

The genetics of depression and suicidal behaviour

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Common disorders

- Lifetime prevalence of MD: 15 to 17%
- Lifetime risk of suicide: 15 to 19%
- Higher risks for substance abuse, chronic illnesses (mainly cardio-vascular)

Multifactorial disorders

- Poor parenting,
- Traumatic experiences,
- Predisposing personality traits,
- Recent stressful life events,
- Genetic liability,
- ...

Sex-differences

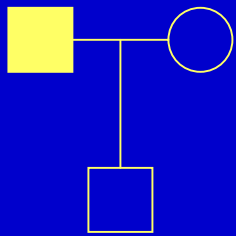
- Higher rates of MD and SA (twice) in women than in men
- But finding replicable differences in risk factors remain difficult.

Family studies of Major Depression

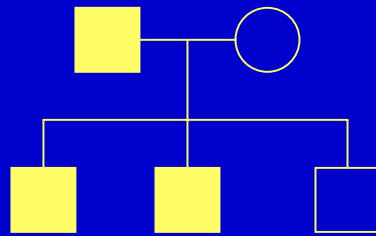
Study	Country	Subjects with major depression		Comparison subjects		Odds ratio	95%CI
		Source of Subjects	Morbidity risk	Source of Subjects	Morbidity risk		
Tsuang et al. 1980	U.S.	Clinical setting	15.2	Unscreened surgical patients	7.5	2.21	1.35-3.62
Gershon et al. 1982	U.S.	Clinical setting	16.6	Screened medical patients	5.8	3.23	1.59-6.58
Weissman et al. 1984	U.S.	Clinical setting	17.6	Screened general population	5.9	3.41	2.23-5.20
Maier et al. 1993	Germany	Clinical setting	21.6	Unscreened general population	10.6	2.32	1.62-3.33
Weissman et al. 1993	U.S.	Clinical plus general population	21	Screened general population	5.5	4.57	2.43-8.60

From Sullivan et al. 2000

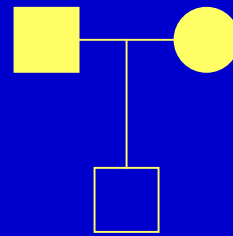
Reccurence risks depend on the family structure



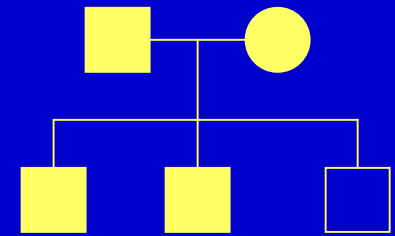
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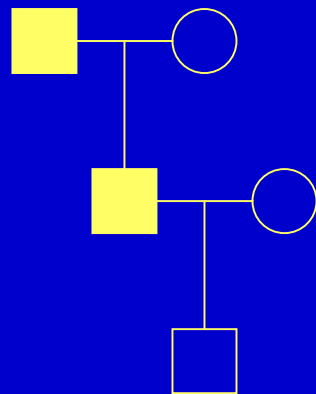
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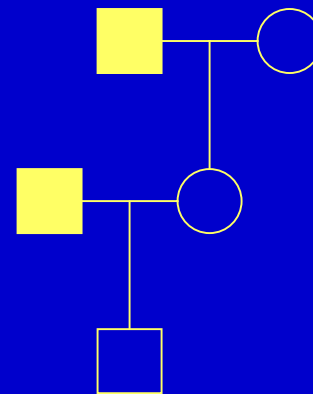
$\lambda=21$



$\lambda=38$

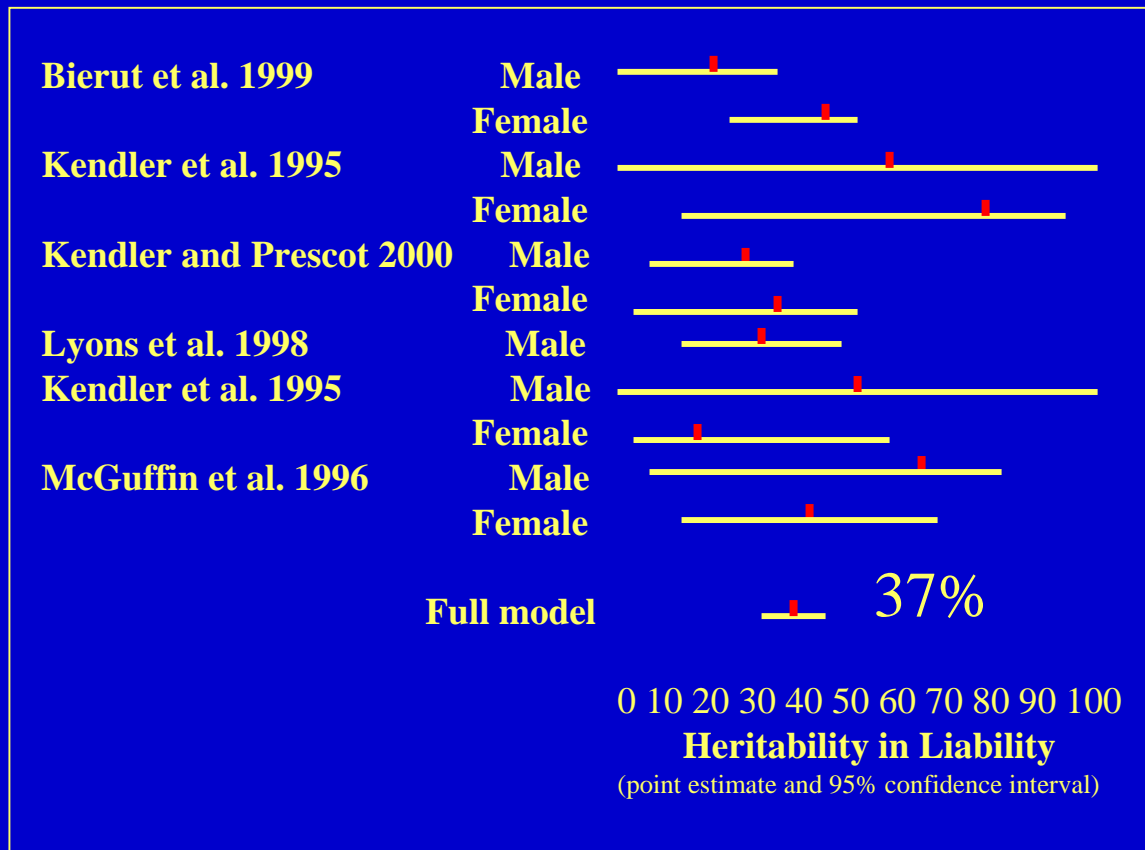


$\lambda=5$



$\lambda=9$

Twin studies - Meta-Analysis



From Sullivan et al. 2000

A Swedish national twin study of lifetime major depression

Arch. Gen. Psychiatry 2006, 163, 109-14

- The largest twin study of MD (15,493)
- Replicates heritability previously estimated by meta-analysis (38%)
- Identifies sex-difference: 42% in women, 29% in men
- Shows that heritability estimates are stable across historical cohorts

Estimates of genetic and environmental components to complex traits

- Combination of family, twin and adoption studies' data
- Additive genetic (heritability), shared (SE) and non shared environment (NSE)
- NSE=environmental influences specific to one or the other member of a twin pair + gene-environment interaction

Estimates of genetic and environmental components to complex traits (2)

- SE : Concordance between adopted and biological children reared in same families
- Major depression : 0-3% .

Estimates of genetic and environmental components to complex traits (3)

- NSE : Concordance between MZ, DZ and fraternal siblings.
- Major depression:
 - MZ : 0.43
 - DZ : 0.15
 - Siblings : 0.12
 - $NSE = 1 - [0.43 - (0.15 - 0.12)] = 0.60$

Suicidal behaviour runs within families

Study	Year	Country	Probands	Controls	Sample size probands/controls	AOR
Qin	2002	Denmark	Suicides, 9-15	Matched community controls	4,262/80,238	2.6 ^{a,b}
Agerbo	2002	Denmark	Suicides, 10-21	Matched community controls	496/24,800	2.3-4.8 ^{a,b,c}
Qin	2003	Denmark	Suicides, all ages	Matched community controls	21,169/423,128	2.1 ^{a,b}
Runeson	2003	Sweden	Suicides, all ages	Matched non-suicide deaths	8,396/7,568	2.0 ^b

^aAdjusted for previous psychiatric admission/care

^bAdjusted for relatives previous psychiatric admission

^cor for suicide in father/mother

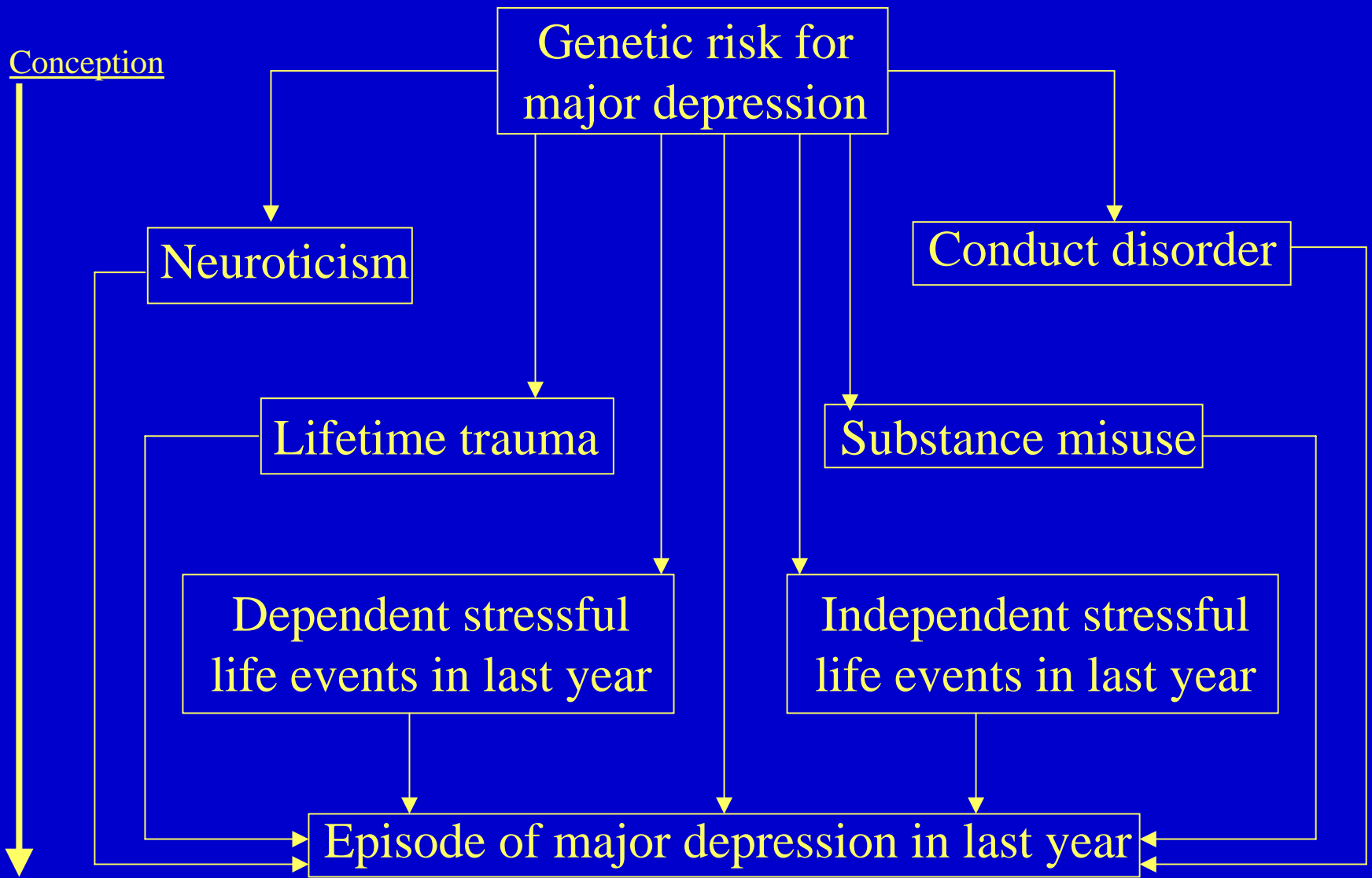
Twin studies also support a genetic component to suicidal behaviour

Study	N° of twins (%) concordant for suicide behaviour		
	MZ	DZ	p
Haberlandt (1967)	14/51 (17.6)	0/98 (0)	<0.001
Juel-Nielsen (1970)	4/19 (21.1)	0/58 (0)	<0.003
Zair (1981)	1/1 (100)		NS
Roy et al. (1991)	7/62 (11.3)	2/114 (1)	<0.01
Roy et al. (1995)	10/26 (38.5)	0/9 (0)	<0.04
Roy and Segal (2001)	4/13 (30.7)	0/15 (0)	<0.04
Combined	40/172 (23.0)	2/294 (0.7)	<0.00001

Heritability of serious suicide attempt: 55%

Synthesis

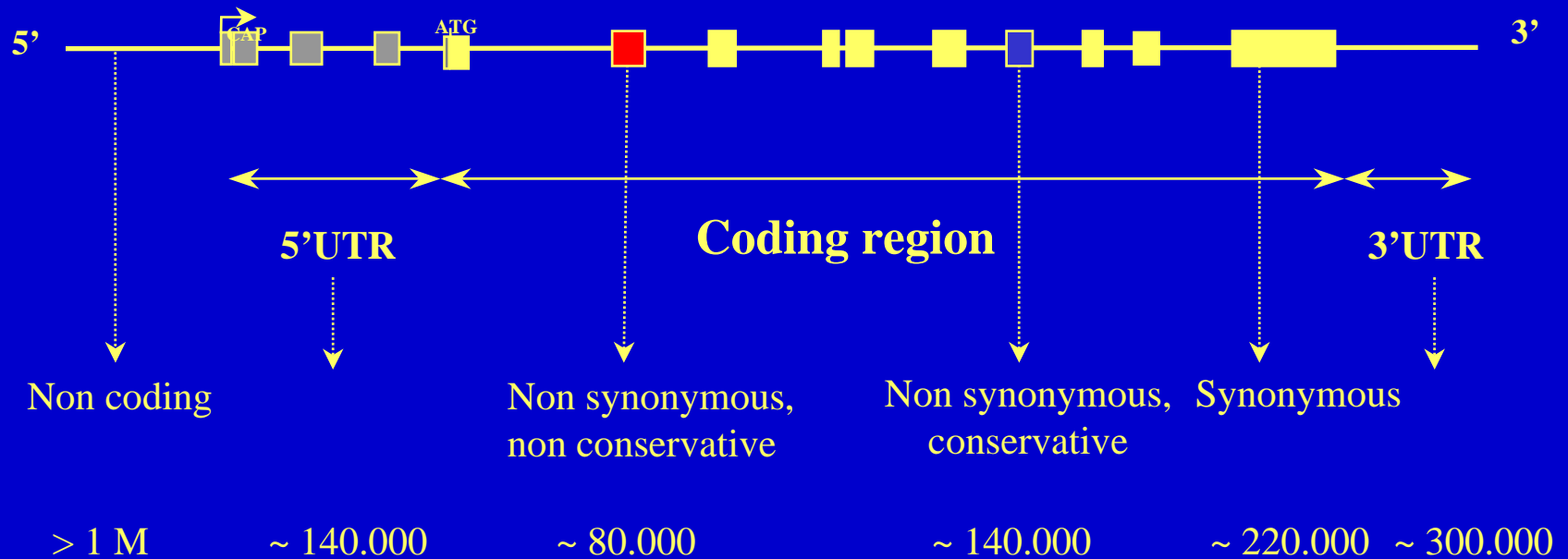
- There are both common and specific genetic contributions to major depression and suicidal behaviour
- Sex-difference in MD. Unknown in SB
- Complex: small size effects of many genes
- Interaction of these genes with environmental and developmental factors



Adapted from Kendler et al. 2006

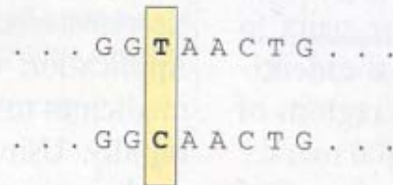
Simple Nucleotidic Polymorphism (SNP)

...ACTTGACCTCAATC...
...ACTTGATCTCAATC...



What is an SNP?

Different people can have a different nucleotide or base at a given location on a chromosome



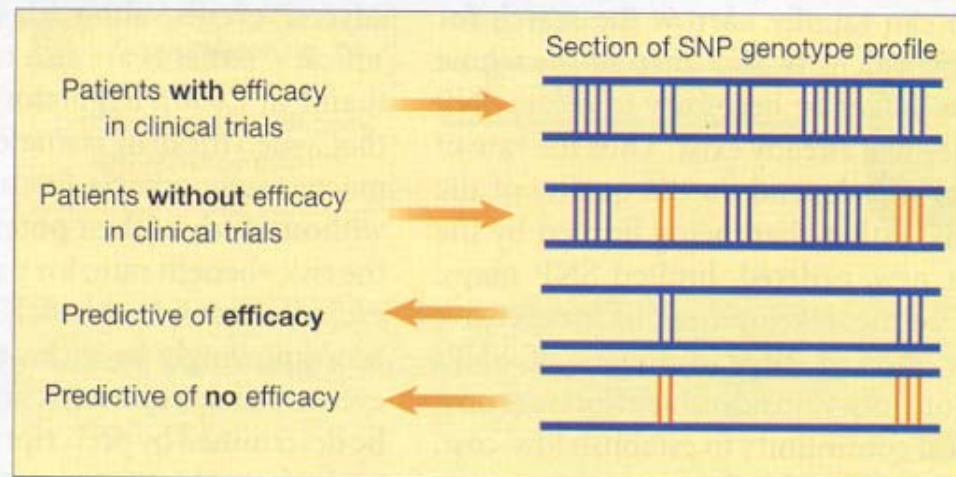
What is an SNP map?

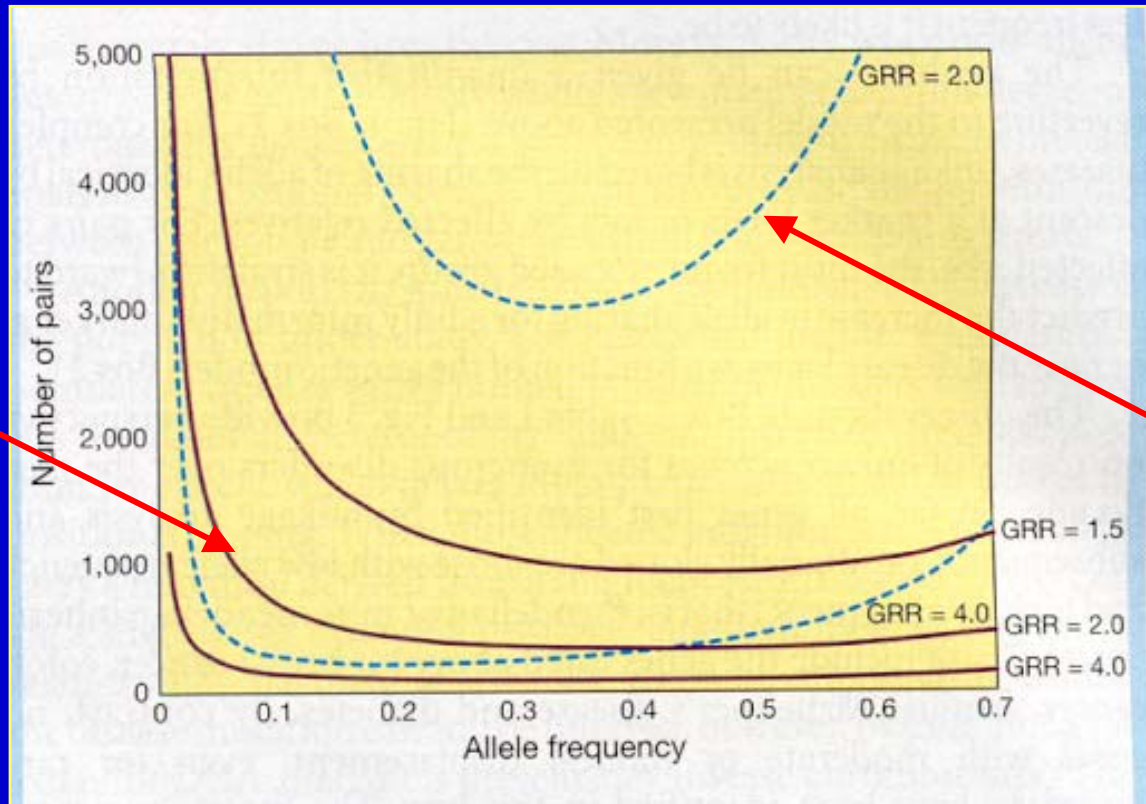
Location of SNPs on human DNA



Human DNA

How can an SNP map be used to predict medicine response?

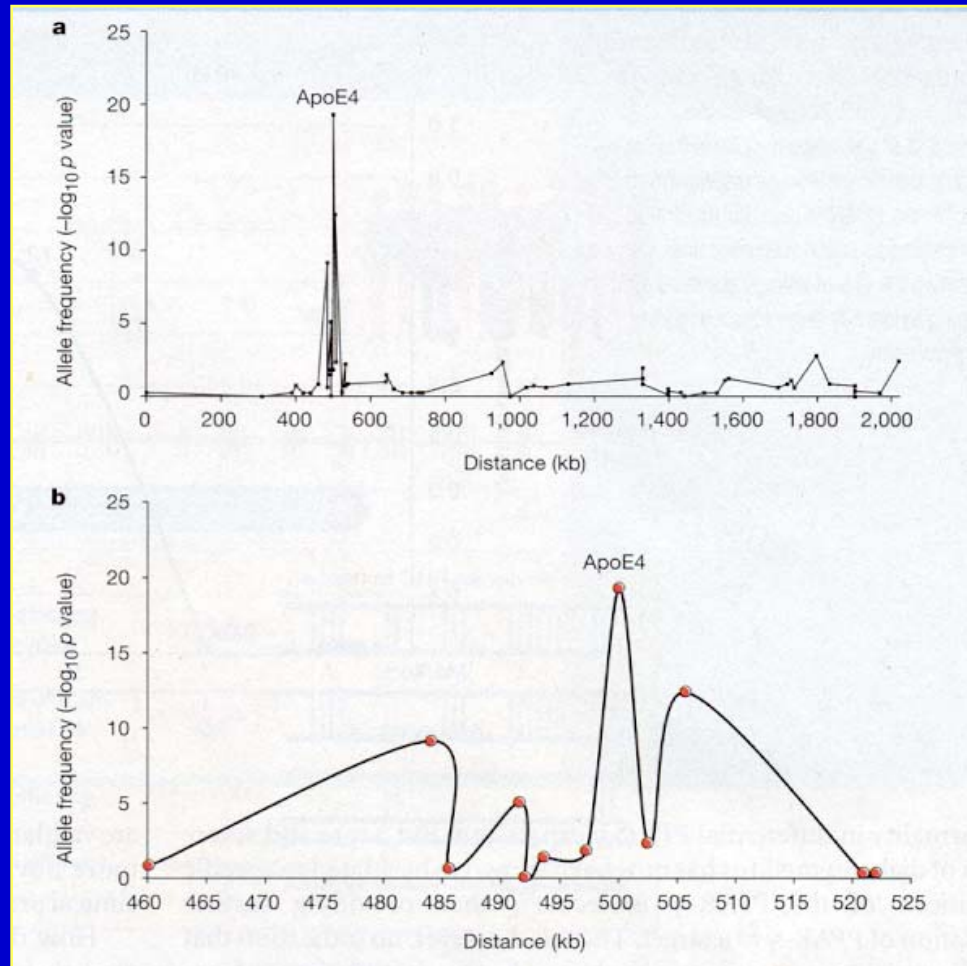




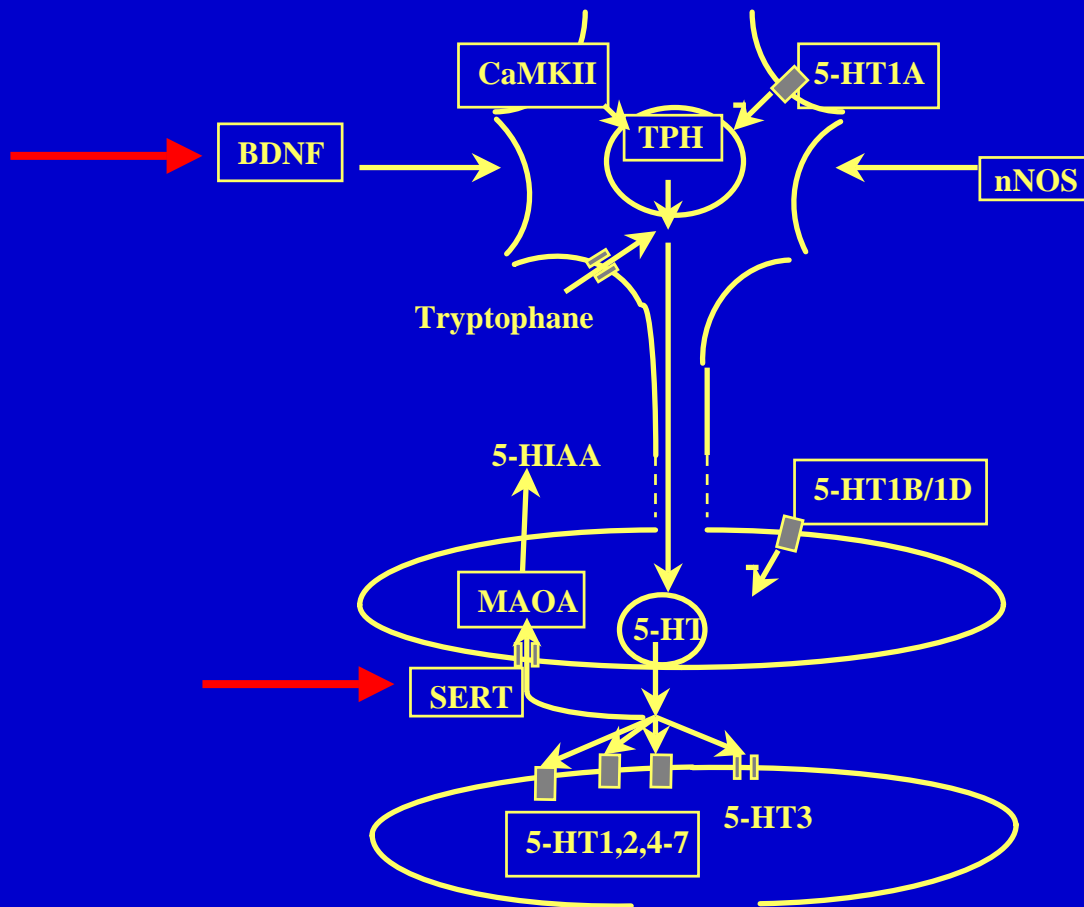
Estimates of the number of pairs required to detect candidate genes with small effect

GRR: genotyping relative risk
 Parameters: power > 90%; $p = 5 \times 10^{-8}$
 (Risch, Nature, 2000, 405, 847-856)

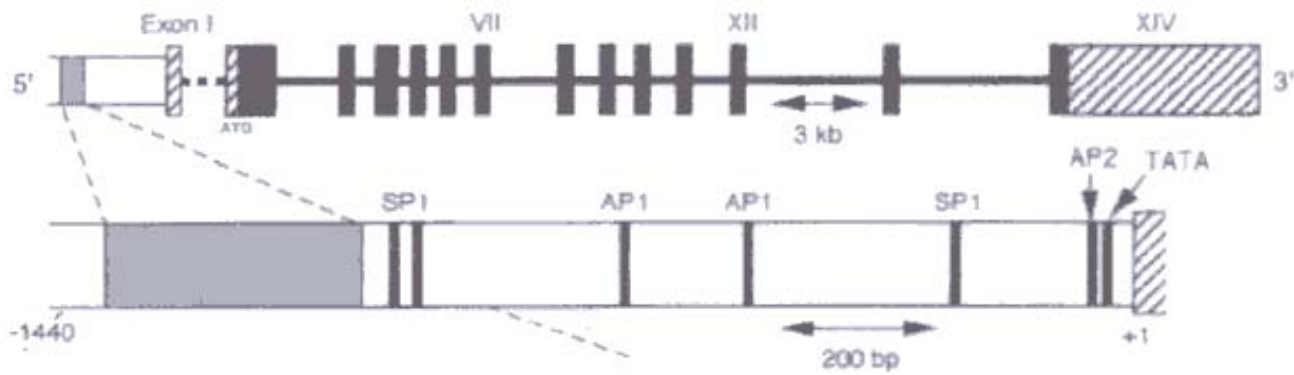
ApoE Alzheimer's disease



Candidate genes



5-HTTLPR

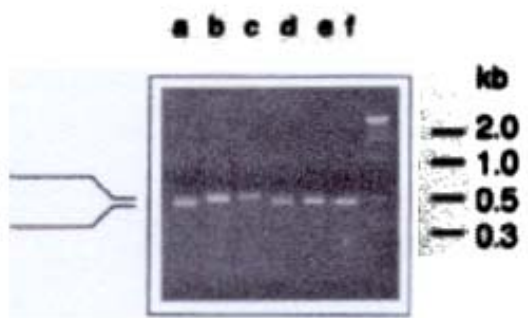
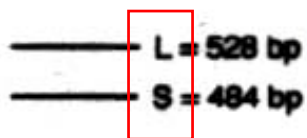


Human serotonin transporter gene (h5-HTT)

h5-HTT gene regulatory region

-1426 TCTCCGCGCTGCGCGTCCCGGCTGAAATGCGCAGCAOCTAACCCCTAATGT

-1376	CCCTAC	TGCA	GCCTCC	AGCAT	I
-1354	CCCCC	TGCA	ACCTCC	AGCA	II
-1333	ACTCC	TGTA	CCCTCCT	AGGAT	III
-1310	CGCTCC	TGCA	TCCTCC	ATTATC	IV
-1288	CCCCC	TTCA	CTCCTCC	GCCAT	V
-1265	CCCCC	TGCA	GGGGG	GGAT	VI
-1244	GGGGG	TGCA	GGGGGGG	GGAT	VII
-1221	GGGGG	TGCA	GGGGG	AGCAT	VIII
-1201	CCCCC	TGCA	GCCTTCC	AGCA	IX
-1179	TCCCC	TGCA	CCTCTCC	AGGAT	X
-1156	CTCCC	TGCA	ACCCC	ATTAT	XI
-1135	CCCCC	TGCA	CCCTCC	AGTAT	XII
-1112	CCCCC	TGCA	CCCCC	AGCATC	XIII
-1090	CCCCC	TGCA	CCCC	GCCAT	XIV
-1070	CCCCC	TGCA	CCCTCC	AGCAT	XV
-1048	TCTCCT	TGCA	CCCTACC	AGTAT	XVI

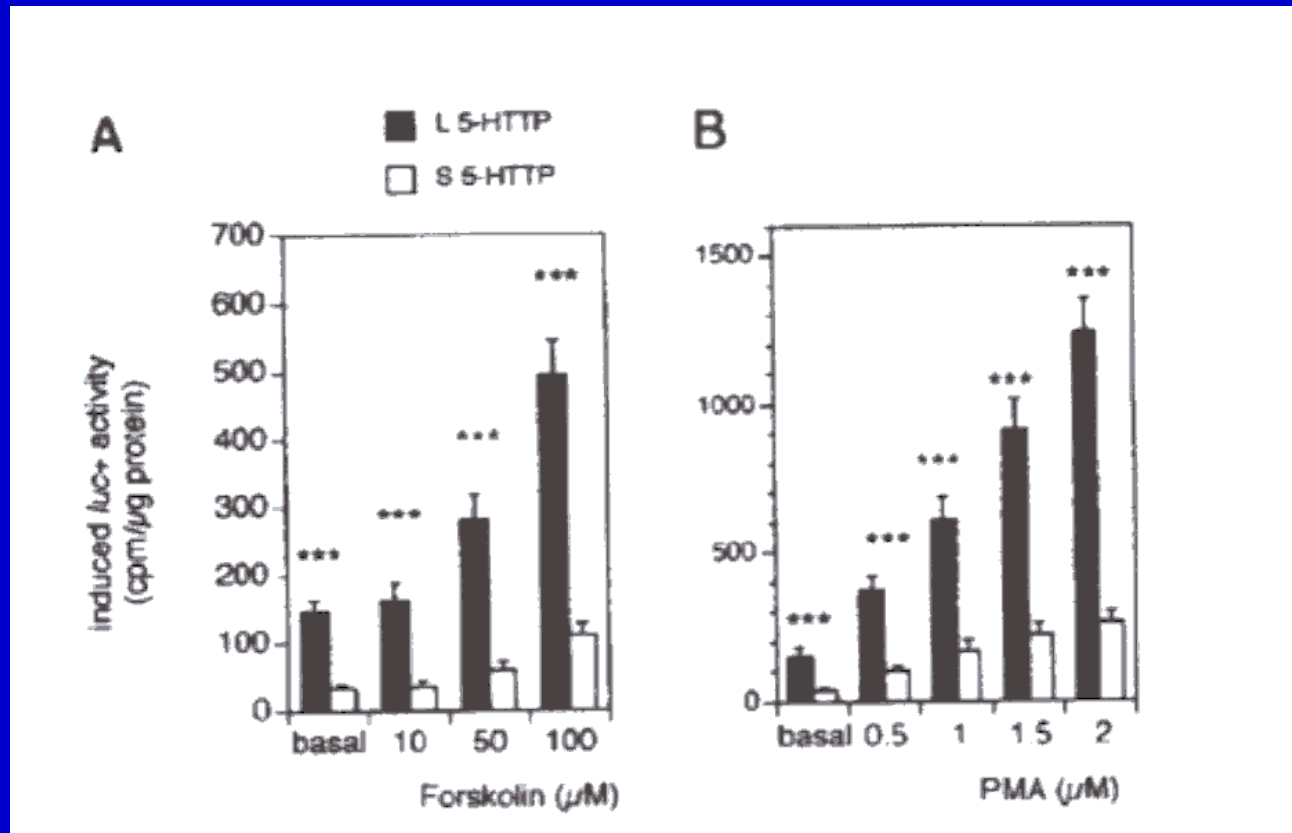


h5-HTT-linked polymorphic region

-1026 TCCCCGATCCCGCCTCCAAAGCCTCCCGCCACCTTGCCTCCCGCC
 -976 CTGGCCTCTAGGTGGCACCAGAAATCCGGGCGGACTCCACCCGCTGGGAG
 -926 CTGCCCCTCCTTCCCGGCTGTCAGGCTCAGTCCCTTAGACGCTCAG

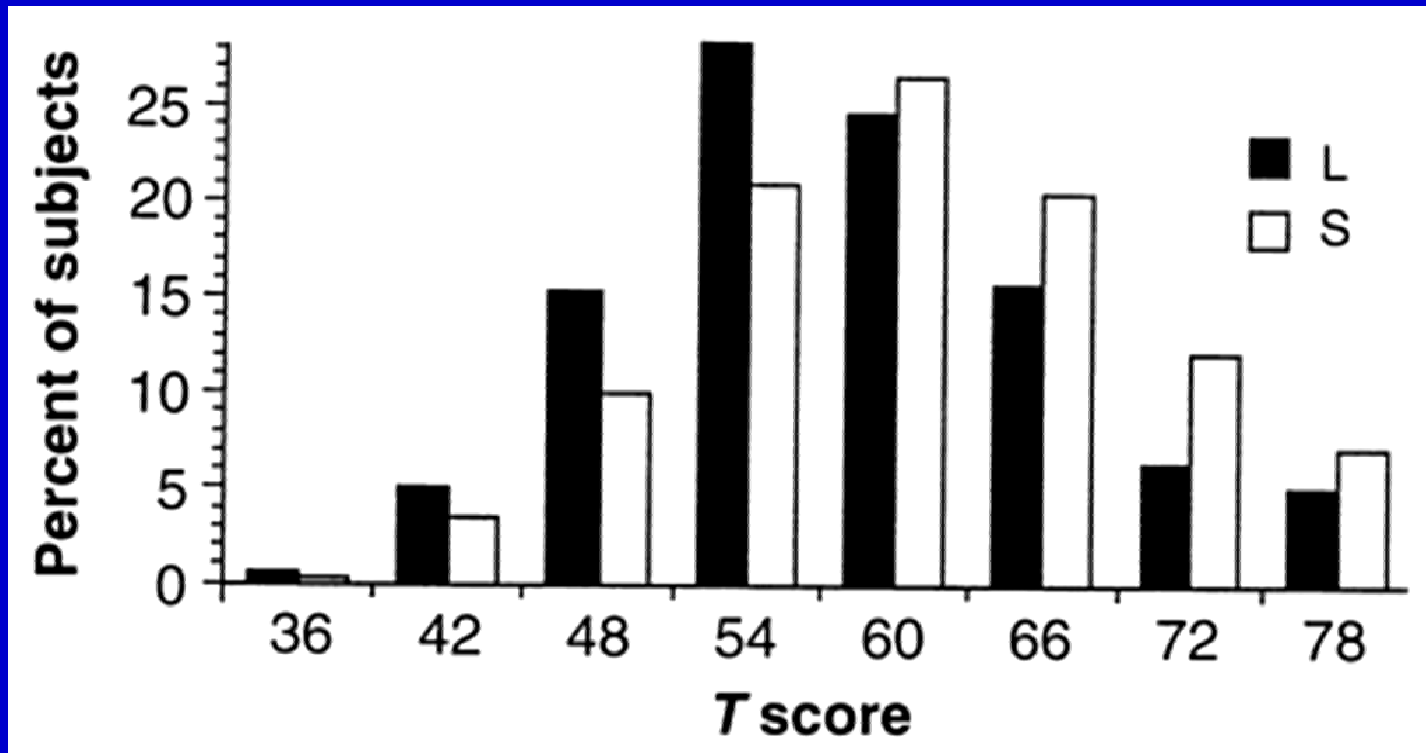
5-HTTLPR (ctd)

Lower level of expression with the 5-HTTLPR s allele



Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region

(Lesch et al, Science 1996)

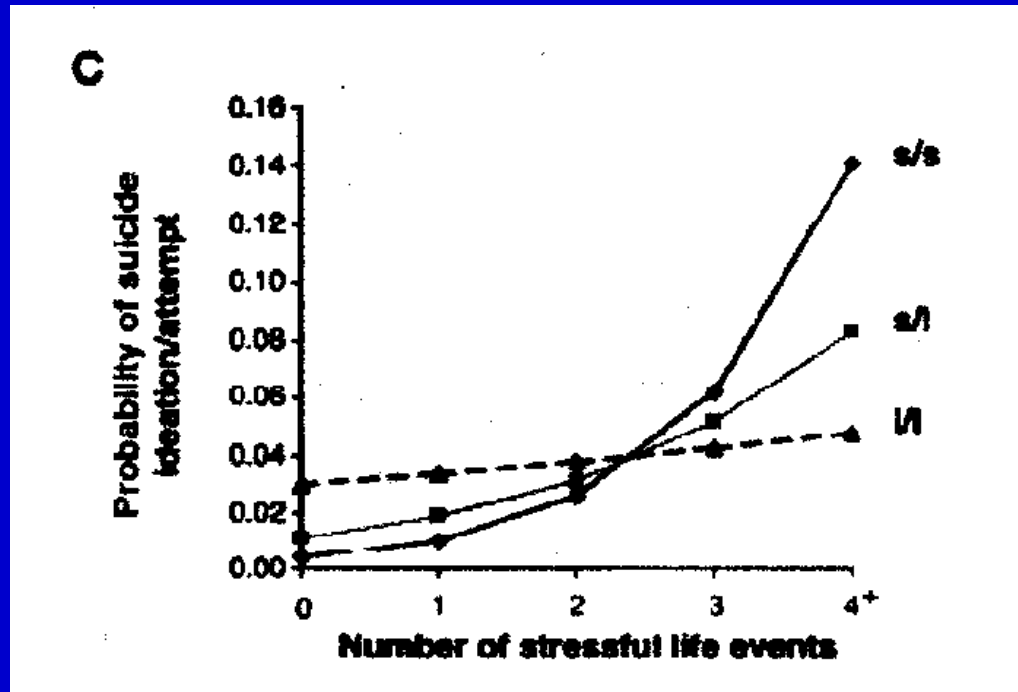


Traits associated to 5-HTTLPR

- Lower mRNA and lower protein
- Neuroticism
- Anxiety
- Depression
- Violent suicidal behaviour
- Less favourable response to SSRI

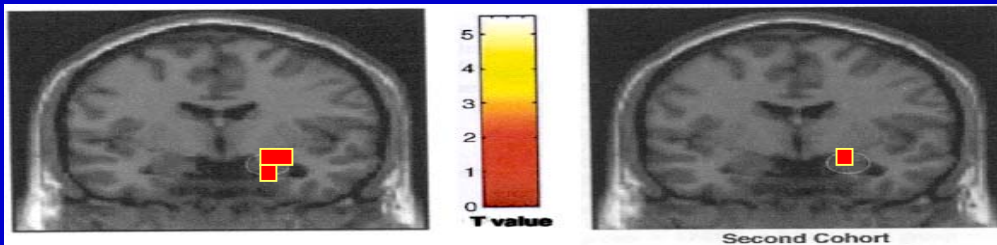
Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene

Caspi et al. Science, 2003, 301, 386-389



Serotonin transporter genetic variation and the response of the human amygdala

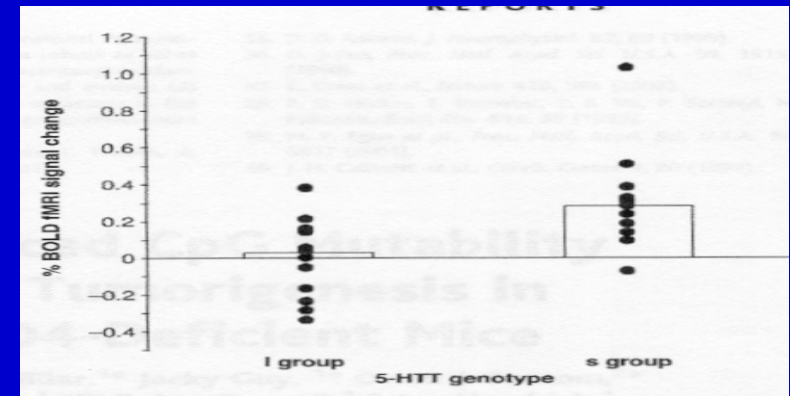
Hariri et al. Science, 2002, 297, 400-403



Sujets avec
l'allele s

Sujets avec
l'allele l

Higher activity in right amygdala in subjects with the 5-HTTLPR S allele



Trois types de corrélations génotype-environnement

- Passif : Les enfants reçoivent des génotypes corrélés avec l'environnement familial.
- Evocateur : Les individus évoquent les réactions d'autres personnes sur la base de leurs prédispositions génétiques.
- Actif : Les individus recherchent ou créent des environnements corrélés avec leurs prédisposition génétique.