Medium Entry - **Genetic Predisposition for Quality of Life** (1637 words)

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Definition

Genetic predispositions can influence human characteristics. Predisposition may refer to the capacity we are born with to learn things (e.g., language or mathematics), or to an inherited tendency to experience life in a certain way (e.g., pessimistic versus optimistic) or to experience symptoms as more or less intense (e.g. high versus low pain level). We may also have a genetic predisposition for developing a disease or condition. How we experience and cope with the stressors of life may also be at least partially determined by genetic predispositions. Hence, there exists a genetic predisposition for quality of life.

Description: evidence for a genetic predisposition of quality of life

Insight into the genetic predisposition of quality of life is based on two types of research. First, studies using a classical twin design (comparing identical and fraternal twins reared together and/or apart) and structural equation modelling has provided empirical evidence of a genetic predisposition for quality-of-life domains, such as self-rated health (Romeis et al., 2000; 2005; Svedberg, Gatz,
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Lichtenstein, Sandin, & Pedersen, 2005), pain (Kato, Sullivan, Evengard, & Pedersen, 2006) and fatigue (Sullivan, Evengard, Jack, & Pedersen, 2005). Genetic influences have also been reported for negative emotional states, such as depression (Sullivan, Neale, & Kendler, 2000) and anxiety (Hettema, Neale, & Kendler, 2001). Anxiety and depression have a common genetic background and they also share a common genetic factor with neuroticism. Thus it is likely that neuroticism is the personality trait underlying these emotional states (Middeldorp, Cath, Van Dyck, & Boomsma, 2005). An increasing number of twin studies also showed substantial heritability of positive emotional states, such as subjective well-being and life satisfaction (Nes, Roysamb, Tambs, Harris, & Reichborn-Kjennerud, 2006). Personality characteristics such as optimism, self-esteem, autonomy, mastery, personal growth, and self-acceptance play important roles in mental health status and subjective well-being (Caprara et al., 2009; Mosing, Zietsch, Shekar, Wright, & Martin, 2009). Thus, these characteristics share a genetic core that might represent the heritable mechanism behind an individual positive orientation. Twin studies have indicated that heritability estimates for quality-of-life-related domains such as self-reported health, symptoms and mood range from 20 to 50%. This level of heritability is comparable or even higher than that of most diseases, including cancer (Lichtenstein et al., 2000).

The second type of research investigates the biological pathways and genetic variables involved in quality-of-life outcomes. For example, biological pathways have been associated with patient-reported outcomes such as pain (Shi et al.,
2010), fatigue (Barsevick et al., 2010), depressed mood, and overall well-being (Sprangers et al., 2010a). Despite high levels of heritability and known biological pathways, the search for the myriad of genes and gene interactions involved in quality of life, is far from straightforward. Whereas a number of genes related to these pathways have been identified, they need to be confirmed in future data sets.

For example, for pain two categories of potential genetic pain-perception pathways were identified: neurotransmission modulators and mechanisms that affect inflammation. These are the major pathways for modulation of pain perception. Additionally, analgesic drug metabolism and transport are two pathways that may modify an individual's response to analgesics. Various genetic variations involved in these pathways and mechanisms that affect inflammation are proposed as candidate genetic markers for pain perception (e.g., the COMT gene, cytokine genes) and for individual sensitivity to analgesics (e.g., Cytochrome P450 enzymes). However, the nature and range of genetic modulation of pain are still not completely understood (Shi et al., 2010).

Much research has been invested in investigating the biological substrate of major depression or anxiety disorders, with many international consortia conducting genome wide association studies and meta-analyses. However, very few candidate genes could be replicated in independent studies (Bosker et al., 2011). The linkage between patient-reported happiness or well-being and genetic
variables has only begun to be explored. The first study aiming to identify genomic regions of interest for happiness found suggestive linkage for genomic regions. However, none of the genes involved play a plausible role in explaining individual differences in happiness (Bartels et al., 2010). Another more promising candidate gene for life satisfaction is the serotonin transporter gene (5-HTTLPR), which has previously been associated with mental health and selective processing of positive and negative emotional stimuli. Individuals with long alleles of the serotonin transporter gene (5-HTTLPR “long”) were found to report significantly higher levels of life satisfaction than those who have short alleles (De Neve, 2011).

Sloan and Zhao (2006) were the first to examine the direct link between polymorphisms and cancer patients’ quality of life, using a large randomized North Central Cancer Treatment Group clinical trial. More than triple the number of relationships between genetic variables and patient-reported quality of life outcomes were observed than would be expected by chance alone. They found evidence for relationships between overall quality of life, symptom distress, and fatigue with variant genotypes of three enzymes involved in folate metabolism. More such studies have been published (Yang et al., 2009; Sloan et al., 2012) or are underway. Clearly, all these findings need to be replicated in future independent samples.
Description: Theoretical underpinnings

The analysis of the genetic disposition of patient-reported quality of life requires a model to delineate the hypothetical relationships among quality-of-life domains, biological mechanisms and genetic variants. Sprangers and colleagues (2010b) have adopted the widely used theoretical model of Wilson and Cleary (1995) that links biological factors and patient-reported quality of life. This model describes a continuum of interrelated levels/measures of health that can be ordered from more biological (left) to more psychological complexity and integration (right).

*Biological and physiological factors* (e.g. cells, organ systems) may affect *symptom status* (e.g., knee pain or worry), which in turn may affect *functional status* (e.g., ability to walk up stairs or handling stressful situations), *general health perceptions* (i.e., subjective evaluations of physical and mental health) and ultimately, *overall quality of life* (e.g., happiness or satisfaction with life in general).

[Insert Figure 1 about here]

Sprangers and colleagues (2010b) proposed a number of refinements of this model by first including the genetic underpinnings of biological/physiological variables (see Figure 1). These molecular and genetic factors thus impact symptom status, functional status, general health perceptions, and overall quality of life indirectly via their involvement in the underlying disease. Second, they have also incorporated *molecular and genetic factors* as a separate category
impacting characteristics of the individual. It follows that these genetic factors impact symptom status, functional status, general health perceptions, and overall quality of life, via individual characteristics. These sets of genes may, in part, be the same genes involved in the underlying condition or disease process. For example, genes involved in the etiology or biology of pain may be similar to those involved in the subjective experience of pain. Other genes may be involved as well, particularly those that impact individual appraisals and experiences of health and life, e.g., via perception, personality, mood, and outlook on life. Third, Wilson and Cleary (1995) built their framework around dominant uni-directional relationships. Sprangers and colleagues (2010b) proposed to add bi-directional arrows from characteristics of the individual to molecular and genetic factors, and biological and physiological variables, respectively. This refinement indicates a mutual influence between individual characteristics and genetic and biological factors, respectively. Fourth, they added uni-directional arrows from environment to molecular and genetic factors and biological and physiological variables to allow for interactions to occur between environment and genetic/biological factors (e.g., epigenetic mechanisms). Finally, the model refinement involves temporal relationships that may change over time, rendering the model explicitly dynamic. Iterative interactions may occur over time (not depicted in the figure). For example, our genetic make up will influence our individual characteristics, such as personality and generalized tendencies to appraise experience (e.g. optimistic versus catastrophizing). This in turn, will not only affect our overall psychological well-being but also our health and symptom experience, by shaping and perhaps
transforming the underlying biological substrate. This in turn may affect an individual's psychosocial environment, and so on.

**Discussion**

Like any human characteristic, quality of life is at least partially determined by genetic influences. Delineating the genetic variables that play a role in (patient-reported) quality of life is a complex endeavor, considering the potential number of genes, the interaction between these genes, the interaction between genes and environmental (e.g., life style) factors, and the number of quality-of-life variables that may be involved. In pursuing the delineation of the relationship between genes and quality of life, it is of paramount importance to join forces among the disparate disciplines, including cellular and molecular biology, behavioral genetics, pharmacogenetics, statistical genetics, genetic epidemiology, medical, clinical and biological psychology, sociology, and importantly, nursing and medicine (e.g., oncology, cardiology dependent on the target disease population). As a consequence, a number of consortia have been established to provide the requisite foundation to stimulate and investigate the biological basis of (patient-reported) quality of life. Examples include the the Mayo Clinic/University of Amsterdam International Consortium for Genetics and Quality of Life Research, the GeneQol Consortium (Sprangers et al., 2009; www.geneqol-consortium.org) and Social Science Genetic Association Consortium (http://www.ssgac.org/index.php).
One of the key challenges for the next decades is the actual translation of genetic knowledge into clinical practice. It is hoped that the biological information will enable the identification of patients who are susceptible to poor quality of life (Sloan & Zhao, 2006; Sprangers et al., 2009; 2010b). As a consequence, we would be able to target preventive strategies, and/or specific support, such as interventions inducing lifestyle and behavioural changes, psychological counseling or therapy, and/or pharmacological treatment. Perhaps at some point in time, diagnostic tests will be designed for personalized medicine to establish not only the patient’s prognosis and the most effective therapy, but also how they will affect a patient’s quality of life (Sloan & Zhao, 2006). Growing insight into the biological basis of patient-reported quality-of-life outcomes might thus ultimately allow the exploration of new ways to improve patient care.

**Note**
This text is based on previously published review papers, including Sprangers et al., 2009; Sprangers, Sloan et al., 2010; and Sprangers, Bartels et al., 2010.

**Cross-References**

- Quality of life
- Self-rated health
- Pain
- Fatigue
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Ddementia

Anxiety

Subjective well-being

Life satisfaction

Appendix A: Glossary

**Allele:** Alternative forms of a gene at a locus (is the site of a specific gene on a chromosome (Plomin et al., 2008).

**DNA (deoxyribonucleic acid):** The-stranded molecule that encodes genetic information (Plomin et al., 2008).

**Epigenetics:** The study of heritable changes in gene expression or cellular phenotype (observable characteristic) caused by mechanisms other than changes in the underlying DNA sequence (wikipedia).

**Gene:** The basic unit of inheritance. A sequence of DNA that codes for a particular protein product (Plomin et al., 2008).

**Genome:** All the DNA sequences of an organism (Plomin et al., 2008).

**Genome wide association study (GWAS):** A study that evaluates association of genetic variation with outcomes or traits of interest by using 100,000 to 1,000,000 markers or more across the genome (Attia et al., 2009).

**Genotype:** The genetic constitution of an individual (Attia et al., 2009).
**Heritability**: The proportion of phenotypic differences among individuals that can be attributed to genetic differences in a particular population (Plomin et al., 2008).

**Polymorphism**: The existence of two or more variants of a gene, occurring in a population, with at least 1% frequency of the less common variant (cf mutation) (Attia et al., 2009).

**Twin study**: Study comparing the resemblance of identical and fraternal twins to estimate genetic and environmental components of variance (Plomin et al., 2008).

**References**


among middle-age, middle-class, male-twins. *Medical Care, 11*, 1147-1154.


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theoretical underpinnings for the investigation of the relationship between genetic variables and patient-reported quality-of-life outcomes.

*Quality of Life Research, 19*(10), 1395-1403.


Figure Legend: Extended model of Wilson and Cleary (2005)

Interrupted arrows and words in italics are added to the original model. Bold arrows were original in standard font and highlight the increasingly acknowledged importance of the relationships they depict.