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University Medical Center Rotterdam

Genetics of PCOS: The insulin receptor pathway

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PCOS consensus meeting. Women's health aspects of PCOS. November 18th

PCOS is a complex genetic trait

Oligo- or Amenorrhea (cycle length > 35 days)
Hyperandrogenism (hirsutism and / or FAI > 4.5)
PCO (> 12 follicles, 2 – 9 mm, in one or both ovaries and/or ovarian volume > 10 mL)

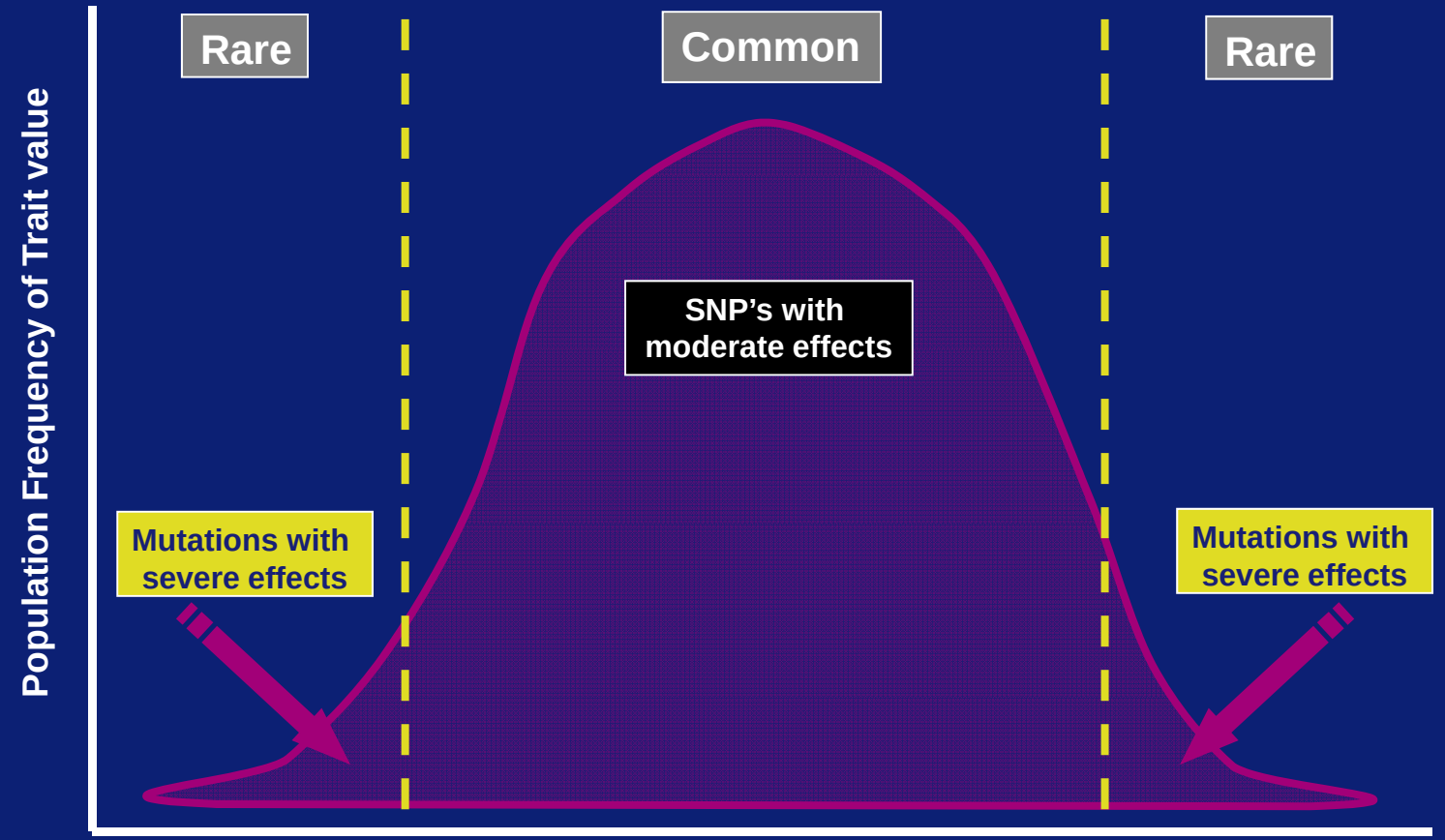
} 2 out of 3: **PCOS**

Rule out:
Hyperprolactinemia,NCAH, Cushing's syndrome, Androgen Secreting Neoplasm, Acromegaly

ESHRE / ASRM sponsored PCOS consensus meeting 2003, Rotterdam, The Netherlands

PCOS is a heterogeneous phenotype indicating a complex genetic background, which might be altered by the environment

Genetics of population variation of traits



Uitterlinden et al, 2004

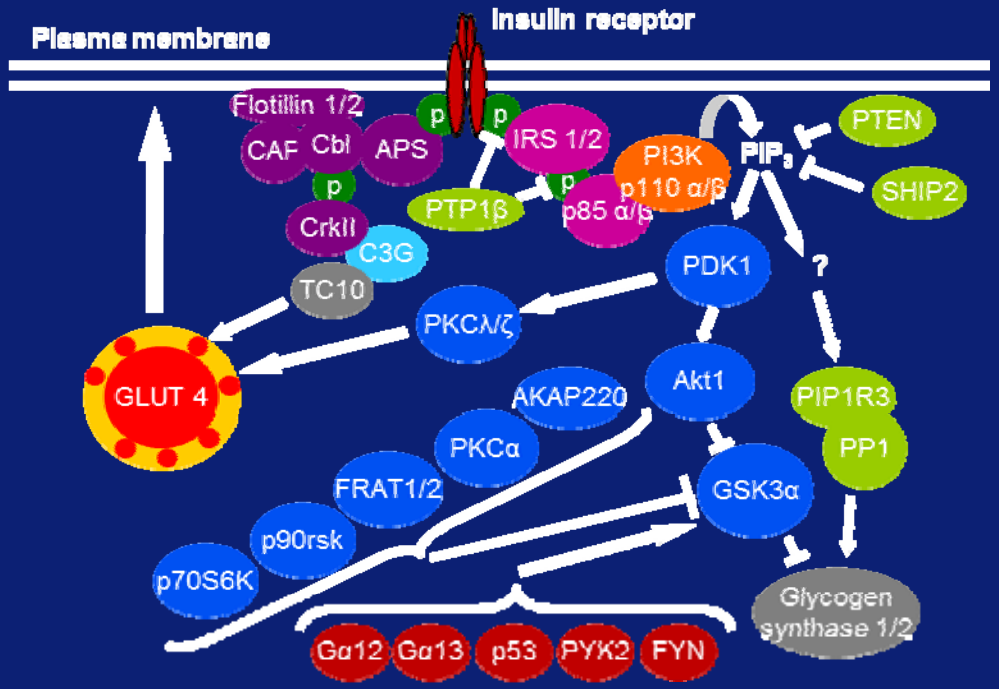
Genetics of PCOS

Two candidate gene studies:

- The insulin receptor pathway: replication of association
  In collaboration with: professor Goodarzi and professor Azziz, Cedars-Sinai Medical Center

- BMI susceptibility genes: genetic risk score
  In collaboration with: professor McCarthy and professor Franks, Oxford University

Insulin signaling pathway



Discovery stage
295 variants in 39 genes

↓

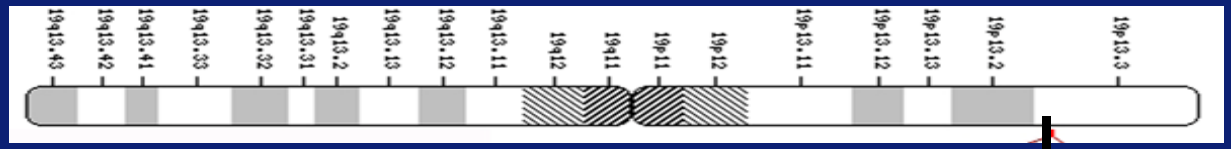
Insulin receptor (INSR)
4 SNPs associated with PCOS

↓

Replication

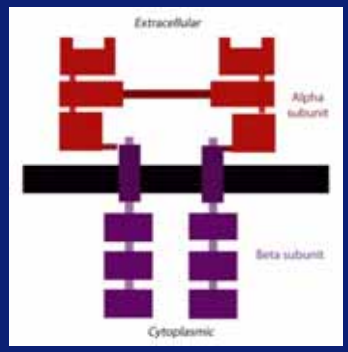
In collaboration with Goodarzi and Azziz et al, unpublished data

Insulin receptor polymorphisms and PCOS



chromosome 19

Insulin receptor (INSR)



SNP	Discovery cohort			Replication cohort			Meta-analysis
	OR	95% CI	P-value	OR	95% CI	P-value	P-value
rs12459488	0.62	0.40-1.0	0.05	1.11	0.92-1.34	0.30	0.71
rs12971499	0.68	0.42-1.11	0.12	1.05	0.86-1.28	0.067	0.21
rs2252673	1.99	1.17-3.58	0.011	1.32	1.08-1.60	0.006	0.00066
rs10401628	0.45	0.255-0.801	0.0065	1.00	0.80-1.25	0.99	0.40

In collaboration with Goodarzi and Azziz et al, unpublished data

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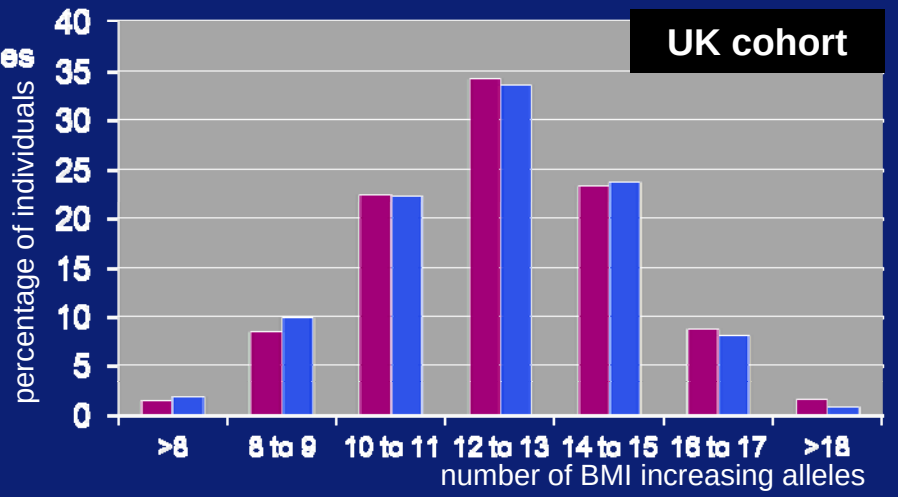
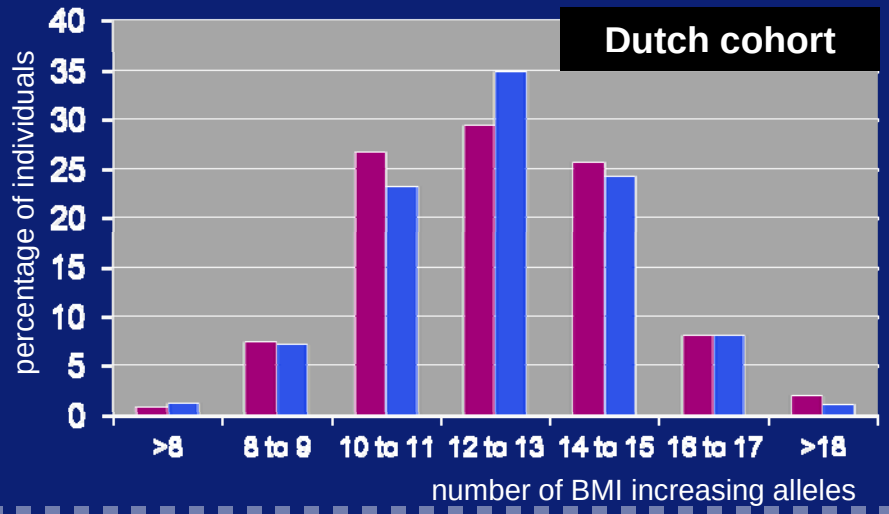
BMI susceptibility genes and PCOS (1)

Genetic Risk Score (GRS)

nearest gene	SNP	chromosome
BDNFOS	rs4074134	11
FAIM2	rs7138803	12
ETV5	rs7647305	3
FTO	rs9939609	16
GNPDA2	rs10938397	4
KCTD15	rs11084753	19
MC4R	rs17782313	18
MTCH2	rs10838738	11
NEGR1	rs2815752	1
SEC16B	rs10913469	1
SH2B1	rs7498665	16
TMEM18	rs6548238	2





In collaboration with McCarthy et al, unpublished data

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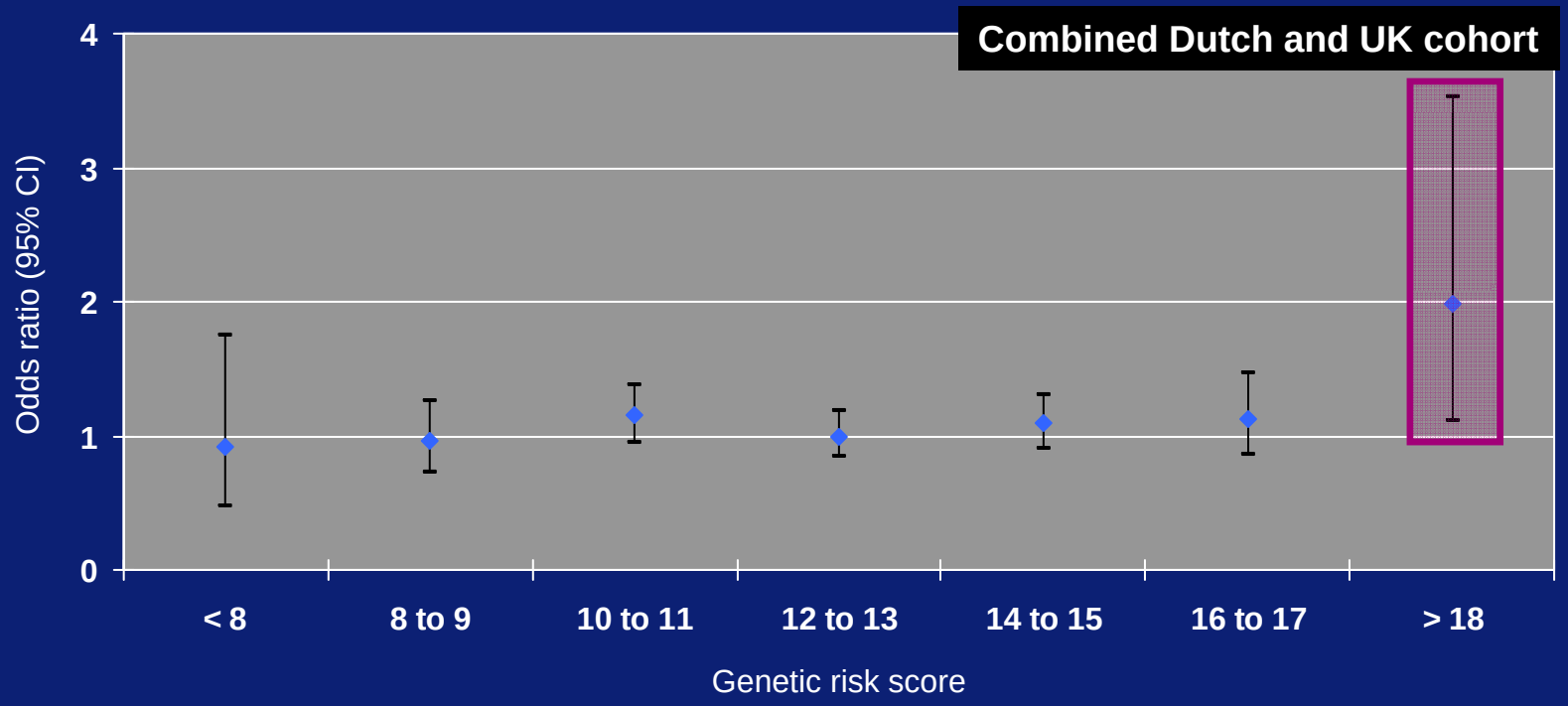
BMI susceptibility genes and PCOS (2)

GRS for BMI increasing alleles and risk for PCOS



Number of BMI risk alleles carried is not associated with an increased risk of PCOS

In collaboration with McCarthy et al, unpublished data

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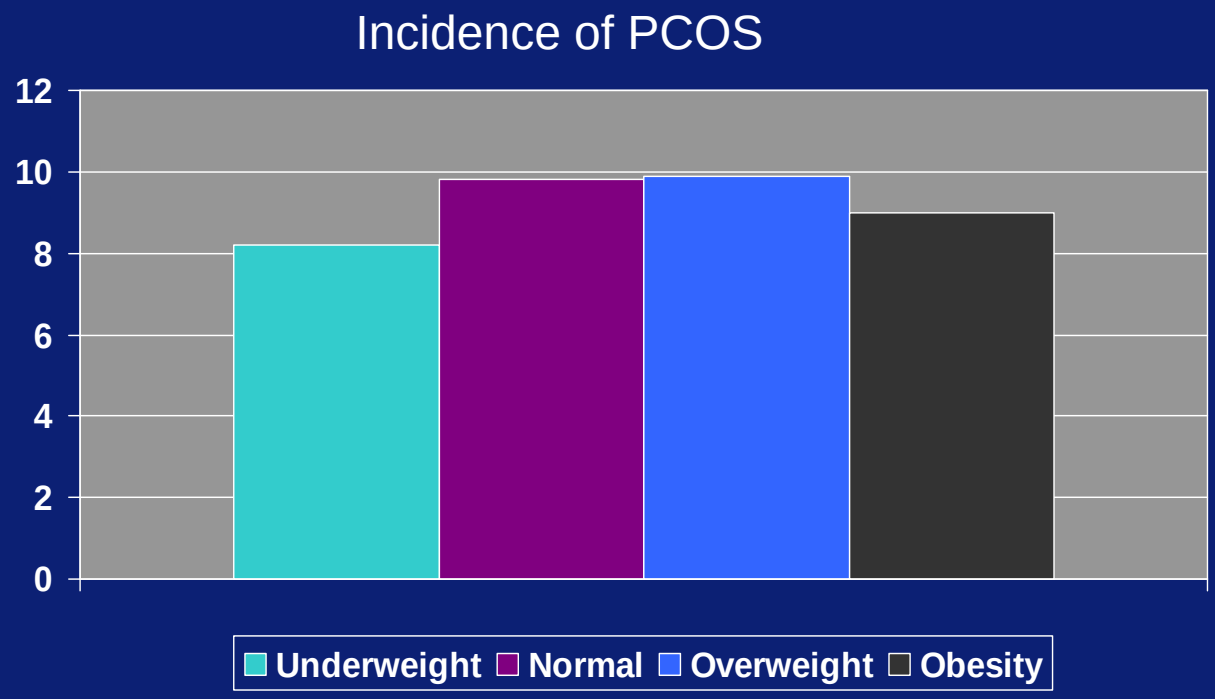
BMI susceptibility genes and PCOS (3)



Yildiz et al. JCEM 2007

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Acknowledgements

ErasmusMC Medical Center

The Netherlands

Joop Laven

Andre Uitterlinden

Lisette Stolk

Cedars-Sinai Medical Center

USA

Mark Goodarzi

Ricardo Azziz

University of Oxford, UK

Mark McCarthy

Steven Franks

Blanca Herrera