CANDIDATE GENES FOR ANXIETY AND MOOD DISORDERS IN HUMANS. A LITERATURE REVIEW.

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Introduction

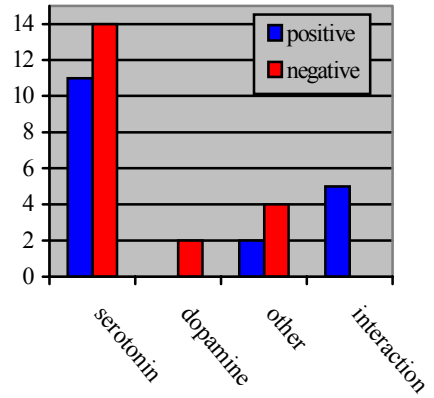
A review of the literature is presented of candidate gene studies on traits that predispose to anxiety and depression.

Methods

The medline database was searched for all reports on adult samples published after 1996 containing the keywords genes, linkage, neuroticism, personality, harm avoidance, reward dependence, anxiety related traits, negative affect, serotonin and dopamine.

Results

In figure 1 studies are presented that focus on genes involved in 1) the serotonin system 2) the dopamine system 3) other systems influencing brain functions and 4) gene-gene interaction. The serotonin system has been most extensively investigated, with 3 negative findings considering the serotonin receptor (5-HT2A) and 11 positive and 11 negative findings regarding the serotonin transporter gene (5-HTTLPR). Noteworthy, in five studies gene-gene interaction effects are found: DRD4×5-HTTLPR× COMT, 5-HTTLPR×COMT, 5HT2C×DRD2× DRD4, DRD4×5-HT2c, chromosomes 8p×18p×20p×21q (a linkage study). These interaction effects are often found between genes which did not seem to influence a trait when studied separately. Included in the category 'other' are studies on genes, who have been investigated just once up till now.



Reasons for contradictory findings:[1]

- Small samples in several studies, lacking the statistical power to detect small gene effects.
- Use of different questionnaires.
- Population stratification.
- Ethnic and gender differences (for example Japanese versus American, ratio males/females).
- Selection of subjects at the high and low ends of the distribution.

Recommendations

- A within family design can prevent the influence of population stratification, which may lead to false negative as well as false positive results. [2] Furthermore, simultaneous linkage and association will strengthen evidence for association.
- Inclusion of large samples preferably of one ethnic group to detect small effects, or gene-gene interaction.[2]
- The use of endophenotypes in multivariate association analyses, may strengthen results.
- Follow-up studies in young children (neonates, 2 months, 4 months) show promising results.[1] Longitudinal designs should be considered.
- Results of animal studies should direct further human studies.

References

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