Qual Life Res (2013) 22:1189–1200
DOI 10.1007/s11136-012-0277-5

REVIEW

Biological pathways and genetic mechanisms involved in social functioning

Juan R. Ordoñana · Meike Bartels · Dorret I. Boomsma · David Cella · Miriam Mosing · Joao R. Oliveira · Donald L. Patrick · Ruut Veenhoven · Gert G. Wagner · Mirjam A.G. Sprangers · The GENEQOL Consortium

Accepted: 21 September 2012 / Published online: 10 October 2012

Abstract
Purpose To describe the major findings in the literature regarding associations between biological and genetic factors and social functioning, paying special attention to: (1) heritability studies on social functioning and related concepts; (2) hypothesized biological pathways and genetic variants that could be involved in social functioning, and (3) the implications of these results for quality-of-life research.
Methods A search of Web of Science and PubMed databases was conducted using combinations of the following keywords: genetics, twins, heritability, social functioning, social adjustment, social interaction, and social dysfunction.
Results Variability in the definitions and measures of social functioning was extensive. Moderate to high heritability was reported for social functioning and related concepts, including prosocial behavior, loneliness, and extraversion. Disorders characterized by impairments in social functioning also show substantial heritability. Genetic variants hypothesized to be involved in social functioning are related to the network of brain structures and processes that are known to affect social cognition and behavior.
Conclusions Better knowledge and understanding about the impact of genetic factors on social functioning is needed to help us to attain a more comprehensive view of health-related quality-of-life (HRQOL) and will ultimately enhance our ability to identify those patients who are vulnerable to poor social functioning.

Keywords Quality of life · Social functioning · Patient-reported outcomes · Genetic variants · Genetic underpinning

J. R. Ordoñana (✉)
Department of Human Anatomy and Psychobiology, University of Murcia, and Murcia Institute for Biomedical Research (IMIB), Murcia, Spain
e-mail: ordonana@um.es

M. Bartels · D. I. Boomsma
Department of Biological Psychology, VU University, Amsterdam, The Netherlands

D. Cella
Department of Medical Social Sciences, Feinberg School of Medicine, Chicago, IL, US

M. Mosing
Queensland Institute of Medical Research, Brisbane, Australia

J. R. Oliveira
Department of Neuropsychiatry, Federal University of Pernambuco, Recife-Pernambuco, Brazil

D. L. Patrick
Department of Health Services, University of Washington, Seattle, WA, USA

R. Veenhoven
Faculty of Social Sciences, Erasmus University Rotterdam, Rotterdam, The Netherlands

G. G. Wagner
Max Planck Institute for Human Development, Berlin University of Technology, and German Institute for Economic Research, Berlin, Germany

M. A.G.Sprangers
Department of Medical Psychology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Introduction

For a long time, studies of social behavior and genetics were parallel areas of research that rarely interfaced. The identification of a network of brain structures which facilitates social cognition and behavior, known as the "social brain" [1, 2], served as an intermediate step between these two fields and genes have since emerged as possible factors influencing an individual's social life. Obviously, genes do not influence or dictate social behavior directly but rather encode molecular products that regulate brain development and function [3]. Thus, behavior, including social functioning, will be the result of brain activity in close interaction with the environment. Biological pathways and specific genetic variants may, indirectly, induce individual variability in social functioning, including individual reactivity to an illness in the social domain, and the degree of interference a given disorder has upon one's usual social activities.

The emerging evidence for a genetic basis of health-related quality-of-life (HRQOL) [4–8], and the need to incorporate new insights about the role of biological and physiological variables in this field have led to the development of the GENEQOL Consortium [9]. GENEQOL is an initiative to investigate potential biological pathways, genes, and genetic variants involved in HRQOL. The GENEQOL Consortium has produced brief reviews on the biological and genetic mechanisms associated with symptoms related to HRQOL, including pain, mood, and fatigue [10–12]. These mechanisms may indirectly affect social functioning, but there may be more direct pathways connecting biological variables and the ability to perform social behaviors. We concentrate on these latter connections for this paper. To our knowledge, this is the first attempt to review the evidence in support of the association of genetic factors on social functioning. We hope it will be a step toward introducing a new perspective that could contribute to the advancement of the HRQOL field.

Social functioning and health-related quality of life

Although the term "social functioning" is frequently used, it is often ill defined. Though we can usually agree on what constitutes negative, or maladaptive social behavior, clear delineation of the range of positive social behavior is more elusive. Positive social functioning should be more than the absence of dysfunction in social interaction. Figure 1 shows a *biopsychosocial model* of disability from the perspective of The International Classification of Functioning, Disability and Health (ICF) [13]. As shown in the figure, social dysfunction related to disorders (i.e., illnesses that disrupt normal function) or diseases (i.e., disorders with a known pathophysiology or structural pathology) [14] may appear in different components of the model reflecting diverse processes. However, these differences are commonly not taken into account in the literature. Such lack of clear definition and multipurpose application is reflected in the variety of measurement instruments. Social functioning has been measured as a dimension in general quality of life questionnaires (often with only one or two questions) [15, 16], as a functional area with specific scales (mainly in psychotic patients) [17] or even by discrete indicators that can comprise very different concepts, such as employment [18] or facial expression recognition [19].

One of the eight scales of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) [15] assesses social functioning by the degree to which physical or emotional problems interfere with usual social life, which is loosely defined as normal social activities (e.g., visiting) with family, friends, or neighbors. The instrument developed by the EuroQoL Group (EQ-5D) [16] includes a dimension (one question) asking about the presence of problems with performing usual activities (i.e., work, study, housework, family, or leisure activities). Other examples of well-known questionnaires with similar dimensions are Multidimensional Index of Life Quality (MILQ) [20], World Health Organization Quality of Life Assessment (WHOQOL-BREF) [21], Quality of Life Index-Mental Health (QLI-MH) [22], European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30) [23], and the Functional Assessment of Cancer Therapy—General (FACT-G) questionnaire [24].

All in all there is a consensus that social functioning should be included as a core component of HRQOL, together with physical and emotional functioning [25]. Several studies report an association between some form of appropriate social functioning with better health and survival, while dysfunction in this area appears to be associated with poorer health outcomes [26–28]. These effects are possibly due to the role of social functioning in the reduction of the deleterious effects of stress or to the positive influence of social environments on health-protective attitudes and behaviors [29].

Social functioning and neuropsychiatric disorders

Social functioning has special relevance for those neurobehavioral and neuropsychiatric disorders that are defined, partially, by some kind of social dysfunction. For example, schizophrenia is, among other symptoms, characterized by social withdrawal and an impaired ability to interact with others. Many patients with schizophrenia experience

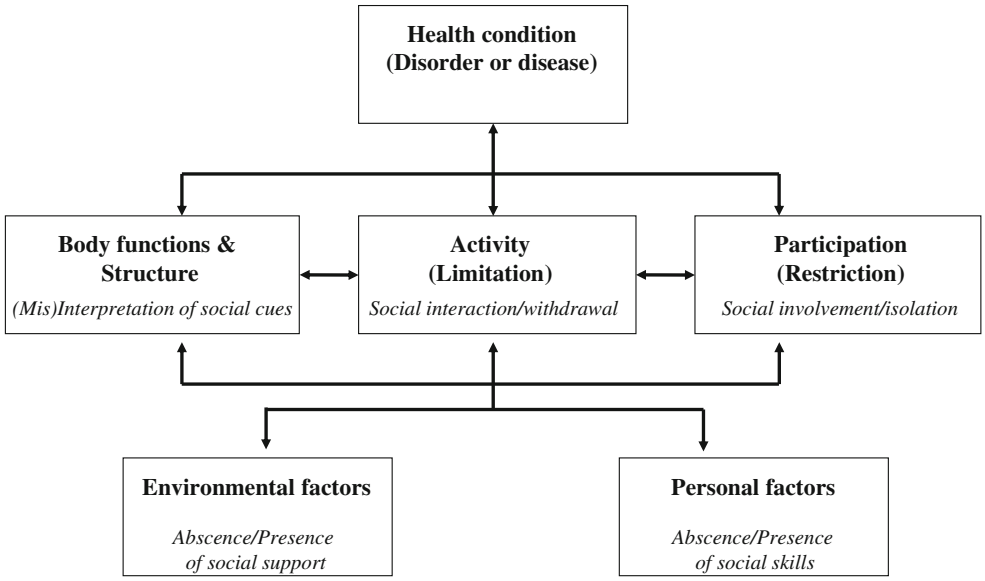

Fig. 1 International Classification of Functioning, Disability, and Health (ICF) *biopsychosocial model* of disability. Adapted and applied to social functioning from WHO (2002)

difficulty caring for themselves and maintaining employment, placing significant burden on families and society. This has led to the development of specific and more detailed instruments that measure social functioning more comprehensively than those used commonly in HRQOL research.

Another example is autism, a neurodevelopmental disorder defined in part by impairment in social functioning, together with deficits in communicative and behavioral areas. Of this triad, social impairment appears to be of special relevance including problems with attention to social stimuli, processing of facial information, or the response to emotional cues from others. [30].

Social functioning and personality

Major models in personality research usually include a trait related to an individual's ability to engage and enjoy social relationships. This can be labeled extraversion, sociability, or reward dependence, among other things [31]. Although there is no consensus among trait theorists regarding a common definition of these constructs, all of these traits, together with related behavioral dispositions, like loneliness or interest in physical activity, can be associated with frequency or intensity of social life. Individuals with a positive attitude toward social relationships are more likely to have satisfying relations and a socially engaged lifestyle. These individuals may actively seek experiences that reinforce their disposition [32]. In fact, personality prior to the experience of disability seems to influence the way in which individuals react and adapt to dysfunction [33].

HRQL, neuropsychiatric disorders, and personality reconciled

Depending upon the illness involved, impairment in social functioning has been regarded as a symptom of an underlying disorder or as a consequence of disease or disability. When the illness appears to be related to alterations in structures and physiology of what has been called the "social brain" [1, 2] (e.g., brain tumors, traumatic injuries, schizophrenia, or autism), its manifestations in individual behavior (including social functioning) are usually considered as symptoms. However, in the context of HRQOL, impairment in social functioning is more often seen as an effect of the disease or its treatment. From this viewpoint, an impaired functional status is the result of symptoms, like fatigue, pain, reduced mobility, or mood.

The role of genetic factors on social functioning must be understood within this frame, taking into account the presence of many other intervening variables. Sprangers et al. [6] presented a revision of the well-known theoretical model of Wilson and Cleary [34] as a framework that incorporates all these factors (Fig. 2). This model describes a continuum of levels/measures that can be ordered from basic biological to more complex psychological and integrated concepts. The revised model includes at the left side the presence of molecular and genetic factors that may affect social functioning through biological and physiological variables, which produce symptoms impacting functional status. Additionally, it acknowledges the impact of genetic and molecular factors on individual characteristics which, in turn, may affect social functioning. The arrows in the model depict the dominant associations, but

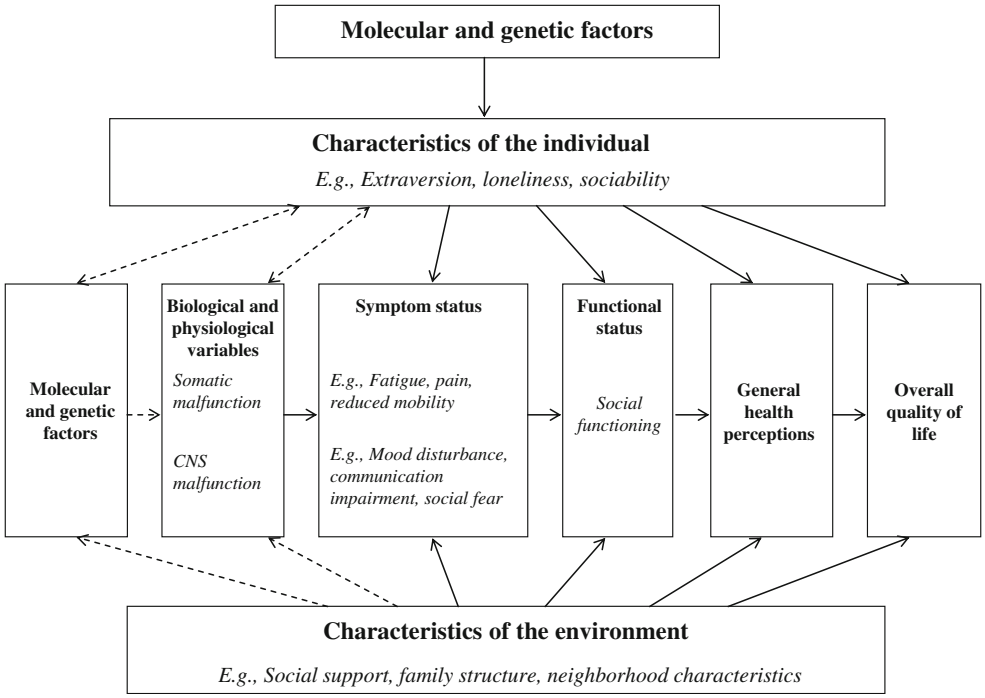

Fig. 2 Extended model of Wilson and Cleary. Adapted and applied to social functioning from Sprangers et al. (2010)

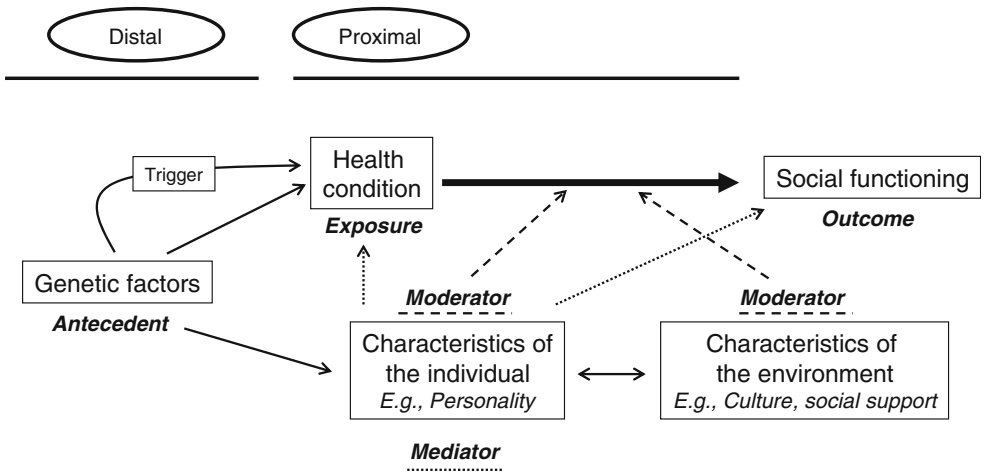

Fig. 3 Pathways for genetic influence on social functioning. This figure represents a simplification of the complex interaction between different factors, through different pathways, to exert effects on social functioning. Proximal factors may induce the outcome directly, while distal factors that feature earlier in the causal chain have the potential to affect the outcome indirectly, via a number of intermediary causes. The role of the variables as mediators, moderators, antecedents, or exposure may vary according to the situation under analysis or a particular research design. For instance, the characteristics of the individual could *moderate* the relationship between health and social functioning (*dashed pathways*) but also act as *mediators* (*dotted pathways*) or even be considered the *exposure* depending on the situation

mutual influences exist (e.g., social support may affect functional status while, in turn, functional status induces changes in social support). Other relationships within the model include possible gene–gene or gene–environment interplay. Hence, genetic influences may exert their effects on social functioning through different pathways, and the set of genes involved may, in part, overlap and, in part, be specific for different disorders.

This is further clarified in Fig. 3, where the character of the different variables as antecedents, mediators, or moderators is described [35]. The central part of the figure represents the relationship between health condition (from absence to presence of disorder or disease) and social functioning. The former is considered the *exposure* that may produce different levels in the *outcome*. Obviously, genetic factors do not influence social functioning directly,

and in fact, they are present earlier in time than any other intervening variable. As *antecedents*, they may influence health condition either directly (e.g., genetic disorder) or indirectly by increasing the susceptibility of the individual to environmental triggers (e.g., a pathogen or an accident). An additional pathway for genetic effects is through their influence on the characteristics of the individual. These characteristics, either alone or interacting with the environment, would act as *moderators* of the relationship between health condition and social functioning or as *mediators* between the antecedents and either the exposure or the outcome. Hence, to the point that personality dispositions are influenced by genetic expression, social functioning would indirectly show genetic influence; and heritable influences on personality would be apparent as heritable influences on social functioning [32].

The figure also considers the possibility of gene–environment interplay (i.e., G–E correlation or G*E interaction) depending on the variables and the pathways involved. Thus, genetic factors favoring low levels of extraversion might act in parallel with an environment that hampers the presence and extension of social networks, to produce a negative influence on social functioning (G–E correlation). In addition, the genetic effects on health and social functioning might be moderated by environmental conditions, such as education (G*E interaction) [36]. While accounting for the complexities of the processes involved, the figure helps to clarify these multifaceted relationships and exemplifies how genetic diversity may act through different channels to produce individual differences in social functioning.

Genetic influences on individual differences in social functioning

Few studies have directly investigated the causes of individual differences in social functioning. Romeis et al. [7] analyzed the responses to SF-36 among 2,928 male middle-aged twin pairs. Their estimation of heritability for the "social functioning" dimension was low (0.2) and non-significant. A preliminary study of the responses to the EQ-5D questionnaire by a sample of 472 female adult twin pairs showed a higher estimate of 0.6 for the "usual activities" dimension, although the comparability of these measures is questionable [37].

McGue and Christensen [38] studied a sample of 1,112 pairs of elderly Danish twins and measured "social activity" with a six-item scale assessing the frequency of social engagement (e.g., leave home, or go to a party) and mental pursuits (hobbies). The study revealed that social activity was moderately but significantly heritable (0.36).

Heritability has also been reported for associated dimensions or constructs (e.g., prosocial behavior or loneliness) [39]. To the point that these constructs are related to the social skills, interests, and behavior of the individual, they should serve as mediators by which genes may exert certain influence on social functioning. The heritability of prosocial behavior was found to be between 0.3 and 0.5 [40]. These estimates are moderated by age. Knafo and Plomin [41] longitudinally studied a group of 9,424 twin pairs and found a significant increase in genetic effects during early childhood, from 0.32 at age two up to 0.61 five years later. Moreover, in another longitudinal study of prosocial behavior through adolescence, the correlation between measures taken at two time points was explained mainly by genetic factors (60% of the covariance), showing that continuity of this dimension seems to be genetically influenced [40]. Social support, assessed by scales like friends/relative support or social integration, was found to have heritability estimates in the range of 0.43–0.75 [42].

Twin studies of loneliness (i.e., a feeling of social isolation and dissatisfaction with one's social relationships [12]) have estimated its heritability to be around 0.5–0.7, both in adults, adolescents, and children [43–46]. Moreover, classical personality traits that can be related to individual differences in social functioning have been extensively studied. Broadly speaking, twin studies have consistently suggested heritabilities in the range of 0.3–0.5 for traits such as extraversion, neuroticism, agreeableness, reward dependence, or sociability, both in adults and adolescents [31, 47–50].

From a clinical perspective, evidence also points to a significant role of genetic factors. Main disorders characterized by impairments in social functioning domains, such as schizophrenia or autism, show substantial heritabilities in the order of 0.80 [14, 30, 47, 51]. Significant heritability has also been reported for specific dimensions within these disorders, such as "child/adolescent sociability" in schizophrenia (0.27) [52] or social autistic-like traits (0.70–0.75) [53].

Biological pathways of social functioning

Our knowledge about potential biological pathways underlying social functioning is incomplete. Nonetheless, we can assume that some biological mechanisms, including neural networks, neurotransmitters, and hormone systems, may be of special interest.

Brain structures and regions which seem to be central to social functioning include, but are not limited to, the superior temporal sulcus (STS), the fusiform gyrus, the amygdala, and the prefrontal cortex (PFC) [1, 30]. The STS and the fusiform gyrus play an important role in the perceptual processing of social information. Facial expression

recognition has been used as an index of social functioning for certain patients, and substantial heritability (0.36–0.64) of neuroelectric indicators of face processing (event-related brain potentials) has been reported [54].

The amygdala and the PFC assign an emotional value to the processed information. The amygdala is thought to be a central structure in complex social behavior [1], and its activity has been related to face processing, identification of emotion, social judgments, empathy, or threat detection [30]. Decreased amygdala activation to fearful stimuli has been linked to increased sociability and decreased social fear in humans [55], whereas increased activation is observed in social avoidance and phobia [56]. This is consistent with the assumption that amygdala activation represents a danger signal in social interaction [57] and would affect social interests and functioning.

Not surprisingly, neurotransmitters potentially involved in social functioning are related to pathways implicated in the processes that take place in the above-mentioned brain regions. Interacting with other neurotransmitter systems, oxytocin and vasopressin have emerged as central players in the regulation of social cognition and behavior [39, 58, 59]. These neuropeptides strongly modulate the functioning of the amygdala [60], and recent advances have suggested that both could play an important role in personality traits relevant to social interaction, trust, social bonding, and ability to infer the emotional state of others [58].

Oxytocin is released during stress, being involved in anxiety and fear responses, but especially it appears to be a key mediator of complex emotional and social behaviors [58, 60]. There is evidence linking oxytocin to prosocial behavior in humans and suggesting that this neuropeptide is involved in affiliative behaviors, such as mother–infant and adult pair bond formation, separation distress, and other aspects of social attachment [30, 58, 61]. Moreover, oxytocin could play a role as an underlying biological mechanism for the stress-protective effects of positive social interactions [62]. Human social interaction appears to be facilitated by this hormone. Kosfeld et al. [63] found that oxytocin affected an individual's willingness to accept social risks arising through interpersonal interactions. Likewise, imaging studies have reported that oxytocin decreases amygdala activity [60]. From a clinical viewpoint, disruption of the oxytocin system appears to have a relevant role in autism spectrum disorders [30]. For example, oxytocin administration facilitated the processing and retention of social information in adults diagnosed with autism or Asperger's syndrome [61]. In fact, this neuropeptide, as well as vasopressin, has been suggested as targets for novel treatment approaches for disorders characterized by social dysfunction [59].

From biological pathways to genetic variants involved in social functioning

The main genetic variants that might influence social functioning are related to the above-mentioned neurotransmitters. The oxytocin receptor gene (OXTR) has recently been associated with social behavioral phenotypes, such as altruism, empathy, maternal sensitivity, or reward dependence [59, 64–67]. Allelic variation in OXTR, linked to social behavior, appears to be associated with both the volume and the functional response of the amygdala [65, 68]. Moreover, the effect of this gene may be moderated by cultural environment. For example, Kim et al. [69] compared Korean and American participants and found that carriers of an allelic variant (rs56576G) were more likely to seek emotional social support under psychological distress, but only among the Americans. Additionally, both the oxytocin gene and the OXTR have been reported to be related to autism spectrum disorders [70, 71].

The arginine-vasopressin (AVP) system is a biomolecular pathway that clearly influences social behavior [72]. These behavioral effects of AVP seem to be mediated through the AVP receptor 1a (AVPR1A), and variation in this locus appears to contribute to sociobehavioral diversity in humans [58]. An allelic variant in this region has been linked to significantly lower scores on the partner bonding scale, but only for males. Homozygous males were twice as likely to have experienced marital problems or threat of divorce and half as likely to be married if involved in a committed relationship [73]. Additionally, carriers of this variant appear to have the highest level of amygdala activation when performing an emotional face-matching task [74] and, from a clinical standpoint, AVPR1A variation has been hypothesized to influence the sociobehavioral deficits characteristic of autism spectrum disorders [58].

Both oxytocin and vasopressin show functional interactions with dopamine and serotonin systems [59]. Genes related to dopamine receptors have also been considered plausible candidates for traits related to motivational behaviors, such as reward seeking or extraversion. A recent meta-analysis found evidence of an association between a polymorphism (C521T) in the dopamine D4 receptor (DRD4) gene and approach-related personality traits. This association appeared weaker for extraversion [75]. There are also reports of associations between other dopaminergic genes and variables that could be related to social functioning [76–78]. Variations in genes associated with serotonin pathways are also likely to influence social functioning and some of them (i.e., the 5′-promoter polymorphism of the serotonin transporter gene) have widely been studied for relations with complex social behavior in humans [39]. Thus, for instance, differences in the response of the amygdala to threatening stimuli have been associated

with this genetic variant [79], and a recent meta-analysis suggests an association between this locus and amygdala activation, accounting for up to 10% of the variance in the response of this neural structure to emotional stimuli (i.e., phenotypic variance) [80].

Other genes could also contribute to social functioning among normal adults. It has been suggested that norepinephrine (NE) is related to social motivation and drive [81], and genes related to NE function appear to be associated with the personality trait "reward dependence", which reflects the degree of susceptibility to reinforcing effects of social rewards [30]. Finally, an association between the brain-derived neurotrophic factor (BDNF) *Val66Met* polymorphism and social functioning (SF-36) has been reported for depressive patients under psychopharmacological treatment [5].

Research toward related traits with a longer history of inquiry in the genetic aspects involved could also provide new candidate genes widening the range of research targets. For instance, social functioning has been associated with cognitive functioning and cognitive decline, such that poor cognitive functioning relates to subsequent decrements in social activity, and more socially active older adults experience less cognitive decline [82, 83]. Cognitive ability shows substantial heritability throughout the lifespan and the quest to identify the genetic variants involved may pave the way pointing to possible candidates [84, 85].

Additionally, we should bear in mind, as mentioned before, that genetic polymorphisms could also interact with other genes or environmental factors resulting in effects on social functioning. Thus, some researchers have reported interactions between several of the above-mentioned genes and environmental conditions, affecting social behavior [86–88].

To date, the candidate gene approach and the study of G*E interaction effects have produced mixed results. Null findings, false positives, replication failures, publication bias, and power concerns are frequently discussed in the literature [89]. In fact, it has been argued that the effect of any single gene would be too small to generate such large variations, especially in complex behaviors, and that we are only beginning to understand how genes exert their influence [90]. These findings have resulted in a call for a more rigorous evaluation of the scientific merits of published results [91].

In trying to overcome these problems, a different strategy for searching relevant genes has been used. Genome-wide association studies (GWAS) analyze hundreds of thousands of single nucleotide polymorphisms (SNPs) distributed across the entire genome in search of allelic variants related to the phenotype of interest [92]. To the best of our knowledge, no GWAS has been conducted for social functioning. However, several GWAS have been published for some of the related phenotypes we have reviewed before. GWAS performed for extraversion and a recent meta-analysis of GWAS on personality traits [93–95] could not find convincing evidence for associations between genetic variants and extraversion. Even new approaches, such as forming Molecular Personality Scales (MPSs) summing the effect of a number of SNPs, although useful for other traits, have also failed for extraversion, suggesting that this trait might be influenced by a vast number of genes, each of them with a very small effect [90].

Conclusions and implications for HRQOL research

We have presented a brief overview of the main molecular and genetic mechanisms that could affect social functioning, and reached some challenging conclusions. By doing so, we came across obvious problems that need to be addressed in future research. First, classical twin and association studies are hampered by the lack of consensus regarding the definition of social functioning and lack of knowledge regarding the proposed candidate genes (biological pathway). Second, this is an enormous field. With this paper, we attempt to bring more attention to the promise in this area, recognizing that much needs to be done. Currently, there only are very few studies relating genes and HRQOL, and social functioning in particular.

While acknowledging these limitations, we have tried to provide a clear overview and suggestions for the future development of this area of research. We have taken concepts and learning points from related domains that can be applied to this field; we have selected relevant material making it available to the HRQOL audience; and we have provided background information about how to approach genetic studies in observational HRQOL settings. We hope this will help avoid pitfalls and stimulate research in this promising area.

Confronted with the scarcity of results from classical twin studies regarding social functioning, we have relied on data regarding associated concepts and personality characteristics (e.g., extraversion, sociability, loneliness, social reward, affiliation). Most of them appear to be moderately but significantly heritable. Additionally, from a clinical standpoint, most disorders characterized by impairments in the social domain are highly heritable. It would be naïve to think that a few specific genes could explain the important behavioral variability encountered in social functioning related to HRQOL. Genetic influences are probably multiple, exerting their effects through different pathways, and correlating and interacting with a great number of environmental factors. We think that the adapted model of Wilson and Cleary offers a frame to integrate and interpret this information, showing the different pathways and

relationships possibly involved in the genetic effects on social functioning.

Current knowledge precludes solid conclusions. Unequivocal associations between single genes and complex phenotypes have not been found and will not likely be found. Nonetheless, more than a deterrent, this should serve as an incentive for including genetics in the HRQOL research agenda. In performing this task, different strategies are worth exploring.

Incorporating the biological underpinnings will enhance the study of social functioning in HRQOL research in a number of ways. Genetically informative approaches are needed to elucidate the complex interplay of genetic and environmental factors in social functioning. Analyzing the presence of shared genetic factors between social functioning and related variables, like personality traits (e.g., sociability), will help to interpret their relationship and the underlying genetic mechanisms, and including social functioning and HRQOL variables in future molecular genetic studies (i.e., candidate gene or GWAS) will help to understand and identify the variability in response to health problems. In addition, merging methods and research interests between both fields will contribute to the analysis of the moderation effects of pure demographic (e.g., age or sex) and environmental (e.g., gender, education or SES) variables on social functioning, helping to identify environmental factors that act on genetically susceptible individuals. Also, it would improve longitudinal models by determining the role of genetic factors in the continuity and change of social functioning.

Based on the evidence reviewed in this paper, a number of mechanisms and directions emerge as particularly promising for future research in this area, including several structures (i.e., amygdala or PFC) at the neural level, and the dopamine and oxytocin/vasopressin systems at the biochemical level. Other related areas (e.g., cognitive functioning or personality) could also supply new candidates widening our research targets.

Additionally, a currently more common, but due to the large sample size needed not easily accomplishable method is the GWAS-approach. A blind search of possible genetic variants that could explain individual differences in social functioning might reveal biological pathways worth further scrutiny. Although these strategies have not always achieved consistent results and, too frequently, genes selected from candidate studies do not replicate effects on GWAS (e.g., cognitive function [84] or depressive disorder [96]), at this point both could provide advances helping to direct future research. A consortium like the GENEQOL facilitates such endeavors. Intensifying our efforts in this area will help us to achieve better insight into the factors underlying variability in HRQOL and, particularly, in the complex domain of social functioning. This knowledge will help us to determine which patients are most vulnerable to poor outcomes and, ultimately, to enhance our efforts at early identification, prevention, and intervention on HRQOL.

Acknowledgments We are grateful to all members of the GENEQOL Consortium for their invaluable contribution to the consortium activities.

Appendix 1: Glossary

Allelic association: An association between allelic frequencies and a phenotype (Allele: an alternative form of a gene at a locus) [47].

Candidate gene: A gene whose function suggests that it might be associated with a trait [47].

Chromosome: Self-replicating structures in the nucleus of a cell that carry the genetic information [97].

Gene: The basic unit of inheritance. A sequence of DNA bases that code for a particular product [47].

Genome:The entire collection of genetic information (or genes) that an organism possesses [97].

Genome-wide association study (GWAS): A study that evaluates association of genetic variation with outcomes or traits of interest by using 100,000–1,000,000 markers or more across the genome [92, 97].

Genotype: The genetic constitution of an individual [97].

Heritability: The proportion of the phenotypic differences among individuals that can be attributed to genetic differences in a particular population [47].

Locus (plural, loci): The site(s) on a chromosome at which the gene for a particular trait is located [97].

Molecular Personality Scale (MPS): A set of SNPs that are collectively associated with personality traits [90].

Personality traits: Relatively enduring individual differences in behavior that are stable across time and across situations [47, 98].

Phenotype: An observed characteristic of an individual that results from the combined effects of genotype and environment [47].

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) [97].

Single Nucleotide Polymorphism (SNP): The most common type of DNA polymorphism which involves a mutation in a single nucleotide [47].

Twin study: Study comparing the resemblance of identical and fraternal twins to estimate genetic and environmental components of variance [47].

Appendix 2: GENEQOL consortium participants per February 2012

Amy P. Abernethy, Duke Cancer Care Research Program, Duke University Medical Center, Durham, NC, US; Frank Baas, Laboratory of Neurogenetics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Andrea M. Barsevick, Nursing Research and Education, Fox Chase Cancer Center, Philadelphia, PA, US; Meike Bartels, Department of Biological Psychology, VU University, Amsterdam, the Netherlands; Dorret I. Boomsma, Department of Biological Psychology, VU University, Amsterdam, the Netherlands; Andrew Bottomley, Quality of Life Department, EORTC Data Center, Brussels, Belgium; Michael Brundage, Department of Oncology, Queen's University Cancer Centre of Southeastern Ontario, Kingston, Ontario, Canada; David Cella, Department of Medical Social Sciences, Feinberg School of Medicine, Chicago, IL, US; Cynthia Chauhan, Cancer Advocay, Wichita, KS, US; Charles S. Cleeland, Department of Symptom Research, The University of Texas M. D. Anderson Cancer Center, Houston, TX, US; Corneel Coens, Quality of Life Department, EORTC Data Center, Brussels, Belgium; Amylou C. Dueck, Section of Biostatistics, Mayo Clinic, Scottsdale, AZ, US; Marlene H. Frost, Women's Cancer Program, Mayo Clinic, Rochester, MN, US; Per Hall, Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden; Michele Y. Halyard, Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, US; Pål Klepstad, Department of Intensive Care Medicine, St Olavs University Hospital, Norwegian University of Technology and Science, Trondheim, Norway; Nicholas G. Martin, Queensland Institute of Medical Research, Brisbane, Australia; Christine Miaskowski, School of Nursing, University of California, San Francisco, CA, US; Miriam Mosing, Queensland Institute of Medical Research, Brisbane, Australia; Benjamin Movsas, Department of Radiation Oncology, Henry Ford Health System, Detroit, MI, US; Cornelis J. F. Van Noorden, Department of Cell Biology and Histology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Joao Ricardo Oliveira, Department of Neuropsychiatry, Federal University of Pernambuco, Recife—Pernambuco, Brazil; Juan Ordoñana, Department of Human Anatomy and Psychobiology, University of Murcia, Murcia, Spain; Donald L. Patrick, Department of Health Services, University of Washington, Seattle, WA, US; Nancy L. Pedersen, Department of Medical Epidemiology and Biostatistics, Karolinska; Institute, Stockholm, Sweden; Hein Raat, Preventive Youth Health Care, Erasmus Medical Center, Rotterdam, the Netherlands; Bryce Reeve, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD, US; Mary E. Ropka, Cancer Prevention and Control Program, Fox Chase Cancer Center, Cheltenham, PA, US; Quiling Shi, Department of Symptom Research, The University of Texas M. D. Anderson Cancer Center, Houston, TX, US; Gen Shinozaki, Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, US; Jasvinder A. Singh, Minneapolis Veterans Affairs Medical Center and University of Minnesota, Minneapolis, MN and Mayo Clinic College of Medicine, Rochester, MN, US; Jeff A. Sloan, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, US; Mirjam A. G. Sprangers, Department of Medical Psychology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Dick Swaab, The Netherlands Institutes for Neuroscience, Amsterdam, the Netherlands; Jayant Talwalker, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, US, Ruut Veenhoven, Faculty of Social Sciences, Erasmus University Rotterdam, Rotterdam, The Netherlands; Gert G. Wagner, Berlin University of Technology, Max Planck Institute for Human Development and German Institute for Economic Research, Berlin, Germany; Ping Yang, Department of Genetic Epidemiology, Mayo Clinic, Rochester, MN, US; Ailko H. Zwinderman, Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

References

1. Adolphs, R. (2003). Cognitive neuroscience of human social behaviour. *Nature Reviews Neuroscience, 4*(3), 165–178.
2. Brothers, L. (1990). The social brain: A project for integrating primate behavior and neurophysiology in a new domain. *Concepts in Neuroscience, 1*, 27–51.
3. Robinson, G. E., Fernald, R. D., & Clayton, D. F. (2008). Genes and social behavior. *Science, 322*(5903), 896–900.
4. Cortina, S. D., Drotar, D., Ericksen, M., Lindsey, M., Patterson, T. L., Myers, J. M., et al. (2011). Genetic biomarkers of health-related quality of life in pediatric asthma. *The Journal of Pediatric, 159*(1), 21–26 e21.
5. Zou, Y. F., Wang, Y., Liu, P., Feng, X. L., Wang, B. Y., Zang, T. H., et al. (2010). Association of BDNF Val66Met polymorphism with both baseline HRQOL scores and improvement in HRQOL scores in Chinese major depressive patients treated with fluoxetine. *Human Psychopharmacology, 25*(2), 145–152.
6. Sprangers, M. A., Sloan, J. A., Barsevick, A., Chauhan, C., Dueck, A. C., Raat, H., et al. (2010). Scientific imperatives, clinical implications, and 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.
7. Romeis, J. C., Heath, A. C., Xian, H., Eisen, S. A., Scherrer, J. F., Pedersen, N. L., et al. (2005). Heritability of SF-36 among middle-age, middle-class, male-male twins. *Medical Care, 43*(11), 1147–1154.

8. Sprangers, M. A., & Schwartz, C. E. (2008). Reflections on changeability versus stability of health-related quality of life: Distinguishing between its environmental and genetic components. *Health Qualification of Life Outcomes, 6*, 89.
9. Sprangers, M. A., Sloan, J. A., Veenhoven, R., Cleeland, C. S., Halyard, M. Y., Abertnethy, A. P., et al. (2009). The establishment of the GENEQOL consortium to investigate the genetic disposition of patient-reported quality-of-life outcomes. *Twin Research and Human Genetics, 12*(3), 301–311.
10. Barsevick, A., Frost, M., Zwinderman, A., Hall, P., & Halyard, M. (2010). I'm so tired: Biological and genetic mechanisms of cancer-related fatigue. *Quality of Life Research, 19*(10), 1419–1427.
11. Shi, Q., Cleeland, C. S., Klepstad, P., Miaskowski, C., & Pedersen, N. L. (2010). Biological pathways and genetic variables involved in pain. *Quality of Life Research, 19*(10), 1407–1417.
12. Sprangers, M. A., Bartels, M., Veenhoven, R., Baas, F., Martin, N. G., Mosing, M., et al. (2010). Which patient will feel down, which will be happy? The need to study the genetic disposition of emotional states. *Quality of Life Research, 19*(10), 1429–1437.
13. WHO. (2002). *Towards a common language for functioning, disability and health: ICF*. Geneva: World Health Organization.
14. Sullivan, P. F., Daly, M. J., & O'Donovan, M. (2012). Genetic architectures of psychiatric disorders: The emerging picture and its implications. *Nature Reviews Genetics, 13*(8), 537–551.
15. Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care, 30*(6), 473–483.
16. EuroQol Group. (1990). EuroQol–a new facility for the measurement of health-related quality of life. The EuroQol group. *Health Policy, 16*(3), 199–208.
17. Burns, T., & Patrick, D. (2007). Social functioning as an outcome measure in schizophrenia studies. *Acta Psychiatrica Scandinavica, 116*(6), 403–418.
18. van der Mei, S. F., Krol, B., van Son, W. J., de Jong, P. E., Groothoff, J. W., & van den Heuvel, W. J. (2006). Social participation and employment status after kidney transplantation: A systematic review. *Quality of Life Research, 15*(6), 979–994.
19. Bonner, M. J., Hardy, K. K., Willard, V. W., Anthony, K. K., Hood, M., & Gururangan, S. (2008). Social functioning and facial expression recognition in survivors of pediatric brain tumors. *Journal of Pediatric Psychology, 33*(10), 1142–1152.
20. Avis, N. E., Smith, K. W., Hambleton, R. K., Feldman, H. A., Selwyn, A., & Jacobs, A. (1996). Development of the multidimensional index of life quality. A quality of life measure for cardiovascular disease. *Medical Care, 34*(11), 1102–1120.
21. The WHOQOL Group. (1998). Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL group. *Psychological Medicine, 28*(3), 551–558.
22. Becker, M., Diamond, R., & Sainfort, F. (1993). A new patient focused index for measuring quality of life in persons with severe and persistent mental illness. *Quality of Life Research, 2*(4), 239–251.
23. Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., et al. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute, 85*(5), 365–376.
24. Cella, D. F., Tulsky, D. S., Gray, G., Sarafian, B., Linn, E., Bonomi, A., et al. (1993). The Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. *Journal of Clinical Oncology, 11*(3), 570–579.
25. Fayers, P. M., & Machin, D. (2007). *Quality of life: The assessment, analysis and interpretation of patient-reported outcomes*. Chichester: John Wiley & Sons Ltd.
26. Herzog, A. R., Ofstedal, M. B., & Wheeler, L. M. (2002). Social engagement and its relationship to health. *Clinics in Geriatric Medicine, 18*(3), 593–609, ix.
27. Rasulo, D., Christensen, K., & Tomassini, C. (2005). The influence of social relations on mortality in later life: A study on elderly Danish twins. *Gerontologist, 45*(5), 601–608.
28. Tse, W. S., Rochelle, T. L., & Cheung, J. C. (2011). The relationship between personality, social functioning, and depression: A structural equation modeling analysis. *International Journal of Psychology, 46*(3), 234–240.
29. Lyyra, T. M., & Heikkinen, R. L. (2006). Perceived social support and mortality in older people. *Journals of Gerontology. Series B, Psychological Sciences and Social Sciences, 61*(3), S147–S152.
30. Neuhaus, E., Beauchaine, T. P., & Bernier, R. (2010). Neurobiological correlates of social functioning in autism. *Clinical Psychology Review, 30*(6), 733–748.
31. Bouchard, T. J., Jr., & Loehlin, J. C. (2001). Genes, evolution, and personality. *Behavior Genetics, 31*(3), 243–273.
32. McGue, M., Osler, M., & Christensen, K. (2010). Causal inference and observational research: The utility of twins. *Perspective on Psychological Science, 5*(5), 546–556.
33. Boyce, C. J., & Wood, A. M. (2011). Personality prior to disability determines adaptation: Agreeable individuals recover lost life satisfaction faster and more completely. *Psychological Science, 22*(11), 1397–1402.
34. Wilson, I. B., & Cleary, P. D. (1995). Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA, 273*(1), 59–65.
35. Singh-Manoux, A. (2005). Commentary: Modelling multiple pathways to explain social inequalities in health and mortality. *International Journal of Epidemiology, 34*(3), 638–639.
36. Johnson, W., Kyvik, K. O., Mortensen, E. L., Skytthe, A., Batty, G. D., & Deary, I. J. (2010). Education reduces the effects of genetic susceptibilities to poor physical health. *International Journal of Epidemiology, 39*(2), 406–414.
37. Ordoñana, J. R., Bartels, M., Rebollo-Mesa, I., Monteagudo, O., & Perez-Riquelme, F. (2010). *Causes of individual differences in quality of life dimensions of the EQ-5D questionnaire*. Paper presented at the 40th annual meeting of the behavior genetics association, Seoul.
38. McGue, M., & Christensen, K. (2007). Social activity and healthy aging: A study of aging Danish twins. *Twin Research and Human Genetics, 10*(2), 255–265.
39. Harris, J. R. (2007). Genetics, social behaviors, social environments and aging. *Twin Research and Human Genetics, 10*(2), 235–240.
40. Gregory, A. M., Light-Hausermann, J. H., Rijsdijk, F., & Eley, T. C. (2009). Behavioral genetic analyses of prosocial behavior in adolescents. *Developmental in Science, 12*(1), 165–174.
41. Knafo, A., & Plomin, R. (2006). Prosocial behavior from early to middle childhood: Genetic and environmental influences on stability and change. *Developmental Psychology, 42*(5), 771–786.
42. Kendler, K. S. (1997). Social support: A genetic-epidemiologic analysis. *American Journal of Psychiatry, 154*(10), 1398–1404.
43. Boomsma, D. I., Cacioppo, J. T., Muthen, B., Asparouhov, T., & Clark, S. (2007). Longitudinal genetic analysis for loneliness in Dutch twins. *Twin Research and Human Genetics, 10*(2), 267–273.
44. Bartels, M., Cacioppo, J. T., Hudziak, J. J., & Boomsma, D. I. (2008). Genetic and environmental contributions to stability in loneliness throughout childhood. *American Journal of Medical Genetic B Neuropsychiatry Genetics, 147*(3), 385–391.
45. Boomsma, D. I., Willemsen, G., Dolan, C. V., Hawkley, L. C., & Cacioppo, J. T. (2005). Genetic and environmental contributions

to loneliness in adults: The Netherlands twin register study. *Behavior Genetics, 35*(6), 745–752.
46. Waaktaar, T., & Torgersen, S. (2012). Genetic and environmental causes of variation in perceived loneliness in young people. *American Journal of Medical Genetic B Neuropsychiatry Genetics, 159*(5), 580–588.
47. Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2008). *Behavioral genetics* (5th ed.). New York: Worth Publishers.
48. Keller, M. C., Coventry, W. L., Heath, A. C., & Martin, N. G. (2005). Widespread evidence for non-additive genetic variation in Cloninger's and Eysenck's personality dimensions using a twin plus sibling design. *Behavior Genetics, 35*(6), 707–721.
49. Bratko, D., & Butkovic, A. (2007). Stability of genetic and environmental effects from adolescence to young adulthood: Results of Croatian longitudinal twin study of personality. *Twin Research and Human Genetics, 10*(1), 151–157.
50. Kandler, C., Riemann, R., & Kampfe, N. (2009). Genetic and environmental mediation between measures of personality and family environment in twins reared together. *Behavior Genetics, 39*(1), 24–35.
51. Flint, J., Greenspan, R. J., & Kendler, K. S. (2010). *How genes influence behavior*. Oxford: Oxford University Press.
52. McGrath, J. A., Avramopoulos, D., Lasseter, V. K., Wolyniec, P. S., Fallin, M. D., Liang, K. Y., et al. (2009). Familiality of novel factorial dimensions of schizophrenia. *Archives of General Psychiatry, 66*(6), 591–600.
53. Ronald, A., Happe, F., & Plomin, R. (2005). The genetic relationship between individual differences in social and nonsocial behaviours characteristic of autism. *Developmental Science, 8*(5), 444–458.
54. Anokhin, A. P., Golosheykin, S., & Heath, A. C. (2010). Heritability of individual differences in cortical processing of facial affect. *Behavior Genetics, 40*(2), 178–185.
55. Meyer-Lindenberg, A., Hariri, A. R., Munoz, K. E., Mervis, C. B., Mattay, V. S., Morris, C. A., et al. (2005). Neural correlates of genetically abnormal social cognition in Williams syndrome. *Nature Neuroscience, 8*(8), 991–993.
56. Stein, M. B., Goldin, P. R., Sareen, J., Zorrilla, L. T., & Brown, G. G. (2002). Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Archives of General Psychiatry, 59*(11), 1027–1034.
57. Amaral, D. G. (2003). The amygdala, social behavior, and danger detection. *Annals of the New York Academy of Sciences, 1000*, 337–347.
58. Donaldson, Z. R., & Young, L. J. (2008). Oxytocin, vasopressin, and the neurogenetics of sociality. *Science, 322*(5903), 900–904.
59. Meyer-Lindenberg, A., Domes, G., Kirsch, P., & Heinrichs, M. (2011). Oxytocin and vasopressin in the human brain: Social neuropeptides for translational medicine. *Nature Reviews Neuroscience, 12*(9), 524–538.
60. Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., et al. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *Journal of Neuroscience, 25*(49), 11489–11493.
61. Hollander, E., Bartz, J., Chaplin, W., Phillips, A., Sumner, J., Soorya, L., et al. (2007). Oxytocin increases retention of social cognition in autism. *Biological Psychiatry, 61*(4), 498–503.
62. Heinrichs, M., Baumgartner, T., Kirschbaum, C., & Ehlert, U. (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biological Psychiatry, 54*(12), 1389–1398.
63. Kosfeld, M., Heinrichs, M., Zak, P. J., Fischbacher, U., & Fehr, E. (2005). Oxytocin increases trust in humans. *Nature, 435*(7042), 673–676.
64. Rodrigues, S. M., Saslow, L. R., Garcia, N., John, O. P., & Keltner, D. (2009). Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *Proceedings of Natural Academy of Science USA, 106*(50), 21437–21441.
65. Tost, H., Kolachana, B., Hakimi, S., Lemaitre, H., Verchinski, B. A., Mattay, V. S., et al. (2010). A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proceedings of Natural Academy of Science USA, 107*(31), 13936–13941.
66. Thompson, R. J., Parker, K. J., Hallmayer, J. F., Waugh, C. E., & Gotlib, I. H. (2011). Oxytocin receptor gene polymorphism (rs2254298) interacts with familial risk for psychopathology to predict symptoms of depression and anxiety in adolescent girls. *Psychoneuroendocrinology, 36*(1), 144–147.
67. Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2008). Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. *Social Cognitive and Affection in Neuroscience, 3*(2), 128–134.
68. Inoue, H., Yamasue, H., Tochigi, M., Abe, O., Liu, X., Kawamura, Y., et al. (2010). Association between the oxytocin receptor gene and amygdalar volume in healthy adults. *Biological Psychiatry, 68*(11), 1066–1072.
69. Kim, H. S., Sherman, D. K., Sasaki, J. Y., Xu, J., Chu, T. Q., Ryu, C., et al. (2010). Culture, distress, and oxytocin receptor polymorphism (OXTR) interact to influence emotional support seeking. *Proceedings of Natural Academy of Science USA, 107*(36), 15717–15721.
70. Yrigollen, C. M., Han, S. S., Kochetkova, A., Babitz, T., Chang, J. T., Volkmar, F. R., et al. (2008). Genes controlling affiliative behavior as candidate genes for autism. *Biological Psychiatry, 63*(10), 911–916.
71. Lerer, E., Levi, S., Salomon, S., Darvasi, A., Yirmiya, N., & Ebstein, R. P. (2008). Association between the oxytocin receptor (OXTR) gene and autism: Relationship to Vineland Adaptive Behavior scales and cognition. *Molecular Psychiatry, 13*(10), 980–988.
72. Wassink, T. H., Piven, J., Vieland, V. J., Pietila, J., Goedken, R. J., Folstein, S. E., et al. (2004). Examination of AVPR1a as an autism susceptibility gene. *Molecular Psychiatry, 9*(10), 968–972.
73. Walum, H., Westberg, L., Henningsson, S., Neiderhiser, J. M., Reiss, D., Igl, W., et al. (2008). Genetic variation in the vasopressin receptor 1a gene (AVPR1A) associates with pair-bonding behavior in humans. *Proceedings of Natural Academy of Science USA, 105*(37), 14153–14156.
74. Meyer-Lindenberg, A., Kolachana, B., Gold, B., Olsh, A., Nicodemus, K. K., Mattay, V., et al. (2009). Genetic variants in AVPR1A linked to autism predict amygdala activation and personality traits in healthy humans. *Molecular Psychiatry, 14*(10), 968–975.
75. Munafo, M. R., Yalcin, B., Willis-Owen, S. A., & Flint, J. (2008). Association of the dopamine D4 receptor (DRD4) gene and approach-related personality traits: Meta-analysis and new data. *Biological Psychiatry, 63*(2), 197–206.
76. Lawford, B. R., Young, R., Noble, E. P., Kann, B., & Ritchie, T. (2006). The D2 dopamine receptor (DRD2) gene is associated with co-morbid depression, anxiety and social dysfunction in untreated veterans with post-traumatic stress disorder. *European Psychiatry, 21*(3), 180–185.
77. Marino, C., Vanzin, L., Giorda, R., Frigerio, A., Lorusso, M. L., Nobile, M., et al. (2004). An assessment of transmission disequilibrium between quantitative measures of childhood problem behaviors and DRD2/Taql and DRD4/48 bp-repeat polymorphisms. *Behavior Genetics, 34*(5), 495–502.
78. Godlewska, B. R., Olajossy-Hilkesberger, O., Limon, J., & Landowski, J. (2010). Ser9Gly polymorphism of the DRD3 gene

is associated with worse premorbid social functioning and an earlier age of onset in female but not male schizophrenic patients. *Psychiatry Research, 177*(1–2), 266–267.
79. Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., et al. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science, 297*(5580), 400–403.
80. Munafo, M. R., Brown, S. M., & Hariri, A. R. (2008). Serotonin transporter (5-HTTLPR) genotype and amygdala activation: A meta-analysis. *Biological Psychiatry, 63*(9), 852–857.
81. Tse, W. S., & Bond, A. J. (2003). Reboxetine promotes social bonding in healthy volunteers. *Journal of Psychopharmacolgy, 17*(2), 189–195.
82. James, B. D., Wilson, R. S., Barnes, L. L., & Bennett, D. A. (2011). Late-life social activity and cognitive decline in old age. *Journal of the International Neuropsychology Society, 17*(6), 998–1005.
83. Small, B. J., Dixon, R. A., McArdle, J. J., & Grimm, K. J. (2012). Do changes in lifestyle engagement moderate cognitive decline in normal aging? Evidence from the Victoria Longitudinal Study. *Neuropsychology*, *26*(2), 144–155.
84. Harris, S. E., & Deary, I. J. (2011). The genetics of cognitive ability and cognitive ageing in healthy older people. *Trends in Cognitive Sciences, 15*(9), 388–394.
85. Lee, T., Henry, J. D., Trollor, J. N., & Sachdev, P. S. (2010). Genetic influences on cognitive functions in the elderly: A selective review of twin studies. *Brain Research Reviews, 64*(1), 1–13.
86. DiLalla, L. F., Elam, K. K., & Smolen, A. (2009). Genetic and gene-environment interaction effects on preschoolers' social behaviors. *Developmental Psychobiology, 51*(6), 451–464.
87. Creswell, K. G., Sayette, M. A., Manuck, S. B., Ferrell, R. E., Hill, S. Y., & Dimoff, J. D. (2012). DRD4 polymorphism moderates the effect of alcohol consumption on social bonding. *PLoS ONE, 7*(2), e28914.
88. Kiser, D., Steemers, B., Branchi, I., & Homberg, J. R. (2012). The reciprocal interaction between serotonin and social behaviour. *Neuroscience and Biobehavioral Reviews, 36*(2), 786–798.
89. Duncan, L. E., & Keller, M. C. (2011). A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *American Journal of Psychiatry, 168*(10), 1041–1049.
90. McCrae, R. R., Scally, M., Terracciano, A., Abecasis, G. R., & Costa, P. T., Jr. (2010). An alternative to the search for single polymorphisms: Toward molecular personality scales for the five-factor model. *Journal of Personality and Social Psychology, 99*(6), 1014–1024.
91. Hewitt, J. K. (2012). Editorial policy on candidate gene association and candidate gene-by-environment interaction studies of complex traits. *Behavior Genetics, 42*(1), 1–2.
92. Pearson, T. A., & Manolio, T. A. (2008). How to interpret a genome-wide association study. *JAMA, 299*(11), 1335–1344.
93. Terracciano, A., Sanna, S., Uda, M., Deiana, B., Usala, G., Busonero, F., et al. (2010). Genome-wide association scan for five major dimensions of personality. *Molecular Psychiatry, 15*(6), 647–656.
94. de Moor, M. H., Costa, P. T., Terracciano, A., Krueger, R. F., de Geus, E. J., Toshiko, T., et al. (2012). Meta-analysis of genome-wide association studies for personality. *Molecular Psychiatry, 17*(3), 337–349.
95. Gillespie, N. A., Zhu, G., Evans, D. M., Medland, S. E., Wright, M. J., & Martin, N. G. (2008). A genome-wide scan for Eysenckian personality dimensions in adolescent twin sibships: Psychoticism, extraversion, neuroticism, and lie. *Journal of Personality, 76*(6), 1415–1446.
96. Bosker, F. J., Hartman, C. A., Nolte, I. M., Prins, B. P., Terpstra, P., Posthuma, D., et al. (2011). Poor replication of candidate genes for major depressive disorder using genome-wide association data. *Molecular Psychiatry, 16*(5), 516–532.
97. Attia, J., Ioannidis, J. P., Thakkinstian, A., McEvoy, M., Scott, R. J., Minelli, C., et al. (2009). How to use an article about genetic association: A: Background concepts. *JAMA, 301*(1), 74–81.
98. John, O. P., Robins, R. W., & Pervin, L. A. (2008). *Handbook of personality: Theory and research* (3rd ed.). New York: Guilford Press.