Pascal Croteau*, Quynh Nguyen-Huu*, Jo
Philip Rosenstiel‡, Andre Franke‡, Gunnar Jacobs‡, Susanna
Nathalie Laplante*, Hilary F. Clark**, René J. Paulussen*, Jo
Abdelmajid Belouchi*, and Stefan Schreiber‡¶

Vol 447 | 28 June 2007 | doi:10.1038/nature05887 nature

ARTICLES

Genome-wide association study identifies novel breast cancer susceptibility loci

Douglas F. Easton[1], Karen A. Pooley[2], Alison M. Dunning[2], Paul D. P. Pharoah[2], Deborah Thompson[1],

nature genetics

OPEN ACCESS Freely available online

Genome-Wide Association Scan Shows Genetic Variants in the *FTO* Gene Are Associated with Obesity-Related Traits

Angelo Scuteri[1,2☯], Serena Sanna[3,4☯], Wei-Min Chen[3], Manuela Uda[4], Giuseppe Albai[4], James Strait[2], Samer Najjar[2],
Ramaiah Nagaraja[2], Marco Orrù[4,5], Gianluca Usala[4], Mariano Dei[4], Sandra Lai[4], Andrea Maschio[4], Fabio Busonero[4],

nature genetics

A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24.21

Ian Tomlinson[1,2], Emily Webb[3,13], Luis Carvajal-Carmona[1,13], Peter Broderick[3,13], Zoe Kemp[1,13],

Robust associations of four new chromosome re from genome-wide analyses of type 1 diabetes

John A Todd[1], Neil M Walker[1,9], Jason D Cooper[1,9], Deborah J Smyth[1,9], Kate Downes[1], Vincent Plagnol[1],

Ovarian Kaleidoscope Database - Microsoft Internet Explorer

Bestand Bewerken Beeld Favorieten Extra Help

Vorige Zoeken Favorieten Media

Adres http://ovary.stanford.edu/ Ga naar Koppelingen

Ovarian Kaleidoscope Database (OKDB)

Home

History

Infertility

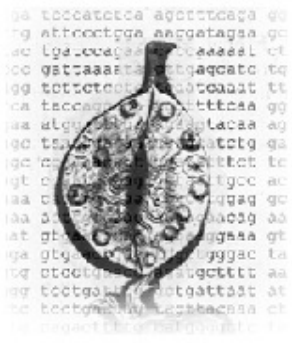
Gene Navigator

Database:

Search

Submit

Update



THE OVARIAN KALEIDOSCOPE DATABASE

- A website to serve the ovarian research community -

Gene Name [ ] Quick Search

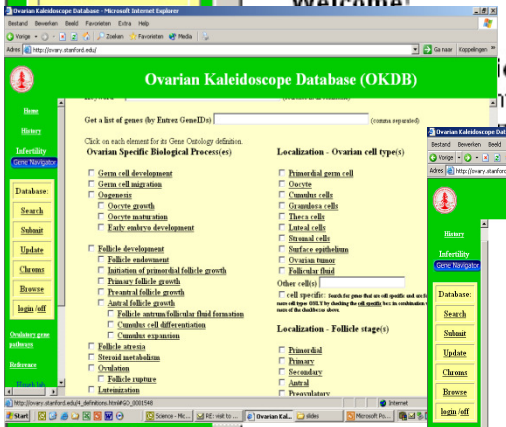
Welcome!

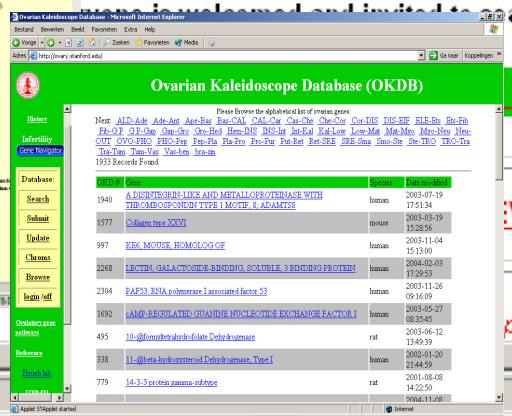
idoscope Database provides information regarding the biological function, expression pattern and regulation of genes expressed
ntains information on gene sequences, chromosomal localization, human and murine mutation phenotypes and biomedical
arch and/or submit genes! Please use the bars on the left of this screen to navigate.

Interpreter

:WS | Useful Links | Ovarian gene maps | BioData Interpreter

ported by the Specialized Cooperative Centers Program





Internet

Start | Science - Mic... | RE: visit to ... | Ovarian Kal... | slides | Microsoft Po... | 17:00

human reproduction update

Human studies on genetics of the age at natural menopause: a systematic review

Marlies Voorhuis[1,2,4], N. Charlotte Onland-Moret[2,3], Yvonne T. van der Schouw[2], Bart C.J.M. Fauser[1], and Frank J. Broekmans[1]

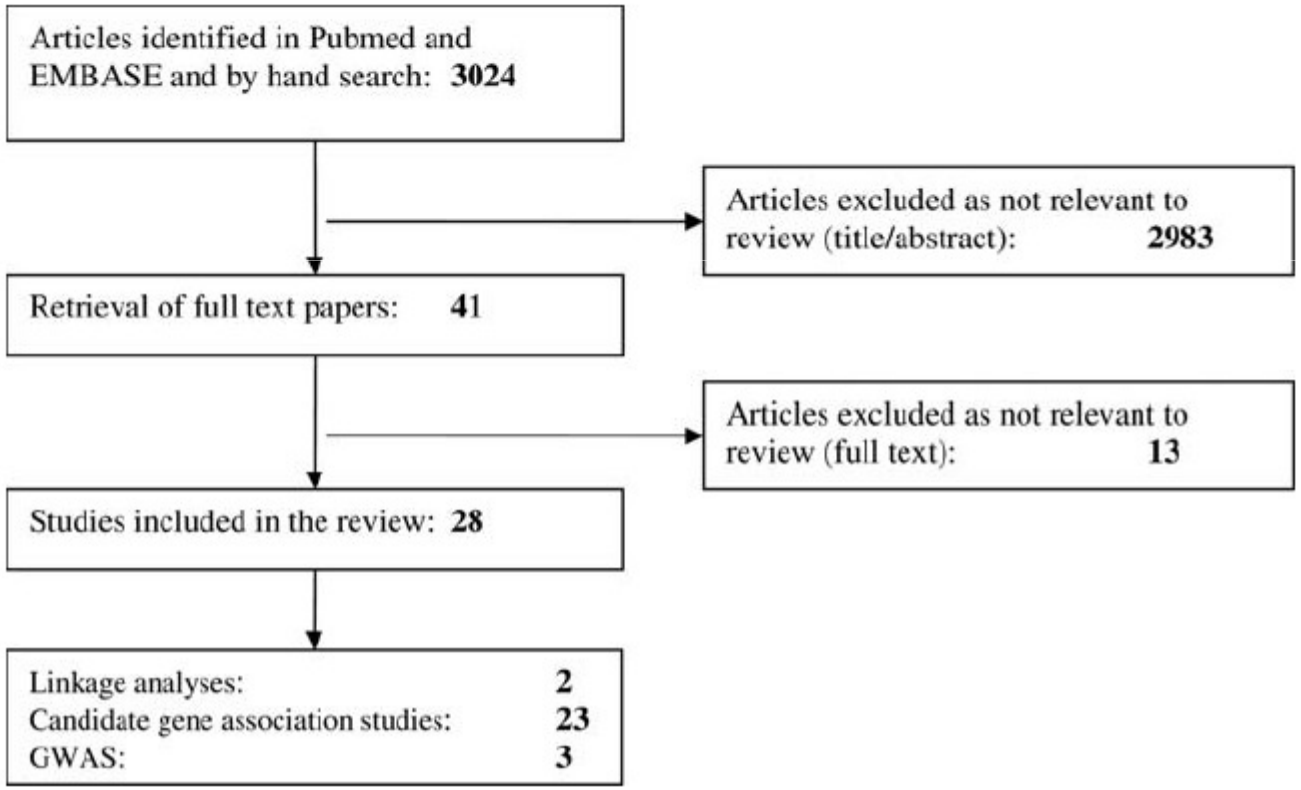


Figure 1 Flowchart of selection of genetic studies on age at natural menopause.

TABLE 5. Summary of candidate gene and genome-wide association (GWA) studies for age at menopause

Chromosome	Study	Effect on AMP in years (minor allele)	Gene or gene region
Candidate gene			
12q13	Keevenaar *et al.*, 2007 (305)	−2.6	AMHR2
13q13	Tempfer *et al.*, 2005 (289)	+1.5	APO-E
	He *et al.*, 2009 (311)	−1.93	
2p21-22	Hefler *et al.*, 2005 (298)	−0.8	CYP1B1
	Long *et al.*, 2006 (331)	−1.0	
	Long *et al.*, 2006 (331)	+1.2	
	Long *et al.*, 2006 (331)	+0.7	
	Mitchell *et al.*, 2008 (332)	+2.6	
6q25	Weel *et al.*, 1999 (299)	−1.1	ERα
13q34	van Disseldorp *et al.*, 2008 (108)	+0.8	F VII
1q23	van Asselt *et al.*, 2003 (290)	−3.1	F V Leiden
	Tempfer *et al.*, 2005 (305)	−2.4	
5q21-22	Zhang *et al.*, 2007 (333)	+1.58	HDC
1p13	Mitchell *et al.*, 2008 (332)	+1.9	HSDB1
GWA studies			
19q13.4	He *et al.*, 2009 (311)	−0.49	BRSK1, THEM224 and SUV420H2
	Stolk *et al.*, 2009 (310)	+0.39	

Universitair Medisch Centrum Utrecht

Table V Genome-wide significant SNPs in association with ANM.

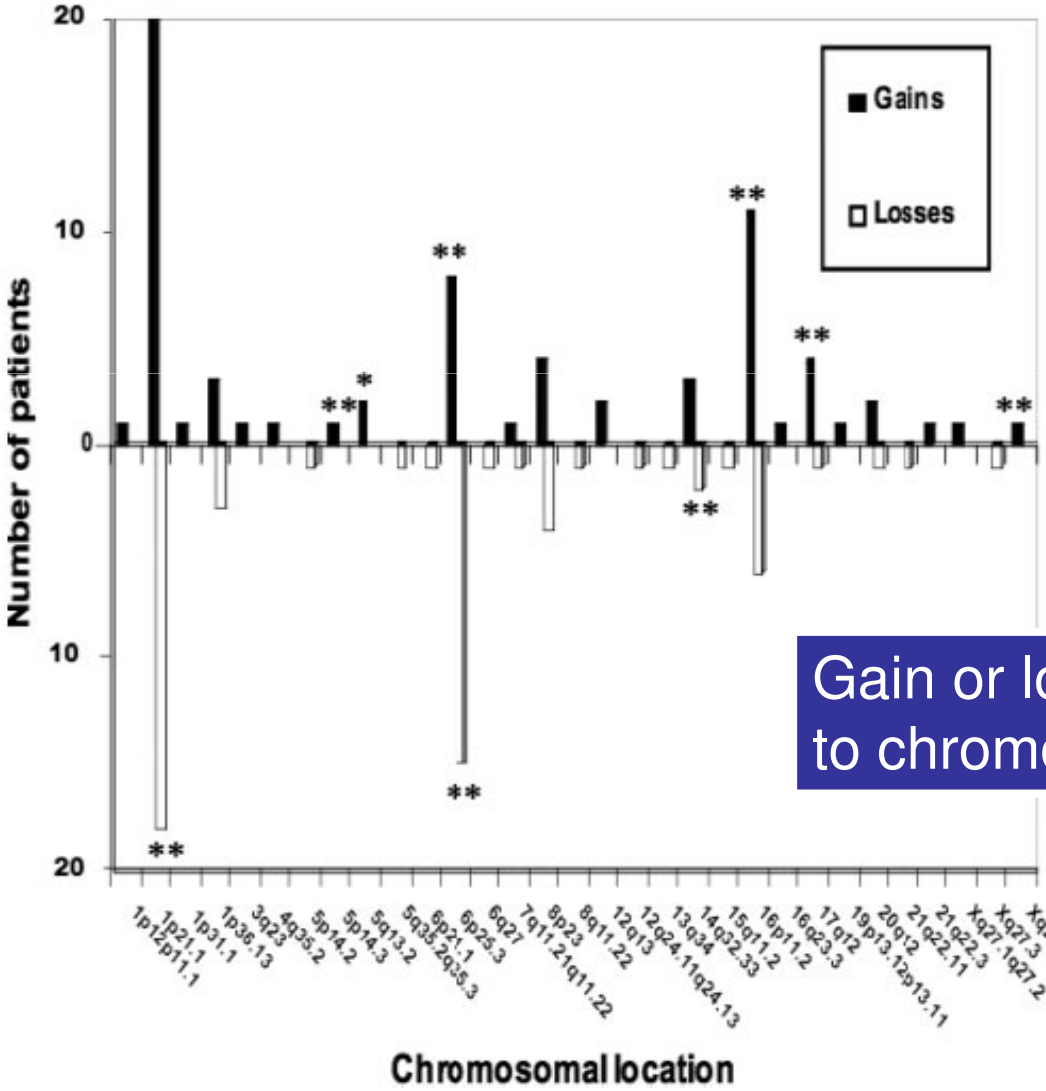
Chromosome	SNP	Study	Effect ANM*	*P*-value	Nearby genes
19q13.4	rs1172822	He *et al.*, 2009a	−0.49	1.8E−19	BRSK1, THEM224 and SUV420H2
		Stolk *et al.* 2009	+0.391	6.28E−11	
	rs2384687	He *et al.*, 2009a	−0.47	2.4E−18	BRSK1, THEM224 and SUV420H2
		Stolk *et al.* 2009	−0.381	1.39E−10	
	rs1551562	He *et al.*, 2009a	−0.43	2.6E−12	BRSK1,THEM224 and SUV420H2
		Stolk *et al.*, 2009	−0.428	1.04E−09	
	rs897798	He *et al.*, 2009a	−0.40	1.1E−14	BRSK1, THEM224 and SUV420H2
		Stolk *et al.* 2009	−0.308	3.91E−08	
	rs7246479	He *et al.*, 2009a	+0.36	2.3E−12	BRSK1
	rs12611091	He *et al.*, 2009a	+0.33	6.6E−10	HSPBP1, BRSK1
20p12.3	rs16991615	He *et al.*, 2009a	+1.07	1.2E−21	TRMT6, MCM8
	rs236114	Stolk *et al.* 2009	+0.495	9.71E−11	MCM8
5q35.2	rs365132	He *et al.*, 2009a	+0.39	8.4E−14	UIMC1
	rs7718874	He *et al.*, 2009a	+0.39	1.3E−13	UIMC1
	rs402511	He *et al.*, 2009a	+0.39	1.4E−13	UIMC1, ZNF346
	rs691141	He *et al.*, 2009a	+0.36	3.9E−12	HK3, UIMC1
	rs2278493	He *et al.*, 2009a	−0.30	7.2E−08	UNC5A, HK3
2	rs10496265	Lunetta *et al.*, 2007	Not stated	1.1E−08	
	rs10496262	Lunetta *et al.*, 2007	Not stated	3.3E−07	
13q34	Rs7333181	Stolk *et al.*, 2009	+0.520	2.50E−08	ARHGEF7
6p24.2	rs2153157	He *et al.*, 2009a	+0.29	5.1E−08	GCM2, SYCP2L

Array Comparative Genomic Hybridization Profiling Analysis Reveals Deoxyribonucleic Acid Copy Number Variations Associated with Premature Ovarian Failure

J Clin Endocrinol Metab. November 2009, 94(11):4540–4546

Azzedine Aboura,* Claire Dupas,* Gérard Tachdjian, Marie-France Portnoi, Nathalie Bourcigaux, Didier Dewailly, René Frydman, Bart Fauser, Nathalie Ronci-Chaix, Bruno Donadille, Philippe Bouchard, and Sophie Christin-Maitre

Universitair Medisch Centrum



Gain or loss of CNV according to chromosome location

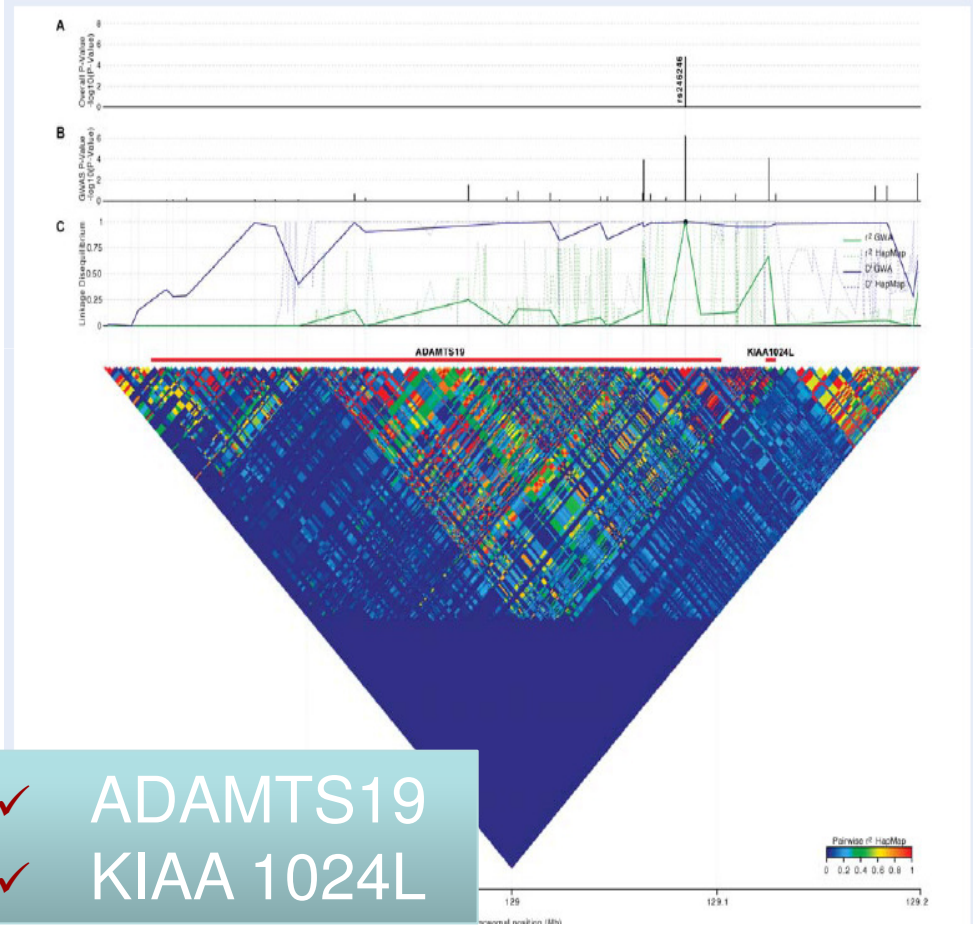
human reproduction ORIGINAL ARTICLE *Reproductive genetics*

Genome-wide association study in premature ovarian failure patients suggests ADAMTS19 as a possible candidate gene

Human Reproduction, Vol.24, No.9 pp. 2372–2378, 2009

Erik A.H. Knauff[1,11,†], Lude Franke[2,3,†], Michael A. van Es[4],

Universitair Medisch Centrum Utrecht



- ✓ ADAMTS19
- ✓ KIAA 1024L

Table II POF patient phenotype characteristics ($n = 99$)

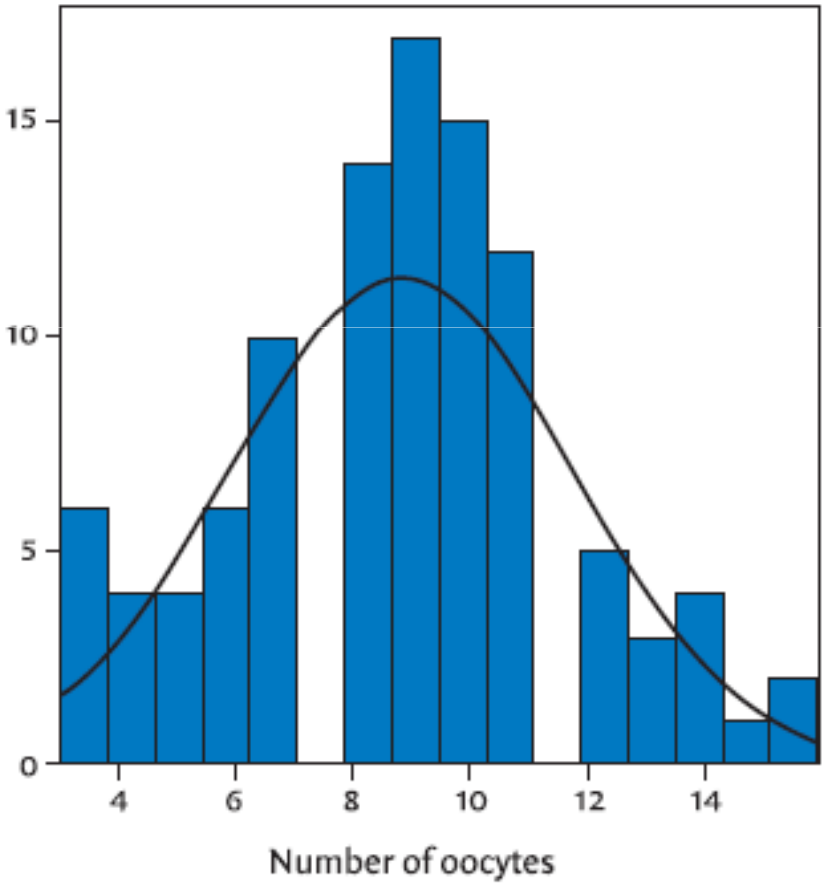
	Mean ± SD	%
Age at screening	36.5 ± 7.3	
1st FSH (IU/l)	82.4 ± 29.5	
2nd FSH (IU/l)	79.7 ± 38.1	
Age at menarche (years)	13.2 ± 1.6	
Age at amenorrhea (years)	31 ± 8.1	
Familial clustering[a] (%)		19
46 XX karyotype (%)		100
FMR1 repeats $n < 40$ (%)		100
Caucasian (%)		100
AMH below menopause threshold[b] (%)		100
Undetectable AMH (%)		93
Positive anti-TPO antibodies (%)		25
Adrenal antibodies (%)		2

Figure 2 Schematic 400 kb haploblock view on the long arm of chromosome five surrounding the rs246246 SNP and covering two genes: ADAMTS19 and KIAA1024L.

Genomic predictors of ovarian response to stimulation for IVF

Universitair Medisch Centrum Utrecht

Poisson distribution
No oocytes



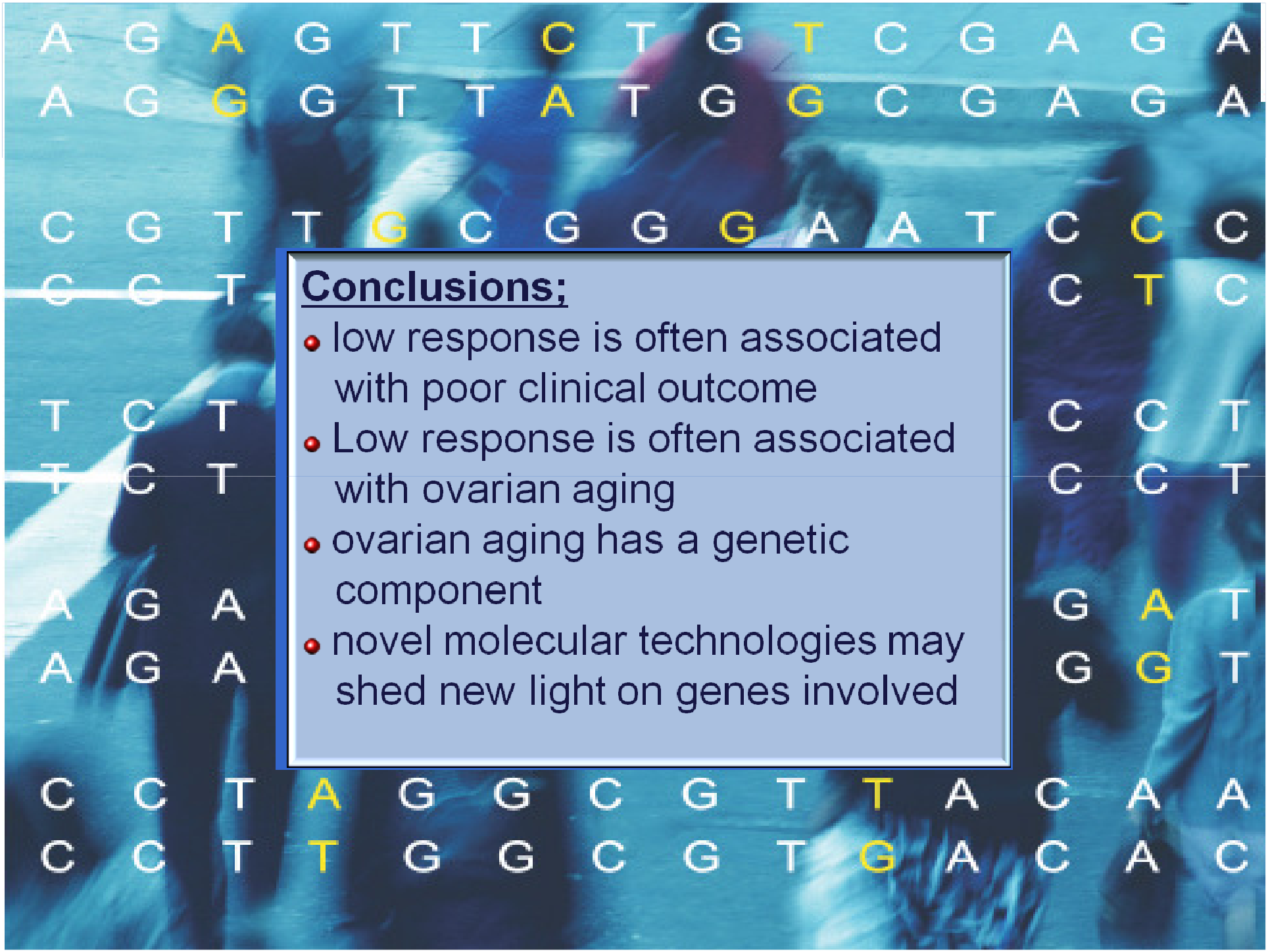
N=102
Homogeneous
Caucasian
Mean age; 33.8
Mean BMI 22.4
Mean FSH 8.0

vDisseldorp et al.
2010; submitted

Possible SNPs involved in ovarian response

Universitair Medisch Centrum Utrecht

POSSIBLE SNPs	Related genes
rs1885678	RAB32; GTPase
rs9403799	RAB32
rs4499783	MAST4
rs8025763	ARRDC4
rs2271463	CUBN
CANDIDATE SNPs	**Related genes**
rs6166	FSHR
rs2234693	ESR1
rs928554	ESR2
rs10407022	AMH
rs2002555	AMHR


Conclusions;
low response is often associated with poor clinical outcome
Low response is often associated with ovarian aging
ovarian aging has a genetic component
novel molecular technologies may shed new light on genes involved