aps ASSOCIATION FOR PSYCHOLOGICAL SCIENCE

The Genetics of Loneliness: Linking Evolutionary Theory to Genome-Wide Genetics, Epigenetics, and Social Science

Perspectives on Psychological Science
2015, Vol. 10(2) 213–226

DOI: 10.1177/1745691614564878
pps.sagepub.com
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Abstract

As a complex trait, loneliness is likely to be influenced by the interplay of numerous genetic and environmental factors. Studies in behavioral genetics indicate that loneliness has a sizable degree of heritability. Candidate-gene and gene-expression studies have pointed to several genes related to neurotransmitters and the immune system. The notion that these genes are related to loneliness is compatible with the basic tenets of the evolutionary theory of loneliness. Research on gene-environment interactions indicates that social-environmental factors (e.g., low social support) may have a more pronounced effect and lead to higher levels of loneliness if individuals carry the sensitive variant of these candidate genes. Currently, there is no extant research on loneliness based on genome-wide association studies, gene-environment-interaction studies, or studies in epigenetics. Such studies would allow researchers to identify networks of genes that contribute to loneliness. The contribution of genetics to loneliness research will become stronger when genome-wide genetics and epigenetics are integrated and used along with well-established methods in psychology to analyze the complex process of gene-environment interplay.

Keywords

behavioral genetics, evolutionary psychology, environment

Loneliness is defined as the negative feelings that arise when a person's social network is found to be deficient in perceived quality or quantity (Perlman & Peplau, 1981). Numerous studies have shown that lonely people experience negative affect more frequently than do non-lonely people (J. T. Cacioppo et al., 2006); are at increased risk for psychiatric syndromes such as clinical depression (Heinrich & Gullone, 2006); show a greater incidence of medical conditions such as cardiovascular incidents (Hawkley & Cacioppo, 2010); and, more generally, become ill more quickly and pass away at an earlier age (Holt-Lunstad & Smith, 2015, this issue). Thus, loneliness should catch the attention of psychologists, psychiatrists, and medical doctors.

Lonely people show these negative outcomes to varying degrees, and this variation may be influenced by biological aspects and genetic makeup. At the same time, loneliness is associated with environmental exposures, such as less frequent contact with family and friends and lower social support (J. T. Cacioppo & Hawkley, 2009a). Intuitively, biology, genes, and environment, including the social environment, are important influences on

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Table 1. Four Topics Addressed in Four Branches of Genetics and Associated General Expectations

Topic	Branch of genetics	General expectation
Degree of heritability	Behavioral genetics	Loneliness shows a sizable degree of heritability
Main effects of candidate genes	Molecular genetics	Variants in candidate genes are associated with loneliness
Conditional effects of candidate genes	Gene-environment interplay	The effects of environmental exposures on loneliness may depend on variants of candidate genes, or the effects of the variants of candidate genes are more or less pronounced depending on the environment
Transcribability of the genetic code	Functional genomics	The degree to which the genetic code, as laid down in the DNA, is expressed may be different in lonely compared to nonlonely individuals

loneliness and might be interconnected in complex ways. Current research, therefore, is increasingly trying to unravel how genetic and environmental factors work together to affect loneliness. The present article discusses empirical work on the genetics of loneliness and the effects of some environmental exposures and social factors. The evolutionary theory of loneliness (J. T. Cacioppo et al., 2006) is used as a general theoretical framework.

Loneliness: An Evolutionary Approach

The evolutionary approach to loneliness (J. T. Cacioppo, Cacioppo, Cole, et al., 2015, this issue; J. T. Cacioppo et al., 2006) calls into question the dominant conceptualization of loneliness as an aversive condition without redeeming features. Instead, loneliness is viewed as an aversive signal that indicates that important social connections are at risk or absent and acts as a motivating force to reconnect with others. As such, loneliness has played an important role in the evolution of the human species, given that reconnecting with others increases one's chances of survival and opportunities to pass on one's genes to the next generation.

The negative sequelae of loneliness that are well-established in the scientific literature emerge when loneliness is sustained over time. Lonely people exhibit specific features, such as hypervigilance to social threat and subdued reactions to positive social situations (J. T. Cacioppo & Hawkley, 2009b), that cause them to be perceived by others as less interesting interaction partners. As these reactions reinforce lonely people's suspicion, they get caught in a vicious circle (Hawkley & Cacioppo, 2010). Initially adaptive bodily changes that prepare lonely people for the optimal response to an unsafe environment lead to long-term changes that help explain why lonely people become ill more easily and tend to pass away at an earlier age. One of these changes is continuous overactivation of the human stress system. The entire set of bodily changes may share important features with the neurobiological reactions to social isolation in other primate species (J. T. Cacioppo, Cacioppo, Cole, et al., 2015) and may well be a target for neuropharmacological treatments of loneliness (S. Cacioppo, Grippo, London, Goossens, & Cacioppo, 2015, this issue). Within the evolutionary theory, loneliness can be viewed as both an outcome and an important predictor of other health-related outcomes. In many cases, loneliness has indirect effects on health. Loneliness may lead to sleep problems, for instance, which, in turn, may lead to increases in blood pressure.

Connecting the Evolutionary Theory of Loneliness to Different Branches of Genetics

The evolutionary approach can be linked to four topics of inquiry that are each addressed in a different branch of genetics. The general expectation regarding each of these topics can be tested in empirical research. Table 1 presents an overview of the four topics, their associated branches of genetics, and the general expectation for each topic. The topics are presented in roughly historical order (i.e., the first topic listed was the first to capture researchers' interest, followed by the second topic, etc.).

Degree of heritability

The general expectation here is that loneliness might exhibit a substantial degree of heritability, given that it is not evolutionarily neutral but served to increase our survival as a species (J. T. Cacioppo, Cacioppo, & Boomsma, 2014). The degree of heritability for loneliness, pitting the genome as a whole against the environment as a whole, can be estimated empirically—for instance, through twin and family studies—in a branch of genetics labeled *behavioral genetics*. In this type of research, no DNA has to be collected or analyzed because the aggregate effects of genes are inferred from a comparison of groups with

varying degrees of biological relatedness (e.g., monozygotic and dizygotic twins).

Main effects of candidate genes

Candidate genes are genes whose function is hypothesized to be related to loneliness in some way. These genes could be linked to the behavioral characteristics of lonely people (e.g., hypervigilance to social threat) or the presumed bodily changes associated with loneliness (e.g., overactivation of the stress system) described in the evolutionary theory of loneliness. The general expectation here is that variants in candidate genes can be expected to have a small association with loneliness. This modest expectation is based on the notion that loneliness is a complex trait that is affected by numerous forms of genetic and environmental influence.

The larger part of the genetic code contained in DNA is identical in all humans, as DNA carries all the instructions for proper bodily functioning. However, there are also many places of known variability in the genetic code. People with one type of variant in a specific place or places may be more lonely, given the same circumstances, than those who have another type of variant at these same locations. Alternatively, people with a specific genetic variant may act in ways to create circumstances that make them more lonely. Statistical links between variants in candidate genes and loneliness are examined in *molecular genetics*. Techniques from molecular biology are used in this branch of genetics to identify the variants of specific genes or specific stretches of the genome. The term *genomics* is increasingly used to refer to research that targets the entire genome rather than candidate genes (Psychiatric GWAS Consortium Coordinating Committee et al., 2009). In this type of research, access to DNA, typically obtained through a saliva sample, is crucial.

Conditional effects of candidate genes

The general expectation here is that the effects of environmental exposures on loneliness may depend on genetic variants. Variants in candidate genes that are related to the behavior and neurobiology of lonely people may act in concert with environmental risk factors or broader social environments. Low social support, compared to high social support, may have limited impact on loneliness in people with one type of variant but a particularly strong effect on carriers of another variant. Conversely, the effect of the genotype (i.e., the variants in a specific candidate gene) on loneliness can be more pronounced depending on the environment (e.g., the degree of social support experienced).

Such effects of the environment that are conditional on genes and effects of genes that are conditional on the environment are examined in studies of *gene-environment interactions*. Of potentially equal interest and importance are the effects of the nonrandom distribution of genotypes over environments, referred to as *gene-environment correlation* or *covariance*. Both gene-environment interactions and gene-environment correlations are examined in a branch of genetics that is referred to here as *gene-environment interplay* (Rutter & Silberg, 2002). In this type of research, researchers need to have DNA to identify the variants in specific locations in the genome and reliable and valid measures of the quality of the social environment (e.g., the degree of social support).

Transcribability of the genetic code

The genetic code, as laid down in the DNA, has to be "read" or "transcribed" by the body. This process is known as *gene expression*. The general expectation here is that the degree to which the genetic code is expressed may be different in lonely versus nonlonely individuals. The evolutionary theory again provides clues to the genes for which the DNA code may be variably expressed. These genes could be related to the way in which lonely people behave in their environment, to how their stress system operates, or to which environments they self-select into.

Genes exert their effects because DNA molecules serve as templates to construct RNA copies, a process that is known as *transcription*. RNA, in turn, codes for a sequence of amino acids that together form the proteins (e.g., hormones and neurotransmitters) that regulate all important bodily processes. The degree to which the body manages to regulate the transcription process, which is referred to as *gene expression*, depends in part on transcription factors (i.e., proteins that bind to DNA; Cole, 2009). Researchers, therefore, may concentrate on the entire set of proteins, called the *proteome*, in a science referred to as *proteomics*, or the entire set of RNA molecules involved in transcription, called the *transcriptome*, in a science referred to as *transcriptomics*.

Another phenomenon of interest are modifications that alter gene activity without changing the genetic code of the DNA (Roth & Sweatt, 2011). As these changes exert their effects on top of the genetic code, so to speak, they are referred to as *epigenetic effects*, using the Greek preposition *epi*, which means "above" (Sweatt, Meaney, Nestler, & Akbarian, 2013). When epigenetic effects are studied across the genome, the term *epigenomics* may be used.

In the present review, gene expression and epigenetic processes are subsumed under the heading *functional genomics*. In this branch of genetics, the emphasis is not on genetic structure (or the genetic code), as is the case

Table 2. Heritability Estimates of Self-Reported Loneliness

Study	Design	*N*	Age (years)	Country	Heritability (h^2)
Boomsma, Cacioppo, Slagboom, and Posthuma (2006)	Twins study (twins and non-twin siblings)	8,387 twins; 2,295 siblings	Range = 18–30	The Netherlands	40%
Boomsma, Willemsen, Dolan, Hawkley, and Cacioppo (2005)	Twin study	3,869 MZ; 4,518 DZ	Range = 18–30	The Netherlands	48%
Distel et al. (2010)	Extended twin study (twins, siblings, partners, and parents)	4,818 twins (half MZ, half DZ); 815 siblings; 3,048 parents; 917 partners	*M* = 34	The Netherlands and Belgium	37%
McGuire and Clifford (2000)					
Colorado study	Adoption study	69 full-sibling pairs; 64 unrelated sibling pairs	Range = 9–12	United States	48%
California study	Twin study (twins and non-twin siblings)	22 MZ pairs; 40 DZ pairs; 80 sibling pairs	Range = 8–14	United States	55%
Waaktaar and Torgersen (2012)	Twin study	536 MZ pairs; 903 DZ pairs	Range = 12–18	Norway	44%

Note: MZ = monozygotic twins; DZ = dizygotic twins.

in molecular genetics and its extension into gene-environment interplay, but on gene functioning. When doing this type of research, researchers need to have access to RNA, extracted from blood, to study gene expression or to DNA to study epigenetic effects.

In the next sections, we present an overview of the research on loneliness conducted in the four branches of genetics. For each branch, we examine whether the findings support the general expectation regarding the selected topic. In addition, we describe new techniques in different branches of genetics that still have to be applied in research on loneliness. The review covers childhood to old age, as loneliness is a problem that affects people of all ages. (See Qualter et al., 2015, this issue, for a review of loneliness across the life span).

Behavioral Genetics

The degree of heritability of a trait such as loneliness can be inferred by comparing the average correlations between pairs of individuals with different degrees of biological or environmental relatedness. Twin studies compare the correlations between monozygotic twins (who share nearly 100% of their genetic material) and dizygotic twins (who share 50% of their segregating genes). Adoption studies concentrate on pairs of relatives in families with, for instance, adopted and biological children. They compare the correlations between full-sibling pairs (who, like dizygotic twins, share 50% of their segregating genes) and pairs of adopted children (who are biologically unrelated and do not share any genetic material). Based on patterns of correlations, a univariate biometric model is tested, using structural equation modeling, in which the total variance of a single trait, that is, loneliness, is decomposed into multiple components, usually additive and nonadditive genetic factors, and shared and nonshared environmental factors. The heritability estimate (Boomsma, 2013) represents the ratio of additive genetic variance over the total variance (narrow-sense heritability) or the total genetic variance over the total trait variance (broad-sense heritability).

An overview of heritability estimates from studies using self-reports of loneliness may be found in Table 2. Just a single study used an adoption design (McGuire & Clifford, 2000); some studies used the classical twin design that compares monozygotic and dizygotic twins (Boomsma, Willemsen, Dolan, Hawkley, & Cacioppo, 2005; Waaktaar & Torgersen, 2012); and other studies also included the siblings of twins, which allows for more precise estimates of the components in the statistical model (e.g., Boomsma, Cacioppo, Slagboom, & Posthuma, 2006). Finally, one study (Distel et al., 2010) used the extended twin design, which also includes the partners and parents of twins and allows for additional controls (i.e., controls for the fact that lonely people tend to marry lonely partners and for transmission from one generation to the next through nongenetic means).

The heritability estimates obtained are remarkably similar and are just below 50%. In two of the larger

studies (Boomsma et al., 2006; Boomsma et al., 2005), the researchers tested whether these estimates were significantly different from zero and found that that was the case. The heritability of loneliness, therefore, is substantial. So, research in behavioral genetics has confirmed the general expectation regarding the first topic in the genetics of loneliness, that is, the degree to which loneliness is a heritable trait. Future developments in this field can make use of methods for estimating heritability based on "genetic relatedness" in unrelated individuals (e.g., see Lubke et al., 2012, for an application to depression).

Future research should try to determine if specific components of loneliness (e.g., hypervigilance to social threat or subdued reactions to positive social situations) are driving this heritability effect. Additional efforts should move beyond the mere partitioning of the variance in heritable and nonheritable parts and engage in quasicausal modeling that links loneliness to health outcomes (Turkheimer & Harden, 2014). Research on pairs of monozygotic twins who are discordant for loneliness, for instance, may allow a better understanding of environmental exposures and their effects on health, given that genetic factors and shared nongenetic factors are controlled for (see Fujiwara & Kawachi, 2008, for an application to the sense of belonging, i.e., the opposite of loneliness).

Molecular Genetics

In genetic-association research, two types of studies can be distinguished. *Candidate-gene studies* are theory-based or hypothesis-driven and therefore represent a top-down approach. *Genome-wide association studies* (GWAS), by contrast, are hypothesis-free or agnostic and therefore represent a bottom-up approach. Both approaches are based on genetic variation and the principle of association.

Genetic variation and the principle of association

The human genome comprises some 3 billion basic units. These units come in four varieties, referred to as adenine (A), cytosine (C), guanine (G), and thymine (T). At a large number of locations in this vast genetic code, different variations (so-called *polymorphisms* or *genetic markers*) can be found. Each of these variants is called an *allele*. There are different types of alleles. One type are referred to as single nucleotide polymorphisms (or SNPs), variants that differ in a single basic unit in the genome (e.g., guanine, or G, vs. cytosine, or C). Another type are repeat polymorphisms, longer sequences of basic units have been inserted at a particular place in the genome in some individuals but not in others (resulting in long vs. short alleles).

Individuals inherit two copies of a gene (one from the mother and one from the father), and their autosomal genotypes can be classified as heterozygote (two different alleles) or homozygote (two similar alleles). For a G/C SNP, for instance, the GC type is heterozygote, and CC and GG are homozygote. Genotypes can be combined to form groups of comparable magnitude. For example, for repeat polymorphisms, the long-long group can be contrasted to all other groups combined (i.e., short-short and long-short). The average level of loneliness in the two genotype groups may be compared and, when a significant difference emerges, a significant association between loneliness and that particular polymorphism has been obtained.

Candidate-gene studies

The selection of candidate genes for loneliness has been inspired by early pathological or neurobiological models in psychiatry, which concentrated on systems related to neurotransmitters (e.g., dopamine and serotonin) or other signaling substances (e.g., oxytocin). Receptors (i.e., chemical substances that are particularly sensitive to a neurotransmitter or signaling substance) occupy a central place in these models. Oxytocin, for instance, is a chemical substance in the human body that is related to different types of social behavior, including attachment, social recognition, and social exploration (MacDonald & MacDonald, 2010). Several SNPs in the oxytocin receptor (OXTR) gene have received particular attention in empirical research. Individuals who have the GG genotype at SNP rs53576 display greater prosociality and greater trust in others (Kumsta & Heinrichs, 2013) and are more sensitive to social cues (Ebstein, Knafo, Mankuta, Chew, & Lai, 2012). Because lower trust is a key characteristic of lonely people, according to the evolutionary theory of loneliness (J. T. Cacioppo & Hawkley, 2009b), the OXTR gene is a promising candidate gene, and this particular SNP is a promising genetic marker.

An overview of the findings of candidate-gene association studies of loneliness may be found in Table 3. It is clear from this table that most associations were nonsignificant, that few replication attempts were undertaken, and that successful replication across two samples was achieved for just a single gene, the OXTR gene. Adolescent girls (van Roekel, Verhagen, Scholte, et al., 2013) and pregnant women (Connelly et al., 2014) who had a GG genotype at SNP rs53576 were significantly less lonely than their counterparts with other genotypes.

A known variant in a candidate gene supposedly linked with sensitivity to social cues has thus shown an association with loneliness that is somewhat consistent. So, research in molecular genetics seems to support the general expectation regarding the second topic in the

Table 3. Genotype–Loneliness Associations

Study	*N*	Population	Country	Gene	Marker	Results
Chou, Cacioppo, Kumari, and Song (2014)	1,374	Older adults	United Kingdom	CRHR1	rs1876831	Not significant
					rs242938	Not significant
Connelly et al. (2014)	7,723	Pregnant women	United Kingdom	OXTR	rs53576	Significant; GG carriers less lonely
					rs2254928	Not significant
Lan et al. (2012)	323	Elderly males	Taiwan	MTFHR	rs1001133	Significant; CC carriers more lonely
Lucht et al. (2009)	285	Adults	Germany	OXTR	rs53576	Not significant
					rs2254298	Not significant
					rs2228485	Not significant
	89	Adolescents			rs53576	Not significant
					rs22254298	Significant; GG carriers less lonely
					rs2228485	Not significant
Tsai et al. (2012)	192	Elderly males	Taiwan	CHRNA4	rs1044396	Significant: CC carriers more lonely
van Roekel, Scholte, Verhagen, Goossens, and Engels (2010)	306	Adolescents	The Netherlands	SLC6A4	5-HTTLPR	Not significant
van Roekel, Goossens, Scholte, Engels, and Verhagen (2011)	307	Adolescents	The Netherlands	DRD2	rs1800497	Not significant
van Roekel, Verhagen, Engels, Goossens, and Scholte (2013)	302	Adolescents	The Netherlands	OXTR	rs53576	Not significant
van Roekel, Verhagen, Scholte, et al. (2013)	300	Adolescents	The Netherlands	OXTR	rs53576	Significant; GG carriers less lonely (girls only)
Verhagen, van Roekel, and Engels (2014)	305	Adolescents	The Netherlands	BDNF	rs62625	Significant; boys: Val/Val carriers more lonely; girls: Met/Met carriers more lonely
Wang et al. (2013)	192	Elderly males	Taiwan	IL-1A	rs1800587	Not significant

Note: BDNF = brain-derived neurotrophic growth factor; CHRNA4 = cholinergic receptor nicotinic A4; CRHR1 = corticotropin releasing hormone receptor 1; DRD2 = dopamine receptor D2; IL-1A = interleukin-1 alpha; MTFHR = methylenetetrahydrofolate reductase; OXTR = oxytocin receptor; SLC6A4 = serotonin transporter; 5-HTTLPR = promoter-linked polymorphic region (serotonin transporter gene).

genetics of loneliness, that is, the main effects of genes on loneliness. However, this result should be interpreted with extreme caution. Research in related areas such as depression has revealed that the average effect size in candidate-gene studies is very small (i.e., odds ratio = 1.10 or 1.15, very close to the value of 1, which represents the absence of any association; Lopez-Leon et al., 2008). The candidate-gene approach, therefore, has never lived up to the high expectations that arose when the method was introduced into the world of genetics. This general finding should not come as a surprise, given that the effects of single polymorphisms (e.g., SNP rs53576) in specific genes (e.g., the OXTR gene) may a priori be expected to have a limited impact on human behavior, although there are traits such as mental retardation in which single-gene mutations have large effects (Veltman & Brunner, 2012). With the breakthroughs in high-dimensional genotyping and sequencing, to which we now turn, candidate-gene association studies are no longer considered a valid method in genetics.

Genome-wide association studies

A promising alternative to candidate-gene studies is studies examining variability across the entire genome (Visscher, Brown, McCarthy, & Yang, 2012). These GWAS concentrate on a single type of polymorphisms, that is, SNPs. Associations are examined between millions of

measured and imputed SNPs, on the one hand, and a particular behavior or trait, such as loneliness, on the other hand. The subsets of SNPs are selected to "tag" or represent a large set of SNP markers, which represent most common genetic variation. Drastic corrections for multiple comparisons need to be applied, of course, but with increasing sample sizes, many markers that achieved genome-wide significance have been documented.

Finding the "best SNP". Most GWAS concentrate on the "best SNP" (i.e., the marker whose association has the smallest *p* value). The SNPs that are thus selected are often found in novel genes (i.e., genes that had not come into the picture yet in candidate-gene research) or in "non-gene" regulatory regions of the genome. No GWAS research has been conducted for loneliness as of yet. However, the results for measures of broader personality constructs, such as neuroticism and depressive symptoms, provide preliminary insight into the rich potential of the method. A GWAS on neuroticism found its "best SNP" in a gene related to circadian rhythms (the retinoic acid receptor-related orphan receptor A, or RORA, gene; Terracciano et al., 2010), which may be linked to sleep fragmentation, which is an important aspect of the clinical picture of loneliness (Cacioppo, Grippo, et al., 2015). However, this finding did not replicate in a much larger GWAS of personality (de Moor et al., 2012). Another GWAS on depressive symptoms found its "best SNP" in a gene that is associated with the sensitivity of the glucocorticoid receptor to cortisol (the FK506 binding protein, or FKBP5, gene; Velders et al., 2011), suggesting involvement of the stress system (i.e., the hypothalamic-pituitary-adrenal, or HPA, axis) in depression and loneliness. However, subsequent large studies of depression did not replicate this finding (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium et al., 2013).

Identifying gene networks. Increasingly, GWAS research is moving beyond "best SNP" analyses. As sets of significant SNPs have been replicated across samples, researchers have checked the function of the genes in which these SNPs can be found, using databases such as the Gene Ontology database (http://geneontology.org). If these genes can be related to sets of genes that have a common biological function, or if they turn out to represent a specific *biological pathway*, as biologists call it (Ramanan, Shen, Moore, & Saykin, 2012), researchers can get hints at the underlying biological system or interacting biological systems (e.g., the HPA axis and the immune system). In subsequent studies, researchers can then test, for instance, whether a particular pathway is overrepresented in terms of significant SNPs. In short, researchers are using GWAS-derived information in multiple ways to identify networks of genes. As of yet, no such studies have been conducted for loneliness.

Polygenic scores. Researchers are also using GWAS-derived information that does not meet the exacting statistical standard associated with the method. Multiple SNP alleles that are associated with the trait at a liberal significance level (i.e., $p < .10$ or $p < .50$) are summed to create a polygenic score. This score, which may be based on several thousands of SNPs, is created by weighting the genotypes by the strength of the association (i.e., the odds ratio) that each SNP has with, for instance, loneliness. These weighted sum scores, called *polygenic profiles*, account for a larger portion of the variance than a single SNP does (Purcell et al., 2009). No analyses using these scores have been conducted for loneliness so far, but an early application to depression (Demirkan et al., 2011) showed that some individuals who received a low polygenic score because they only had a limited number of genetic variants associated with depression (i.e., they exhibited low genetic susceptibility) had lower incidence of depression and anxiety.

With the advent of newer methods that focus on gene networks and polygenic scores, the GWAS approach, which is based on statistical principles rather than theoretical arguments, has firmly established itself as the dominant method for association studies in molecular genetics. Future research on the molecular genetics of loneliness, therefore, should adopt this approach—with a focus on gene networks and polygenic scores—rather than the candidate-gene approach that has dominated the field until now.

Gene-Environment Interplay

Current research on gene-environment interplay still relies on candidate genes, an approach that is heavily criticized, as we have just seen. We will illustrate this approach with another example of a candidate gene and end this section with a brief description of what a genomic (GWAS) approach to gene-environment interplay could look like. Both approaches are based on assumptions that genetic associations show up more easily under adverse social conditions or that genetic variants moderate the effects of known environmental factors on top of main genetic associations.

Candidate genes

The serotonin transporter (SLC6A4) gene, which comes in a long and a short variant, is a good candidate gene for loneliness. The short allele is thought to be linked to less efficient dampening of negative emotions (Collier et al., 1996). This less efficient dampening, in turn, can be

linked to hypervigilance to social threat, which is a key characteristic of lonely people in the evolutionary theory of loneliness (J. T. Cacioppo & Hawkley, 2009b).

Examining the variation in the SLC6A4 gene (short vs. long) and using a measure of perceived social support, two different phenomena can be observed. The first phenomenon, *gene-environment interactions* (G × E), which has attracted much attention, indicates that the effect of the social environment (in this case, low or high parental support) may be more or less pronounced depending on the genotype or that the effect of the genotype may be more or less pronounced depending on the environment. The typical expectation here would be that the carriers of the short allele who experience a low level of social support clearly feel more lonely than do carriers of that same allele who experience a high level of social support. Among carriers of the long allele, by contrast, the degree of loneliness would be similar across all levels of experienced social support. This joint effect of the specific gene and the environment on loneliness will show up as a significant interaction effect. The second phenomenon, *gene-environment correlations* (rGE), which has been relatively neglected, implies that participants with different genotypes report that they are treated differently in the social environment (Kendler & Eaves, 1986; Plomin, Defries, & Loehlin, 1977). The typical expectation here would be that carriers of the short allele report lower levels of social support than carriers of the long allele do.

An overview of the results of G × E analyses may be found in Table 4. Because the studies in this table used environmental measures in addition to candidate genes, they are a subset of the studies in Table 3. Significant G × E findings were observed for four genes related to the HPA axis (the corticotropin releasing hormone receptor 1, or CRHR1, gene; Chou, Cacioppo, Kumari, & Song, 2014), the serotonin system (the serotonin transporter, or SLC6A4, gene; van Roekel, Scholte, Verhagen, Goossens, & Engels, 2010), the dopamine system (the dopamine receptor D2, or DRD2, gene; van Roekel, Goossens, Scholte, Engels, & Verhagen, 2011), and oxytocin (the OXTR gene; van Roekel, Verhagen, Scholte, et al., 2013). The observed pattern of results was in line with the general expectation in research on gene-environment interactions. In each case, carriers of a particular genotype (e.g., those with at least one short allele for the SLC6A4 gene) showed higher levels of loneliness when they experienced more adverse social conditions (i.e., lower social support from their parents in adolescence and lower support from and less frequent contact with their children in old age); for the other genotype examined (e.g., two long alleles), levels of loneliness were comparable across adverse and supportive social situations. Two of the studies also checked for gene-environment correlations (van Roekel et al., 2011; van Roekel et al., 2010) and found them to be nonsignificant. So, some support was found for one of the hypothesized phenomena (gene-environment interactions) but not for the other (gene-environment correlations).

The association between a well-established environmental factor (social support) and loneliness thus depends on variants in four candidate genes that are related to neurotransmitters and the stress system. So, research on gene-environment interplay seems to support the general expectation regarding the third topic in the genetics of loneliness, that is, conditional effects of candidate genes that depend on the environment or conditional effects of the environment that depend on specific genotypes. However, this pattern should again be interpreted with great caution. No attempts at replication have been published for any of the obtained interactions as of yet. Interactions are notoriously hard to replicate and require much larger samples for successful replication than main effects do. Unsurprisingly, a review of the first 10 years of research on gene-environment interactions for psychiatric conditions revealed that gene-environment interactions are indeed hard to replicate (Duncan & Keller, 2011).

Loneliness may also act as an "environmental" moderator in G × E interactions. The evolutionary theory frames loneliness as both an important outcome and an important intermediate variable predicting other, health-related outcomes. One study, for instance, found that adults who had a specific variant of the apolipoprotein E (APOE) gene and felt very lonely exhibited more depressive symptoms (Chou, 2010). The most problematic aspect of current research on gene-environment interactions and the limited work on gene-environment correlations is, of course, that it represents an extension of the candidate-gene approach, which has been all but abandoned in current genetics.

Genome-wide association studies

The use of polygenic scores that represent an overall index of genetic susceptibility (as described in the Molecular Genetics section) is currently recommended by many authors for future research on G × E interactions (Boomsma, 2013; Iyegbe, Campbell, Butler, Ajnakina, & Sham, 2014; Plomin & Simpson, 2013) and should be adopted in future research on loneliness. The general expectation is that the effect of social-environmental factors, such as low social support, on loneliness will be moderated by the polygenic score. Recent research on depression effectively found that adults who had suffered from maltreatment as children and had a high genetic susceptibility for depression (as indicated by their high polygenic score) were diagnosed more frequently as clinically depressed (Peyrot et al., 2014).

Table 4. Gene × Environment Interactions for Loneliness

Study	*N*	Population	Country	Gene	Marker	Environmental variable	Results
Chou, Cacioppo, Kumari, and Song (2014)	1,374	Older adults	United Kingdom	CRHR1	rs1876831	Support from children	Significant; CT and TT carriers with low support more lonely
						Contact with children	Significant; CT and TT carriers with infrequent contact more lonely
					rs242938	Support from children	Not significant
						Contact with children	Not significant
Connelly et al. (2014)	7,723	Pregnant women	United Kingdom	OXTR	rs53576	Childhood abuse	Not significant
					rs2254928		Not significant
van Roekel, Scholte, Verhagen, Goossens, and Engels (2010)	306	Adolescents	The Netherlands	SLC6A4	5-HTTLPR	Parental support	Significant; SS and SL carriers with low support more lonely, but SS and SL carriers with high support less lonely
van Roekel, Goossens, Scholte, Engels, and Verhagen (2011)	307	Adolescents	The Netherlands	DRD2	rs1800497	Parental support	Significant; A2/A2 carriers with low support more lonely, but A2/A2 carriers with high support less lonely
van Roekel, Verhagen, Engels, Goossens, and Scholte (2013)	302	Adolescents	The Netherlands	OXTR	rs53576	Parental support	Not significant
van Roekel, Verhagen, Scholte, et al. (2013)	300	Adolescents	The Netherlands	OXTR	rs53576	Negative perceptions of company	Significant; A carriers more lonely when negative perceptions are high

Note: CRHR1 = corticotropin releasing hormone receptor 1; DRD2 = dopamine receptor D2; OXTR = oxytocin receptor; SLC6A4 = serotonin transporter; 5-HTTLPR = promoter-linked polymorphic region (serotonin transporter gene).

Functional Genomics

Two approaches to studying the transcribability of the genetic code have become feasible through new technologies (e.g., microarrays or chips). One approach, labeled *transcriptomics*, concentrates on RNA and gene expression. The second approach, labeled *epigenetics* (or *epigenomics*), focuses on DNA and how epigenetic marks affect the "readability" of the genetic code.

Gene expression

A popular design in gene-expression studies entails comparing a group of individuals with a specific psychiatric or medical condition to a control group. In loneliness research, a group of people with very high scores on a loneliness scale is compared to a group of people with very low scores on that same measure. Researchers then look for genes whose expression is upregulated (i.e., relatively overexpressed in lonely individuals) or downregulated (i.e., relatively overexpressed in nonlonely individuals; Cole, 2009). The complete pattern of upregulated and downregulated genes represents the specific gene-expression profile of loneliness. Such profiles are a function of tissue and condition, but also genotype (Wright et al., 2014). Once such a profile is obtained, researchers check the function of each of the genes involved in a gene database to better understand which

biological systems are involved, much like they do for GWAS, as described in the Molecular Genetics section.

A first small-scale study on older adults, which compared six lonely individuals to eight nonlonely individuals, found upregulated expression in 78 genes and downregulated expression in 131 genes (Cole et al., 2007). Different biological systems were of course involved, such as cell growth and differentiation, transcription control, and immune functioning. A possible global interpretation has been advanced implicating the immune system, which defends and protects our body against all sorts of invading organisms. Genes involved in the first, nonspecific line of defense in this system are selectively upregulated, whereas other genes involved in the second, more specific line of defense are selectively downregulated in lonely older adults compared to their nonlonely counterparts. These results help illuminate why lonely people show heightened vulnerability to cardiovascular diseases (which are thought to emerge through excessive nonspecific immune activity) and impaired reactions to viral infections (which are thought to be linked to insufficient specific immune activity). The overall pattern of results of this discovery study were confirmed in a larger replication study on older adults that compared 25 chronically lonely individuals to 68 controls (Cole, Hawkley, Arevalo, & Cacioppo, 2011).

The specific gene-expression profile associated with perceived social isolation could be a remnant of our evolutionary history. When we are socially connected, protection against viral infections by our conspecifics is all-important. However, when we are on the social periphery, we stand a much greater chance of getting wounded and being infected by bacteria. It is adaptive to set inflammatory genes to express themselves more strongly under these circumstances, and our body spontaneously shifts to this alternative type of defense when we feel lonely (Cole et al., 2011).

Expression of loneliness-associated genes or related data may also help explain other findings from loneliness research. In cancer research, lonely individuals tend to pass away at an earlier age than do nonlonely individuals. The fact that expression of loneliness-associated genes proved related to survival time in cancer patients (You, Yeh, & Su, 2013) could provide a glimpse into the mechanism underlying the loneliness-mortality link. In intervention research, specific types of cognitive behavioral therapy, such as Mindfulness-Based Stress Reduction training, reduced loneliness in the experimental group relative to a control group. The fact that a larger reduction of protein markers of the nonspecific immune response was observed in the former group (Creswell et al., 2012) suggests that changes in the immune system may provide the underlying mechanism for the observed effect.

Epigenetic processes

Here, we will briefly explain only one of the many epigenetic processes, referred to as *methylation*, because it is the only process that can be studied in large human cohorts. This particular process involves a methyl molecule binding to a cytosine (C) basic unit, which leaves an epigenetic "mark" and impairs gene transcription. Particularly when this process takes place in the *promoter region*, a segment of the gene to which transcription factors have to bind if the genetic code is to be read properly, transcriptional efficiency may be reduced (Sweatt et al., 2013). Researchers compare the degree of methylation in a group of individuals with a specific psychiatric or medical condition and a control group. Unusual methylation patterns are found in the clinical groups (Roth, 2013). In loneliness research, one would expect to find, for instance, a greater degree of methylation, either across the entire genome or in specific places (e.g., promoter regions of specific genes) in lonely compared to nonlonely individuals. However, such research still has to be conducted for loneliness.

So, research on gene expression seems to support the general expectation regarding the fourth topic in the genetics of loneliness, that is, the transcribability of the genetic code. The degree to which the genetic code is expressed is different in lonely compared to nonlonely individuals. As a result, the body functions less efficiently in lonely people. Convergent lines of evidence point to the role of the immune system, which may be impaired in a specific way. Future research on epigenetic marks—a topic that is currently attracting increasing attention—may expand on the extant body of findings. However, this pattern of findings once again has to be interpreted with great caution. Given that all of the available evidence is correlational in nature, with the exception of the intervention study, one cannot exclude the possibility that a third factor that is associated with both gene expression and immune functioning explains the correlations observed.

A research program on the functional genomics of loneliness needs to consider how environmental exposures can regulate the expression of the genome, while simultaneously recognizing that the genome also influences its own expression. The heritability of epigenetic processes (Gordon et al., 2012) and gene expression (Wright et al., 2014) has been well documented, and future research needs to take this into account—for instance, by designing studies in related individuals, collecting (genome-wide) genotype data, and integrating across different levels of "-omics" (e.g., genomics, transcriptomics, and epigenomics).

Each of these methods yields signals that have to be carefully checked for consistency, much like the results

of functional MRI. Researchers should have multiple competing hypotheses in mind and should test each hypothesis by deliberately trying to demonstrate its falsity (Arue, Lavelle, & Cacioppo, 2009). One objective of genetics research is to improve patient care through personalized medicine, that is, by adapting the treatment to the patient's specific genetic background. In the social sciences, information on specific alleles or specific polygenetic profiles that may render individuals more sensitive to the adverse effects of stressful social environments can inform targeted prevention and intervention efforts that are tailored specifically to the needs of genetically sensitive youth (Reiss, 2010).

Conclusion

The genetics of loneliness is a fascinating research domain that cuts across numerous fields such as immunology, psychology, psychiatry, and medicine. Well-established methods such as gene-expression and candidate-gene studies in molecular genetics have pointed to several genes related to various neurotransmitters, signaling substances, and the immune system that can all be linked easily to the evolutionary theory of loneliness. However, significant advances in the field are expected if the entire range of "-omics" approaches (e.g., genomics and epigenomics), along with the social sciences, is targeted and integrated.

In future research, new methods will have to be used that identify networks of genes whose altered structure (i.e., genomics) or transcribability (i.e., epigenomics) are indexed by multiple genetic variants or methylation patterns. It is still unclear at which level these networks will be found (e.g., at a basic level and closely related to neurotransmitter functions or at a higher level and linked to brain regions) and whether they will be small or large in size. In fact, we do not even know whether any gene network uncovered will tell a sensible biological story (Kendler, 2013).

Finally, genetics is just one of the factors that contribute to individual differences in loneliness (Kendler, 2012). Given that people show different trajectories of loneliness over time and that individuals are exposed to non-supportive social environments to varying degrees, it is by no means certain, for instance, that conducting GWAS research on loneliness is indicated right now. Only widespread application of the most advanced genetic technologies available, along with the best methods psychology has to offer (e.g., identification of developmental trajectories, in-depth study of negative social experiences, and analyses of social attention and cognition through eye tracking and brain imaging techniques; Goossens, 2012), can provide more definitive answers regarding the true contribution of genetics to the study of loneliness.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

Funding

Preparation of this review was supported by KU Leuven Special Research Fund Grant GOA/12/009 (STRATEGIES project).

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