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The Genetic Influence on Subjective Well-Being: A review of the current knowledge on the role of genetics on our sense of subjective well-being and the implications it has for future research in improving well-being at both a population and individual level.

Abhishek Gupta
abhishek.gupta@uconn.edu

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Abhishek Gupta

Thesis Advisor: Dr. Theodore Rasmussen

Honors Advisor: Dr. Joerg Graf

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Abstract

This thesis project explores the genetic underpinnings of one of the most cherished attributes in the world, well-being.[1] Specifically, it attempts to understand the influence of the genome on subjective, or experienced, well-being. An investigation was conducted into current literature concerning both the structure of measurement devices of well-being as well as association studies to determine the scope of the correlation that exists between the genome and well-being and identify genetic findings of interest. Ultimately, being able to provide evidence of causality between the genome and sense of well-being at this iteration of well-being and genome research is limited, however, the correlations detailed in this work suggest overwhelmingly that genetics plays a significant role in the development of our sense of subjective well-being. It also suggests that the key to better understanding subjective well-being may be more concrete and lie, to some degree, in genetic expression. This presents a path forward that can be utilized in the foreseeable future to the advantage of optimizing public policy and in improving quality of life in populations, as well as presents another avenue by which epigenetic research can be utilized to modulate quality of life at an individual level. However, in order for such avenues to be explored, current measures of well-being must be expanded and improved. Thus, this work also presents an argument for making the measure of well-being a metric of importance that is comparable to that of GDP or GNP and utilizing the advent of biotechnological monitoring to collect real-time data on this topic to create the

infrastructure necessary to develop a greater understanding of subjective well-being.

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Introduction

Subjective well-being, herein referred to as SWB, is defined as “how people *experience* and *evaluate* their lives and specific domains and activities in their lives”. [2] It is characterized by a person’s affective and cognitive evaluation of their life. [3] Well-being measurement is a relevant assessment because it is a helpful and effective indicator in assessing quality of life and economic success in nations across the world. [4,5] From an economic perspective, subjective well-being is of interest because it can inform concepts such as “National Time Accounting” which help paint a more accurate picture on the welfare of citizens of a country and how that contributes to economic markers like GDP and GNP. [4]

Furthermore, research from Diener et al. highlights that elements of well-being including life satisfaction and happiness have been shown to be rated higher than material success across cultures and will continue to become more important as more and more of the basic needs of people are met globally. [1]

Beyond this perspective, we currently live in a time where mental illness stigma is decreasing and awareness is increasing [6] – and studying subjective well-being can not only inform the overall health of our populations, but also inform policy on how to improve quality of life. In the context of the United States, this is especially relevant as studies are showing anxiety and depression amongst adolescents is on the rise. [7,8]

As evidenced, SWB is a highly relevant concept to our current society, however, due to its subjective nature, its method of study is variable and relies on a variety of factors including perspective and environment. Thus, its results can be

interpreted to reflect different domains of well-being from short term happiness to more eudaimonic conceptions. [2] Utilizing SWB data to improve the levels that people experience requires understanding the concept in more concrete terms and understanding how the different aspects of their lives and lifestyles impact SWB. One way to do this is through investigating the genetics of SWB. Studies have shown that associations exist between SWB and genetic structure. [9] In fact, Bartels and Boomsma, have estimated that the heritability of SWB is approximately 30-50%. [3] In addition to having an association with genes, SWB has also been shown to be correlated to domains such as personality and psychiatric disorders. [9] The genetic correlates of these domains have been more intensely studied and present another avenue to further understand SWB at a cellular level. [10-12] The correlation of SWB to personality is particularly noteworthy as researchers Bouchard and Loehlin have suggested that genetic effects account for approximately 50% of the domains of the five-factor model domains of personality, meaning that SWB could potentially have a similar composition. [13] Additionally, current research suggests that the genetic influence on SWB may be more concrete than it appears. Through genetic studies, specific genes and gene markers that show significance in relation to SWB have been identified. However, truly understanding the genetic influence of SWB will require more comprehensive and higher-powered studies. Further investigation of this topic could grant insights into mechanisms concerning specific gene functions in the development of SWB. This could yield findings that support the usage, and possibly the creation, of interventional practices and potential therapies that

modulate well-being at an individual level. It could also be utilized to influence both public and health policy to create healthier communities and increase the levels of SWB of a population.

Objective

The objective of this review is to:

- Define the different aspects of SWB in more concrete terms and provide an overview of methods of assessment.
- Investigate the role of genetic makeup in determining SWB and its method of study by reviewing GWAS studies associated with measures of SWB.
- Present genes or gene markers that are potentially influential in the development of SWB.
- Postulate on future research of SWB including: the need for a more comprehensive and better utilized method of assessment, investigation into health policy and the possibility of SWB modulation at a population level, and the study of how genes and neural networks respond to positive SWB interventions at an individual level.

Part I: Measuring Subjective Well-Being

Well-being, as it is referred to in scientific literature does not have a singular definition. A variety of different concepts including negative and positive affect and short- and long-term evaluation all fit under its umbrella. This can lead to

some confusion, especially when colloquial terminology such as “happiness” is utilized. For example, depending on the context happiness can refer to your short term, hedonic experience of receiving one’s paycheck, or to one’s life satisfaction over a period of 50 years. As a result, two important elements of well-being need to be acknowledged when measuring it. The first element is that well-being exists on a continuum. This continuum, as the Panel on Measuring Subjective Well-Being in a Policy-Relevant Framework, et al. describes it, has “real-time assessments of experience, emotional state, or sensations at one end...and overall evaluations of life satisfaction, purpose, or suffering at the other end”. The second element is that well-being is a composite trait. In other words, the different points on this continuum, also known as domains, co-exist and collectively make up the trait of well-being. [2] In social science literature, well-being is stratified into separate dimensions based off these domains. Most notably, a distinction is drawn between eudaimonic and hedonistic well-being with perspectives evaluating hedonic well-being as subjective and eudaimonic well-being as psychological. [14] Eudaimonic well-being is characterized as one’s sense of meaning or purpose in life and is associated with a more evaluative sense of well-being. Hedonistic well-being is characterized as one’s interaction with emotional experiences that determine the pleasure they derive from their life and is associated with an experiential sense of well-being. The multifaceted nature of well-being results in a variety of methods and measures to study it and these measures can vary in focus. Specifically, categorizations of the study of well-being have been broken into eudaimonic, evaluative, and experienced

dimensions. [2] To conduct these measurements, the assessments make use of statements measuring happiness and satisfaction that participants respond to on a likert (rating) scale and evaluate quality of life using the cantril ladder of life scale. The cantril ladder measurement is conducted as follows:

> Please imagine a ladder with steps numbered from zero at the bottom to ten at the top. Suppose we say that the top of the ladder represents the best possible life for you and the bottom of the ladder represents the worst possible life for you. [15]

Some popular assessment models for SWB include: The Satisfaction with Life Scale, a 5-item scale that assess the aspect of life satisfaction in SWB; the Positive and Negative Affect Schedule (PANAS), a 10 item affect measurement scale; and the Experience Sampling Method (ESM) which is a self-reporting tool that respondents fill out throughout the day for a designated period of time. [16-18] While these methodologies are effective in assessing domains of well-being, they do not reflect the composite nature of well-being in subject matter nor assessment method. This has led to a lack of comprehensive data concerning some well-being datasets. One potential solution can be seen in assessments such as the Dutch Health and Behavior Questionnaire (DHBQ). This questionnaire combines four separate domain assessments of well-being, measuring perspective and attitude in the short and long term as well as assessing cognitive and affective well-being, to create a more holistic approach. [3] However, even with an improved assessment scale, well-being data remains limited by inaccuracies in self reporting and a lack of longitudinal data. [19]

In investigating the influence of genetics on well-being, correlative studies are excellent ways to overcome the limitations facing SWB data sets regarding comprehensiveness. Additionally, studies suggest that the domain distinctions created at the social science level are not reflected at the genetic level. [3,14,20,21] Furthermore, SWB (represented by life satisfaction (r=0.88) and positive affect (r=0.80)), depression (r=-0.91), and neuroticism (r=-0.93) have all been found to be significantly correlated and to make up a spectrum of well-being at the genetic level. [9] Thus, correlative methodologies of analysis have been able to discover associations between well-being and genetic structure as well as between the genome, the domains of well-being, and other aspects of psychological health. Given this overlap, study results may have connotations for multiple psychological traits, however, for the purpose of this review, findings will be interpreted in reference to well-being and SWB.

Part II: The Genetics of It All

The study of genetics involves the analysis of heritable traits or genes and understanding how these genes become expressed or silenced in a lifeform's phenotype. In order to assess SWB on a genetic level, SWB assessment scores must somehow be related to the genome. One of the most achievable ways to do this is through correlative studies. These studies, namely Twin Studies and Genome Wide Association Studies, allow us to quantify SWB measures, and thus provide a more concrete, objective way to utilize qualitative data. While these methods lend little, if any, information to developing theories of a causal

mechanism between genetic correlates and SWB, they are the crucial first steps to understanding the role of genetics in the development of an individual's sense of well-being. In a twin study, identical or fraternal twins are observed to research the effect of environmental factors and genetic factors in development. Cohorts of both monozygotic twins who are nearly genetically identical and dizygotic twins who share ~50% of their genetics (about the same as any pair of non-identical siblings) are utilized and analysis of variance in responses are then attributed to genetic or environmental influences. While such studies provide a strong method for genetic effect validation, their requirements also result in limited sample sizes that make it difficult for results to be generalized and the for the focus of data collection to be exclusive to well-being. [20] This is where Genome Wide Association Studies (GWAS) can be very helpful. In GWAS a metric such as satisfaction with life can be analyzed against the genetic make-up of the participants in the study, and correlations based on the population data are collected. Unlike traditional twin studies, it is not uncommon for GWAS studies to have significantly large sample sizes that can be analyzed due to their use of data sets such as the UK Biobank or Netherlands Twin Registry.[9,22] A GWAS study requires collecting DNA samples from participants and scanning markers to look for variations in genetic makeup. These markers are known as single nucleotide polymorphisms (SNP) and variations in them make up different haplotypes (combinations of alleles for different SNPs along the same chromosome). When haplotypes are more or less frequent than expected this indicates linkage disequilibrium. Analyzing linkage disequilibrium not only

highlights patterns of genetic inheritance, but also demonstrate the genetic forces acting on a population and can be utilized to identify a gene or genes of interest.[23] This method is helpful if the traits being analyzed are all assumed to be resulting from a collection of genes that are alike. For example, the analysis of data obtained from the DHBQ in the Bartels et al. study was able to utilize GWAS as they found that at the genetic level "all four measures [of well-being]...load on a similar set of genes". [3] However, in cases where data from multiple assessments is utilized or the gene sets cannot be assumed to be homogenous, possible adaptations to a GWAS study include performing a multivariate genome wide association study (multivariate GWAS), a multivariate genome-wide-association meta-analysis (GWAMA), a multivariate adaptive shrinkage analysis (MASH), or a multi-trait analysis of genome wide association analysis (GWAS MTAG). [12,22,24,25] Despite evidence presented previously concerning the overlap of well-being with other aspects of the psychological domains and with itself, studies show that well-being is a polygenic trait subject to environment and is not in a 1:1 ratio concerning genetic influence.[26] In this context, multivariate / multi-trait analyses can prove very useful in the analysis of SWB data. Nonetheless, these methods also have drawbacks that those who utilize them must be cognizant of. An analysis by Okbay et al. critiques that, "...mixing different measures may make any discovered associations more difficult to interpret" and "...doing so may reduce the heritability of the resulting phenotype if the measures are influenced by different genetic factors". Additionally, they highlight that while studies can discover associations between compiled SWB measures and genetic

factors, the accuracy of these associations are limited in their scope of application as they “are unlikely to attain enough predictive power to be clinically useful”. [11] Furthermore, in utilizing a polygenic approach, the chance of type I error occurring in regard to correlates obtained increases. Thus, false error correction as well as high powered GWAS data are essential to producing accurate analyses in this approach.[22,27,28]

Utilizing these methodologies, a variety of associations can be discovered between SWB and the genome. However, as there is no way to determine causality in these relationships it is important to bear in mind that such findings are only a starting point. Further investigation must occur to truly understand the genetic mechanisms of SWB, and well-being in general. One immediate pathway that presents for future research from GWAS or its multi-trait/ multi-variate adaptions is evaluating the methylation and function of genes at CpG sites through Epigenome Wide Association Studies (EWAS). [20] By better understanding the expression profiles of certain genes in relation to traits concerning SWB the mechanisms by which SWB is modulated by the genome could be better understood. Additionally, the findings of correlative studies present a battery of genes to investigate directly against well-being. These findings can inspire future investigations by directly comparing SWB and quality of life to the expression of specific genes. For example, gene expression modulation study designs such as the one conducted by Epel et al., where expression was monitored by biomarkers could be applied to other candidate genes identified through GWAS. [29] Additionally animal model studies utilizing

gene knockouts could be utilized to better understand gene function regarding well-being. For example, Kimura et. al, has demonstrated that the MAPT gene is necessary for the induction of long-term depression in mice models using such a study design.[30]

Part III: Genetic Findings of Interest

The research to date on the genetic influence on SWB has highlighted a variety of genetic associations responsible for creating both positive and negative effects in well-being. Additionally, SWB has been found to correlate to metabolic disorders and associate with a variety of other facets of the human emotional domain including depression, neuroticism, personality, and loneliness. [9,10,27,31,32] Thus, understanding SWB from a genetic perspective can have huge implications on the way society interacts with health at both a population and individual level. In this section, candidate genes and findings linking SWB to other aspects of the human emotional domain, and genetic responses will be discussed to better depict the current state of SWB genetic research. This information will be utilized to inform a discussion of avenues for future work in the next section.

The genes that have been found to be associated with SWB are numerous. Studies have shown that SWB is linked to genes responsible for brain morphology and development, neurotransmitter availability and transmission, nervous system function, sleep, iron utilization, telomere activity, hypertension and PTSD, immune response, stress response, susceptibility to loneliness and

psychiatric disorders, cell growth and function, neurodegenerative disease, and metabolic disorders. [11,12,25,27,31,33-41] While there certainly seems to be numerous possibilities for genetic influence, this number can be narrowed, and the roles of specific genes can be better defined through future studies designed to assess the effects of the expression or silencing of these genes.

The following tables highlight the specifics of pertinent genetic findings discovered through the literature review conducted for the construction of this paper. Table 1 presents genetic correlative findings discovered through GWAS, multivariate GWAS, and MASH. The findings of two studies utilizing GWAMA and MTAG were omitted as their power was such that that the number of associations and novel loci reported numbered into the hundreds. [22,24] While these findings are certainly relevant, the focus of this review is to present an outlook on how gene association study data can be utilized in future work. Thus, it was deemed appropriate to present data from potential study designs that could create such future work instead. In Tables 2 and 3 the findings of study designs that are more evaluative of the direct interaction of the genome with SWB are presented. Table 2 presents findings directly relating well-being interventions to gene expression. Table 3 presents epigenetic correlative findings from an EWAS. While the study in Table 3 presents data concerning association with well-being as opposed to SWB, the data is worth highlighting as the analysis of gene methylation through this type of study presents data, that while still correlative, suggests a potential mechanism of influence concerning the genes studied on SWB.

Table 1:

Genetic associations discovered through GWAS

Gene	SNP	Function	SWB Association
INTS8 [25]	rs10100651	Linked to human brain development and hypertension	-
TP53INP1 [25]	rs10100651	Releases antioxidant in response to hypertension and PTSD	-
STEAP3 [40]	rs6735649	Involved in iron availability for the brain	+
CLQL2 [40]	rs6735649	Involved in glutamatergic pathway which plays a role in CNS	+
GRIK3 [36]	rs490647	Involved in glutamatergic pathway; Strongest predictor of suicide and associated with neuroticism	-
KLHL2 [36]	rs62353264	Encodes actin-binding protein involved in ubiquitination and neurodegeneration	+
CRHR1 [36,42]	rs111433752	Encodes a corticotropin-releasing hormone receptor which is central to stress response	+
MAPT [30,36]	rs111433753	Encodes Tau protein, a protein associated with microtubules and present in neurons	+
CELF 4 [36]	rs1187264	Involved in regulation of excitatory neurotransmission	+
FTO [31,43]	rs1421085	Expression associated with fat mass and obesity	-
RAPGEF6 [11,44]	rs3756290	Guanine-nucleotide releasing factor	+
CSE1L [11,45]	rs2075677	Involved in protein transport to and from cell nucleus	+
NMUR2 [11,46]	rs4958581	Encodes a protein receptor involved in regulation of food intake and body weight	+
KSR2 [11,47]	rs7973260	Encodes kinase suppressor protein of Ras 2	-
DCC [11,48]	rs62100776	Involved in the development of the nervous system and implicated in tumor suppression	-
PER3 (VNTR polymorphism) [38]	rs57875989	Influences time preference for sleeping and waking. A longer allele is associated with better rest	+
CLDN23 [12]	rs2428; rs2921077*	Involved in maintaining cell polarity and signal transduction	-
MSRA [12]	rs2409691; rs9286062*	Candidate gene for SCZ	-

XKR6 [12]	rs4240673; rs2572433*	Risk site for lupus	-
BLK [12]	rs11250099; rs10108511*	Encodes non-receptor tyrosine kinase involved in cell proliferation/ differentiation and linked to autoimmunity	-
5-HTTLPR polymorphism [37,49]	rs25531; rs25532	Longer allele codes for more serotonin transporters	+
COMT [35,50]	rs737865; rs165599	Encodes enzyme involved in one of the major degradative pathways of the catecholamine transmitters.	+
COMT val 158met polymorphism [35,51]	rs4680	Associated with ~40% enzyme activity increase of COMT gene	-
MEIS1 [39]	rs113851554	Implicated in Restless Legs Syndrome (RLS)	-
DIO1 [26]	rs2294512; rs4926616	Encodes enzyme involved in thyroid hormone regulation	-

*Table 1 Genetic associations identified between the genome and SWB using GWAS, multivariate GWAS, and MASH studies are presented. A brief description of function as well as the directionality of association with SWB for each gene is presented. Where possible lead SNPs are indicated. *- multiple SNPs. CLDN23: rs4841042; MSRA: rs10096421; XKR6: rs11250099, rs4840542, rs6601569, rs2409691, rs2736313.*

Table 2:

Genetic expression measured through biomarker presence in blood

Gene	Function	SWB Association	Response to Physiological Changes
MME [29]	Linked to NFIL3 gene found in immune cells and stress response. It is downregulated with relaxation interventions.	-	Suppression observed in response to relaxation effect from meditation
FOXO3 [29]	Expression is part of behavioral stress response activated by psychological stress and glucocorticoid pathway	-	Suppression observed in response to relaxation effect from meditation
ODC1, OAZ1, OAZ2 [29]	Involved in polyamine synthesis pathway; suppression in response to relaxation interventions	-	Suppression observed in response to relaxation effect from meditation
NOP2, PPRC1 [29]	Involved with DKC1 gene and its role in ribosome biogenesis and TERC pathway (RNA component of telomerase)	+	Upregulation observed in response to relaxation effect from meditation
PSEN1 [29]	Familial AD gene expression	-	Suppression observed in response to relaxation effect from meditation

Table 2 The findings of a study measuring gene expression in response to meditation interventions are presented. A brief overview of the function, directionality of association with SWB, and the response of genes modulated by

this study are provided. Gene expression was analyzed using biomarker presence in blood samples collected at varying time points. [29]

Table 3:

Genetic associations discovered through methylation levels

Gene	CpG Site	Function	Well-being Association
NEURL1B [20]	cg10845147	Involved in cell survival and proliferation as well as mammary development	+
ALPPL2 [20]	cg01940273; cg03329539	Encodes alkaline phosphatase; Involved in the metabolism of protein and associated w/ cancers and premature birth	-
CG018 [20,52]	cg09716613	Unknown function associated with Inflammatory Leiomyosarcoma	-
ZFPM1 [53]	cg04387347	Transcription regulator involved in cell differentiation and associated with anemia	-
ZNF687 [20,54]	cg02290168	Encodes protein involved in bone differentiation and development	+

Table 3 The findings of an EWAS between genetics and well-being are presented. [20] *A brief overview of the methylation site (CpG), gene function, and the directionality of association with well-being is provided.*

The tables above demonstrate not only that current correlative research suggests that SWB is subject to polygenic influence, but also that this influence can be further studied to present a better picture of the mechanism by which the genome and SWB interact. Further investigation of this topic could help improve understanding not only of mental health but also that of physiological health. As cane be seen, research in this field has the potential to revolutionize society's interaction with both individual and community health through greater emphasis on the mind-body connection. [55] However, in order to achieve this SWB research methods need to be expanded and improved.

Part IV: Future Work and Potential Implications

As demonstrated above, current research has been successful in providing evidence of the association of the genome with SWB. However, the potential for this work's current application in our conception of health is limited as there is a need for future work to improve data sets and investigate causal effects. Thus, in this section arguments will be constructed concerning how to improve current SWB methods of assessment and data collection and will postulate on the prospective downstream effects that achieving this goal could have on health decisions at a population level and individual level.

As mentioned at the beginning of this paper, two key aspects of understanding well-being are recognizing that it exists on a temporal continuum and that it is a composite trait with multiple domains. [2] Assessing well-being in its entirety would be beneficial in differentiating it and its potential genetic correlates from other aspects of the psychological domain. To do so will require creating more holistic and longitudinal study designs. One way to do this is to fund higher powered studies that measure the experienced, evaluative, and eudaimonic well-being of their respondents and collect genetic samples over a period of time. A potential model for this more universal well-being assessment method lies in the DHBQ which not only takes a holistic approach but also benefits from being able to gather cross-cultural data and assess cross-cultural variation as a result of the fact that the cantril ladder scale is considered a "culture free" metric. [3] Thus, an assessment such as the DHBQ could be easily applied to diverse populations and demographics and produce greater sample sizes without needing to create specialized cultural assessment scales. Additionally, applying a more

comprehensive assessment model longitudinally to SWB assessment could benefit studies greatly by providing the opportunity to evaluate gene association longitudinally. For example, in the two gene expression studies of the e4 allele of apolipoprotein E (APOE)'s looked at in this review, both were found to be limited by their small sample sizes and lack of longitudinal data. [56] A more comprehensive data set would have benefitted the authors in being able to better understand the allele's impact on quality of life as well as its onset. Beyond the impact that improved study designs could have on research findings, they could also help inform policy and legislative changes concerning SWB.

In evaluating the need for better well-being data sets for genetic studies, it also becomes apparent that such data could also be particularly useful for governments seeking to improve the lives of their citizens. In fact, there is a potential symbiotic benefit in improving the quality and scope of well-being studies both for the scientific community and governing purposes. As Fox highlights, methods of measuring national success such as Gross Domestic Product (GDP) or Gross National Product (GNP) are criticized for being uncomprehensive and somewhat arbitrary. [5] Measuring the well-being of a population, while more qualitative in approach than these metrics, could provide a more comprehensive picture of a population by not being solely limited to evaluating its economic aspects. [1] Furthermore, by emphasizing the idea of well-being as a performance metric representative of national success in countries such as the United States, the data collected could be utilized to evaluate the relationship of issues such as mental health, obesity, and poverty with

physiological health and epigenetic effects in the genome. [3,57,58] More importantly, such information could inform and galvanize policy makers and legislators to address these issues more comprehensively at an institutional or national level because their long-term impact would be more apparent. [59] The development of evaluative models concerned with more of the social and qualitative aspects of life can already be seen in examples such as the Measuring National Well-being program in the United Kingdom and the World Happiness Report. [60] By building off such examples, the potential exists to develop a better understanding of well-being at a global level This would in turn also benefit SWB research as greater insights would be available in assessing the influence of external influences such as environmental effects on SWB as well as genetic effects. Another way that SWB data sets could be improved is by modernizing collection techniques at the individual level.

As previously discussed, the measurement of well-being is limited in that it often does not provide longitudinal data, and it is crucial for assessments to acknowledge that its domains exist on a continuum and should be evaluated regularly. In the case of SWB, its experiential nature means that it can change over short time scales of weeks, days, or even hours. [2] While ESM questions attempt to collect data at this scale, the current widespread utilization of wearable biotechnology and mobile devices offers a more comprehensive method of achieving this. As evidenced by Berkel et al., real time data collection concerning ESM through the use of vital monitoring and the administration of assessments via mobile devices are a viable design study in this day and age. [61] This potential

study design presents a way to better understand both how SWB fluctuates on a daily basis as well as any physiological responses that may be associated with this change. Through such a methodology, the amount and quality of data collected from SWB studies could be dramatically improved. Concerning mental health interventions and the treatment plans for mental health patients, this type of assessment could even become part of the standard of care. The efficacy of a therapeutic in an individual patient could potentially be monitored with real-time vital and evaluative data as opposed to only qualitative reports. Additionally, therapy practices, such as those concerning stress management, could be bolstered by the integration of mind-body therapies that are validated by both subjective and objective measures. [55] Furthermore, such methodology could also provide more quantitative evidence of the neural modulation effects of mindfulness techniques such as meditation, journaling, and breathing exercises. In instituting such a practice, health care professionals could have improved means to evaluate the mental health of their patients. In a similar vein, utilizing such methodology could be applied to better understanding the relationship of SWB with brain morphology and neurological correlates as well. [33]

Conclusion

While there is room for improvement in the assessment methods utilized in studying well-being, the study of well-being is an exciting and worthy effort. As evidenced by current literature, the correlation of well-being to the genome, specifically in regard to SWB, indicates a relationship between our mental and physical health that impacts a variety of domains of our health. These

associations, as evidenced in Table 1, range from stress response and psychiatric disorders to metabolic disease and telomerase activity. Through the application of GWAS and muti-trait / multi-variate association studies, the relationship of well-being to the genome can be further delineated through gene expression studies and EWAS such as those evidenced in Table 2 and Table 3. Improving the data sets utilized for such studies could occur by developing the infrastructure necessary to study well-being as a metric indicative of national success such as GDP/GNP and utilizing biotechnology and mobile devices to create real time well-being evaluations. Doing so could result in new avenues by which to influence health policy and legislation to improve population health and better and more comprehensive individual health intervention and treatment plans. In conclusion, SWB research has the potential to revolutionize not only our understanding of health, but also how we live our lives, but in order to do so future work must endeavor to improve and expand both its scope and influence.

References

1. Diener E. Subjective well-being. the science of happiness and a proposal for a national index. *Am Psychol*. 2000;55(1):34-43. doi: 10.1037//0003-066X.55.1.34.

2. Panel on Measuring Subjective Well-Being in a Policy-Relevant Framework, Committee on National Statistics. *Subjective well-being : Measuring happiness, suffering, and other dimensions of experience.* Washington, District of Columbia : The National Academies Press; 2013.

3. Bartels M, Boomsma DI. Born to be happy? the etiology of subjective well-being. . 2009;39(6). https://doi.org/10.1007/s10519-009-9294-8.

4. Krueger A, National Bureau of Economic Research. Measuring the subjective well-being of nations : National accounts of time use and well-being. *University of Chicago Press.* 2009.

5. Fox J. The economics of well-being. *Harvard Business Review*. 2012. https://hbr.org/2012/01/the-economics-of-well-being. Accessed Dec 17, 2020.

6. Moukheiber Z. Mental health awareness is on the rise, but access to professionals remains dismal. *Forbes.* , May 22 2019. Available from: https://www.forbes.com/sites/zinamoukheiber/2019/05/22/mental-health-awareness-is-on-the-rise-but-access-to-professionals-remains-dismal/?sh=458c16e37ba5.

7. McCarthy C. Anxiety in teens is rising: What's going on? *HealthyChildren.org*. , September 20 2019. Available from: https://www.healthychildren.org/English/health-issues/conditions/emotional-problems/Pages/Anxiety-Disorders.aspx.

8. Cassada Lohmann R. What's driving the rise in teen depression? . *U.S. News & World Report.* 2019.

9. Baselmans BML, van de Weijer, M. P., Abdellaoui A, et al. A genetic investigation of the well-being spectrum. *Behav Genet*. 2019;49(3):286-297. doi: 10.1007/s10519-019-09951-0 [doi].

10. Weiss A, Bates TC, Luciano M. Happiness is a personal(ity) thing: The genetics of personality and well-being in a representative sample. *Psychol Sci*. 2008;19(3):205-210. https://doi.org/10.1111/j.1467-9280.2008.02068.x. doi: 10.1111/j.1467-9280.2008.02068.x.

11. Okbay A, Baselmans BML, De Neve J, et al. Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. . 2016;48(6):633. https://doi.org/10.1038/ng.3552.

12. Chu X, Liu L, Wen Y, et al. A genome-wide multiphenotypic association analysis identified common candidate genes for subjective well-being, depressive symptoms and neuroticism. *J Psychiatr Res*. 2020;124:22-28. doi: S0022-3956(19)31392-5 [pii].

13. Bouchard Jr T,J., Loehlin JC. Genes, evolution, and personality. *Behav Genet*. 2001;31(3):243-273. doi: 10.1023/A:1012294324713.

14. Baselmans BML, Bartels M. A genetic perspective on the relationship between eudaimonic –and hedonic well-being. *Scientific reports*. 2018;8(1):1-10. doi: 10.1038/s41598-018-32638-1.

15. Organisation for Economic Co-operation and Development, (OECD). ANNEX A, illustrative examples of subjective well-being measures. In: *OECD guidelines on measuring subjective well-being.* Paris: OECD Publishing; 2013. https://www.ncbi.nlm.nih.gov/books/NBK189562/?report=classic.

16. Pavot W, Diener E. The satisfaction with life scale and the emerging construct of life satisfaction. *The journal of positive psychology*. 2008;3(2):137-152. doi: 10.1080/17439760701756946.

17. Thompson ER. Development and validation of an internationally reliable short-form of the positive and negative affect schedule (PANAS). *Journal of cross-cultural psychology*. 2016;38(2):227-242. doi: 10.1177/0022022106297301.

18. Kubey R, Larson R, Csikszentmihalyi M. Experience sampling method applications to communication research questions. *J Commun*. 1996;46(2):99-120. doi: 10.1111/j.1460-2466.1996.tb01476.x.

19. Schwarz N, Strack F. Evaluating one's life: A judgment model of subjective well-being. In: Elmsford, NY, US: Pergamon Press; 1991:27-47.

20. Baselmans BM, van Dongen J, Nivard MG, et al. Epigenome-wide association study of wellbeing. *Twin Res Hum Genet*. 2015;18(6):710-719. doi: 10.1017/thg.2015.85 [doi].

21. Brown NJ, MacDonald DA, Samanta MP, Friedman HL, Coyne JC. A critical reanalysis of the relationship between genomics and well-being. *Proc Natl Acad Sci U S A*. 2014;111(35):12705-12709. doi: 10.1073/pnas.1407057111 [doi].

22. Turley P, Walters RK, Maghzian O, et al. Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nat Genet*. 2018;50(2):229-237. doi: 10.1038/s41588-017-0009-4 [doi].

23. Genome-wide association studies fact sheet. https://www.genome.gov/about-genomics/fact-sheets/Genome-Wide-Association-Studies-Fact-Sheet. Updated 2017.

24. Baselmans BML, Jansen R, Ip HF, et al. Multivariate genome-wide analyses of the well-being spectrum. *Nat Genet*. 2019;51(3):445-451. doi: 10.1038/s41588-018-0320-8 [doi].

25. Schijven D, Geuze E, Vinkers CH, et al. Multivariate genome-wide analysis of stress-related quantitative phenotypes. *Eur Neuropsychopharmacol*. 2019;29(12):1354-1364. doi: S0924-977X(19)30886-7 [pii].

26. Young Cho Y, Jeong Kim H, Won Jang H, et al. The relationship of 19 functional polymorphisms in iodothyronine deiodinase and psychological well-being in hypothyroid patients. *Endocrine*. 2017;57(1):115-124. doi: 10.1007/s12020-017-1307-4 [doi].

27. Abdellaoui A, Nivard MG, Hottenga JJ, et al. Predicting loneliness with polygenic scores of social, psychological and psychiatric traits. *Genes Brain Behav*. 2018;17(6):e12472. doi: 10.1111/gbb.12472 [doi].

28. Yang J, Weedon MN, Purcell S, et al. Genomic inflation factors under polygenic inheritance. . 2011;19(7):812. https://doi.org/10.1038/ejhg.2011.39.

29. Epel ES, Puterman E, Lin J, et al. Meditation and vacation effects have an impact on disease-associated molecular phenotypes. *Translational psychiatry*. 2016;6(8):e880. doi: 10.1038/tp.2016.164.

30. Kimura T, Whitcomb DJ, Jo J, et al. Microtubule-associated protein tau is essential for long-term depression in the hippocampus. *Philosophical transactions of the Royal Society of London.Series B, Biological sciences*. 2013;369(1633):20130144. https://pubmed.ncbi.nlm.nih.gov/24298146 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3843876/. doi: 10.1098/rstb.2013.0144.

31. Wootton RE, Lawn RB, Millard LAC, et al. Evaluation of the causal effects between subjective wellbeing and cardiometabolic health: Mendelian randomisation study. *BMJ*. 2018;362:k3788. doi: 10.1136/bmj.k3788 [doi].

32. van den Broek N, Treur JL, Larsen JK, Verhagen M, Verweij KJH, Vink JM. Causal associations between body mass index and mental health: A mendelian randomisation study. *J Epidemiol Community Health*. 2018;72(8):708-710. doi: 10.1136/jech-2017-210000 [doi].

33. Van 't Ent D, den Braber A, Baselmans BML, et al. Associations between subjective well-being and subcortical brain volumes. *Sci Rep*. 2017;7(1):6957-z. doi: 10.1038/s41598-017-07120-z [doi].

34. Song L, Meng J, Liu Q, et al. Polygenic score of subjective well-being is associated with the brain morphology in superior temporal gyrus and insula. *Neuroscience*. 2019;414:210-218. doi: S0306-4522(19)30386-0 [pii].

35. Liu J, Gong P, Gao X, Zhou X. The association between well-being and the COMT gene: Dispositional gratitude and forgiveness as mediators. *J Affect Disord*. 2017;214:115-121. doi: S0165-0327(16)31632-9 [pii].

36. Smith DJ, Escott-Price V, Davies G, et al. Genome-wide analysis of over 106 000 individuals identifies 9 neuroticism-associated loci. *Mol Psychiatry*. 2016;21(6):749-757. doi: 10.1038/mp.2016.49 [doi].

37. De Neve JE. Functional polymorphism (5-HTTLPR) in the serotonin transporter gene is associated with subjective well-being: Evidence from a US nationally representative sample. *J Hum Genet*. 2011;56(6):456-459. doi: 10.1038/jhg.2011.39 [doi].

38. Lázár AS, Slak A, Lo JC, et al. Sleep, diurnal preference, health, and psychological well-being: A prospective single-allelic-variation study. *Chronobiol Int*. 2012;29(2):131-146. doi: 10.3109/07420528.2011.641193 [doi].

39. Hammerschlag AR, Stringer S, de Leeuw CA, et al. Genome-wide association analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric and metabolic traits. *Nat Genet*. 2017;49(11):1584-1592. doi: 10.1038/ng.3888 [doi].

40. Kim S, Jang H, Myung W, et al. Heritability estimates of individual psychological distress symptoms from genetic variation. *J Affect Disord*. 2019;252:413-420. doi: 10.1016/j.jad.2019.04.011.

41. Troadec MB, Loréal O, Brissot P. The interaction of iron and the genome: For better and for worse. *Mutat Res*. 2017;774:25-32. doi: S1383-5742(17)30009-1 [pii].

42. Tseng LA, Bixby JL. Interaction of an intracellular pentraxin with a BTB-kelch protein is associated with ubiquitylation, aggregation and neuronal apoptosis. *Mol Cell Neurosci*. 2011;47(4):254-264. Accessed Dec 17, 2020. doi: 10.1016/j.mcn.2011.04.005.

43. Fawcett KA, Barroso I. The genetics of obesity: FTO leads the way. *Trends Genet*. 2010;26(6):266-274. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2906751/. Accessed Dec 17, 2020. doi: 10.1016/j.tig.2010.02.006.

44. X G, T S, Y L, et al. Identification and characterization of RA-GEF-2, a rap guanine nucleotide exchange factor that serves as a downstream target of M-ras. *J Biol Chem*. 2001;276(45):42219-42225. https://europepmc.org/article/MED/11524421. Accessed Dec 17, 2020. doi: 10.1074/jbc.m105760200.

45. Gaudet P, Livstone MS, Lewis SE, Thomas PD. Phylogenetic-based propagation of functional annotations within the gene ontology consortium. *Brief Bioinform*. 2011;12(5):449-462. https://doi.org/10.1093/bib/bbr042. Accessed 12/18/2020. doi: 10.1093/bib/bbr042.

46. Howard AD, Wang R, Pong SS, et al. Identification of receptors for neuromedin U and its role in feeding. *Nature*. 2000;406(6791):70-74. Accessed Dec 17, 2020. doi: 10.1038/35017610.

47. Dhawan NS, Scopton AP, Dar AC. Small molecule stabilization of the KSR inactive state antagonizes oncogenic ras signalling. *Nature*. 2016;537(7618):112-116. Accessed Dec 17, 2020. doi: 10.1038/nature19327.

48. Haddick PCG, Tom I, Luis E, et al. Defining the ligand specificity of the deleted in colorectal cancer (DCC) receptor. *PLoS One*. 2014;9(1):e84823. Accessed Dec 17, 2020. doi: 10.1371/journal.pone.0084823.

49. Nuñez-Rios DL, Chaskel R, Lopez A, Galeano L, Lattig MC. The role of 5-HTTLPR in autism spectrum disorder: New evidence and a meta-analysis of this polymorphism in latin american population with psychiatric disorders. *PLoS One*.

2020;15(7):e0235512. Accessed Dec 17, 2020. doi: 10.1371/journal.pone.0235512.

50. Grossman MH, Emanuel BS, Budarf ML. Chromosomal mapping of the human catechol-O-methyltransferase gene to 22q11.1----q11.2. *Genomics*. 1992;12(4):822-825. Accessed Dec 17, 2020. doi: 10.1016/0888-7543(92)90316-k.

51. Stein MB, Fallin MD, Schork NJ, Gelernter J. COMT polymorphisms and anxiety-related personality traits. *Neuropsychopharmacology (New York, N.Y.)*. 2005;30(11):2092-2102. https://www.ncbi.nlm.nih.gov/pubmed/15956988. doi: 10.1038/sj.npp.1300787.

52. Couch FJ, Rommens JM, Neuhausen SL, et al. Generation of an integrated transcription map of the BRCA2 region on chromosome 13q12-q13. *Genomics*. 1996;36(1):86-99. Accessed Dec 17, 2020. doi: 10.1006/geno.1996.0428.

53. Dyserythropoietic anemia and thrombocytopenia: MedlinePlus genetics. https://medlineplus.gov/genetics/condition/dyserythropoietic-anemia-and-thrombocytopenia/. Accessed Dec 17, 2020.

54. Nagase T, Kikuno R, Ishikawa KI, Hirosawa M, Ohara O. Prediction of the coding sequences of unidentified human genes. XVI. the complete sequences of 150 new cDNA clones from brain which code for large proteins in vitro. *DNA Res*. 2000;7(1):65-73. Accessed Dec 17, 2020. doi: 10.1093/dnares/7.1.65.

55. Muehsam D, Lutgendorf S, Mills PJ, et al. The embodied mind: A review on functional genomic and neurological correlates of mind-body therapies. *Neurosci Biobehav Rev*. 2017;73:165-181. doi: S0149-7634(16)30325-6 [pii].

56. Martin P, Jazwinski SM, Davey A, et al. APOE ϵ4, rated life experiences, and affect among centenarians. *Aging Ment Health*. 2014;18(2):240-247. doi: 10.1080/13607863.2013.827624 [doi].

57. Miller GE, Chen E, Fok AK, et al. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. *Proc Natl Acad Sci U S A*. 2009;106(34):14716-14721. doi: 10.1073/pnas.0902971106 [doi].

58. Vickers MH. Early life nutrition, epigenetics and programming of later life disease. *Nutrients*. 2014;6(6):2165-2178. doi: 10.3390/nu6062165 [doi].

59. Meyer C, Kirby J. Runaway capitalism. *Harvard Business Review*. 2012. https://hbr.org/2012/01/runaway-capitalism. Accessed Dec 17, 2020.

60. Helliwell JF, Layard R, Sachs J, De Neve J. World happiness report 2020. . 2020. http://worldhappiness.report/. Accessed Dec 17, 2020.

61. van Berkel N, Ferreira D, Kostakos V. The experience sampling method on mobile devices. *ACM computing surveys*. 2018;50(6):1-40. doi: 10.1145/3123988.