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REVIEW

Biological pathways, candidate genes, and molecular markers associated with quality-of-life domains: an update

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Abstract
Background There is compelling evidence of a genetic foundation of patient-reported quality of life (QOL). Given the rapid development of substantial scientific advances in this area of research, the current paper updates and extends reviews published in 2010.
Objectives The objective was to provide an updated overview of the biological pathways, candidate genes, and molecular markers involved in fatigue, pain, negative (depressed mood) and positive (well-being/happiness) emotional functioning, social functioning, and overall QOL.
Methods We followed a purposeful search algorithm of existing literature to capture empirical papers investigating the relationship between biological pathways and molecular markers and the identified QOL domains.
Results Multiple major pathways are involved in each QOL domain. The inflammatory pathway has the strongest evidence as a controlling mechanism underlying fatigue. Inflammation and neurotransmission are key processes involved in pain perception, and the catechol-O-methyltransferase (COMT) gene is associated with multiple sorts of pain. The neurotransmitter and neuroplasticity theories

On behalf of the GeneQol Consortium.

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have the strongest evidence for their relationship with depression. Oxytocin-related genes and genes involved in the serotonergic and dopaminergic pathways play a role in social functioning. Inflammatory pathways, via cytokines, also play an important role in overall QOL.
Conclusions Whereas the current findings need future experiments and replication efforts, they will provide researchers supportive background information when embarking on studies relating candidate genes and/or molecular markers to QOL domains. The ultimate goal of this area of research is to enhance patients' QOL.

Keywords Biological pathways · Genes · Molecular markers · Quality of life · Patient-reported outcomes (PROs)

Introduction

In 2004, empirical support was found for the provocative hypothesis that there is a genetic basis to patient-reported quality of life (QOL) [1]. In response to this preliminary work [2], an international and interdisciplinary research consortium (GeneQol) was formed to set out the state of the science at that point and to design and implement a program of research [3]. A theoretical framework was published to facilitate and focus the investigation into the biological foundation of self-perceived QOL [4].

Multiple publications and studies ensued laying the groundwork for methodological approaches and identifying candidate molecular markers, e.g., [5–7]. Replication of preliminary work has been seen alongside new markers [8]. Reviews documented the biological pathways and molecular markers that were found to be associated with QOL domains, including the most prevalent symptoms pain [9] and fatigue [10], and emotional [11] and social functioning [12].

As a result of this collective work, there is now compelling evidence of a genetic foundation of QOL. Given the rapid development of substantial scientific advances in this area of research, the current paper updates and extends the previous work. The objective was to provide an updated overview of the biological pathways, candidate genes, and molecular markers for these domains and those for overall QOL. This information will provide researchers supportive background information when embarking on studies relating candidate genes and/or molecular markers to QOL.

Methods

To provide an overview of the state of the science, we started by including the references provided in our earlier reviews [2, 3, 9–12]. To update these references, we conducted a computerized literature search on PubMed for the years November 2007–November 2012. However, we did not set a limitation on year of publication for overall QOL as the GeneQol Consortium had not previously published a review on this subject. Due to the large number of hits on depression and pain, up-to-date publications were limited to the last three years (2010–2012). Articles or book chapters found through reference checking or personal communication (until June, 2013) were also included.

Specific search terms are provided as supplementary material (see Supplementary information 1). Empirical papers investigating the relationship between biological pathways/molecular markers and the following QOL domains were included: fatigue, pain, emotional functioning (depression, well-being/happiness), social functioning, and overall QOL. We limited our search to publications in English on human subjects.

A gene or molecular marker is included if there is at least one publication (either empirical, meta-analysis or review) reporting its significant association with a QOL domain. The findings are provided in Tables 1, 2, 3, 4, 5, and 6 for each QOL domain, respectively. References included in the tables are provided as supplementary information. The text will only elaborate on new information since our previous reviews.

The primary source for identifying the biological pathways was the KEGG website (Kyoto Encyclopedia for Genes and Genomes) (http://www.genome.jp/kegg/) and supplemented by Genecards website (http://www.genecards.org/).

Results

Fatigue

To the best of our knowledge, no genome-wide association studies (GWAS) on fatigue have been published to date. Several biological pathways show promise as underlying mechanisms of fatigue: inflammation, serotonin, dopamine, and glutathione metabolic pathways [10, 13].

Saligan [14] synthesized the evidence for inflammatory pathway involvement. In cross-sectional studies, various markers of immunity and inflammation obtained at various time points from blood, plasma, serum or in vitro were inconsistent in predicting fatigue depending on the covariates included in the analysis [15]. In a small number of longitudinal studies, primarily in women with early-stage breast cancer, fatigue was associated with elevations in immune response and inflammation. Significant associations have also been demonstrated between fatigue and genomic markers. Higher morning and evening fatigue in cancer patients and caregivers was found to be related to single nucleotide polymorphisms (SNPs) of the interleukin

Table 1 Biological pathways, candidate genes, and molecular markers in fatigue

Quality-of-life domains	Biological pathways[a]	Candidate genes	Molecular markers	Literature
Fatigue				[1]
	Serotonergic synapse/ metabolic pathway	*TPH1*	5-HT	[2–5]
	Dopaminergic synapse	*COMT, DRD4, DAT1*	Cortisol	[6, 7]
	Glutathione metabolic pathway	*GSTZ1, ABCC4, DPYD, GSTP1, OPRT/UMPS*	NR	[8–10]
Inflammation	Cytokine–cytokine receptor interaction			[11]
	Pro-inflammatory	*IL-1β, IL-6, TNF-α, CD19+β*	IL-1β, IL-6, TNF-α, CD19+β, TNF-R1,	[12–25]
	Anti-inflammatory	*IL-1RN, IL-1Rα, IL-10*	IL-1RN, IL-1Rα, IL-10	[13–15, 17]
	Immunity	*IL-2, IL-4, IL-5, IFN-γ*	IL-2, IL-4, IL-5, IFN-γ	[12, 26]
	Cell migration	*CXCL9, CXCL11*	CXCL9, CXCL11	[27]
	Inflammation	*CRP*	CRP, neopterin	[4, 13]
Cortisol production, serotonin dysregulation, catecholamine	HPA	NR	CRH, ACTH, cortisol, melatonin, norepinephrine, epinephrine	[28–31]
Circadian rhythm disruption—i.e., through modulation of arousal and sleep patterns	SCN	*PER2, PER3, TIMELESS*	EGF, TGF-α, neuregulin-1, prokineticine-2, cardiotrophin-like cytokine, PER2, PER3, cortisol, melatonin	[28, 32–37]
	EGFR	NR	NR	[28]
Peripheral fatigue (muscle strength)	Skeletal muscle	NR	ATP	[37, 38]
Vagal afferent nerve activation (suppress somatic muscle activity—'sickness behavior')	Cytokine–cytokine receptor interaction			
	Pro-inflammatory	*IL-1, IL-6, TNF-α*	IL-1, IL-6, TNF-α	[39]

References are included in Supplementary Material 2: References to Tables 1–7

[a] Biological pathways are according to KEGG (Kyoto Encyclopedia of Genes and Genomes), http://www.genome.jp/kegg/or Genecards, http://www.genecards.org/

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(IL)-6 gene [15], while in lung cancer survivors, fatigue was associated with SNPs of the IL-1β, IL-1ra, and IL-10 genes [6]. Among breast cancer survivors, fatigue was related to the IL1β-511 and the IL6-174 polymorphism [16] (Table 1).

There is some evidence of serotonin system involvement in fatigue. In various forms of cancer, tryptophan is catabolized by enzymes produced by the tumor cells, i.e., indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO). By decreasing tryptophan levels, the tumor creates an immunosuppressive environment protecting itself against the immune system [17]. High fatigue in cancer patients was associated with low concentration of tryptophan and high kynurenine/tryptophan ratio [18]. High fatigue in women with irritable bowel syndrome was associated with the 5-HT marker on the tryptophan hydroxylase (TPH) gene [19].

There is evidence of association between fatigue and the dopamine system. In a sample of 100 breast cancer survivors, fatigue was found to be related to the catechol-O-methyltransferase (COMT) gene [20]. In a sample of 332 healthy university students and staff, time on task and subjective indicators of energy level were evaluated for association with genes governing dopamine [21]. Polymorphisms in COMT and dopamine transporter gene (DAT1) were associated with differences in time taken for task completion, while subjective declines in mental energy were associated with dopamine receptor D4 (DRD4) polymorphisms.

Table 2 Biological pathways, candidate genes, and molecular markers in pain

Quality-of-life domains	Biological pathways[a]	Candidate genes	Molecular markers	Literature
Pain				[40]
Disease-related pain/pain perception	Dopaminergic synapse	*COMT, CRHBP*	NR	[41–50]
	Serotonergic synapse	*5-HTT (SLC6A4), 5-HTR2A, HTR1A, TPH1*	NR	[2, 46, 51–56]
	Cytokine–cytokine receptor interaction			
	Pro-inflammatory	*CX3CR1*	CX3CR1	[57]
	Neuroactive ligand–receptor interaction	*OPRM1, HTR1A*	NR	[50, 56, 58]
	Phagosome	*HLA-DRB1*	NR	[55]
	Endocrine and other factor-regulated calcium reabsorption	*ER-α*	Estrogen	[46]
	Neuroactive ligand–receptor interaction	*ADR-β2, MC2R*	NR	[46, 49]
	Glucocorticoid/mineralocorticoid receptor	*SERPINA6*	NR	[49]
	Adipocytokine signaling pathway	*POMC*	NR	[49]
	Sodium channel transporter	*SCN9A*	NR	[59, 60]
	Apoptosis	*CASP9*	NR	[61]
	PI3K/Akt signaling	*WNK1/HSN2, TCL1A*	NR	[62, 63]
	Transcription	*BCL11A*	NR	[64]
	Metabolic pathway	*NOS3, GCH1*	eNOS	[65–68]
	mRNA surveillance pathway	*HBS1L-MYB*	NR	[64]
	?	*FAM173B*	NR	[68]
	?	*CCT5*	NR	[68]
Medication consumption, pain treatment efficacy/side effect (morphine, opioid), response to pain, pain relief	Dopaminergic synapse	*COMT, CREB1*	NR	[69–72]
	Protein methylation	*METTL21A*	NR	[72]
	Serotonergic synapse	*5-HTT (SLC6A4)*	NR	[73]
	Cytokine–cytokine receptor interaction			
	Pro-inflammatory	*TNF-α, IL-6*	TNF-α, IL-6	[74]
	Anti-inflammatory	*IL-1RA*	IL1-RA	[75]
	Neuroactive ligand–receptor interaction/ morphine addiction	*OPRM1*	DAMGO(?)	[76–80]
	Drug metabolism	*CYP3A4*	NR	[81]
	Proteolysis/protein transport	*RHBDF2*	NR	[82]
Drug transportation and metabolism of specific analgesics/painkillers	ABC transporter	*ABCB1*	NR	[83–87]
	Drug metabolism	*CYP2B6, CYP2D6, CYP2C9, UGT2B7*	NR	[85, 88–98]
Pain severity, duration	Cytokine–cytokine receptor interaction			
	Pro-inflammatory	*IL-1α, IL-1β, IL-6, IL-8, TNF-α*	IL-1α, IL-1β, IL-6, IL-8, TNF-α	[12, 74, 99–102]
	Anti-inflammatory	*IL-1RNA*	IL-1RNA	[102]
	Immunity	*IL-4*	IL-4	[12]
	Glutathione metabolic pathway	*ABCC4*	NR	[9]
	Neuroactive ligand–receptor interaction/ morphine addiction	*OPRM1*	NR	[103]
	Neuroactive ligand–receptor interaction	*CRHR1, CRHR2,*	CRH, cortisol, substance P, angiotensin, vasopressin, melatonin, nerve growth factor, cholecystokinin	[104]

[a] Biological pathways are according to KEGG (Kyoto Encyclopedia of Genes and Genomes), http://www.genome.jp/kegg/or Genecards, http://www.genecards.org/

References are included in Supplementary Material 2: References to Tables 1–7

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Table 3 Biological pathways, candidate genes, and molecular markers in negative emotional functioning

Quality-of-life domains	Biological pathways[a]	Candidate genes	Molecular markers	Literature
Emotional functioning				[105]
Negative affect	Amygdala-medial prefrontal cortex	NR	NR	[106]
Depression	?	*PCLO*	NR	[107, 108]
	Dopaminergic synapse	*MAO-A, GNB3, SLC6A3, DRD4, DβH, PRKACA, GNAS, GNAL, AKT1, CREB1, CAMK2A, GRIN2B, GRIN2A, VMAT2, DRD2, COMT, DAT*	DβH, COMT, MAO-A	[109–119]
	Metabolic pathway	*MTHFR, NOS2A, PLA2G2A, SYNJ2, TYMS, OPRT/UMPS, ATP6V1B2, TPH*	Tryptophan	[8, 109, 110, 115, 120–123]
	Dopaminergic/ serotonergic pathway (?)	*CACNA1C*	NR	[124]
	Serotonergic synapse	*5-HTR2A, SLC6A4 (5-HTT, 5-HTTLPR), GNB3, PTGS2, PRKACA, GNAS, HTR1A, VMAT2, TPH1*	NR	[2, 109, 111, 112, 115, 121, 125–128]
	Glutamatergic synapse	*PRKACA, GNB3, ADCY7, GNAS, GRIN2B, GRIN2A, GRIN1, GRM7*	NR	[112, 123, 129]
	?	*SP4*	NR	[123]
	Cholinergic synapse	*CHRNA7, PRKACA, GNB3, ADCY7, AKT1, CREB1, CAMK2A,*	NR	[111, 112, 116, 130]
	Neurotrophin signaling pathway	*BDNF, GSK3B, NGFR, CAMK2A, $p75^{NTR}$*	BDNF	[111, 112, 116, 131, 132]
	Phagosome	*MPO*	NR	[121]
	Proteasome	*PSMB4*	NR	[133]
	Immune response	*TBX21*	NR	[133]
	Neurodegeneration (Alzheimer's disease)	*APOEε2, APOEε3, APOEε4*	APOEε4	[109, 134, 135]
	Chemokine signaling pathway	*CCL2, AKT1, PRKACA, ADCY7*	NR	[112]
	Cytokine–cytokine receptor interaction			
	Pro-inflammatory	*IL-1α, IL-1β, IL-6, IL-8, MCP1, TNF-α, CCL2*	IL-1α, IL-1β, IL-6, IL-8, MCP1, CCL2, TNF-α	[12, 24, 26, 111, 136–138]
	Anti-inflammatory	*IL-1RN, IL-10*	IL-1RN, IL-10	[17, 26, 136, 139]
	Immunity	*IL-2, IL-4, IL-4R, IL-7, IL-12p70, IL-15, IFN-γ, GM-CSF*	IL-2, IL-4, IL-4R, IL-7, IL-12p70, IL-15, IFN-γ, GM-CSF	[12, 136]
	Cell migration	*CXCL9, CXCL11, Eotaxin, MIP-1α*	CXCL9, CXCL11, Eotaxin, MIP-1α	[27, 136]
	Inflammation	*CRP*	CRP	[137]
	Glucocorticoid/ mineralocorticoid receptor	*FKBP5*	Cortisol	[140]
	Neuroactive ligand–receptor interaction/ morphine addiction	*AVPR1A, AVPR1B, HCRTR2, OXTR, CRHR1, CRHR2*	AVP, orexin, oxytocin, CRH	[141–148]
	Nucleosides transport	*SLC29A3*	NR	[149]

Table 3 continued

Quality-of-life domains	Biological pathways[a]	Candidate genes	Molecular markers	Literature
	GABAergic synapse	*GABA*	GABA	[150, 151]
	Endocrine and other factor-regulated calcium reabsorption	*ER-α, AR*	Estrogen, androgen	[152, 153]
	Nicotinate and nicotinamide metabolism	*NUDT12*	NR	[154]
Anhedonia	Neuroactive ligand–receptor interaction	*CNR1*	NR	[155]
Circadian rhythm disruption—through modulation of arousal and sleep patterns	SCN	*PER3, CLOCK, CRY2*	PER, CLOCK, CRY	[36, 156, 157]
Antidepressant medication response/ non-response	Neuroactive ligand–receptor interaction	*CRHR1, CRHR2*	CRH	[147]
	Neurotrophin signaling pathway	*BDNF, VGF*	BDNF	[158, 159]
	Serotonergic synapse	*5-HTTLPR*	NR	[160]
	Glucocorticoid/ mineralocorticoid receptor	*UCN3, FKBP5*	Cortisol	[133, 159, 161]
	Nitrogen metabolism pathway	*GLDC*	Glycine	[162]
	Cytokine–cytokine receptor interaction			
	Pro-inflammatory	*IL-1β, MIF, TNF-α*	IL-1β, MIF, TNF-α	[159]
	T-cell receptor signaling	*CD3E*	NR	[133]
	Proteasome	*PSMD9*	NR	[133]
Anxiety	HIF-1 signaling pathway (?)	*SERPINE1*	PAI	[163]
	Serotonergic synapse	*SLC6A4 (5-HTTLPR), TPH1*	NR	[2, 164–168]
	Dopaminergic synapse	*DRD2*	NR	[119]
	?	*NPSR1*	NPSR1	[169, 170]
	Metabolic pathway	*SYNJ2*	NR	[122, 171]
	Tight junction pathway	NR	NR	[171]
	Adipocytokine signaling pathway	*NPY*	Neuropeptide Y	[172]
	Neuroactive ligand–receptor interaction	*OXTR*	NR	[173]
Loneliness	Cholinergic synapse	*CHRNA4*	NR	[168]
	Metabolic pathways	*MTHFR*	NR	[174]
	Neuroactive ligand–receptor interaction	*OXTR*	NR	[175]

[a] Biological pathways are according to KEGG (Kyoto Encyclopedia of Genes and Genomes), http://www.genome.jp/kegg/or Genecards, http://www.genecards.org/

References are included in Supplementary Material 2: References to Tables 1–7

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The glutathione metabolic pathway has been associated with differential reports of fatigue. In a case–control study of lung cancer patients with high and low QOL scores (including fatigue), two SNPs in the glutathione S-transferase super family were associated with fatigue during cancer therapy: ABCC4 and GSTZ1 [22].

In summary, the inflammatory pathway has the strongest evidence as a controlling mechanism underlying fatigue

Table 4 Biological pathways, candidate genes, and molecular markers in positive emotional functioning

Quality-of-life domains	Biological pathways[a]	Candidate genes	Molecular markers	Literature
Positive affect	NR	NR	NR	[176, 177]
	Dopaminergic system (ventral tegmental area)	*COMT, OPRM1*	CART	[178]
	Serotonergic synapse	*SLC6A4 (5-HTTLPR), MAOA*	NR	[179–181]
	Neuroactive ligand–receptor interaction	NR	Oxytocin	[178]
	Adipocytokine signaling pathway	*NPY*	Neuropeptide Y	[178]
	Cytokine–cytokine receptor interaction			
	Pro-inflammatory	*TNF-α*	TNF-α	[17]
Emotional appraisal	Serotonergic synapse	*SLC6A4 (5-HTTLPR)*	NR	[182]

[a] Biological pathways are according to KEGG (Kyoto Encyclopedia of Genes and Genomes), http://www.genome.jp/kegg/or Genecards, http://www.genecards.org/

References are included in Supplementary Material 2: References to Tables 1–7

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Table 5 Biological pathways, candidate genes, and molecular markers in social functioning

Quality-of-life domains	Biological pathways[a]	Candidate genes	Molecular markers	Literature
Social functioning				[183]
Social behavior (empathy, altruism, bonding, social skills)	Neuroactive ligand–receptor interaction	*OXTR, AVPR1A*	Oxytocin, arginine vasopressin	[184–196]
	Dopaminergic synapse	*DRD4*	NR	[197]
	Serotonergic synapse	*SLC6A4 (5-HTT)*	NR	[185]
Motivational behavior (reward seeking, extraversion)	Dopaminergic synapse	*DRD4, DRD2, DRD3*	NR	[119, 198–200]
Social function	Cytokine–cytokine receptor interaction			
	Pro-inflammatory	*IL-6, TNF-α*	IL-6, TNF-α	[17]
	Anti-inflammatory	*IL-1RN*	IL-1RN	[17]
	Amygdala-medial prefrontal cortex	NR	NR	[106]
	Serotonergic synapse	*HTR2A*	NR	[201]
	Neuroactive ligand–receptor interaction	*OXTR*	NR	[202, 203]
Social function in response to treatment	Dopaminergic synapse	*DRD2*	NR	[204]
	Neurotrophin signaling pathway	*BDNF*	NR	[205]
Social acceptance/rejection	Dopaminergic synapse	*COMT*	NR	[206, 207]
	Neuroactive ligand–receptor interaction	*OPRM1*	NR	[208]
Antisocial behavior	Dopaminergic synapse	*MAO-A*	NR	[209]
Personality traits				
Self-transcendence (to be an integral part of universe and its source)	Amino sugar and nucleotide sugar metabolism	*CHI3L1*	Serum YKL-40	[210]
Neuroticism	-NR	NR	NR	[211, 212]
	Olfactory transduction	*OR1A2*	NR	[213]
	Monoamine transport	*SCAMP2*	NR	[214]
Openness	Aldosterone-regulated sodium reabsorption	*KCNJ1*	NR	[212]

Table 5 continued

Quality-of-life domains	Biological pathways[a]	Candidate genes	Molecular markers	Literature
Coherence (perceived comprehensibility, manageability and meaningfulness of internal and external demands)	Dopaminergic/serotonergic pathway (?)	*CACNA1C*	NR	[124]
Neural processing of facial expression	?	*TMEM212*	NR	[215]

References are included in Supplementary Material 2: References to Tables 1–7

[a] Biological pathways are according to KEGG (Kyoto Encyclopedia of Genes and Genomes), http://www.genome.jp/kegg/or Genecards, http://www.genecards.org/

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Table 6 Biological pathways, candidate genes, and molecular markers in overall quality of life

Quality-of-life Domains	Biological pathways[a]	Candidate genes	Biomolecular markers	Literature
Overall quality of life	DNA repair pathway	*MGMT*	NR	[9]
	Cytokine–cytokine receptor interaction			
	Pro-inflammatory	*IL-6*	IL-6	[17]
	Inflammation	NR	CRP, neopterin	[4]
	Metabolic pathway	*TYMS, UGT1A1*	NR	[8]
	Serotonergic synapse	*TPH1*	tryptophan	[2, 4]

References are included in Supplementary Material 2: References to Tables 1–7

[a] Biological pathways are according to KEGG (Kyoto Encyclopedia of Genes and Genomes), http://www.genome.jp/kegg/or Genecards, http://www.genecards.org/

NR the relevant information was not reported

? the relevant biological pathway could not be identified

during the cancer experience. However, most pathways described here need further replication and validation studies. Other pathways also need exploration. For example, adipose tissue could play a role in fatigue because it secretes numerous cytokines, chemokines, and other proteins [23]. Additionally, there is evidence of links between stress and fatigue involving the HPA-axis and norepinephrine (another catecholamine) that need exploration [13].

Pain

Findings from GWAS studies on pain are limited to single cohorts in specialized settings. None of these were replicated. Moreover, the identified gene candidates are not intuitively biological plausible. A large-scale GWAS meta-analysis on chronic widespread pain [24] revealed that the minor C-allele of rs13361160 on chromosome 5p15.2 was associated with a 30 % higher risk of chronic widespread pain presence. In another GWAS including 335 patients with postoperative pain, several SNPs located close to the FAM119A and CREB genes were associated with more opioid requirements [25]. Another GWAS identified SNP TCL1A as being associated with musculoskeletal pain in women on adjuvant therapy for breast cancer [26]. Those works support the notion of inflammation as a promising target in the regulation of pain [9]. Finally, Galvan et al. [27] in a pooled GWA analysis observed that several SNPs related to neuronal transmission were associated with a good response from opioids used for cancer pain.

Most published studies continue to focus on pathways involved in pain. As addressed in our previous review [9], biological pathways related to neurotransmission, inflammation, and response to analgesics have served as major targets for pain genomic study. SNPs and haplotypes of COMT gene were associated with multiple phenotypes, such as osteoarthritis-related pain [28], neck pain, and pressure pain hypersensitivity in the neck and shoulder area in breast cancer survivors [29], pain sensitivity in major depressive disorder patients [30], and pain impact on daily positive affect in fibromyalgia [31]. Two of those studies revealed sex-specific effect of COMT gene variations [28, 30]. Gene-related pain modulation is more likely to be seen

in females, which indicates a possible role of estrogen in pain modulation (Table 2).

Polymorphisms of serotonin transporter gene (5-HTT) and serotonin HTR1A receptor gene were associated with perception of thermal pain [32, 33] and joint pain in chronic fatigue syndrome [34]. The A118G polymorphism in the opioid receptor mu 1 (OPRM1) gene was associated with pain intensity in patients with disk herniation [35]. Variability in the SCN9A gene can cause loss of function of the sodium channel transporter pathway. Additionally, patients with osteoarthritis, sciatica, or phantom pain due to amputation may experience differing amounts of pain on the basis of their SCN9A rs6746030 genotype [36].

In summary, the current work supports inflammation and neurotransmission as key processes involved in pain perception. Again, these findings need replication and extension (Table 2), preferably using large-scale GWAS studies.

Emotional functioning

Negative emotional functioning: depressed mood

The past decade has witnessed a variety of large-scale and individual genetic studies, which have suggested numerous candidate genes for depression. A range of GWAS studies have also been conducted. Sullivan [37], Muglia [38], Shi [9], and their respective colleagues did not identify any SNP that achieved GWAS significance in relation to major depression, whereas Shyn et al. [39] found significant SNPs in ATP6V1B2, SP4, and GRM7. Hek et al. [40] conducted a GWAS study with the self-reported Center for Epidemiologic Studies Depression Scale. Using over 50,000 individuals, one SNP, rs161645, in the 5q21 region reached GWAS significance. Kao et al. [41] concluded that the results are inconclusive, due to small effect size.

Whereas the hypothalamo–pituitary–adrenal (HPA) axis is described as the 'final common pathway' for most depressive symptoms [42], recent studies generated new hypotheses for biological mechanisms of depression (Table 3). For example, much research has been directed at the cytokine–cytokine receptor interaction of the inflammatory pathway. A meta-analysis of 24 studies measuring cytokines in patients with major depression found significantly higher concentrations of tumor necrosis factor (TNF)-alpha and IL-6 [43]. Cytokines were also found to be related to self-reported depressive symptoms in a wide variety of patient populations. For example, the allele of IL4 rs 2243248 was associated with high depression levels in oncology outpatients [44], and TNF-308 and IL6-174 polymorphisms that were found to be associated with fatigue were also associated with depression in breast cancer patients [45]. Moreover, polymorphisms of IL-10 were associated with depressed mood in patients attending their GP with acute infection [46] or who had end-stage renal disease [47]. Moreover, patients with Marfan disease who reported the lowest levels of mental QOL could also be distinguished on the basis of high expression levels of CXCL11, a gene coding for cytokines [7].

Since numerous susceptible genes for depression have been suggested without conclusive results, Kao et al. [41] reviewed and integrated the available data. They included 5,055 candidate genes, which they ranked (prioritization) on the basis of the magnitude of evidence multiplied by a source-specific weight. They thus identified 160 genes that have a high likelihood to be associated with depression. The top seven genes are dopamine beta-hydroxylase (DBH), serotonin transporter (SLC6A4), brain-derived neurotrophic factor (BDNF), nerve growth factor receptor (NGFR), tumor necrosis factor (TNF), glycogen synthase kinase 3 beta (GSK3B), and the alpha7 neuronal nicotine acetylcholine receptor subunit gene (CHRNA7).

Two of these top genes support the neurotransmitter theory. DBH catalyzes the biosynthesis of the neurotransmitter noradrenaline from dopamine. Low DBH activity is a likely risk factor for depression. SLC6A4, belonging to the serotonergic synapse pathway, is most likely related to the etiology of depression. The neurotrophin signaling pathway is supported by three top genes. BDNF is a neuroprotective protein which changes the balance of neuroprotective and neurotoxic responses to stress. GSK3B is an enzyme involved in neuronal cell development and energy metabolism, and has a key role in the action of mood stabilizer. NGFR modulates the activity of tyrosine kinases for neurotrophin family and may have a protective effect against developing depression.

In summary, the neurotransmitter and neuroplasticity theories have the strongest evidence for their relationship with depression [41]. However, these and other pathways (Table 3) need future experiments and replication efforts to disentangle the molecular mechanisms underlying depression.

Positive emotional functioning: well-being/happiness

No GWAS studies on well-being or happiness have been published to date. In fact, this QOL domain has been the subject of few genetic studies. Bartels et al. [5] were the first to conduct a genome-wide linkage study of 1157 offspring from 441 families. A suggestive linkage signal was obtained at the end of the long arm of chromosome 19 for marker D19S254 at 110 cM. A second suggestive linkage peak was found at the short arm of chromosome 1 for marker D1S534 at 153 cM. These two regions are not

overlapping with the regions found for contrasting phenotypes, such as depression.

The first candidate gene study [48] reported an association of the serotonin transporter gene (5-HTTLPR) with satisfaction of life in a representative sample of 2,574 Americans. However, follow-up work using data from the Framingham Heart Study and an augmented sample from the same data did not replicate this finding [49].

Chen et al. [50] report an association between the monoamine oxidase (MAOA) gene and happiness in women. This study, based on a sample of 193 and 152 Caucasian women and men, respectively, suggests that the low expression allele of the MAOA gene (MAOA-L) predicts higher self-reported happiness in women after correction of several covariates such as age, gender, education, but also mental disorder, and self-esteem (Table 4).

Rietveld et al. [51] are the first who demonstrate that genetic variants as measured in the current laboratory protocols are of significance for well-being. In a sample of over 11,500 unrelated Swedish and Dutch individuals, they found that 5–10 % of the variance in responses to single-question survey measures of subjective well-being is accounted for by the additive effects of the SNPs measured on presently used genotyping platforms. A correction for measurement error in the subjective well-being measures raises the point estimates to 12–18 %. These results warrant optimism about the prospects of using genetic data in well-being research because the contributing polymorphisms could be discovered with a sufficiently large sample of individuals.

Social functioning

Recent reports on the biological foundations of social functioning remain focused on previously identified biological pathways [12]. More specifically, recent studies support the posited intervention of the medial prefrontal cortex and associated neural structures (i.e., amygdala) on social functioning. Holmes et al. [52] reported a strong relationship between those structures and social avoidance or facial recognition. They found that decreased thickness in the left medial prefrontal cortex was associated with social withdrawal, reduced social functioning, and an increased likelihood of errors in the identification of facial emotions. They also found that individual differences in this circuitry could arise, in part, from common genetic variability contributing to the risk of depression, which is compatible with the previously observed phenotypic relation between negative mood and difficulty adjusting to social circumstances [53].

To the best of our knowledge, no GWAS has been yet published about social functioning specifically. However, genome-wide approaches have been performed on associated personality and behavioral variables. Suggestive results were found in areas of neural activation of specific brain regions and personality traits (i.e., extraversion), pointing to new variants that could ultimately be related to social functioning [54–58]. Although promising, they have not produced yet conclusive results.

Recent literature on candidate genes confirms the previously reviewed evidence regarding the role of genetic variants on individual differences in social functioning. Oxytocin-related genes have continued being the variants most commonly associated with areas related to social functioning, and with impacts of social environments on the individual, in a variety of samples [59–61]. However, the picture is far from clear; the relationships between oxytocin and social behavior are complex, and epigenetic mechanisms play a crucial role [62, 63]. Moreover, given the known influence of estrogens on oxytocin receptor activity, gender could also impact the intensity and/or direction of this association [59, 61]. Additionally, gene variants that appear to be related to serotonergic pathways (e.g., HTR2A [53]) and dopaminergic pathways (e.g., DRD4 [64] and MAOA [65]), or to psychiatric vulnerability, have continued to be reported as associated with social functioning domains [53, 64, 66].

In summary, recent reports appear to support the initial interest in some specific genetic variants as related to social functioning. However, many questions regarding this relationship are still unresolved and subject to further scientific enquiry (Table 5).

Overall QOL

To the best of our knowledge, no GWAS study has been conducted on overall QOL. However, several candidate gene studies have expanded our knowledge of the relationship between genetic variables and QOL (Table 6). The biological pathways and genetic variants involved in the individual QOL domains mentioned previously also apply to overall QOL.

Jun et al. [19] examined whether polymorphisms in TPH gene were associated with disease morbidity and overall QOL in a community-based sample of 199 Caucasian women with irritable bowel syndrome. SNP4 polymorphism of TPH1 was significantly associated with overall QOL. These associations strengthened further when analyses were adjusted for gastro-intestinal symptoms and global severity index of current psychological distress.

Rausch et al. [6] examined the association of SNPs in six cytokine genes with QOL in 1,319 patients with non-small-cell lung cancer. After Bonferroni correction, rs2069861 and rs 2069843 SNPs in IL-6 gene were significantly associated with overall QOL. SNP polymorphisms in IL-1β,

IL-6, and IL-1RN were significantly associated with a clinically significant difference in overall QOL. In another analysis from this cohort that consisted of 1,299 lung cancer patients, 470 SNPs in 56 genes of three biological pathways were assessed for association with QOL [22]. The study reported that three SNPs on the MGMT gene (rs3858300, rs10741191, and rs10741191) were associated with 34, 36, and 30 % higher risk of reporting a deficit in overall QOL, respectively.

In summary, these three studies provide evidence of association of genetic polymorphisms in genes for cytokines and receptors involved in important pathways with QOL. The biological plausibility and existing evidence of association of these pathways with other domains of QOL make it likely that this is not a mere fishing expedition. Clearly, much more studies are needed to disentangle the biological and molecular mechanisms underlying the complex construct of QOL.

Biological pathways

Biological pathways and individual genes have more than one function and can therefore impact more than one QOL domain. Table 7 reorganizes and summarizes Tables 1, 2, 3, 4, 5, and 6 by presenting the biological pathways and genes that are involved in the different QOL domains. Genes are included in this table if an association was found with at least two QOL domains.

There is substantial evidence that inflammatory pathways, via cytokines, play an important role in the QOL domains. Additionally, the dopaminergic and serotonergic synapse pathways demonstrate consistent involvement in emotional functioning, but play a role in other QOL domains. The neurotrophin signaling pathway seems to be more restricted to involvement with the emotional and social domains of QOL. The neuroactive ligand–receptor interaction pathway is related to a range of QOL domains.

Table 7 Common biological pathways, candidate genes, and molecular markers associated with QOL domains

Biological pathways	Candidate genes	Quality-of-life domain	Literature
Cytokine–cytokine receptor interaction	*IL-1β*	General health	[17]
Pro-inflammatory		Fatigue	[17]
		Pain	[100, 102]
		Emotional functioning—depression	[112, 136]
		Anti-depressant response	[159]
	IL-6	Overall quality of life	[17]
		General health	[17]
		Fatigue	[13, 24, 39]
		Pain	[39, 74, 101]
		Emotional functioning—depression	[24, 26, 112, 136–138]
		Social functioning	[17]
	IL-8	Pain	[99]
		Emotional functioning—depression	[12, 136)
	TNF-α	Fatigue	[14, 20, 24, 39)
		Pain	[74, 100)
		Emotional functioning—depression	[138, 159)
		Social functioning	[17]
Inflammation	*CRP*	Fatigue	[13]
		Emotional functioning—depression	[137]
Anti-inflammatory	*IL-1RN*	General health	[17]
		Fatigue	[17]
		Pain	[17]
		Emotional functioning—depression	[17]
		Social functioning	[17]
	IL-1RA	Fatigue	[13, 14)
		Pain	[75, 102)
	IL-10	General health	[17]
		Fatigue	[17]
		Pain	[39]
		Emotional functioning—depression	[26, 112, 136, 139)

Table 7 continued

Biological pathways	Candidate genes	Quality-of-life domain	Literature
Dopaminergic synapse	*COMT*	Fatigue	[6]
		Pain	[41–43, 45–48, 50, 69–71]
		Emotional functioning—depression	[118]
		Emotional functioning—Positive affect	[178]
		Social functioning	[206, 207]
	DRD2	Emotional functioning—depression	[118, 119]
		Emotional functioning—Anxiety	[119]
		Social functioning	[119, 199, 204]
	DRD4	Fatigue	[7]
		Emotional functioning depression	[110]
		Social functioning	[198]
	CREB1	Pain	[72]
		Emotional functioning—depression	[116]
Dopaminergic synapse/serotonergic synapse	*MAOA*	Emotional functioning –depression	[110]
		Emotional functioning—positive affect	[181]
		Social functioning	[209]
Serotonergic synapse	*5-HTT (SLC6A4)*	Pain	[46, 51, 52, 73]
		Emotional functioning—depression	[125–128, 182]
		Emotional functioning—anxiety	
		Emotional functioning—positive affect	[164–168]
		Social functioning	[179]
	TPH1	Overall quality of life	[185]
		Fatigue	[2]
		Pain	[2]
		Emotional functioning—depression	[115]
		Emotional functioning—anxiety	[2]
Neuroactive ligand–receptor interaction	*OPRM1*	General health	[216]
		Pain	[58, 76–80, 103]
		Emotional functioning	[178]
		Social functioning	[208]
	AVPR1A	Emotional functioning—depression	[146]
		Social functioning	[184, 187, 190–193]

Genes are included in this table if association is found with at least two QOL domains

Biological pathways are according to KEGG (Kyoto Encyclopedia of Genes and Genomes), http://www.genome.jp/kegg/or Genecards, http://www.genecards.org/

References are included in Supplementary Material 2: References to Tables 1–7

Discussion

The idea for exploring the relationship between genetic variables and QOL domains is now almost ten years old. What began as an exploratory investigation from a devil's advocate perspective has evolved into a broad program of research with established theoretical underpinnings and empirical evidence. This review provides promising evidence of genetic involvement in multiple QOL phenotypes through a variety of biological pathways. It speaks to the multi-dimensional nature of QOL and to the complex physiological mechanisms that underly a person's subjective experience. The exploration of the relationship between QOL and genetic variables has evolved into research involving a myriad of biological mechanisms instead of just one or two isolated pathways/genes.

Two potentially limiting aspects of this review merit attention. First, we included any genetic variable that was reported as being significant at least once. Many genetic findings fail the test of replication, so we undoubtedly have included some genetic variables that will ultimately fail to demonstrate a relationship with QOL domains. However,

given the novelty of this area of research, we felt it was too early to be more restrictive and to discard potential genetic biomarkers. Second, the number of genetic studies published to date varied across the different QOL domains, resulting in a varied level of evidence for individual biomarker relationships.

The findings presented in this review provide a platform for the inclusion of pathways and genes/molecular markers in the design of future studies. As most studies are cross-sectional, we need more longitudinal studies, preferably hypothesis-driven, to disentangle the causal biological pathways. Further, the vast majority of studies reviewed is involving pre-specified candidate genes. This knowledge-based approach runs the risk of missing important genes. GWAS can help to more fully investigate not only initial candidate genes but might uncover unexpected relationships. Whereas GWAS studies are still scarce, the decreasing costs will make such large-scale studies increasingly more feasible. Finally, as the current review was restricted to a limited number of QOL domains, we need additional reviews that collate evidence of the biological foundation for other QOL domains (e.g., physical functioning, cognitive functioning, and symptoms, such as nausea, cough, and appetite loss).

Ultimately, the goal of this research is to identify and use genetic markers for QOL deficits in clinical practice. Better understanding of the genetic basis of QOL will lead to innovations and discoveries that will help us improve patient care in the same way that the understanding of cellular and molecular mechanisms of diseases, such as diabetes and heart disease, has helped us better treat our patients with new drug discoveries targeting these mechanisms. Screening for predispositions to deficits in QOL holds the same clinical implications as screening for predispositions to disease and treatment outcomes. For example, there is a preponderance of evidence that cytokines are involved in various QOL domains. Moreover, they are easy to obtain in clinical practice. Perhaps it is time to begin screening patients for cytokine markers to provide prophylactic interventions to prevent QOL deterioration. More specifically, based on cytokine screening results, patients may be allocated to different prophylactic programs to reduce fatigue, e.g., provision of B12 supplements, steroids, blood transfusions, exercise programs, or cognitive therapy.

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Appendix 1: Glossary

Allele Is one of a number of alternative forms of the same gene or same genetic locus (generally a group of genes). It is the alternative form of a gene producing different effects. Sometimes, different alleles can result in different observable phenotypic traits.

Blood plasma Is the liquid component of blood, consisting 90 % of water, with the 10 % remainder including proteins, minerals, waste products, clotting factors, hormones, and immunoglobins.

Blood serum Is the blood plasma without the clotting elements.

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

DNA (deoxyribonucleic acid) The double-stranded molecule that encodes genetic information.

Epigenetics The study of heritable changes to DNA structure that do not alter the underlying sequence.

Gene The basic unit of inheritance. A sequence of DNA that codes for a particular protein product.

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

Ligand Ligand is an ion or molecule (functional group) that binds to a central metal atom to form a coordination complex.

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.

Genotype The genetic constitution of an individual.

Haplotype Is a combination of alleles (DNA sequences) at adjacent locations on a chromosome that are inherited together.

Heritability The proportion of phenotypic differences among individuals that can be attributed to genetic differences in a particular population.

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

Linkage study Study to identify physical segments (e.g., chromosomal regions) that are associated with given traits.

Nucleotides Organic molecules that are the building blocks of nucleic acids, like DNA and RNA.

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

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).

SNP A single nucleotide polymorphism is a variation in a DNA sequence when a single nucleotide in the gene differs between paired chromosomes.

Note: definitions are taken from text books and Wikipedia.

Appendix 2: GENEQOL Consortium Participants per September 2013

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