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Genetic Support for Longevity-Enhancing Drug Targets: Issues, Preliminary Data, and Future Directions

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Abstract

Interventions meant to promote longevity and healthy aging have often been designed or observed to modulate very specific gene or protein targets. If there are naturally occurring genetic variants in such a target that affect longevity as well as the molecular function of that target (eg, the variants influence the expression of the target, acting as "expression quantitative trait loci" or "eQTLs"), this could support a causal relationship between the pharmacologic modulation of the target and longevity and thereby validate the target at some level. We considered the gene targets of many pharmacologic interventions hypothesized to enhance human longevity and explored how many variants there are in those targets that affect gene function (eg, as expression quantitative trait loci). We also determined whether variants in genes associated with longevity-related phenotypes affect gene function or are in linkage disequilibrium with variants that do, and whether pharmacologic studies point to compounds exhibiting activity against those genes. Our results are somewhat ambiguous, suggesting that integrating genetic association study results with functional genomic and pharmacologic studies is necessary to shed light on genetically mediated targets for longevity-enhancing drugs. Such integration will require more sophisticated data sets, phenotypic definitions, and bioinformatics approaches to be useful.

Keywords: Longevity, Mortality, Human Aging

The identification of interventions, such as nutritional supplements, specific diets, and drugs that can reduce age-related disease risk and enhance longevity, is receiving a great deal of attention. The reasons for this are not just rooted in an age-old fascination with mortality, but also the belief that it might be possible to slow the aging process, simultaneously reducing the risk of many age-related diseases and morbidities, maintaining health, and ultimately increasing longevity (1–5). However, the identification of relevant targets for the development of longevity-enhancing drugs, such as specific genes or proteins, is complicated by the fact that human longevity and the aging process are complex and ultimately influenced by a number of genetic and nongenetic factors (3,6–9). This makes it difficult to identify compelling longevity-enhancing drug targets because the effects of any one potential gene or protein target could be obscured by the effects of others.

There are strategies to identify longevity-enhancing drug targets that overcome this complexity, and many have been used with some level of success. For example, many researchers have studied longevity in nonhuman species since relevant experiments can be performed in ways that are not feasible in humans. These studies range from the comparison of, for example, genes and their expression levels across species exhibiting variation in life span (10–13),

exploring natural variation in life span among individual animals within a species (14–16), using contrived gene manipulation techniques (such as knocking out a gene or controlling its expression using various genetic engineering strategies) and assessing their effects on life span (17,18), or simply screening drugs against individual animals to see which have a positive effect (19,20). The biological insights into the aging processes from these studies have been varied, with many offering important observations on evolutionarily conserved processes involved in aging. However, given the fundamental differences between humans and other species at the molecular and physiologic levels, it is still an open question as to whether these insights can be readily translated into findings that can form the basis for human longevity-enhancing interventions (21).

An alternative to identifying drug targets involving nonhuman species is to use human genetic studies, in particular genome-wide association studies (GWAS), which seek to identify naturally occurring DNA sequence variants that are associated with, for example, longevity, healthspan, and susceptibility/resistance to diseases. A number of GWAS have been pursued to date that have focused on human longevity, healthspan, and protection from disease (3,14,22–26). Unfortunately, the results of many of these studies have not been replicated, in part due to the multifactorial nature of human longevity, but also due to difficulties in assembling relevant cohorts necessary for such studies (eg, large numbers of very long-lived individuals; large cohorts with longitudinal data reflecting health trajectories over time, etc.) (27).

Despite complications with many GWAS initiatives, it has been shown that a drug designed to modulate or affect a gene or protein target, which harbors variants associated with the specific disease that the drug was designed to treat, actually yields better outcomes during the drug development process than a drug that targets a gene that does not harbor such variants (28–31). This is plausible because naturally occurring genetic variations that have an impact on a phenotype of relevance must work through some mechanism that could, in theory, be modulated pharmacologically (32). Many success stories exist in which drugs have been developed that target or modulate genes harboring variants associated with a specific disease (see, eg, research on the development of Ivacaftor for cystic fibrosis (33) and *PCSK9* inhibitors for treating hypercholesterolemia (34)). In fact, these successes are consistent with, and have motivated, the growing interest in tailoring medicine to individuals' genetic (and other) profiles via precision medicine initiatives (35,36).

Identifying drug targets based on genetic association study results is not trivial, however, because the mere association of a genetic variant with a phenotype, especially one as complex as longevity, is insufficient. One must identify the actual molecular mechanism or process through which the variant alters the phenotype before a genetic association can reveal a viable drug target. Unfortunately, many variants found to be associated with longevity-related phenotypes via GWAS—as well as most other phenotypes—do not actually reside in genes or their more obvious surrounding regulatory elements. As an example, these variants may reside in intergenic regions or regulatory elements, which are not well characterized, making their immediate functional effects hard to discern (37). In addition, the genes that harbor variants are not always found to be amenable to pharmacologic modulation (ie, they might not be "druggable") (38). Finally, many variants associated with a disease or trait, even those in genes that are thought to be druggable, do not implicate or suggest specific or obvious mechanisms for pharmacologic modulation. For example, it might not be obvious whether or not a variant causes overexpression of a gene in a specific tissue of relevance whose pharmacologic inhibition would lead to consistent and favorable phenotypic outcomes (39). As a result, the use of genetic information to identify or prioritize drug targets is likely to require integrated approaches which draw on the insights from a number of disciplines beyond genetics, including molecular, systems and evolutionary biology, genomics, pharmacology, and chemoinformatics (see the Discussion section for more detail) (2,3,27,40).

One approach to determining whether a variant found to be associated with, for example, longevity is likely to reveal a viable drug target is to determine whether that variant is also known to influence, or correlate with, a molecular phenotype that could be amenable to pharmacologic modulation in a tissue of relevance. For example, if the associated variant is known to affect the expression level of a gene (ie, is an "expression quantitative trait loci" or "eQTL") or the abundance of a particular protein (ie, is a "pQTL") in muscle, cardiac, or brain cells, there is a possibility that the variant influences this molecular phenotype in a causal pathway leading from the variant to the longevity phenotype. Evidence for a causation would make that molecular phenotype a logical longevity-enhancing drug target (41). In fact, databases are available that catalog variants that have been found to be eQTLs, pQTLs, or other molecular phenotypes, as in the GTex database (42). In addition, statistical strategies have been developed to test the hypothesis that, for example, an eQTL, or other molecular (or "intermediate") phenotype, is in a causal pathway leading from the relevant variant to an overt, clinically meaningful, phenotype like longevity (43).

We surveyed the available literature and interrogated a number of resources focused on associations with genetic variants, and their known effects, to determine whether the research community might be able to exploit information about genetic associations involving longevity and longevity-related phenotypes to identify possible longevity-enhancing drug targets. We pursued this in two ways. We first identified a number of drugs thought to be candidates for enhancing longevity in humans based on their effects on longevity in nonhuman species, their mechanisms of action, and/or their impacts on age-related diseases. We then determined whether there was evidence that those drugs modulate or target genes harboring variants associated with human longevity-associated phenotypes and/or a potential mechanism amenable to pharmacologic modulation (eg, if the variants are known eQTLs or pQTLs.)

We also identified individual variants found to be associated with human longevity, healthspan, and disease protection based on GWAS (3,22–25,44). We then determined whether these longevity phenotype-associated variants, or more precisely the alternate alleles at the locus harboring the variants, are associated with age-related disease phenotypes. We also determined whether these variants reside in druggable genes, are known QTLs (eQTLs, pQTLs, etc.), or are in linkage disequilibrium (LD > 0.8) with variants that are QTLs and/or associated with other phenotypes. We cataloged eQTLs in LD with the sourced eQTLs, as well as variants associated with longevity phenotypes because they give an indication of how complex a regulatory setting a target gene may be operating within. For example, if perturbations within a gene induced by naturally occurring sequence variants have ripple effects involving a number of other genes, then modulating that gene pharmacologically could affect multiple pathways or molecular networks, for better or worse. For genes harboring associated variants, we also determined whether there were pharmacology studies published in the chemoinformatics literature suggesting that a drug or compound exhibited activity against genes whose DNA sequences were homologous to that gene (45,46). Activity against a homologous gene sequence may suggest

that the drug or compound in question may also exhibit activity against the gene harboring the associated variant. It may also indicate that, if the homologous gene has a similar function to the gene harboring the associated variant, the modulation of that gene may affect the longevity-related phenotype.

We emphasize eQTLs as relevant molecular phenotypes in much of our analyses because they have received the most attention in the literature, have the most information about their influence on different tissues, and have the most resources cataloging them. In addition, by focusing on eQTLs in potential target genes and their LD relationships to other variants, we expose the potential that a variant associated with longevity could reveal a molecular mechanism worthy of scrutiny as a drug target. We admit that there may be other variants in the genes of interest that are not themselves eQTLs, nor in LD with eQTLs, that may actually induce or contribute to an as-yet uncharacterized molecular function that could be pharmacologically modulated. We also emphasize that the definition of longevity is widely debated and a crucially important topic for putting aspects of our findings into perspective. We make no attempt to resolve this debate but rather use the published data based on the authors' definitions of longevity to make broader claims about genetic information and putative longevity-enhancing drugs and drug targets. Figure 1 provides a schematic summarizing our sources of information for longevity-associated variants as well as putative longevity-enhancing drugs. Figure 1 also provides the main databases and query tools used in our analyses, which are discussed in greater detail in the Methods section.

Methods

Longevity Drug and Compound Data Sources

There are many drugs and compounds that have been hypothesized to influence human longevity based on a wide variety of studies (see, eg, the DrugAge database (47)). We limited the number of drugs we considered in the present analysis to those receiving the most attention based on our internet and literature searchers, although we are pursuing more complete analyses of a larger collection of drugs. Note that many "drugs" we list are actually experimental compounds not yet approved for use but are rather in various stages of development. We first considered the drugs and compounds found to significantly increase longevity in mice from the NIA-sponsored Interventions Testing Program (ITP) (20). The ITP follows a rigorous standard protocol to test drugs and compounds for their effects on mouse longevity. We also considered drugs and compounds that have been proposed to be evaluated in human clinical trials based on the credibility of the published science behind them. URLs and relevant references with information describing these efforts are provided in Supplementary Tables where appropriate. Finally, we considered the drugs and compounds ranking highly as likely to affect human longevity based on the systems biology and cross-species analysis of Fuentealba and colleagues (48) because the authors did *not* include more comprehensive human genetic association study result information in their otherwise very thorough analysis of candidacy and properties of the drug targets.

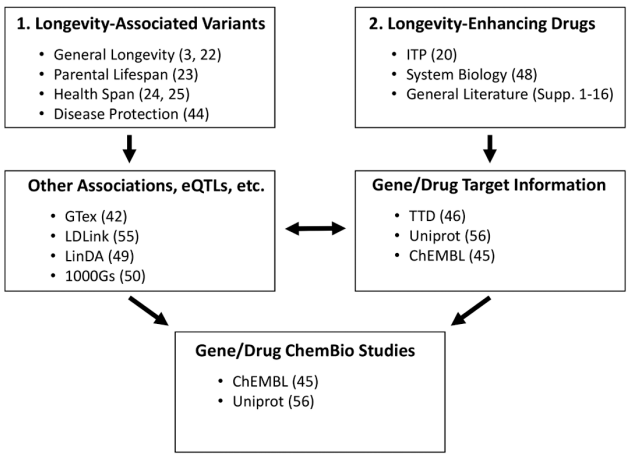

Figure 1. Schematic of the resources used for both determining: (i) if a gene harboring a longevity-associated variant is a reasonable drug target and (ii) if there is genetic evidence supporting the targets of potential longevity-enhancing drugs. Note that numbers in parentheses denote references.

Identifying Variants and Their Associations in the Gene Targets of Longevity-Enhancing Drugs

For each putative longevity-enhancing drug and compound we considered, we identified the primary gene targets of those drugs and compounds using the Therapeutic Target Database (TTD) (45). We emphasize that TTD, although well curated, does not contain exhaustive information about drug targets that could be obtained from an analysis of, for example, the downstream effects of a drug on genes in a particular pathway. For each gene target, we used the LinDA web-based query tools (49) to determine the number of eQTL variants within them that could reflect compelling genetically mediated molecular phenotypes for drug development purposes (eg, pharmacologic modulation studies of the expression of a gene that varies naturally between long-lived and short-lived individuals or between carriers and noncarriers of specific genetic variants). Note that we used conventional statistical significance criteria also used on the website to determine eQTL status, though of course it would be important to explore how the use of different criteria would change our findings. For each of the eQTL variants we also used the LinDA query tools to identify variants that were in LD with these eQTLs (LD > 0.8) that were associated with (i) longevity; (ii) diseases and other clinical phenotypes; and/or (iii) other molecular phenotypes (eQTLs; sQTLs [splicing QTLS]; aseQTLs [allele-specific expression QTLs]; polyAQTLs [alternative polyA QTLs]; repeatQTLs [repeats expansion expression-level QTLs]; pQTLs: dhsQTL [DnaseI hypersensitive sites QTLs]; hQTLs [Histone modifications QTLs]; mQTLs [DNA methylation QTLs]). Variants in LD with eQTLs were based on the use of the European cohort from the 1000 Genomes Project (50). Note that we chose an LD cutoff of 0.8 because the effect sizes of most variants associated with longevity are weak. If a true functional variant is in weak LD with a variant with a weak effect on longevity, it is difficult to argue that the influence of that variant on longevity is due to the molecular phenotype induced by the variant for which it is in weak LD. Of course, further studies assuming different LD strengths could be revealing and should be pursued. We did not weigh the evidence for reported phenotypic associations, but merely point to published studies claiming an association with a particular phenotype. Further exploration is needed to accurately assess the strength of the evidence for each association and how it may support the belief that the gene harboring that variant is a reasonable drug target. For eQTL information, we summarized studies involving different tissues using the GTex database (42). To summarize genetic association information, we summed the number of associated variants (for longevity and other phenotypes, including

the molecular phenotypes) falling into various categories and report these categories here.

Associated Variants With Longevity, Healthspan, and Disease Protection Sources

We gathered information about genetic variants associated with human longevity, healthspan, and protection against disease from multiple publications. For variants associated with longevity, we used the recent review by Partridge and colleagues focusing on variants with replication studies (3,22,51–54), the meta-analysis of GWAS studies by Sebastiani and colleagues (22), and the GWAS study of parental life span using the UK Biobank and LifeGen study data by Timmers and colleagues (23). For variants associated with healthspan, we used the study involving the UK Biobank by Zenin and colleagues (24) as well as the study on *TTR* gene variants by Hornstrup and colleagues (25). For genes harboring rare variants that appear to protect individuals from getting certain diseases, we used the list in the review by Harper and colleagues (44).

Characteristics and Drug Information for Genes Harboring Variants Associated With Longevity-Related Phenotypes

For variants associated with longevity, healthspan, and protection against diseases, we first identified the genes reported to harbor, be near, or modulated by, the variant from the publications cited. We then determined these genes' druggability based on information in Chembl (45) and TTD (46). We determined if the associated variants were themselves eQTLs using the LinDA resources (49). We also used the LinDA resources to determine whether the associated variants were in LD (>0.8) with variants associated with longevity, other age-related phenotypes, or various molecular phenotypes (eg, eQTLs or pQTLs). To capture additional information about the various tissues affected by the eQTLs, we used the LDLink resources and query tools using the European cohort information of the 1000 Genomes Project (50,55). We queried each of the single-nucleotide polymorphisms (SNPs) in LD with other variants associated with various phenotypes, and summed the count of disease/trait associations across different disease categories to get a total number of SNPs. When eQTLS were in LD with a longevity phenotype-associated variant, we also catalogued the various tissues that these eQTLs affected—based on the GTex database (42). For each protein-coding gene harboring the variants, we identified its protein equivalent in UniProt (56) using the BioConductor package "Uniprot.ws." Known and experimental drugs targeting these proteins were identified with custom functions querying a downloaded SQLite instance of the ChEMBL database (Version 24) (45). The drug-target annotation functions developed for this step have been implemented as an R software package (Girke and colleagues, manuscript in review). Representative drugs were provided for any gene encoding druggable proteins identified from both TTD and ChEMBL. Because many genes in the human genome are part of gene families, we included in an extra panel of our drug-target annotation routine all nearest neighbor proteins. They had to share with each protein, encoded by a variant harboring gene, a sequence identity of at least 90% based on the UniRef90 entries in UniProt. Including nearest neighbor protein sequences is important because closely related proteins are usually targeted by the same drugs. Yet, drug development and screening efforts can only focus on one or a few targets within a protein family. Thus, incorporating these family relationships reduces the false-negative rate of our approach.

Results

Candidate Longevity-Enhancing Drugs and Compounds

ITP drugs

We first considered the drugs and compounds shown to have an effect on longevity in mice from the ITP (20). Table 1 summarizes the results. For some drugs and compounds, multiple target proteins are listed in the TTD (46). We note that experimental evidence may not suggest that a drug exhibits activity against all of these targets. In addition, information in the TTD (and other databases) may simply be wrong. Note that despite its having a positive effect on longevity based on ITP studies, we did not include the dietary supplement Protandim (a mixture of milk thistle, bacopa extract, ashwagandha, green tea extract, and turmeric extract) because it is not a defined active small molecule with a specific target as indicated in the TTD. Protandim may affect a number of genes possibly relevant to longevity based on association studies; however, from Table 1, it can be seen that none of the drugs and compounds with an effect on mice interact with human gene targets that harbor variants associated with longevity. However, some drugs target genes that harbor variants associated with age-related diseases (eg, 17-alpha-estradiol and target gene *ESR1*). In addition, it is important to point out that 17-alpha-estradiol and acarbose exhibited sex-specific effects in mice based on the ITP studies, complicating their relationships to a target gene or protein. Many other target genes harbor eQTLs and other variants that are in LD with many other phenotypes and eQTLs that affect longevity-related tissues (eg, acarbose targets gene *MGAM* with variants in LD with eQTLs affecting the expression levels of genes in the brain). These findings do not suggest that the drugs found to affect longevity, as defined by the ITP, in mice will not affect human longevity, but rather that variation in the genes they target are not overtly associated with human longevity.

Proposed longevity-enhancing clinical trial drugs

We identified multiple drugs that have been proposed as potential longevity-enhancing compounds and for which some claim about them being evaluated in a clinical trial has been made (see Supplementary Tables for references). Supplementary Table 1 describes the results. None of the reported drugs targets a gene that harbors a variant associated with longevity. A few genes (eg, *Alki5i*, alternatively named *TGFBR1*) harbor variants that have been shown to be associated with age-related diseases, but the reproducibility of these associations needs to be considered and explored. Many of the drugs listed in Supplementary Table 1 target gene products that harbor variants that are themselves eQTLs, are in LD with variants that affect gene function, or are associated with age-related diseases and phenotypes (eg, Fisetin and the *FABG* gene; J147 and the *ATP5A1* gene). This provides evidence that a rich genetically mediated set of phenomena exists that could make these genes even more compelling longevity-enhancing drug targets, either through their ability to stave off age-related diseases, slow the aging rate, or both, if explored in greater depth.

Highly ranked drugs by Fuentealba and colleagues

Fuentealba and colleagues (48) conducted a series of analyses to evaluate the evidence that certain drugs target genes that, if modulated, are likely to affect fundamental processes implicated in aging and longevity. These analyses leveraged state-of-the-art systems biology analyses and databases and resulted in two lists of prioritized drugs. The first list (Table 1 in Fuentealba and colleagues (48))

Table 1. Human Genetic Information Related to Drugs That Exhibited Statistically Significant Positive Effects on Mouse Longevity From the NIA-Sponsored Interventions Testing Program (20)

Drug/Compound Information				Variants		Associations Involving Variants in LD With Target Gene eQTLs						eQTL Tissues							
Drug	Gene Target	TTD Mechanism	Indication	eQTLs	# LD	Long	Age Rel	Other	LD eQTLs	LD pQTLs	LD mQTLs	LD Other	Adipose	Artery	Brain	Heart	Muscle	Skin	WB	Total
Rapamycin	*OPRK1*	A	C	8	185	0	0	0	27	0	8	12	0	0	59	0	0	0	0	59
Rapamycin	*MTOR*	I	C	24	1,753	0	22	7	548	0	143	217	0	0	2	0	9	17	212	437
Rapamycin	*FKBP1A*	B	C	33	524	0	0	0	178	0	16	82	15	32	1	0	9	27	1	132
17Aalpha estradiol	*ESR1*	A	M	15	890	0	42	8	48	0	206	47	0	53	0	0	1	3	0	204
17-alpha-estradiol	*ESR2*	A	M	28	881	0	10	25	360	0	81	284	0	0	58	9	226	486	76	1,348
Acarbose	*MGAM*	M	D	41	3,167	0	1	2	4,789	26	143	1,256	0	0	1,599	0	0	0	9	2,134
NDGA	*ERBB2*	M	P	12	531	0	0	25	569	0	159	134	7	0	0	110	0	161	0	736

Notes: TTD mechanism = mechanism of action per the Therapeutic Target Database, where A = agonist, I = inhibitor, B = binder, and M = modulator (TTD) (46). Indication = indication of drug on disease where C = CAS, multiple myeloma, M = menopause, D = diabetes, cardiovascular disease, and P = prostate cancer. eQTLs = number of eQTLs in the gene target based on the LinDA eGENE query tool (49). # LD = number of variants in linkage disequilibrium (LD > 0.8 among the 100 genomes European cohort) with the eQTL variants in the gene target per the LinDA eGENE query. Long = number LD variants associated Longevity from the literature based on the LinDA eGENE GWAS summary. Age Rel = comparable number LD variants with GWAS associations to age-related diseases (cancer, cardiovascular disease, metabolic diseases such as diabetes, osteoporosis, and other age-related bone diseases, and Alzheimer's and Parkinson's diseases). Other = number LD variants with GWAS associations associated other phenotypes; LD eQ, LD pQ, LD mQ, LD Other = number of variants eQTL, pQTL and mQTLs themselves in LD (>0.8) with variants with eQTLs in the gene target based on the LinDA molecular QTL summary. eQTL Tissues = number of variants associated with the Gene Target in GTex that affect certain tissues where WB = whole blood and Total = sum of eQTLs including all other tissues.

considers drugs whose gene targets contribute to processes and networks of relevance to longevity and aging. Of the drugs in this list, six drugs had been shown to influence longevity in nonhuman species (resveratrol, genistein, simvastatin, epigallocatechin gallate, celecoxib, and sirolimus). The second list of drugs (Table 2 in Fuentealba and colleagues (48)) was based on multiple criteria including their reported biological activity. Of the drugs in this list, three drugs had been shown to influence longevity in nonhuman species: trichostatin, geldanamycin, and celecoxib. Despite the sophistication of the approach taken to identify candidate drugs for enhancing human longevity, Fuentealba and colleagues (48) did not consider human genetic support in the form of GWAS, eQTL, and other association studies. We note that we could not identify information necessary to conduct our assessments for a few of the drugs listed by Fuentealba and colleagues (48) including cAMP, epigallocatechin gallate, dorsomorphin, doxorubicin, selenium, indole-3 carbinol, cisplatin, and etoposide. Also, the potential side effects of many of these drugs in humans need further attention given their use as chemotherapeutic agents.

Supplementary Table 2 (reflecting drugs in Table 1 of Feuntealba and colleagues (48)) and Table 2 (reflecting drugs in Table 2 of Feuntealba and colleagues (48)) provide the results of our assessments of the genetic support for the two lists of drugs. It is interesting that none of the drugs/compounds target a gene that harbors variants associated with longevity. However, all of the target genes harbor eQTLs, suggesting that functional variants affect those genes. In addition, several of the drugs and compounds target genes, which contain variants in LD with eQTLs that are associated with many age-related diseases and additional functional variants such as eQTLs, pQTLs, and mQTLs. For those target genes enriched for eQTLs, many of the tissues affected by these eQTLs are important in aging (eg, the *NOS2* gene targeted by resveratrol; the *HSP90AA1* gene targeted by tanespimycin and geldanamycin).

Variants Associated With Longevity-Related Phenotypes

Variants associated with longevity

The review on aging research by Partridge and colleagues (3) discusses a number of variants in specific genes that have been shown to be strongly associated with human longevity. Table 3 provides our assessment of those variants and genes. We find that at least two of the genes harboring longevity-associated variants are not considered druggable because they are noncoding genes and hence not considered in the TTD (*LINC02227* and *USP2-AS1*). Two of the variants are themselves eQTLs, suggesting that they could reveal mechanisms for their association with longevity that could motivate the genes they reside in as potential drug targets (*FOXO3A* and *RAD50/IL13*). Many of the variants were in LD with eQTLs, and other variants were associated with a wide variety of phenotypes, with the exception of the rs28926173 variant in the *MC2R* gene and the rs139137459 variant in *USP2-AS1*. These SNPs do not appear to be in strong LD with other variants of functional significance, raising questions about the biology behind their associations with longevity. Interestingly, two of the genes harboring longevity-associated variants have been the focus of pharmacologic studies (eg, the #Ch columns in Table 3): *FOXO3A* and *MC2R*. Further exploration of the studies focused on *FOXO3A* suggests that resveratrol (which has been extensively studied and considered a candidate longevity-enhancing drug despite not exhibiting effects on longevity in mice) has an effect on that gene (57) and that the efficacy of

Table 2. Human Genetic Information Related to Drugs Identified by Fuentealba and Colleagues as Being Good Candidate for Promoting Healthy Aging Based on These Drugs' Multiple Levels of Biological Action (48)

Drug/Compound Information						Variants		Associations Involving Variants in LD With Target Gene eQTLs							eQTL Tissues							
Drug	Extend	Toxic	Status	Gene Target	Mechanism	eQTLs	# LD	Long	Age Rel	Other	LD eQTLs	LD pQTLs	LD mQTLs	LD Other	Adipose	Artery	Brain	Heart	Muscle	Skin	WB	Sum
Tanespimycin	N	N	I	*HSP90AA1*	I	19	401	0	0	4	103	0	18	57	35	4	3	0	92	250	0	393
Imatinib	N	N	A	*KIT*	I	8	511	0	0	11	133	0	133	42	0	0	0	0	0	0	0	114
Imatinib	N	N	A	*PDGFRB*	I	22	425	0	1	7	160	0	404	106	0	32	0	22	1	0	0	107
Imatinib	N	N	A	*ABL1*	I	18	734	0	0	3	32	0	7	9	0	3	0	4	0	0	0	19
Sunitinib	N	N	A	*KDR*	M	13	309	0	0	0	16	0	4	0	0	3	5	0	0	0	0	812
Trichostatin	Y	N	E	*HDAC1*	I	15	1,054	0	0	1	50	0	3	11	4	4	5	4	2	5	0	32
Geldanamycin	Y	N	I	*HSP90AA1*	I	19	401	0	0	4	103	0	18	57	0	4	3	0	92	250	0	358
Sorafenib	N	N	A	*KDR*	M	13	309	0	0	0	16	0	4	0	0	3	5	0	0	0	0	812
Sorafenib	N	N	A	*KIT*	M	8	511	0	0	11	133	0	133	42	0	0	0	0	0	0	0	114
Sorafenib	N	N	A	*PDGFRB*	M	22	425	0	1	7	160	0	404	106	0	32	0	22	1	0	0	107
Dasatinib	N	N	A	*SRC*	I	20	216	0	0	2	273	0	46	25	0	0	0	0	0	0	0	6
Dasatinib	N	N	A	*ABL1*	I	18	734	0	0	3	32	0	7	9	0	3	0	4	0	0	0	19
Dasatinib	N	N	A	*LCK*	I	15	1,792	0	0	0	52	2	28	19	0	0	10	0	0	0	0	36
Dasatinib	N	N	A	*FYN*	I	34	618	0	1	5	193	0	56	46	0	184	0	1	0	0	0	373
Erlotinib	N	N	A	*EGFR*	I	17	87	0	1	0	23	0	6	0	0	0	8	9	7	146	0	245
Celecoxib	Y	N	A	*PTGS2*	I	17	1,154	0	0	10	194	5	21	130	0	0	0	0	0	0	0	9

Notes: See Table 1. Extend = evidence that the drug can increase life span in model species per Fuentealba and colleagues (48); toxic = evidence exists that the drug is toxic per Fuentealba and colleagues (48). Extend: Y = yes, N = no. Toxic: Y = yes, N = no. Status: I = Investigational, A = approved, E = experimental. Mechanism: I = inhibitor, M = modulator.

Table 3. Variant Effect Annotations and Drug-Target Information on Variants Found to Be Associated With Human Longevity as Reviewed by Partridge and Colleagues (3)

Associated Variant Information				Druggable?		Annotations		Associations Involving Variants in LD With Target SNP							Chem Studies on Gene				
SNP	Gene	Refs	Chrom	PCh	TTD	eQTL?	# LD	Long	Age Rel	Other	LD eQ	LD pQ	LD mQ	LD O	#Ch	#Ch A	#TTD	#I/M	#Ant
rs6857	*APOE*	22	19	N	Y	N	1	0	18	2	0	0	0	0	0	0	2	2	0
rs2149954	*LINC02227*	51	5	N	N	Y	34	2	10	0	1	0	1	3	0	0	0	0	0
rs10457180	*FOXO3A*	52	6	Y	N	Y	26	0	17	8	2	0	1	0	9	2	0	0	0
rs2706372	*RAD50/IL13*	53	5	Y	N	Y	106	0	0	17	4	0	18	5	0	6	8	5	1
rs2892613	*MC2R*	54	18	Y	Y	N	1	0	0	0	0	0	0	0	34	4	1	0	0
rs139137459	*USP2-AS1*	54	11	N	N	N	1	0	0	0	0	0	0	0	0	0	0	0	0

Notes: See Table 1. SNP = SNP found to exhibit a statistically significant association with human longevity. Druggable PCh, TTD = the gene harboring the associated variants status as "druggable" according to ChEMBL (45) and the TTD (46), respectively, where Y = yes and N = no. eQTL = whether or not the associated variant is an eQTL based on GTEX query, where Y = yes and N = no (42). Chem Studies on Genes: #Ch = number of ChEMBL (45) entries with reported activity against gene sequences homologous to the sequence of the gene harboring the longevity-associated variant. #Ch A = number of ChEMBL entries with in-depth annotation information without leveraging paralogs, #TTD = number of entries for the gene in the TTD (46). #I/M = number of drugs in the TTD that modulate or agonize the gene. #Ant = number of drugs in the TTD antagonize the gene.

corticotropin administration is influenced by variants in the *MC2R* gene (58). The eQTL effects of the longevity-associated *FOXO3A* variant rs10457180 are on tibial nerve and artery tissue, making their relevance to pharmacologic modulation and potential connection to resveratrol in need of further investigation.

The meta-analysis of four GWAS studies described by Sebastiani and colleagues (22) led to the identification of 8 longevity-associated variants, including an *APOE* variant. Supplementary Table 3 provides our assessment of those variants. We note that Sebastiani and colleagues (22) did compile some information about eQTLs in LD with those variants but did not have access to the most recently developed tools and databases. Unfortunately, only one of the genes harboring longevity-associated variants is thought to be druggable, though a few of the genes have variants, which are in LD with other variants exhibiting functional effects (eg, the rs7185375 variant in the *SIAH1* gene and the rs72834698 variant in the *HIST1H2BD* gene).

Timmers and colleagues (23) conducted a very large GWAS on parental life spans as a proxy for an individual life span among participants in the UK Biobank Study and LifeGen study data (23). This study focused on natural variation in life span and not exceptional longevity as a unique phenotype. They identified 12 associated variants using standard GWAS (reviewed in our Supplementary Table 4a) as well as 7 additional variants using a Bayesian analysis that accommodated mortality risk factors in the association test with longevity (reviewed in our Supplementary Table 4b). Our assessment of these variants again suggests that many are within genes that are not thought to be druggable, or at least within gene products for which no known or experimental drugs are available, despite many being in LD with a variant associated with a wide variety of age-related diseases, phenotypes, and functional effects. A few of the genes harboring longevity-associated variants have been the focus of a large number of pharmacologic studies (eg, the *HTT* gene harboring the rs61348208 variants and the *ATXN2* gene harboring the rs11065979 variant).

Timmers and colleagues (23) also pursued an in-depth set of analyses seeking to identify genes whose expression levels are in likely variant-mediated causal pathways involving longevity based on Mendelian randomization tests (43). Table 4 provides the results of our assessments of these variants. Note that the authors identified multiple genes whose expression levels passed statistical criteria for being in a causal pathway from an associated variant to longevity. We present information about the reported associated variants only, but note that other variants in each of the implicated genes that might be of interest. Unfortunately, only a few of these variants implicate genes in a causal pathway involving longevity that are thought to be druggable, although all of them, being eQTLs themselves, are in LD with a number of variants associated with other phenotypes and a wide variety of functional variants. Many of the tissues affected by the longevity-associated eQTL variants are relevant to aging (eg, skeletal muscle, associated variant rs4970836 within gene *CELSR2*).

Table 4. Variant Effect Annotations and Drug-Target Information on eQTL Variants With Statistically Significant Evidence That They Are in a Causal Pathway Associated With Human Longevity Based on Analyses by Timmers and Colleagues (23)

Associated Variant Information					Drug?		Annot.	Associations Involving Variants in LD With Target SNP									Chem Studies on Gene				
SNP	Gene	Chr	Example Tissue	Number of Tissues	PCh	TTD	eQTL?	# LD	Long	Age Rel	Other	LD eQ	LD pQ	LD mQ	LD O	#Ch	#Ch A	#TTD	#I/M	#Ant
rs429358	*AC006126.4*	19	Testis	1	N	N	Y	1	2	14	32	0	0	1	0	0	0	0	0	—
rs429358	*CEACAM19*	19	Thyroid	2	N	N	Y	1	2	14	32	0	0	1	0	0	0	0	—	—
rs429358	*APOC1*	19	Esophagus mucosa	1	N	N	Y	1	2	14	32	0	0	1	0	0	0	0	—	—
rs11065979	*ALDH2*	12	Sun-exposed skin	1	Y	Y	Y	24	0	95	93	22	0	39	1	0	1	3	2	6
rs11065979	*CUX2*	12	Muscle skeletal	1	N	N	Y	24	0	95	93	22	0	39	1	0	0	0	—	—
rs1230666	*AP4B1-AS1*	1	Transformed fibroblasts	1	N	N	Y	1	0	1	2	0	0	0	0	353	0	0	—	—
rs3130507	*CCHCR1*	6	Sun-exposed skin	2	N	N	Y	18	0	0	0	2	0	5	2	0	0	0	—	—
rs3130507	*PSORS1C1*	6	Artery aorta	4	N	N	Y	18	0	0	0	2	0	5	2	0	0	0	—	—
rs4970836	*CELSR2*	1	Muscle skeletal	3	N	N	Y	11	0	16	56	52	0	2	11	0	0	0	—	—
rs4970836	*PSRC1*	1	Liver	3	N	N	Y	11	0	16	56	52	0	2	11	0	0	0	—	—
rs6224	*FES*	15	Transformed fibroblasts	9	N	Y	Y	10	0	6	0	11	0	3	0	1,835	0	2	0	2
rs6224	*FURIN*	15	Artery aorta	1	N	Y	Y	10	0	6	0	11	0	3	0	511	0	3	0	3
rs6224	*RCCD1*	15	Brain cerebellum	2	N	N	Y	10	0	6	0	11	0	3	0	0	0	0	—	—
rs113160991	*PMS2P3*	7	Esophagus muscularis	6	N	N	Y	13	0	0	0	30	0	1	15	0	0	0	—	—
rs8042849	*RP11-650L12.2*	15	Lung	2	N	N	Y	41	2	13	149	13	0	10	16	0	0	0	—	—
rs11133005	*SLC22A1*	6	Pituitary	6	N	N	Y	33	0	0	0	6	0	0	0	437	0	0	—	—

Notes: See Table 3. A dash (—) in a cell indicates that we could not find information about the gene or variants in the gene with the resources we used. Drug = Druggable? Annot. = Annotations. PCh: Y = yes, N = no. TTD: Y = yes, N = no. eQTL: Y = yes, N = no.

Variants associated with healthspan

Zenin and colleagues recently pursued a GWAS exploring the age at which an individual likely succumbed to disease and was in a healthy state prior to that age over their life and identified 12 "healthspan"-associated variants (24). Along with these health-enhancing variants, we also gathered information about a variant in the *TTR* gene that has been shown to influence healthspan and longevity as discussed by Hornstrup and colleagues (25). Supplementary Table 5 provides the results, with the first 12 rows corresponding to the variants identified by Zenin and colleagues (24) and the last row corresponding

to the *TTR* variant discussed by Hornstrup and colleagues (25). As with the longevity-associated variants, many of the variants found to be associated with healthspan are not located in genes coding for proteins for which drug-target information is available, although many themselves are eQTLs or in LD with eQTLs and variants associated with nonlongevity phenotypes.

Variants shown to be protective against diseases

We finally considered genes that harbor multiple rare variants that have been associated with protection against diseases (ie, they seem to confer health benefits to those that possess them) as reviewed Harper and colleagues (44). These protective variants may or may not protect against all or most age-related diseases, however. Given the number and rarity of the variants exhibiting protective effects, we considered the properties of the genes they were identified in, rather than the individual variants themselves. Supplementary Table 6 provides the results. All but one (*SLC30A8*) is considered to be druggable, which makes sense since these genes have gathered a great deal of interest as drug targets. There are many eQTLs and variants associated with phenotypes other than longevity, but whether these variants are in LD with the rare variants thought to have functional effects, and induce the positive phenotypes they are associated with, needs further exploration.

Discussion

The genomics era has resulted in a number of major initiatives focusing on naturally occurring human genetic variation, such as the Human Genome Project (59), the International Hapmap Project (60), the 1000 Genomes Project (50), and The Cancer Genome Atlas (TCGA) project (61), among many others. We considered the utility of genetic information in prioritizing or validating drug targets for longevity-enhancing interventions. We identified drugs and compounds thought to have potential to enhance human longevity, collated naturally occurring variants in the gene and protein targets for these drugs, and looked to see whether these variants have been associated with longevity, or if they influence the molecular functions of those targets. We also brought together, from published literature, lists of variants allegedly associated with longevity, healthspan, or protection from disease, and asked if the genes they reside in are reasonable targets for drug development.

The fact that we found that no drug hypothesized to modify human longevity targets a gene that harbors variants found to be associated with longevity to date and that no associated variants have led to a longevity-enhancing drug development campaign, suggests, among other things, that (i) many proposed drugs are not targeting relevant biology related to human longevity (at least as revealed by GWAS); (ii) the genetic associations from GWAS are too weak and ambiguous to reveal compelling targets; and/or (iii) more comprehensive data sets and studies are needed to make genetic association data "actionable" at some level. We believe that the third explanation is likely the best because we did find that there is an incredibly rich biology uncovered by the effects of genetic variants on mechanisms, like gene expression levels, that could be exploited in drug-target identification studies with more systematic analysis. In this light, our work can be seen as a starting point for more comprehensive assessments of genetically mediated biological targets for longevity-enhancing drugs. For example, we believe our work can motivate more sophisticated consideration of genetic association and, for example, eQTL and pQTL studies in work like that of Partridge and colleagues (48) and Cardoso and colleagues (62), which seek to integrate different sources of information in analyses designed to prioritize drugs and biomarkers for further study (27). In fact, a very recent study exploring the utility of genetic association studies in drug target analysis for immune-related diseases provides an excellent example of the type of integration that we feel is necessary (63). Unfortunately, the data sets and information that the authors exploited, including study results using assays on humans interrogating processes known to be of fundamental importance to immune diseases, are lacking with respect to human longevity. It is noteworthy, however, that the National Institutes on Aging (NIA) of the U.S. National Institutes of Health (NIH) have recently funded initiatives designed to generate more sophisticated data and methods that could enable longevity-enhancing drug-target identification and validation (eg, the Longevity Consortium (https://www.longevityconsortium.org) and the Longevity Genomics (https://www.longevitygenomics.org) initiatives.

Given the hype surrounding genetic studies and the somewhat humbling results of our studies, which suggest no obvious connections between genetic associations and drugs currently hypothesized to enhance human longevity exist, we believe our work exposes a number of serious shortcomings with the use of genetic data for identifying, prioritizing, or validating drug targets for human longevity that are also touched on in the study by Fang and colleagues (63). We describe a few of these shortcomings below—many of which are relevant to our very specific analyses—but feel these descriptions are less of a focused critique of what we have produced and more of an indication of what needs to be done going forward, so that better integration of genetic information into bioinformatics analyses can be pursued (27).

Exploitation of Results of GWAS Involving Other Ancestral Groups

We used variant and LD information obtained from individuals of European descent, though many variants are population specific and/or exhibit different LD relationships in individuals of non-European descent.

Consideration of Different Levels of LD

We chose to only consider variants with an LD strength > 0.8 for target variants or those in LD with eQTLs within a gene. Different LD strengths could provide a different picture of the functional landscape of a gene.

Consideration of the Direction of Effect of a Variant's Associations

A variant could increase or decrease, for example, the expression level of a gene. If this variant is associated with a relevant phenotype as well, then the direction of effect on gene expression level could indicate whether a drug should enhance or antagonize the expression of the gene to achieve the same phenotypic effect.

Leveraging Pleiotropy and Unpacking Diseases Associated With Variants

We cataloged variants associated with many age-related diseases, but if many variants are associated with the same disease, this provides a different picture of the pleiotropic effects of the gene than if many variants are associated with different diseases.

Unpacking the Number of Associations for a Gene

We summed up the number of variants associated with different phenotypes, but the resulting sum may involve different variants in varying degrees of LD or variants in very strong LD. These two scenarios have different biological consequences, wherein variation induced by a gene's functional differences attributable to individual variants is due to a single haplotype that deviates from the others functionally or whether there are multiple haplotypes (alleles) that each differs from the others. In addition, the mere assignment of a variant to an individual gene can be problematic if the variant resides in DNA sequence that does not encode a particular gene or if the sequence does encode a gene but that gene is alternatively spliced such that the variant may not affect all forms of protein translated from that gene's sequence.

Exploring the Effects of Multiple eQTLs Within a Gene

A gene that harbors many eQTLs, pQTLs, etc. is likely to regulate a wider range of molecular phenomena. This could indicate that the gene participates in a network filled with feedback and redundancy mechanisms, which could affect its candidacy as a drug target.

Making Better Use of Orthology Information

Many drugs and compounds have been tested in model organisms for their effects on longevity, such as those pursued by the ITP (20), but the relevance of the effects observed in model species to humans is an open question. Exploring the degree of homology between nonhuman and human genes and incorporating this information into cross-species analyses may be useful in this context.

Better Phenotyping and Indices of Health

Individual life span is a very crude phenotype and does not capture the underlying "subclinical" aspects of health that might exist in people who die early of nongenetic causes (eg, accidents, malnutrition, war, etc.) nor what might be possessed by people who would have died earlier without extensive health care or a favorable but rare environment. Therefore, better measures of underlying robustness, vitality, and functional enhancements (eg, muscle strength, excellent vision, etc.) are needed for GWAS and related studies.

Better Molecular Phenotyping of Longevity-Related Processes

Disease-focused research communities often exploit extensive molecular phenotyping (eg, lipid biology in cardiovascular disease, inflammation in rheumatic disease, etc.) to help put drug targets and potential interventions into biological perspective. Researchers investigating longevity need better phenotyping of aging-related processes, such as "rate of aging measures" or measurable facets of the hallmarks of aging, that could be subjected to GWAS (64,65). This activity could lead to better biomarkers of aging to be considered in causal analyses of longevity (see below).

Incorporating Biomarker Data

eQTLs, pQTLs, and so forth capture the effects of variants on measurable molecular phenotypes. These molecular phenotypes could themselves be tested for association with longevity (eg, a gene's expression level in whole blood or skin may correlate with longevity). Many molecular phenotypes have been treated as biomarkers and tested for association with longevity and aging-related phenotypes (62). Information about whether such biomarkers are associated with longevity-related phenotypes could help solidify causal chains leading from a variant to a longevity-related phenotype, but the tissue in which that biomarker has been measured is important to consider. Note that systematically testing such causal chains for prioritization is crucial if there are many such potential causal connections (43).

Exploiting the Power of Network Biology

The role of a gene within a broader network of genes is important for placing drug candidates into context. For example, a gene may harbor a variant associated with a longevity phenotype, but its druggability has not been demonstrated yet. However, if that gene is known to modulate another gene in an extended causal chain leading from the variant to the longevity phenotype, then the gene that is modulated by the other could be thought of as a drug target. Thus, including network module and pathway information into studies like ours may be of crucial importance.

As we have emphasized, although our efforts to compile and process relevant information on the genetic support for longevity-enhancing drug targets are hardly exhaustive, we pursued it to show the potential, and limitations, of the use of such information. We ultimately find that there is a great deal of potential in using genetic association information for longevity-enhancing drug-target studies, particularly with respect to prioritization and lead development. However, we also believe that more detailed and focused mining of the information, along with relevant query tool and resource development, will be necessary to have a broader impact. We hope that our efforts will motivate the pursuit of appropriate studies and tool development.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None reported.

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