STRESS AND DEPRESSION.

THE INTERPLAY BETWEEN

GENETIC FACTORS AND LIFE EVENTS

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“The sequencing of the human genome offers the greatest opportunity for epidemiology since John Snow discovered the Broad Street pump”.

Shpilberg O, J Clin Epidemiol 1997, 50; 633-8

DIRECT vs INDIRECT EFFECTS

GENE-ENVIRONMENT CORRELATION

GENE-ENVIRONMENT INTERACTION

CONCLUSIONS

DIRECT vs INDIRECT EFFECTS

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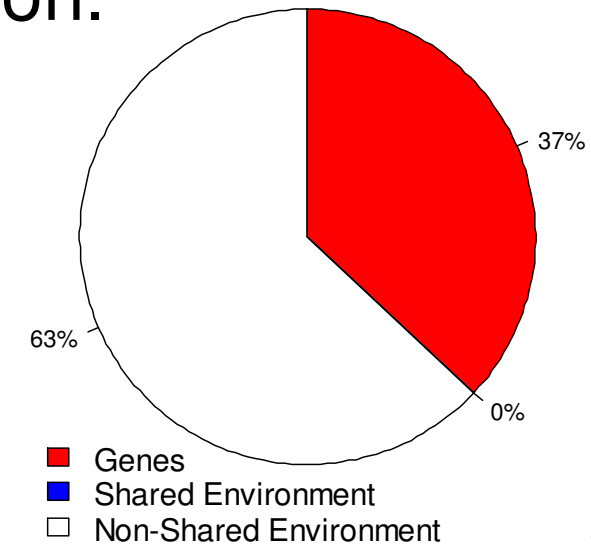
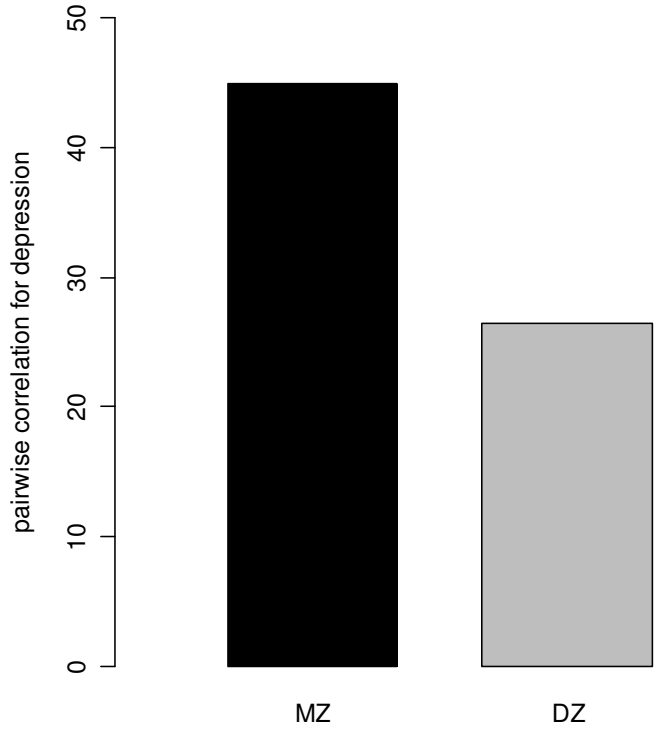
STRESS & DEPRESSION: GENETICS

QUANTITATIVE GENETICS

- First-degree relatives of depressed individuals are 2.8 times as likely to suffer from depression.

- Genetic factors account for 37% of the variance for depression.



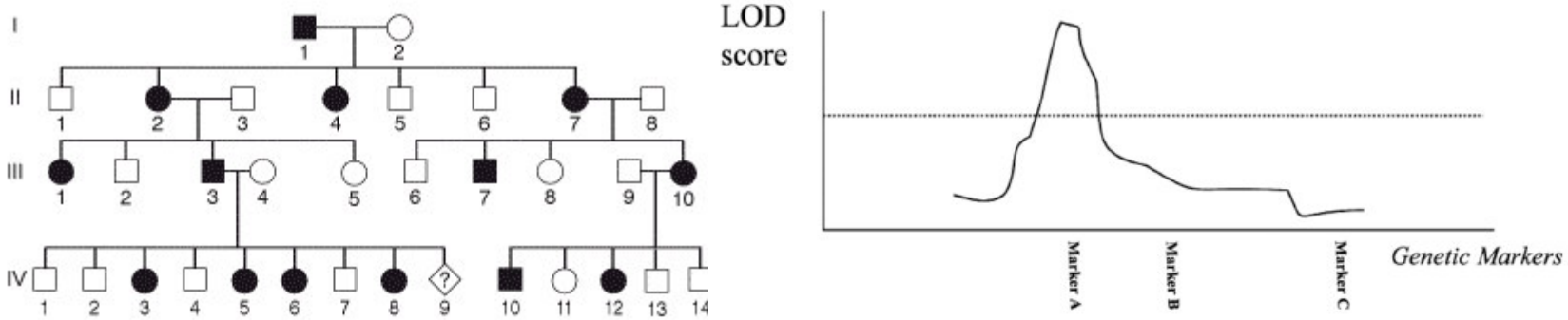


Sullivan PF, Am J Psychiatry 2000, 157;1552-62

STRESS & DEPRESSION: GENETICS

DIRECT GENETIC EFFECTS

- Linkage studies: 1p, 2q, 3centr, 8p, 12q, 15q, 18q.



- Allelic association studies: e.g., 5HTTLPR, TPH, BDNF, COMT, GR, 5HT1A.

- Small effect sizes and false positives are common.

Levison DF, Biol Psychiatry 2006, 60;84-92

STRESS & DEPRESSION: EPIDEMIOLOGY

DIRECT ENVIRONMENTAL EFFECTS

- Stressful life events (SLE) have repeatedly been associated to depression.

- The risk of depression after SLE is higher at the onset of depression than in recurrences.

- The risk of depression after SLE tends to decay over several months, with the strongest effect in the month immediately after SLE.

Kessler RC, Annu Rev Psychol 1997, 48; 191-214

STRESS & DEPRESSION: EPIDEMIOLOGY

DIRECT ENVIRONMENTAL EFFECTS

- The association between stressful life events (SLE) and depression varies considerably depending on prior characteristics of the individuals exposed.

- Because of the observational nature of most studies, it is not possible to rule out the occurrence of selection processes.

Kessler RC, Annu Rev Psychol 1997, 48; 191-214

“If all factors that determine disease are taken into account, then 100% of disease can be said to be inherited. Analogously, 100% of any disease is environmentally caused”.

Rothman K, 1986. In: Modern Epidemiology

GENE-ENVIRONMENT INTERPLAY

INDIRECT EFFECTS

- There is a bidirectional association between the environment and the person, and heritable characteristics of the individual may influence the exposure to the environment (G-E *correlation*).

- There are factors that can modify the effect of the environment, and heritable characteristics of the individual may influence one's vulnerability to the environment (G-E *interaction*).

Rutter M, J Child Psychol Psychiatry 2006, 47; 226-261

DIRECT vs INDIRECT EFFECTS

GENE-ENVIRONMENT CORRELATION

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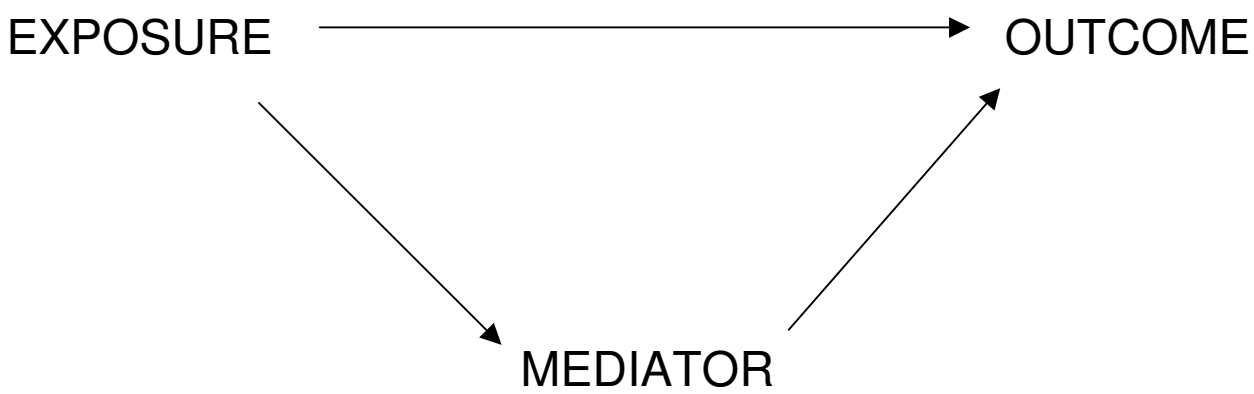
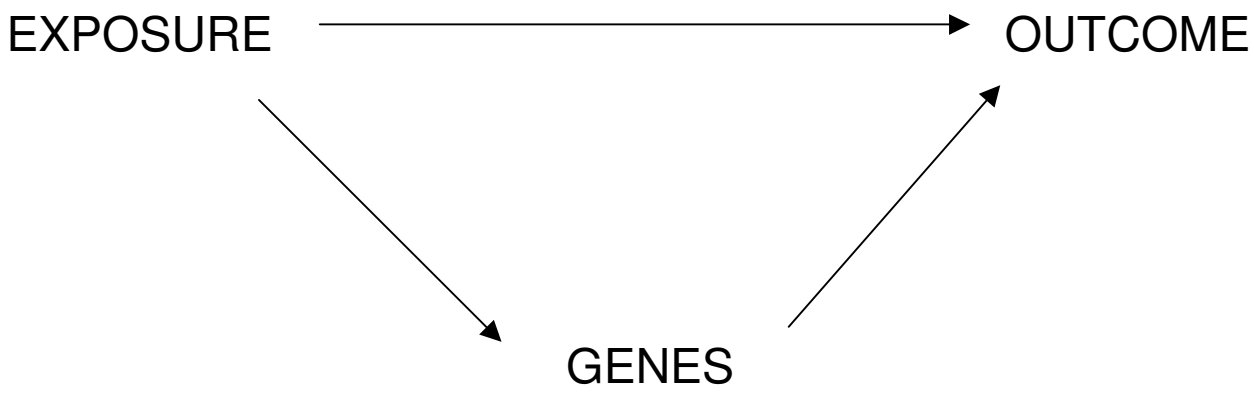
MEDIATION



Kraemer H, Am J Psychiatry 2001, 158;848-856

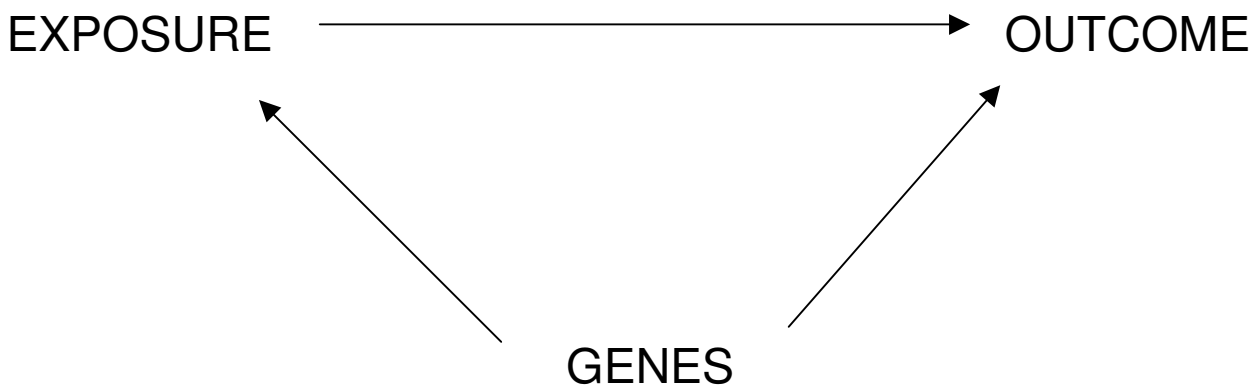
GENETIC MEDIATION

GENE-ENVIRONMENT CORRELATIONS



GENETIC MEDIATION

GENE-ENVIRONMENT CORRELATIONS



GENETIC MEDIATION

GENE-ENVIRONMENT CORRELATIONS

- The heritability of stressful life events is 28% (dependent SLE 37%, independent SLE 17%).

- The heritability of social support is 27%.

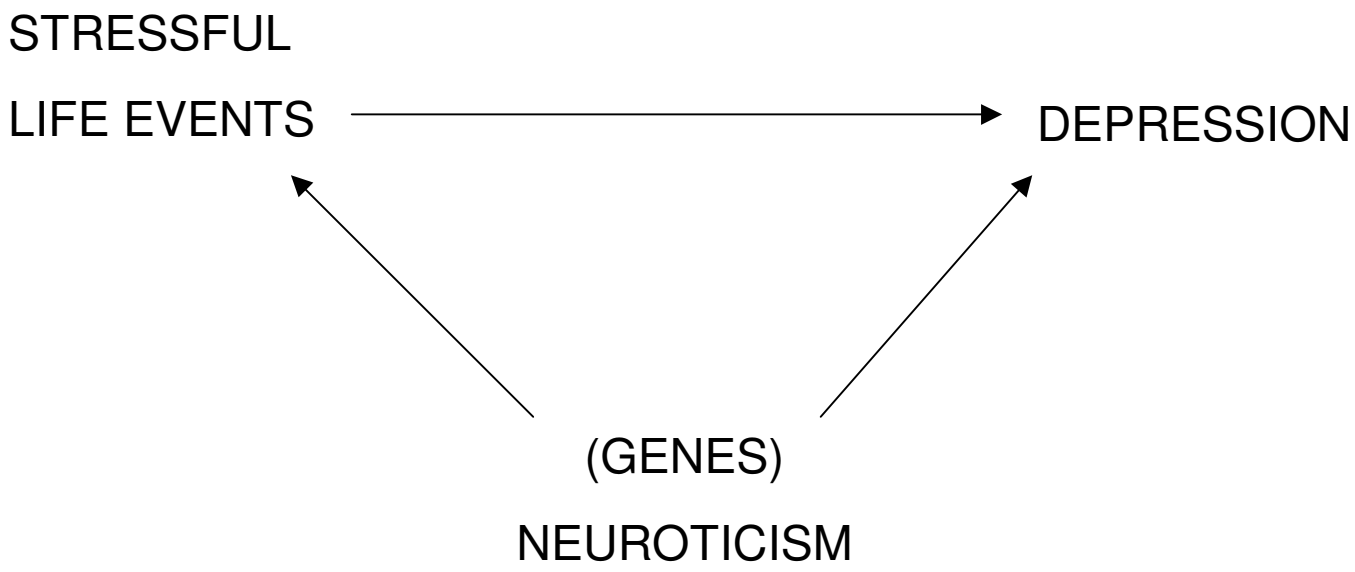
- Alcohol/tobacco/drug consumption, risk-taking behaviours also show an heritable component.

- Personality is a mediator of the effect of genes on the environment.

Kendler K, Psychol Med 2007, 37; 615-26

GENETIC MEDIATION

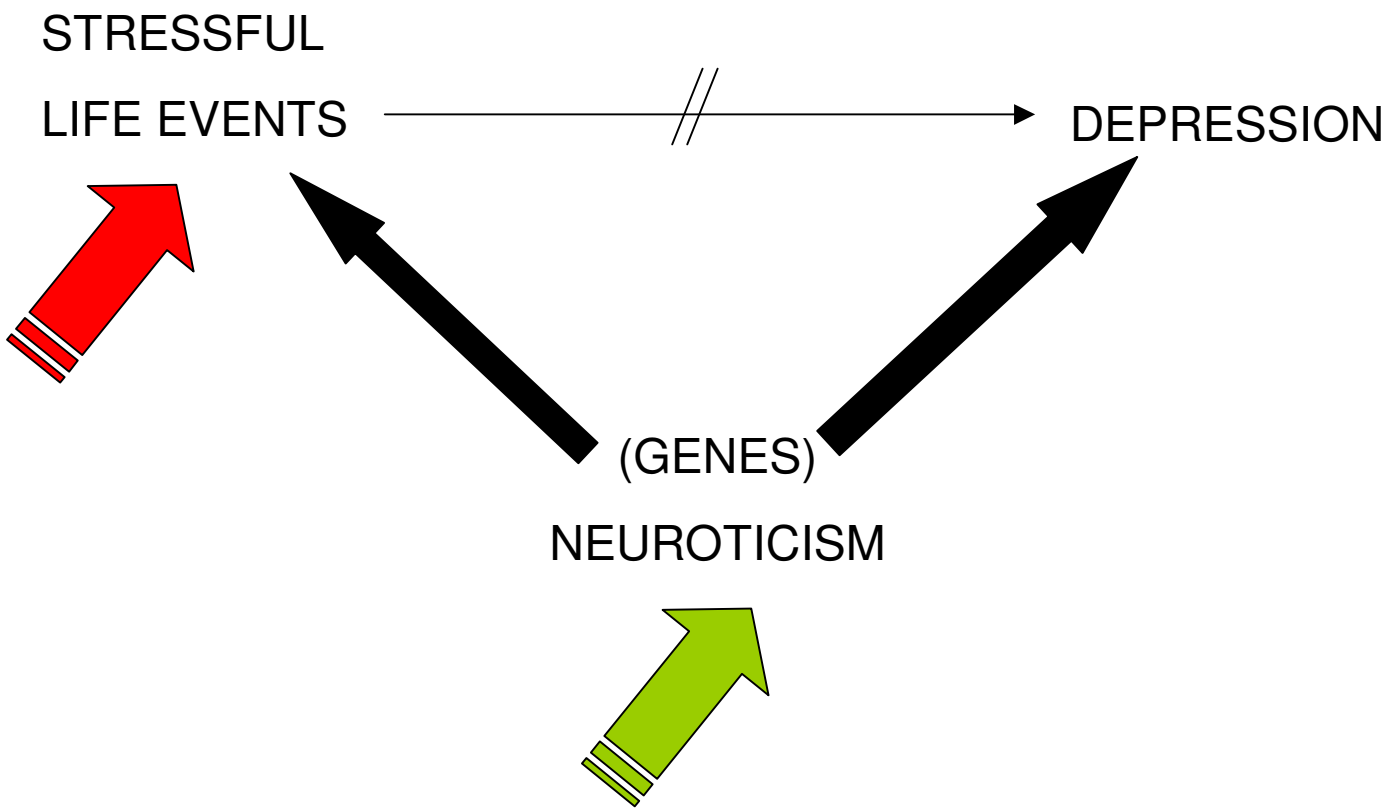
AN EXAMPLE



Kendler K, Psychol Med 2003, 33; 1193-202

GENETIC MEDIATION

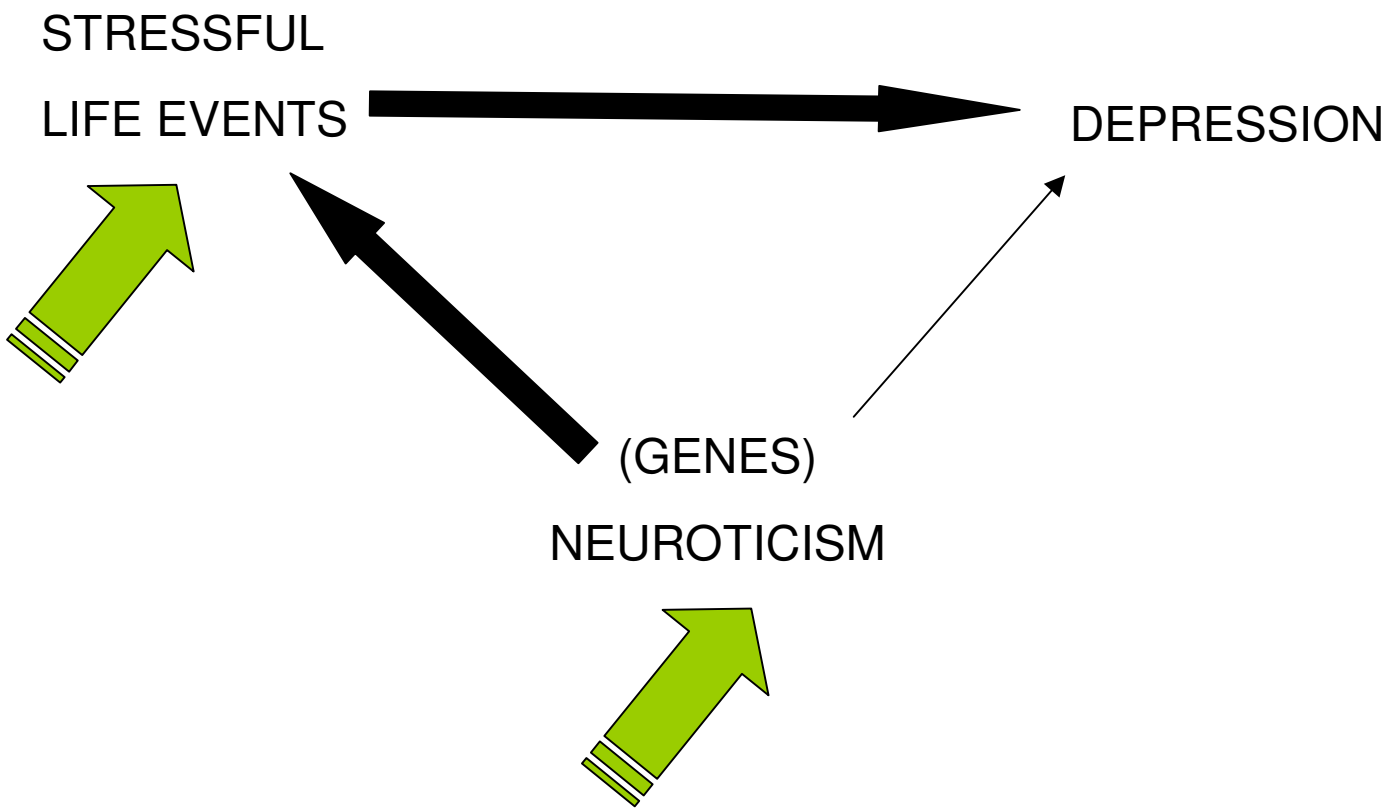
IMPLICATIONS: REFINED INTERVENTIONS



Jaffe S, Mol Psychiatry 2007, 12; 432-442

GENETIC MEDIATION

IMPLICATIONS: REFINED INTERVENTIONS



Jaffe S, Mol Psychiatry 2007, 12; 432-442

DIRECT vs INDIRECT EFFECTS

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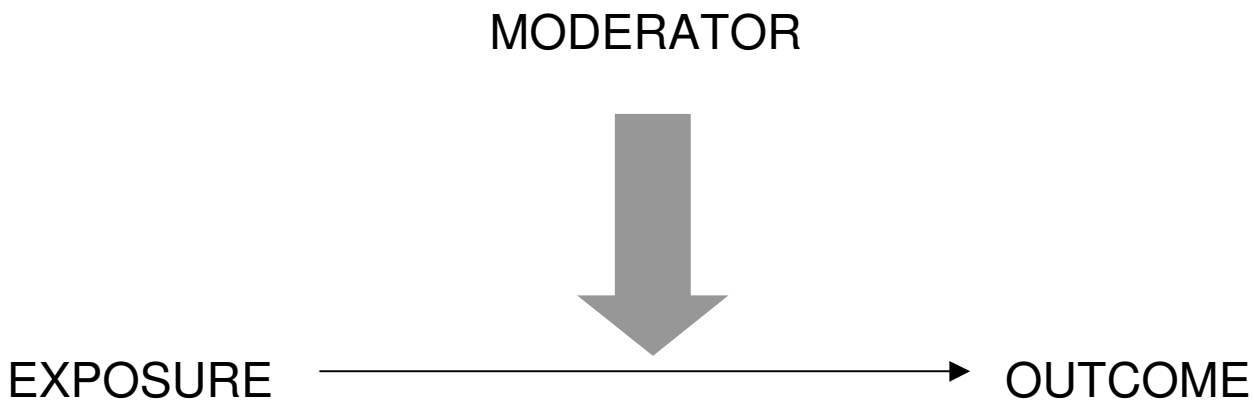
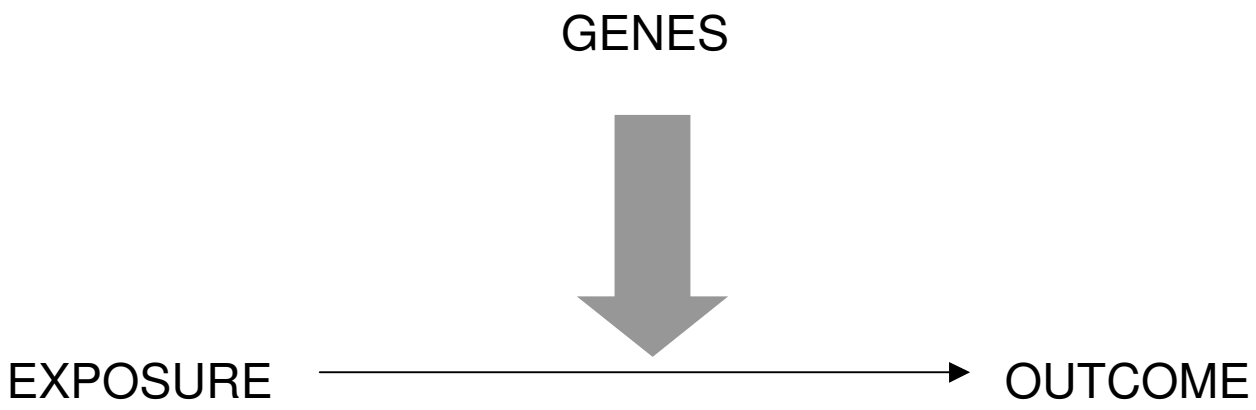
MODERATION



Kraemer H, Am J Psychiatry 2001, 158;848-856

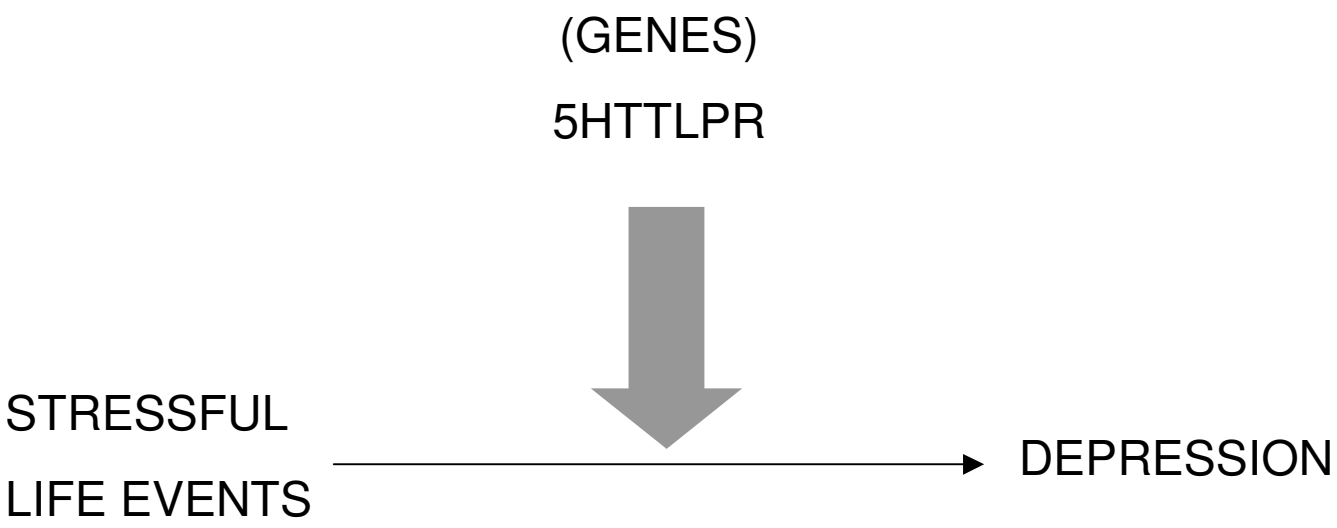
GENETIC MODERATION

GENE-ENVIRONMENT INTERACTIONS



GENETIC MODERATION

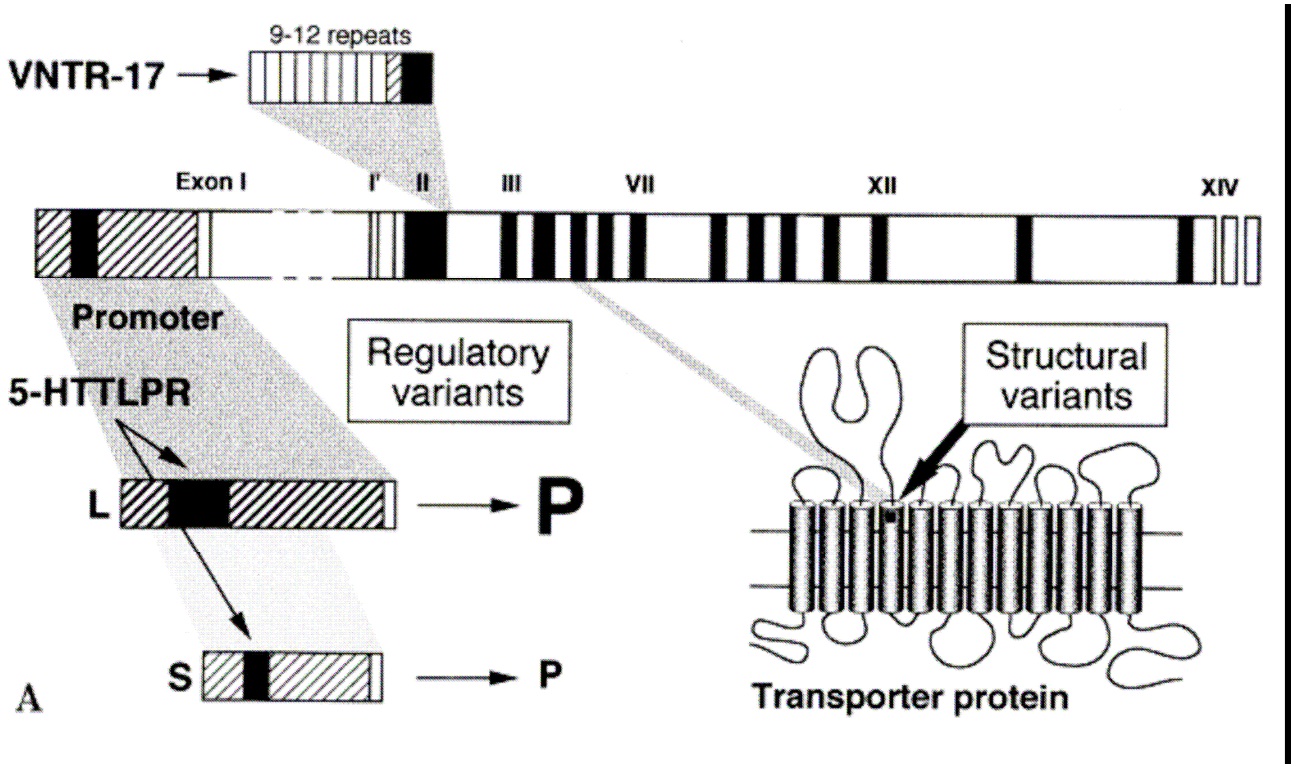
AN EXAMPLE



Caspi A, Science 2003, 301; 386-9

GENETIC MODERATION

AN EXAMPLE

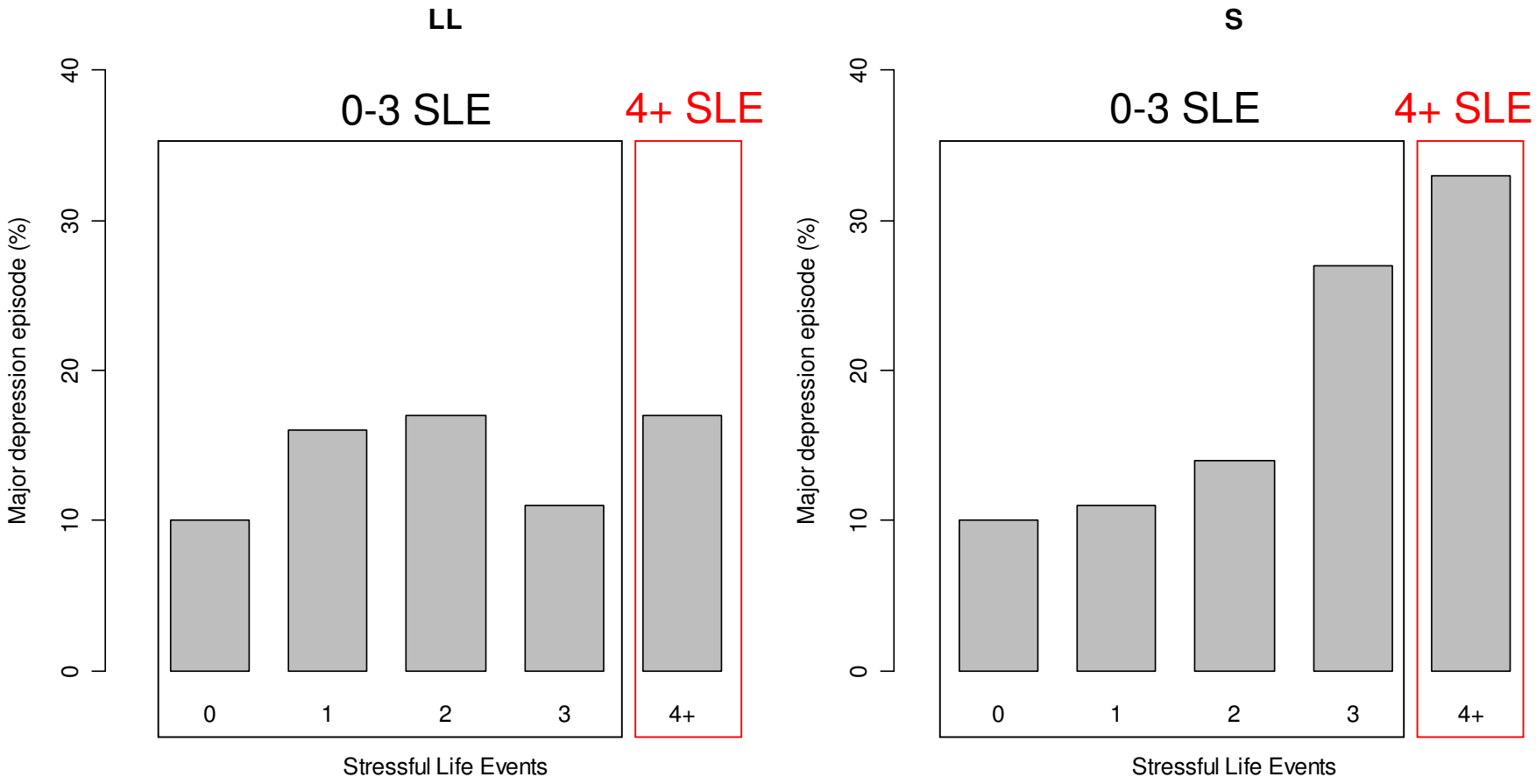


SS: .2, **SL**: .5, **LL**: .3

Lesch KP, Biol Psychiatry 1998, 44; 179-92

GENETIC MODERATION

AN EXAMPLE



Caspi A, Science 2003, 301; 386-9

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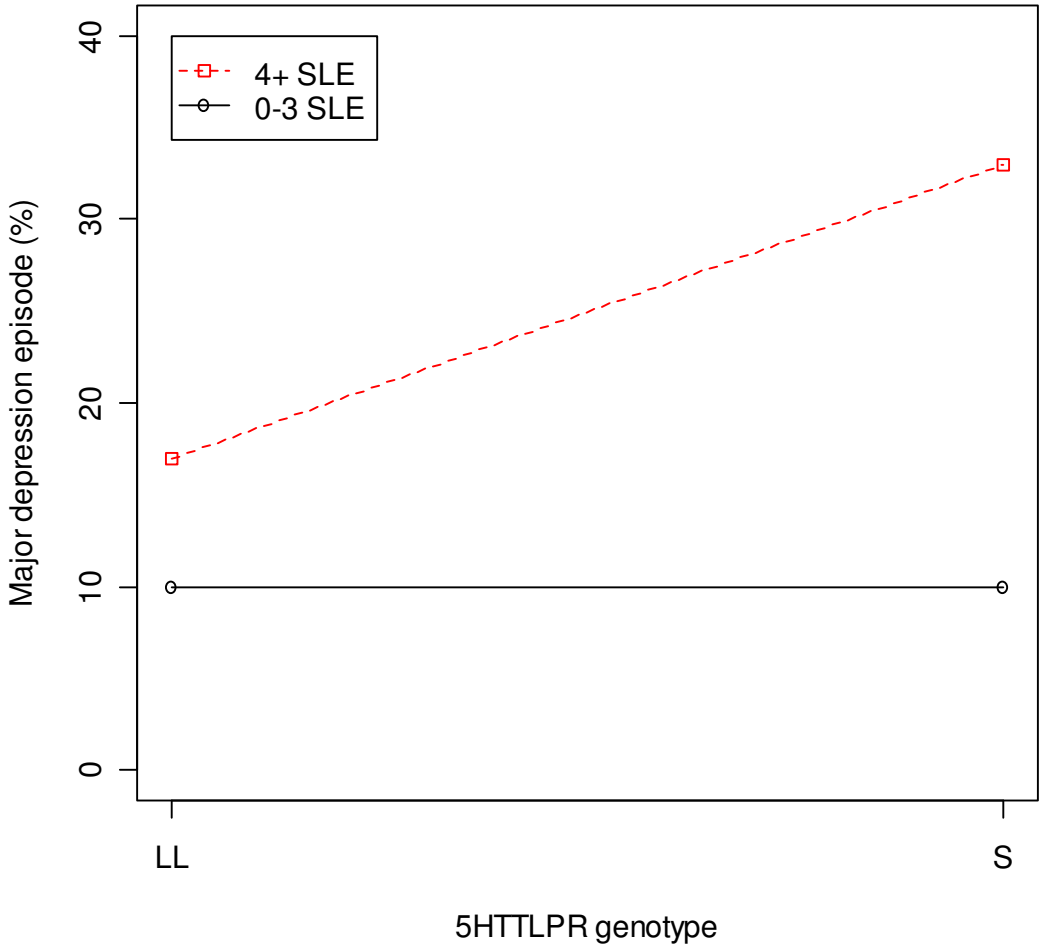
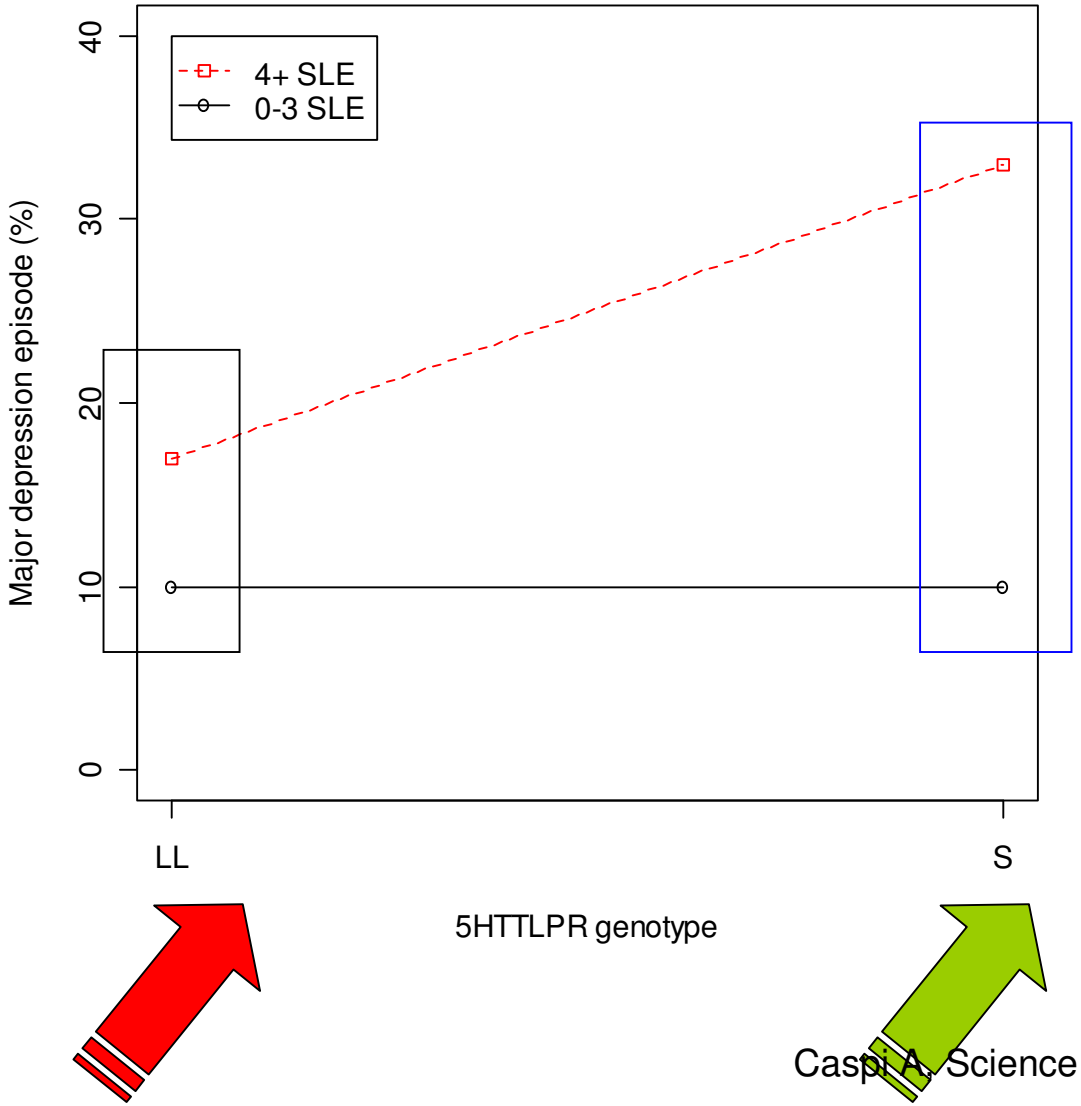


Caspi A, Science 2003, 301; 386-9

GENETIC MODERATION

IMPLICATIONS: TARGETED INTERVENTIONS



Caspi A. Science 2003, 301; 386-9

GENETIC MODERATION

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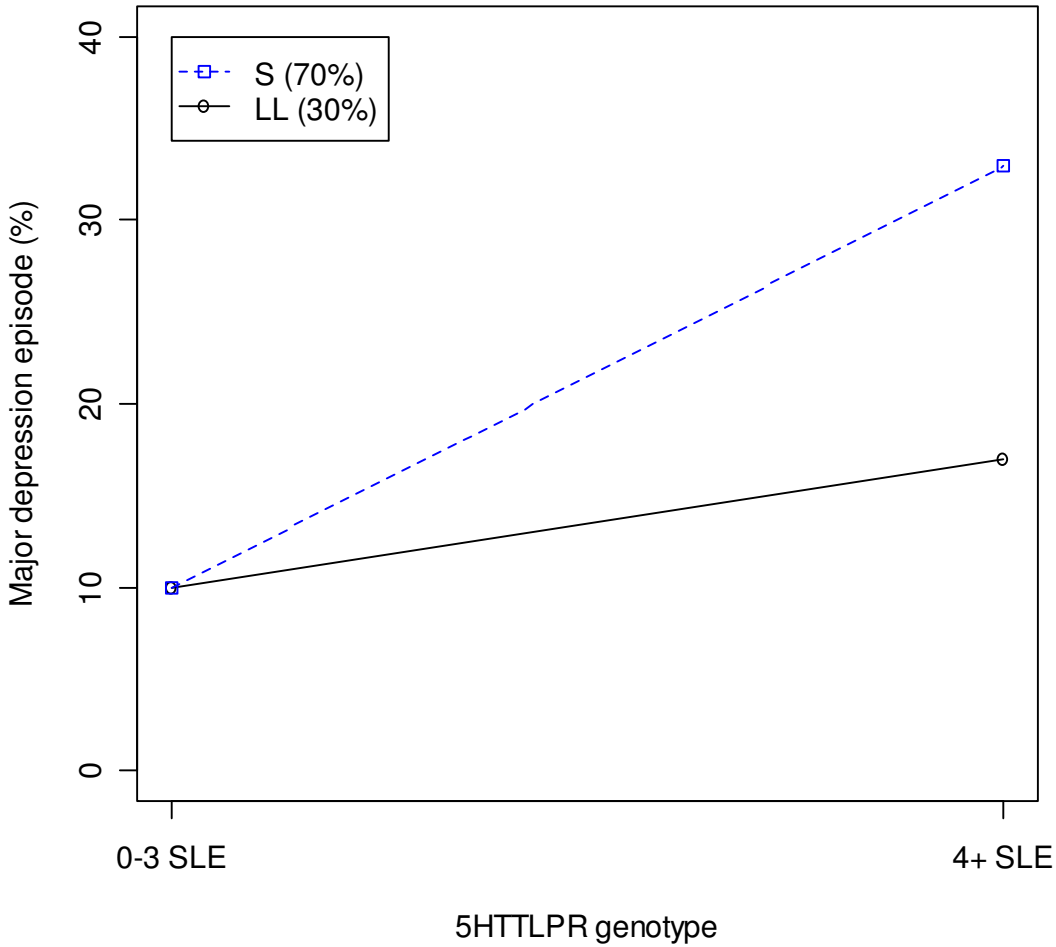

Caspi A, Science 2003, 301; 386-9

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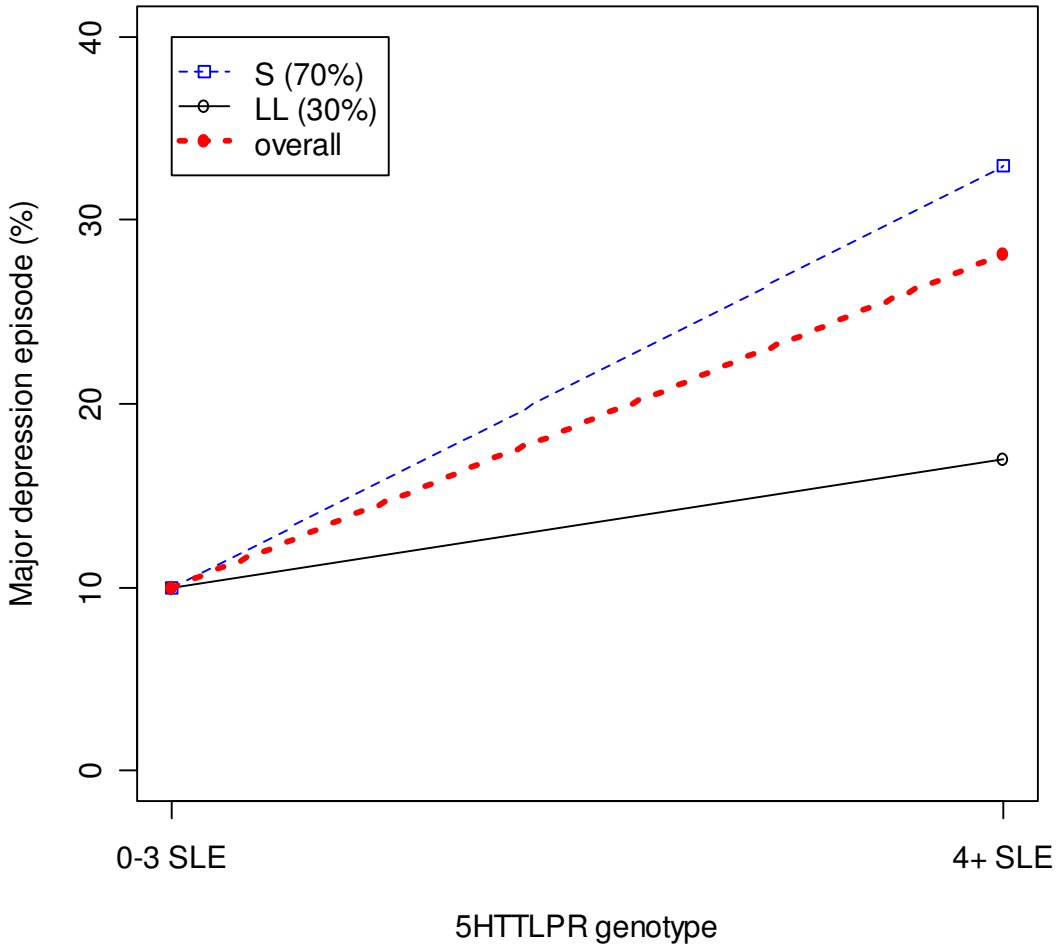

Caspi A, Science 2003, 301; 386-9

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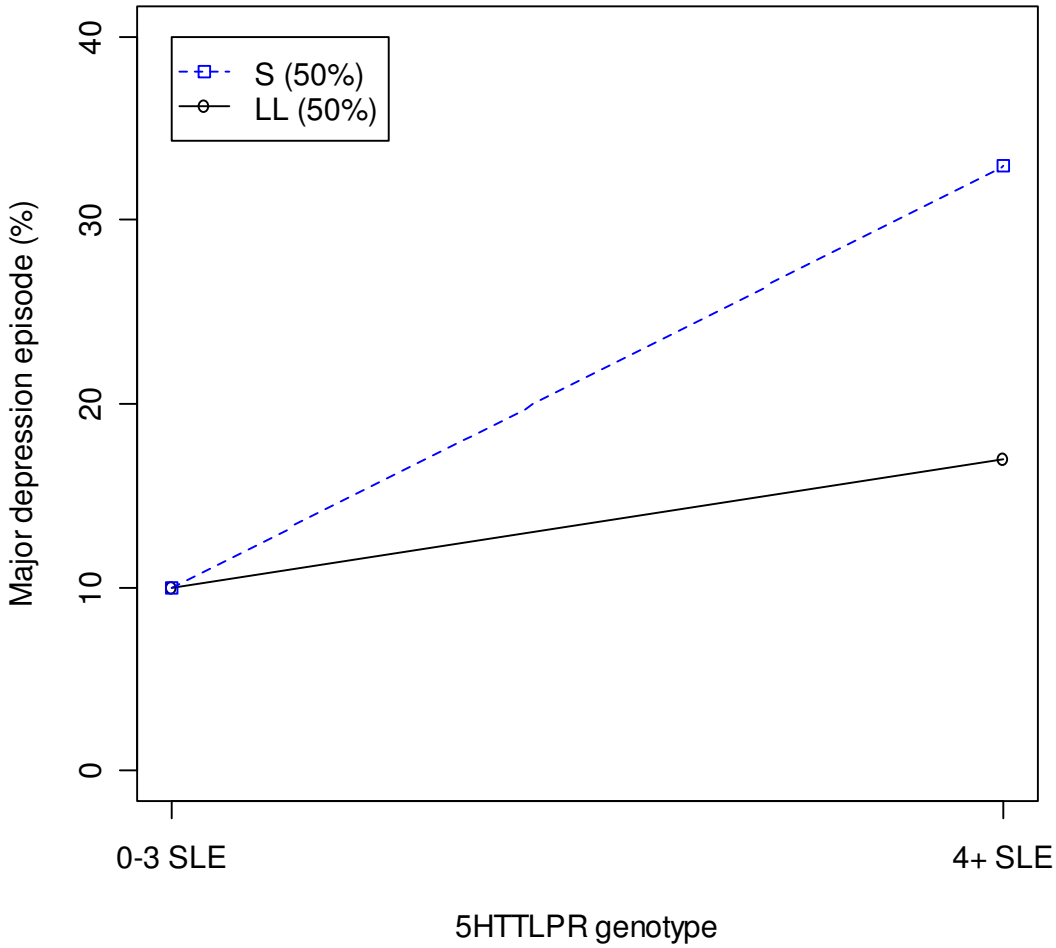

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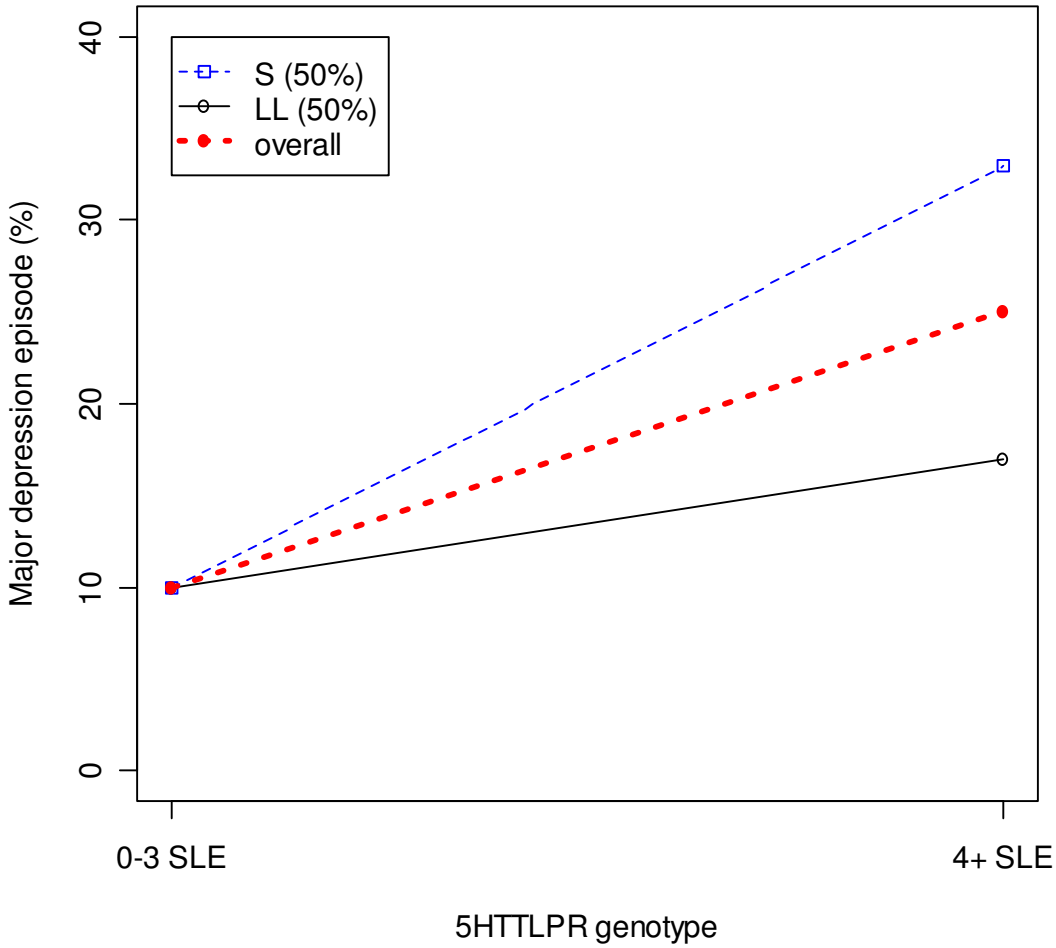

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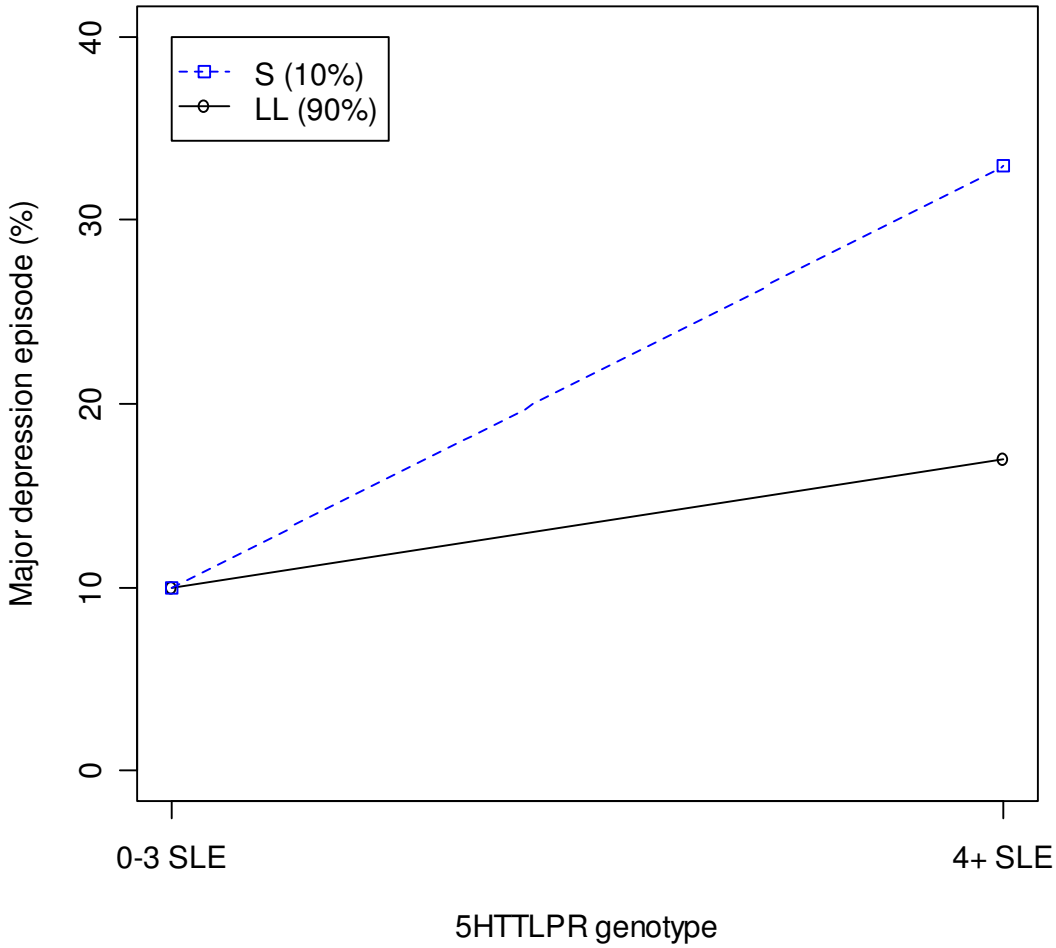
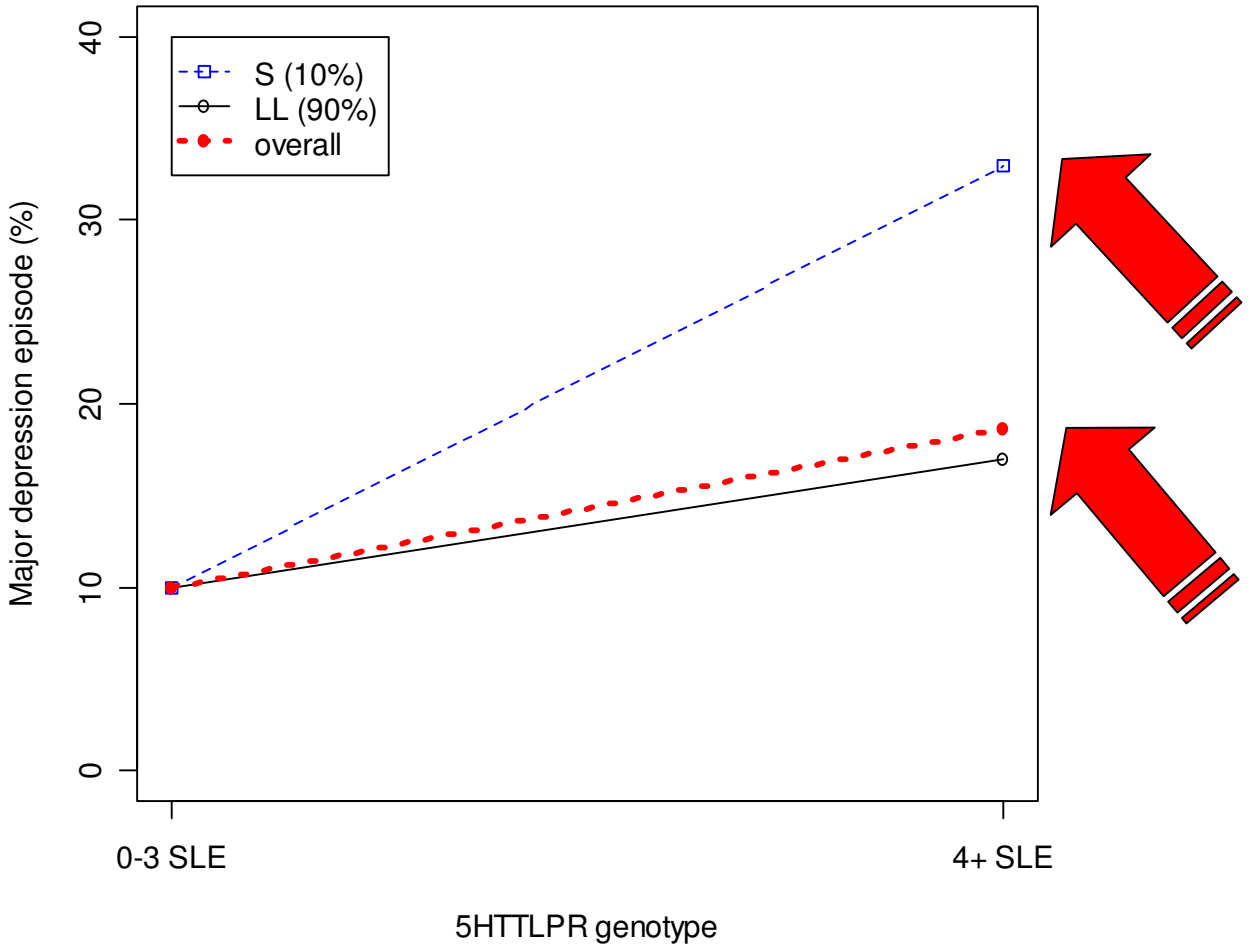


GENETIC MODERATION

IMPLICATIONS: DETECTION OF STRATA-SPECIFIC EFFECTS



DIRECT vs INDIRECT EFFECTS

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CONCLUSIONS

CONCLUSIONS

LIMITATIONS

- Statistical effects do not imply biological effects.

> Need to pair biological/epidemiological research

- Limited contribution of single genes to complex processes hampers optimal outcome prediction.

> Need to implement genetic profiles

Danese A, Epidemiol Psichiatr Soc 2006, 15;185-93

CONCLUSIONS

IMPLICATIONS FOR RESEARCH

- GE *correlations* can inform research about the (genetic and/or environmental) origins of putative environmental risks.

- GE *interactions* can inform research about mechanisms of vulnerability or resilience to environmental risks.

Danese A, Epidemiol Psichiatr Soc 2006, 15;185-93

CONCLUSIONS

IMPLICATIONS FOR HEALTH

- GE *correlations* can suggest strategies to refine health interventions.

- GE *interactions* can suggest strategies to target health interventions.

Danese A, Epidemiol Psichiatr Soc 2006, 15;185-93

ACKNOWLEDGEMENT

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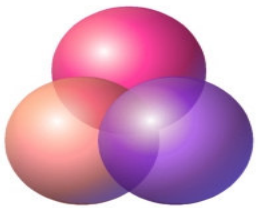

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