Gene – QOL consortium
Homework in preparation for conference in Rochester February 26-28 2009

Team II:
Positive Psychology Attributes

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1) Which potential biological pathways have been considered and/or shown to describe a possible genetic disposition for the indicated quality-of-life outcome?

Several studies indicate that the prefrontal cortex is the candidate brain area for happiness and positive emotional states, e.g., related to taste (Kringelbach et al., 2003), smell (Rolls et al., 2003a) or other input via the somatosensory system (Rolls et al., 2003b). Some EEG studies show suggest that positive affect states are associated with increased left cortical power in the alpha frequency compared to the right hemisphere (Davidson, 2004; Tomarken et al., 1992).

From the neurotransmitters present in this part of the brain, dopamine is a good candidate. Animal studies have shown that dopamine mediates the transfer of signals associated with positive emotions between the left prefrontal area and the emotional centers in the limbic area of the brain, such as the nucleus accumbens, situated within the ventral striatum. A summary of studies that show evidence that dopamine modulates positive affect states is given in Burgdorf and Panksepp (2006, p. 178)

At the subneocortical level, a number of peptide systems have been implicated in positive affective states, e.g., Neutensin and CART (both closely associated with Dopamine), Neuropeptide Y, Oxytosin (for an overview see Burgdorf and Panksepp, 2006).

All pathways considered to be of interest for depression might be associated to happiness and subjective wellbeing as well. This is however under the (not frequently tested) assumption that depression and happiness are the two extremes of the same distribution. A significant relationship between frontal assymetry of EEG alpha power and the risk for anxiety and depression is found in young adult females. This relation was explained by shared genes influencing both EGG and disease risk (Smit et al., 2007).

2) Which genes and genetic variants have been considered and/or shown to have a potential association with the indicated quality-of-life outcome?

So far, 7 studies investigated the etiology of subjective wellbeing (SWB). These studies showed significant heritabilities with estimates in the range of 40 to 50%.
The remaining variance was accounted for by environmental influences unique to an individual and no effects of environmental influences shared by members of the same family were found (Tellegen et al., 1988; Lykken & Tellegen, 1996; Roysamb et al., 2002; 2003; Stubbe et al., 2005; Nes et al., 2006; Bartels et al., submitted). The latter, using four measures of SWB (Quality of life in general, Satisfaction with life, Quality of life at the moment of measurement, Subjective Happiness) found no evidence for a distinction between a cognitive and affect component of SWB. The clustering of quality of life in general, satisfaction with life, quality of life at present, and subjective happiness was explained by one underlying genetic factor. The finding of a common factor for both additive and non-additive genetic effects and the low to non existing measurement specific genetic effects, indicate that one underlying sets of genes explains large parts of the variance of measures of SWB. This finding, in conjunction with the absence of age effects on the genetic architecture, informs future gene finding studies for SWB. Pooling of data over age and if necessary over measure, is acceptable and will be the way to go in future large scale collaboration project to facilitate genome-wide association studies.

To our knowledge only one attempt to identify genomic regions of interest has been undertaken. A variance components-based linkage scan, using SWB data of adults of the Netherlands Twin Register and marker data from a genome-wide 10.6-cM microsatellite scan, was carried out. Suggestive linkage and near suggestive linkage has been found for chromosome 19 (19q13, LOD = 2.41) and chromosome 1 (1p12., LOD 1.74) (Bartels et al, in preparation). These regions have not previously been reported in linkage studies on depression, or neuroticism. Overlapping peaks of interest have been found for Anxiety (Middeldorp et al., 2008) and loneliness (Boomsma et al., 2006).

GWA studies of SWB are not available. There a few studies on neuroticism (van den Oord, et al.; 2008; Terracciano et al. 2008; Shifman et al., 2008). The First GWA of depression (Sullivan et al, in press) suggested evidence for a gene (PCLO on chr 7).

3) What datasets are available to explore the association of genes and the indicated quality-of-life outcome?

At the NTR a GWA dataset (originally for the GAIN project, Boomsma et al., 2008) is available for 1669 adults that filled out questions on satisfaction with life and subjective happiness in a questionnaire send out in 2002. At the end of 2008 a new questionnaire will be send to over 37,000 individuals (18-years or older) of the NTR. This new questionnaire contains the satisfaction with life scale and the Cantril ladder to measure Quality of Life. Genetic data are available for part of this sample.

Information on Quality of life in general, Satisfaction with life, Quality of life at the moment of measurement, and Subjective Happiness is collected in adolescent twins and siblings of the NTR. So far 5323 individuals participated once, 2640 individuals participated twice, and 432 individuals participated three time. The latter two indicate that we are building on a longitudinal database spanning the age range 14 to older. Part of these subject will now be part of the new adult questionnaire that is described above. Furthermore a new wave of adolescent data will also be collected at the end of 2008.
Both the new adults and the new adolescent questionnaires will be web-based for the first time.

4) How would you design a new prospective study to explore the association of genes and the indicated quality-of-life outcome?

The design is actually already set up (see large scale questionnaire project described above). What is currently missing is the DNA and/or SNP typing for GWA’s (and in that matter the money to collect DNA and type SNPs genome wide). The adolescent dataset of the NTR is a growing dataset. Twins in this dataset are followed since birth, and for these individuals many variables (such as pre, peri, and postnatal information, birth weight, psychopathology at several ages, scholastic ability and achievement, family functioning, self-esteem, parental divorce) has been collected longitudinally over the past 20 years (for an overview see Bartels et al., 2007). For a relative small part of the sample DNA is available. Ideally, DNA will be collected in all twins and their family members (sibs and parents) when they turn 18. In combination with the large longitudinal dataset this will provide unique possibilities.

For the adult dataset GWA data are available for about 2000 subjects. DNA, is however, available for over 7000 subjects.

To improve the chances of actually finding genes large scale collaboration (as will be part of the consortium) needs to be launched. As has been described in the paper by Bartels et al (submitted), the method of measurement, the age of the subjects and the sex of the subjects will probably not interfere with the gene finding attempts. Both the adolescent and the adult dataset could be part of a large scale GWA within the consortium or one or both could be used for replication of promising genes.

Summary of discussion in response to the first draft:

a) Wider fitness
We should not only focus on well-being but also on the wider fitness of the organism. Multivariate analyses including measures such as: 1) brain functioning (EEG, MRI); 2) mental health (depression, anxiety); 3) personality (extraversion) 4) physiological functioning (HPA axis, immune system, autonomic nervous system) 5) cognitive/neuropsychological ability could be very informative. Several of these phenotypes are or will become available at the Netherlands Twin Register.

b) Data sources
Gene finding studies are not restricted to twin samples and can also be conducted in large panel studies. Genetic analyses with unmeasured genotypes (and unmeasured environment) need genetically related subjects such as twins and their family member.

Household panels such as the British Household Panel Survey (BHPS) and the German Socio-Economic Panel (GSOEP). These studies follow large samples of the general population and involve yearly interviews with all members of
selected households. Items on happiness are in the core-questionnaires. Since short a few of these studies have started using bio-markers.

*Developmental studies,* such as the Dutch ‘GenerationR’ study that follows 10,000 children born in Rotterdam from early pregnancy into young adulthood. Such studies involve detailed biological information and often allow comparison with parents and siblings.

c) *Happiness-depression continuum?*

Is it still under debate whether well-being and depression are the other ends of the same continuum. Preliminary analyses show that the genetic correlation between quality of life and internalizing (depression/anxiety) is about .6/.7 which means that the genetic influences do not completely overlap. To could be an indication that well-being/ depression cannot only be considered to be the two extremes of one underlying distribution. Further analyses is needed, e.g. multivariate analyses as suggested under 1 or analyses on well-being after correction for depression.

d) *Different basis for variants of SWB?*

A multivariate genetic analyses with over 5000 genetically related individuals reveals that four measures of SWB (subjective happiness, satisfaction with life, quality of life in general and quality of life at present) all load on one underlying genetic factors. Genetic factors specific to the four measures are negligible, indicating that we are dealing with a SWB construct that can be measured in different ways, but is actually based on one underlying biological construct.

e) *Different basis for positive and negative affect?*

An additional point of discussion is raised by several consortium members is if there any information on the genetic overlap between positive and negative affects. Preliminary analyses with data of the NTR reveal a significant negative phenotypic correlation between QoL and Internalizing Problems (r=-.25) (interestingly enough is the larger correlation between Qol and Externalizing behavior of - .40). In boys this correlation is mainly accounted for by genetic effects (84%) and in girls by genetic (54%) and environmental effects. Genetic correlations are -.75 for boys and -.62 for girls, indicating overlapping set of genes with opposite effects. Shared environmental correlations are similar for boys and girls and are estimate to be -1.0, indicating that identical shared environmental influences are of importance.

Altogether this is a first indication that there is an genetic overlap between positive and negative affect. It would be optimal to conduct genetic analyses in samples in which both information on positive as well as negative affect is available.

**References**


British Household Panel Survey: http://www.iser.essex.ac.uk/survey/bhps


GenerationR: http://www.generationr.nl/

German Socio Economic Panel: http://www.diw.de/deutsch/soep/29012.html


Smit DJA, Posthuma D, Boomsma DI, Geus de EJC. The relation between frontal EEG asymmetry and the risk for anxiety and depression. Biological Psychology, Volume 74, 26-33, 2007


