Polygenic risk score for disability and insights into disability-related molecular mechanisms

Alexander M. Kulminski · Chansuk Kang · Stanislav A. Kolpakov · Yury Loika · Alireza Nazarian · Anatoliy I. Yashin · Eric Stallard · Irina Culminskaya

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Abstract Late life disability is a highly devastating condition affecting 20% or more of persons aged 65 years and older in the USA; it is an important determinant of acute medical and long-term care costs which represent a growing burden on national economies. Disability is a multifactorial trait that contributes substantially to decline of health/wellbeing. Accordingly, gaining insights into the genetics of disability could help in identifying molecular mechanisms of this devastating condition and age-related processes contributing to a large fraction of specific geriatric conditions, concordantly with geroscience. We performed a genome-wide association study of disability in a sample of 24,068 subjects from five studies with 12,550 disabled individuals. We identified 30 promising disability-associated polymorphisms in 19 loci at $p < 10^{-4}$; four of them attained suggestive significance, $p < 10^{-5}$. In contrast, polygenic risk scores aggregating effects of minor alleles of independent SNPs that were adversely or beneficially associated with disability showed highly significant associations in meta-analysis, $p = 3.13 \times 10^{-45}$ and $p = 5.60 \times 10^{-23}$, respectively, and were replicated in each study. The analysis of genetic pathways, related

diseases, and biological functions supported the connections of genes for the identified SNPs with disabling and age-related conditions primarily through oxidative/nitrosative stress, inflammatory response, and ciliary signaling. We identified musculoskeletal system development, maintenance, and regeneration as important components of gene functions. The beneficial and adverse gene sets may be differently implicated in the development of musculoskeletal-related disability with the beneficial set characterized, e.g., by regulation of chondrocyte proliferation and bone formation, and the adverse set by inflammation and bone loss.

Keywords Disability · Polygenic risk score · Genetic architecture · Biological function

Introduction

The recent demographic transition from high to low birth/death rates resulted in population aging worldwide. According to the World Health Organization (WHO), the proportion of individuals aged 60 years or older is expected to increase from 900 million (12%) in 2015 to 2 billion (22%) in 2050. About 80% of such persons are projected to be living in low- and middle-income countries. Age-related processes are among the most important risk factors for diseases (e.g., cardiovascular diseases [CVD], cancer, Alzheimer's disease), chronic conditions (e.g., hearing loss, cataracts, arthritis), disability, and frailty (Guarente 2011; Jitapunkul et al. 2003; Zhavoronkov and Moskalev 2016).

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A. M. Kulminski (✉) · C. Kang · S. A. Kolpakov · Y. Loika · A. Nazarian · A. I. Yashin · E. Stallard · I. Culminskaya
Biodemography of Aging Research Unit, Social Science Research Institute, Duke University, Durham, NC 27708-0408, USA
e-mail: Alexander.Kulminski@duke.edu

In the USA, nearly 20% of the elderly (aged 65+ years) had chronic disabilities in 2004/2005 (Manton et al. 2006). Chronic disability is broadly defined as difficulty or dependency in carrying out activities essential to independent living, including essential roles, tasks needed for self-care and living independently in a home, and desired activities important to the individual's quality of life (Adams et al. 1999; Pope and Tarlov 1991). Chronic disability in late life is an important determinant of acute medical and long-term care costs which represent a growing burden on national economies (Okoro et al. 2018; Trupin et al. 1995).

Dealing with population aging requires strategies that could extend health span by compressing late life morbidity and disability while extending the life span (Fries 1980; Manton 1982; Robine 2003; Stallard 2016; Stallard 2019). Identifying the genetic architecture of factors contributing to these processes could yield major breakthroughs in advancing the understanding of biological mechanisms of successful aging. Progress in genome-wide sequencing has created the potential for discovering genes influencing various health-related traits. The vast majority of such studies focus on the genetic bases of different traits assuming that they have independent mechanisms. As conceptualized by geroscience (Kaeberlein et al. 2015), age and aging are major risk factors of geriatric traits of distinct etiologies (Franco et al. 2009; Olshansky et al. 2007; Sierra et al. 2008). Accordingly, the same mechanisms can predispose not to just one, but to a large fraction of geriatric conditions (Franceschi and Garagnani 2016; Martin 2007).

One strategy to identify the common genetic architecture of various traits is to search for pleiotropic variants (Kulminski et al. 2016; Kulminski et al. 2019; Pickrell et al. 2016; Visscher and Yang 2016). An alternative strategy is to attempt to discover the genetic architecture of complex multifactorial traits contributing substantially to decline of health and wellbeing, such as disability. The few studies to date of the genetic architecture of disability have been mostly limited to specific conditions and factors such as physical performance, anthropometry, and muscle strength (Garatachea and Lucia 2013; Heckerman et al. 2017). To address this critical gap in the literature, we perform a genome-wide analysis of the genetic predisposition to disability using a more comprehensive definition based on impairments in any of four basic activities of daily living (ADL):

bathing, dressing, getting out of bed, and walking (Katz and Akpom 1976). These ADLs represent the primary musculoskeletal components of late life disability. We will separately address the other components (e.g., cognitive) in future analyses.

Methods

Study cohorts

We use data from five large-scale studies (Table 1): the Women's Health Initiative (WHI) Genomics and Randomized Trials Network (WHI GARNET), the WHI Memory Study (WHIMS) (The Women's Health Initiative Study Group 1998), the Cardiovascular Health Study (CHS) (Fried et al. 1991), the Framingham Heart Study (FHS) (Cupples et al. 2009), and the Health and Retirement Study (HRS) (Juster and Suzman 1995). We used data available for participants of the FHS original and offspring cohorts who had information on disability. The analyses focused on subjects of European ancestry.

Disability

Disability in the WHI, CHS, FHS, and HRS was measured using the ADL scale which included individual's daily self-care activities, such as bathing, dressing, eating, getting out of bed, and walking (Katz and Akpom 1976). If an individual reported problem executing an activity during follow-up, the individual was considered having an impairment in performing that activity. We created a composite binary index of disability as having at least one of four ADL impairments (bathing, dressing, getting out of bed, and walking) vs. none of them, to better capture the multidimensional concept of disability. Because disability was reported at multiple examinations in these studies, we defined the control variable "age" using age at first report of disability in the disabled (case) group and average age over the entire follow up in the non-disabled (control) group. All individuals in our study were 50 years or older (WHI and HRS ≥ 50 , FHS ≥ 60 , and CHS ≥ 65).

Table 1 Basic descriptive statistics for the genotyped participants in the selected studies

Factor	WHI GARNET	WHIMS	CHS	FHS	HRS
<i>N</i>	3311	5167	4308	2430	8852
Disability cases (%)	1433 (43%)	2200 (43%)	2573 (60%)	233 (10%)	6111 (69%)
Disabled, mean age (SD)	74.84 (6.71)	77.78 (5.13)	78.19 (5.63)	70.69 (4.82)	71.6 (10.47)
Non-disabled, mean age (SD)	72.54 (6.54)	75.33 (5.71)	75.78 (5.10)	67.79 (4.70)	64.5 (9.86)
Women (%)	100%	100%	56%	56%	59%

N indicates the number of genotyped participants after quality control check (see section “Genotypes” in “Methods”). SD indicates standard deviation

WHI GARNET Women’s Health Initiative (WHI) Genomics and Randomized Trials Network; *WHIMS* WHI Memory Study, *CHS* Cardiovascular Health Study, *FHS* Framingham Heart Study, *HRS* Health and Retirement Study

Genotypes

Genotyping was performed using the same customized Illumina iSelect array (the IBC-chip, ~ 50 K single nucleotide polymorphisms [SNPs]) in the FHS and CHS cohorts, Affymetrix 500 K and 50 K chips in the FHS, Illumina HumanCNV370v1 chip (370 K SNPs) in the CHS, Illumina HumanOmni 2.5 Quad chip (~ 2.5 M SNPs) in the HRS, Illumina HumanOmni1-Quad_v1-0_B chip (1 M SNPs) in WHI GARNET, and Illumina HumanOmniExpress-12v1 chip (706 K SNPs) in WHIMS. To facilitate cross-platform comparison, we imputed about 2.5 M autosomal SNPs in FHS and CHS. Genome coordinates of SNPs in our data (NCBI build 38/UCSC hg38) were lifted over to NCBI build 37/UCSC hg19 using liftOver software (Hinrichs et al. 2006). After removing duplicate SNPs, pre-imputation QC was performed using PLINK (Purcell et al. 2007) to remove low-quality SNPs/subjects by setting the following QC criteria: minor allele frequency (MAF) < 5%, SNPs and subject call rates < 95%, Hardy-Weinberg disequilibrium *p* values < 10^{-6} . Because the FHS has family-based designs, a Mendel error rate of 2% was set to remove SNPs and subjects/families with high Mendelian errors. Strand alignment was checked using the SHAPEIT2 (i.e., Segmented Haplotype Estimation and Imputation Tool) package (Delaneau et al. 2011) to ensure that allele calls are consistent between our and reference data. Haplotype phasing was then conducted using SHAPEIT2 to estimate the haplotypes for subjects in each dataset. Finally, genotypes were imputed by Minimac3 software (Das et al. 2016) over pre-phased haplotypes. SHAPEIT2 and Minimac3 were run using default

values for input arguments and European population (EUR) haplotypes from 1000 Genomes Phase 3 data as the reference panel. Only high-quality imputed SNPs (with squared correlation $r^2 > 0.8$ between imputed and expected true genotypes) were retained. Directly genotyped and imputed SNPs were then subject to post-imputation QC using the same criteria as above with the exception of retaining directly genotyped SNPs with MAF > 2%.

Genome wide association study and meta-analysis

We used a three-step approach to perform genome wide association study (GWAS) of disability. In the first step, a logistic regression model (PLINK (Purcell et al. 2007)) was fitted to evaluate the associations between SNPs and the binary disability index in each study. All models were adjusted for age (all studies) and sex (CHS, FHS, and HRS). The models were not adjusted for principal components because of their trivial effect in these populations of European ancestry. In the second step, we selected SNPs that attained nominal significance ($p < 0.05$) in GWAS of FHS. We re-evaluated these associations using a generalized estimating equation (GEE) mixed-effects model (*GWAF* package in R) to correct for potential familial clustering in the FHS family-based data (Manichaikul et al. 2012). In the third step, we performed meta-analysis (fixed-effect meta-regression) using METAL software (Willer et al. 2010) to increase the power to detect statistically significant associations by pooling the results from step 1 (all studies except FHS) and step 2 (FHS only). We followed the discovery-replication strategy selecting SNPs

attaining nominal significance ($p < 0.05$) either in WHI GARNET (9,076 SNPs) or HRS (4,984 SNPs) studies. Then, we performed meta-analysis for these selected SNPs using all studies.

Polygenic risk scores

We computed polygenic risk scores (PRS) by aggregating statistical effects for minor alleles of all SNPs (PRS_{all}) and of SNPs that have positive (PRS_P) or negative (PRS_N) effect beta separately. We evaluated PRS as simple counts (unweighted) and weighted sums of disability-associated alleles identified by our GWAS meta-analysis. We conducted logistic regression analyses in each study using the GEE model to examine the associations between PRS and disability, after controlling for age and sex. Finally, we conducted meta-analysis using METAL software (Willer et al. 2010).

Heterogeneity

We used Cochran's Q test for heterogeneity implemented in METAL software (Willer et al. 2010) and evaluated the heterogeneity coefficient I^2 and p value. The I^2 can be interpreted as the percentage of the total variability in a set of effect sizes due to between-sample variability.

Mapping to genes

SNPs were mapped to genes using the Ensembl genome browser 97 (<https://ensembl.org>) and NCBI SNP database (assembly GRCh38.p13). If an index SNP was not within protein coding gene, the closest up- and/or downstream gene(s) was(were) assigned. We considered distance within ± 700 Kb flanking region of the gene(s) as affected genes can be far away (often up to 2 Mb) from the associated SNP (Brodie et al. 2016).

Bioinformatics analysis

We used the core analysis function in the Ingenuity Pathway Analysis (IPA) bioinformatics tool (www.qiagenbioinformatics.com) to examine enrichment of genes for the disability-associated SNPs in pathways, diseases, and biological functions. IPA was also used to carry out a comparative analysis between different gene sets. The results were scored on the basis of the negative

base-10 logarithm of the p value or the untransformed p value provided by the Fisher's exact test implemented in IPA. These analyses were supported by manual analysis of gene functions.

Results

Associations with disability

Disability-associated SNPs selected based on nominal significance ($p < 0.05$) at the discovery stage (see "Methods") either in WHI GARNET or HRS studies were examined in the other three independent datasets (WHIMS, CHS, and FHS). Meta-analysis of the results identified 30 SNPs in 19 loci at $p < 10^{-4}$ (Table 2). Loci on the same chromosome were considered as independent if SNPs were spaced by more than ~ 1 Mb. Four SNPs on chromosomes 2, 8, and 12 attained suggestive level of significance, $p < 10^{-5}$. For most SNPs, the effect directions were consistent across all studies. Minor alleles of 11 SNPs in 7 loci showed beneficial association with disability whereas minor alleles of the remaining 19 SNPs were adversely associated with disability.

Linkage disequilibrium (LD) analysis identified 22 SNPs in 19 loci considered as non-correlated, with pairwise LD $r^2 < 20\%$. Although two SNPs on chromosome 2 were in the same locus 3, LD between them was $r^2 = 2\%$ and, therefore, they were considered as independent. These 22 SNPs (Table 2) were used to construct PRS_P and PRS_N (see "Methods"). In addition, we also constructed PRS_{all} , which aggregated effects of minor alleles of all 30 SNPs.

PRS_P attained genome-wide significance ($p < 5 \times 10^{-8}$) in each of the two discovery studies, WHI GARNET and HRS, whereas PRS_N in the HRS only (Table 3). As expected, PRS_{all} showed the least significant associations because positive and negative effects of minor alleles tended to cancel out. The effect of each PRS was replicated in independent studies, although the association of PRS_N with disability did not attain nominal significance in the FHS. Because we used weights to construct PRS from our own meta-analysis of all five studies (Table 2), we verified that weights did not bias the results of replication of PRS in independent studies. This was done by evaluating unweighted PRS as simple count of the effect alleles (Table S1 in Online Resource 2). These estimates resembled those for the weighted PRS.

Table 2 GWAS meta-analysis results for associations of the top 30 SNPs with late life disability

Chr	SNP ID	Location	MAF*	Alleles	Locus	Effect	SE	P value	ES sign	I^2 , %	P-het	PRS
1	rs12123186	238,903,098	0.129	T/c	1	0.125	0.032	9.01E-05	+++++	0	0.727	P
2	rs17642263	138,637,196	0.429	T/g	2	0.087	0.021	4.68E-05	+++++	34.7	0.19	
2	rs11691636	138,638,997	0.375	C/t	2	0.094	0.022	1.50E-05	+++++	24.1	0.261	P
2	rs1840641	138,685,102	0.445	G/t	2	0.088	0.021	3.48E-05	+++++	15.3	0.317	
2	rs11691125	208,530,365	0.393	T/g	3	0.087	0.022	6.58E-05	+++++	3.9	0.384	P
2	rs2576810	209,332,455	0.218	T/a	3	− 0.1	0.026	9.10E-05	-----	46.8	0.111	N
2	rs13428970	215,122,782	0.231	T/c	4	− 0.11	0.025	1.37E-05	-----	0	0.818	N
2	rs6720010	215,145,421	0.225	T/c	4	− 0.107	0.025	2.25E-05	-----	0	0.719	
2	rs1064767	241,816,010	0.188	C/t	5	0.106	0.027	7.61E-05	+++++	0	0.533	
2	rs15129	241,817,649	0.193	C/t	5	0.105	0.026	7.47E-05	+++++	9.8	0.351	P
2	rs7568	241,940,416	0.188	G/a	5	0.119	0.028	1.48E-05	+++++	0	0.569	
2	rs16843642	242,000,052	0.187	G/t	5	0.118	0.028	1.92E-05	+++++	0	0.46	
2	rs764081	242,042,814	0.295	T/g	5	0.106	0.024	8.15E-06	+++++	12.9	0.332	P
3	rs7623610	70,005,281	0.457	A/g	6	0.091	0.022	3.57E-05	+++++	0	0.909	P
4	rs3796434	96,250,600	0.475	A/g	7	0.085	0.021	5.53E-05	+++++	19.4	0.291	P
5	rs6876015	95,189,713	0.261	C/t	8	− 0.097	0.025	8.48E-05	-----	0	0.887	N
5	rs1948429	115,994,775	0.312	C/a	9	0.091	0.023	9.04E-05	+++++	15.8	0.314	P
7	rs10270664	46,260,765	0.395	A/c	10	0.089	0.022	3.95E-05	+++++	13.1	0.33	P
8	rs1470969	115,810,385	0.382	G/a	11	− 0.085	0.022	9.65E-05	-----	0	0.725	N
8	rs9297534	115,843,061	0.33	C/t	11	− 0.091	0.022	5.59E-05	-----+	0	0.847	
8	rs7004742	115,851,352	0.329	T/c	11	− 0.1	0.022	7.11E-06	-----	0	0.786	N
8	rs6986502	115,853,096	0.307	T/c	11	− 0.103	0.024	1.20E-05	-----	0	0.963	
12	rs7138679	40,378,647	0.39	T/c	12	− 0.098	0.022	8.52E-06	-----	0	0.477	N
12	rs4766836	116,157,399	0.099	A/c	13	0.169	0.036	2.60E-06	+++++	0	0.795	P
13	rs16972472	109,091,885	0.084	G/a	14	0.154	0.037	3.19E-05	+++++	0	0.638	P
16	rs11149598	82,254,927	0.143	A/g	15	− 0.12	0.031	9.05E-05	-----	0	0.62	N
18	rs894769	45,995,224	0.341	C/t	16	0.096	0.023	3.24E-05	+++++	15.2	0.317	P
19	rs12460407	8,087,037	0.27	C/t	17	− 0.099	0.024	3.23E-05	-----	23.5	0.265	N
21	rs2835682	37,544,604	0.424	C/t	18	0.091	0.022	2.20E-05	+++---	68.3	0.013	P
22	rs5769520	49,671,776	0.283	G/t	19	0.094	0.024	8.23E-05	++++-	34.9	0.189	P

Alleles: upper/lower case letters denote major/minor alleles. ES signs: signs of the effect sizes in the WHI GARNET, WHIMS, HRS, CHS, and FHS cohorts, respectively. I^2 is the heterogeneity coefficient and P-het denotes p value from the Cochran's Q test for heterogeneity. Column PRS (polygenic risk score) indicates SNPs included in the PRSs aggregating the effects of minor alleles of (1) SNPs with positive effect (P) and (2) SNPs with negative (N) effect

*Minor allele frequencies (MAF) were the same in all studies; they were representatively taken from the WHI GARNET study. *Chr*, chromosome; *Location*, location in base pairs; *SE*, standard error

Biological role

The identified 30 SNPs were mapped to 25 genes (see “Methods”) (Table 4). Of them, 16 SNPs were located within 13 functional genes. Eleven SNPs were either located in regulatory regions or were in strong LD ($r^2 \geq 0.7$) with variants in regulatory regions. Three sets of genes were selected for further analyses:

(i) all 25 genes, (ii) 18 genes corresponding to SNPs with adverse effects of the minor alleles (positive direction of the effect beta), and (iii) seven genes corresponding to SNPs with beneficial effects of the minor alleles (negative direction of the effect beta). These sets were referred to as PRS_{all}, PRS_P, and PRS_N, respectively, as these genes were for the corresponding SNPs.

Table 3 Associations of weighted polygenic risk scores (PRS) with disability

Study	PRS _{all}			PRS _P			PRS _N		
	Effect	SE	P value	Effect	SE	P value	Effect	SE	P value
WHI_GARNET	0.304	0.113	6.83E–03	1.141	0.151	3.65E–14	– 0.810	0.171	2.06E–06
WHIMS	0.266	0.090	3.07E–03	0.986	0.122	7.27E–16	– 0.662	0.137	1.27E–06
HRS	0.152	0.074	4.11E–02	0.728	0.095	2.05E–14	– 0.791	0.121	6.83E–11
CHS	0.235	0.126	6.31E–02	0.732	0.161	5.75E–06	– 0.564	0.203	5.44E–03
FHS	0.182	0.255	4.75E–01	0.705	0.314	2.45E–02	– 0.643	0.402	1.10E–01
Meta-analysis	0.221	0.047	2.09E–06	0.859	0.061	3.13E–45	– 0.723	0.073	5.60E–23

PRS_{all}, PRS_P, and PRS_N indicate PRS aggregating effects for minor alleles of all SNPs, and SNPs with positive and negative directions of the effects, respectively

SE standard error, WHI GARNET Women's Health Initiative (WHI) Genomics and Randomized Trials Network, WHIMS WHI Memory Study, CHS Cardiovascular Health Study, FHS Framingham Heart Study, and HRS Health and Retirement Study

The IPA core analysis identified 15 canonical pathways that attained conventional ($p < 0.05$) significance in any of these three sets (Fig. 1, Table S2 in Online Resource 3). Pathways enriched for genes from the adverse PRS_P set were not enriched in the beneficial PRS_N set and vice versa. The top pathways for the PRS_N set, *Glutathione redox reactions II* and *Ascorbate recycling (cytosolic)* pathways, accent on a role of glutathione/glutaredoxin system in defense against oxidative stress. The top pathway for the adverse PRS_P set *Citrulline-nitric oxide cycle* (along with the related pathways including *nNOS signaling in skeletal muscle cells* and *nNOS signaling in neurons*) suggests a role of nitric oxide (NO) production and neuronal nitric oxide synthase (NOS1) signaling in tissue homeostasis. Central to the regulation of inflammation, immunity, and acute phase responses, *NF-κB signaling* is linked with NO production and NOS1 (Baig et al. 2015; Qu et al. 2001).

The IPA analysis identified relevant categories of diseases and biological functions, and their associated genes. Top 50 categories of diseases and functions and their subcategories are listed in Table S3 (Online Resource 4) for the PRS_{all} set. Figure 2 shows top subcategories of diseases and functions characteristic for the PRS_{all} set in comparison with their enrichment in the PRS_P and PRS_N sets. Table S4 in Online Resource 5 presents the results of the IPA analysis specified for diseases and disorders for the three sets. Each functional category in Table S4 (Online Resource 5) represents a collection of associated subcategories each of which has an associated p value.

In general, the most significant diseases and functions were related to organismal development,

organismal injury and abnormalities, cardiovascular, nervous and visual systems development and function, cell morphology, cellular assembly and organization, cellular function and maintenance, cellular growth and proliferation, and cell signaling (Table S3 in Online Resource 4). The top subcategories for the PRS_{all} set were related to vision (i.e., retinal neovascularization, development of choroid), formation of cellular protrusions, proliferation and maturation of chondrocytes, etc. (Fig. 2 and Table S3 in Online Resource 4). Comparative analysis showed overlap of some significant subcategories of diseases and functions between the adverse PRS_P and beneficial PRS_N sets, i.e., retinal neovascularization, transmembrane receptor protein serine/threonine kinase signaling, and proliferation and maturation of chondrocytes. The PRS_P set was characterized by subcategories related to nervous system and bone volume. In line with the pathway analysis, the beneficial PRS_N-specific subcategories *linkage of glutathione* and *deglutathionylation of L-cysteine* supported a role of glutathione/glutaredoxin system.

The IPA analysis links the most significant disease categories to the disability-related health conditions such as neurological and psychological disorders, ophthalmic diseases, musculoskeletal/connective tissue disorders, cancer, and cardiovascular diseases (Table S4 in Online Resource 5). Disease categories such as *organismal injury and abnormalities* and *skeletal and muscular disorders* were consistently higher ranked in each of the three gene sets. Apart from these categories, the beneficial PRS_N set was characterized by developmental/hereditary disorders, gastrointestinal, endocrine, and dermatological diseases, whereas the adverse PRS_P set included larger number of

Table 4 Functional annotation of the 30 disability-associated SNPs

Chr	SNP ID	Function	Regulation	Gene
1	rs12123186	Intergenic		CHRM3*
2	rs17642263	Intergenic		HNMT*
2	rs11691636	Intergenic		HNMT*
2	rs1840641	Intergenic		HNMT*
2	rs11691125**	Intron	PFR	PLEKHM3
2	rs2576810**	Intron	PFR, TF-BS, CTCF-BS	PTH2R
2	rs13428970**	Intron	Enhancer, TF-BS	VWC2L
2	rs6720010**	Intron	Enhancer, TF-BS	VWC2L
2	rs1064767	3'-UTR		HDLBP
2	rs15129	3'-UTR		HDLBP
2	rs7568	3'-UTR	PFR, TF-BS	SEPTIN2
2	rs16843642	Intron	PFR, TF-BS	FARP2
2	rs764081	Intron		FARP2
3	rs7623610	Intron		MITF
4	rs3796434**	Intron	Enhancer, TF-BS	BMPRI1B
5	rs6876015	Intergenic		GLRX*
5	rs1948429	Intergenic		SEMA6A*
7	rs10270664	Intergenic		IGFBP3*
8	rs1470969	Intergenic		TRPS1*
8	rs9297534	Intergenic		TRPS1*
8	rs7004742	Intergenic		TRPS1*
8	rs6986502	Intergenic		TRPS1*
12	rs7138679	Intron		SLC2A13
12	rs4766836	Intron	CTCF-BS, TF-BS	NOS1
13	rs16972472	Intron	OCR, TF-BS	MYO16*; TNFSF13B*
16	rs11149598	Intron		CDH13
18	rs894769	Intergenic		MYO5B*; CFAP53*
19	rs12460407**	Intron	PFR, TF-BS	FBN3
21	rs2835682	Intron	PFR, TF-BS	VPS26C
22	rs5769520	Intergenic		TAF5*; BRD1*

Chr chromosome, *PFR* promoter flanking region, *TF-BS* transcription factor binding site, *CTCF-BS* CTCF-binding site, *OCR* open chromatin region

*Nearest protein-coding (biologically plausible) gene(s) within ± 700 Kb of the intergenic SNPs

**Regulatory function is given for proxies in high linkage disequilibrium with $r^2 \geq 0.8$

disability-related disease categories such as nervous system diseases and mental disorders, visual system and auditory diseases, cancer, and cardiovascular diseases.

The IPA and manual analyses identified 23 genes involved in nervous system development, maintenance of neurological processes, and neurological disorders, i.e., *BMPRI1B*, *BRD1*, *CDH13*, *CHRM3*, *FARP2*, *FBN3*, *IGFBP3*, *GLRX*, *HDLBP*, *HNMT*, *MITF*, *MYO16*, *MYO5B*, *NOS1*, *PTH2R*, *SEMA6A*, *SEPTIN2*, *SLC2A13*,

TAF5, *TNFSF13B*, *TRPS1*, *VPS26C*, *VWC2L*. Most of these genes were also related to musculoskeletal system development, maintenance and repair, and/or were associated with musculoskeletal disorders (all the above, apart *HNMT*, plus *PLEKHM3*). IPA implicates eight genes in formation and function of cellular protrusions (see Table S3 in Online Resource 4, *formation of cellular protrusions* subcategory), which are important for cell migration and cell-cell communication. Indeed, five of

Fig. 1 Enrichment of canonical pathways in three gene sets. PRS_{all}, PRS_p and PRS_n indicate polygenic risk scores aggregating effects for minor alleles of all SNPs, and SNPs with positive and negative directions of the effects, respectively. Color coding for $-\log_{10}(p \text{ value})$ is given in the inset. Numerical estimates are given in Table S2 in Online Resource 3

these genes (*CFAP53*, *MYO5B*, *NOS1*, *SEPTIN2*, *VPS26C*) complemented by two genes identified by the manual analysis (*CHRM3*, *FBN3*) were involved in formation and function of primary cilia, microtubular protrusions present on the apical surface of most vertebrate cells, and/or in ciliopathies.

Genes implicated in development of chondrocytes (the only resident cells in the articular cartilage), differentiation of osteoblasts or bone-forming cells, mineralization of bone matrix, and osteoarthritis (OA) were characteristic for the beneficial PRS_n set. For the adverse PRS_p set, genes affecting musculoskeletal system contributed to bones, cartilage, and skeletal muscles formation and age-related changes. Specifically, *BRD1*, *CHRM3*, *FARP2*, *IGFBP3*, *MITF*, *NOS1*, *SEMA6A*, *TAF5*, and *TNFSF13B* genes were involved in bone-resorbing osteoclasts formation and function, and/or mediated bone loss-related diseases including osteoporosis and rheumatoid arthritis.

Discussion

We performed GWAS of disability following the discovery-replication strategy using the WHI GARNET study and HRS as discovery sets and independent

Fig. 2 Enrichment of diseases and biological functions in three gene sets. PRS_{all}, PRS_p and PRS_n indicate polygenic risk scores aggregating effects for minor alleles of all SNPs, and SNPs with positive and negative directions of the effects, respectively. Color coding for $-\log_{10}(p \text{ value})$ is given in the inset. Numerical estimates for PRS_{all} are given in Table S3 in Online Resource 4

WHIMS, CHS, and FHS datasets as replication studies. Our analysis identified 30 promising disability-associated SNPs in 19 loci at $p < 10^{-4}$, although only four of them attained suggestive level of significance, $p < 10^{-5}$. In contrast, the PRS aggregating statistical effects of minor alleles that were adversely (PRS_p) or beneficially (PRS_n) associated with disability showed highly significant associations in meta-analysis, $p = 3.13 \times 10^{-45}$ and $p = 5.60 \times 10^{-23}$, respectively, and were replicated in each study.

The discovery of adverse and beneficial PRS for a complex trait such as late life disability supports the general concept of geroscience, which postulates age/aging as major risk factors for geriatric traits of distinct etiologies (Kaeberlein et al. 2015). Indeed, disability results from chronic conditions, including both acute events, such as hip fracture and stroke, and slowly progressive diseases, such as arthritis and CVD (Fried

and Guralnik 1997). The presence of a single chronic condition is already a significant risk factor for functional decline with a steep increase in the risk in the case of multimorbidity (Guralnik et al. 1993). An increased risk of disability was associated with cognitive impairment, depression, increased and decreased body mass index, lower extremity functional limitation, low frequency of social contacts, low level of physical activity, no alcohol use compared to moderate use, poor self-perceived health, smoking and vision impairment (Stuck et al. 1999). Disability may also develop due to non-specific factors such as frailty (Fried et al. 2001; Kulminski et al. 2006; Rockwood and Mitnitski 2011).

Our bioinformatics analysis supports the results of the statistical analyses by highlighting pathways, diseases and biological functions which include the aging/disability-related genes. Indeed, the top pathways and specific functions characteristic for the beneficial set of genes for SNPs associated with PRS_N highlighted the glutathione/glutaredoxin system playing a role in redox balance and antioxidant defense reactions (Hayes and McLellan 1999). Oxidative stress is associated with aging and various pathological conditions including cardiovascular and neurodegenerative diseases, macular degeneration, autoimmune disorders, and cancer (Davies et al. 2017; Liguori et al. 2018; Martin et al. 1996; Pham-Huy et al. 2008; Xiong et al. 2011). Genes for these pathologies tend to be less enriched in the beneficial PRS_N set (Table S4 in Online Resource 5). For the adverse PRS_P set, we identified a role of NO production by NOS1. NO and NOS1 are linked with the immune-related *NF-κB* signaling pathway—highlighting a role of redox molecules, such as NO, and the immune system in cell/tissue damage or protection (Bogdan 2001; Finch 2018; Wink et al. 2011).

The top categories of diseases in all sets included organismal injury and abnormalities, and musculoskeletal disorders. While the latter are not highly lethal, they often lead to disability affecting about 50% of US adults and about 75% of the elderly aged 65+ years (Theis et al. 2019; Yelin et al. 2016) representing thus the most common cause of disability (Lewis et al. 2019).

The analysis of diseases and functions complemented by gene analysis also showed enrichment of genes implicated in the formation of primary cilia, which play a role in sensing both mechanical and chemical changes in the extracellular environment and signal transduction

(Wheway et al. 2018). Primary cilia coordinate signaling pathways involved in development and tissue homeostasis. Particularly, they are important in coordinating neuronal migration, in photoreception, development and maintaining cartilage, bone and skeletal muscle cells (Haycraft and Serra 2008; Veland et al. 2009; Wheway et al. 2018). Ciliary defects can cause various human diseases (ciliopathies) (Baker and Beales 2009).

Gene analysis further strengthens the connections of genes with disability due to musculoskeletal disorders. For example, the beneficial PRS_N set supported enrichment of genes that contribute to chondrogenesis or chondrocyte hypertrophy and bone-forming osteoblast differentiation, which may regulate human articular cartilage homeostasis and affect osteoarthritis (OA) progression (Findlay and Atkins 2014; Goldring 2012). Specifically, transcription factor *TRPS1*, which is associated with trichorhinophalangeal syndrome, an autosomal dominant skeletal dysplasia, is involved in chondrogenesis through the control of several signaling molecules (Wuelling et al. 2009) and regulates the global acetylation of histones in chondrocytes (Wuelling et al. 2013). Also, *TRPS1* contributes to osteoblast differentiation (Piscopo et al. 2009). The parathyroid hormone-2 receptor (*PTH2R*) plays a role in the control of proliferation and differentiation of growth plate chondrocytes (Akesson et al. 2015; Panda et al. 2009). Variation in the *PTH2R* is associated with age-related vertebral degenerative changes (Akesson et al. 2015) and may contribute to early-onset generalized OA (Meulenbelt et al. 2006). Interestingly, *TRPS1* may inhibit the hypertrophic differentiation of chondrocyte through regulation of another member of the parathyroid hormone family, *PTHrP*, which is inactive on *PTH2R* (Nishioka et al. 2008). This function supports a role of the parathyroid hormone system in the regulation of chondrocyte proliferation and differentiation in the beneficial PRS_N set that may promote OA (Sun and Beier 2014). A loss of articular cartilage is a key factor in development of OA, which is one of the major causes of disability (Rahmati et al. 2017).

Overexpression of glutaredoxin (*GLRX*), an endogenous antioxidant enzyme, inhibits oxidative stress and apoptosis in OA chondrocytes that may prevent cartilage degeneration (Sun et al. 2017). *VWC2L* gene accelerates bone formation by modulating Osterix, an osteoblast-specific transcription factor (Ohya et al. 2012). Fibrillin *FBN3*, primarily expressed during development, may be involved in chondrocyte

differentiation and bone growth and development (Sabatier et al. 2011). Expression of *CDH13* adiponectin receptor gene was detected in cartilage chondrocytes and it may play role in cartilage development (Khanshour et al. 2018). Adiponectin is a novel key element in the maintenance of cartilage homeostasis and it has been implicated in the pathogenesis of OA (Kang et al. 2010). Proton-coupled myo-inositol cotransporter *SLC2A13* plays a key role in the control of brain myo-inositol (Uldry et al. 2001). Myo-inositol is important for the osmoprotective response in brain. Changes in myo-inositol levels are observed in brain injury and aging (Harris et al. 2014). It also may affect osteogenesis and bone formation (Dai et al. 2011).

Thus, the results of our biological analysis support the connections of genes for the identified SNPs with disabling and age-related conditions. Our analysis highlights the contributions of oxidative/nitrosative stress, inflammation, and signaling through the primary cilium to various disability-related conditions. Development and maintenance of the musculoskeletal system are important components in the identified pathways, diseases, and biological functions that is consistent with the selected ADLs representing the primary musculoskeletal components of late life disability. The beneficial PRS_N and adverse PRS_P gene sets may be differently implicated in the development of musculoskeletal-related disability. Regulation of chondrocyte proliferation/apoptosis and bone formation/mineralization, and degenerative joint diseases such as OA were characteristic for the beneficial gene set. Bone degradation by osteoclasts as well as bone loss and inflammatory conditions such as osteoporosis and rheumatoid arthritis were characteristic for the adverse set.

Despite rigor of this work, we acknowledge its limitations. First, this study oversamples women because it includes two women focused cohorts. Second, we partly relied on imputed SNPs as not all of them were directly genotyped in all studies. Third, while HRS was designed to characterize disability in a nationally representative sample, this was not the focus of the other studies.

Author contributions A.M.K. conceived and designed the experiment and wrote the paper; C.K., S.A.K., and Y.L. performed statistical analyses; C.K., A.I.Y., and E.S. contributed to drafting of the paper. C.K., A.N., and I.C. prepared data. I.C. performed biological analysis

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

- Adams PF, Hendershot GE, Marano MA (1999) Current estimates from the National Health Interview Survey, 1996. Vital and health statistics. Series 10, Data from the National Health Survey ; no. 200. U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, Hyattsville, Md.
- Akesson K, Tenne M, Gerdhem P, Luthman H, McGuigan FE (2015) Variation in the PTH2R gene is associated with age-related degenerative changes in the lumbar spine. *J Bone Miner Metab* 33:9–15. <https://doi.org/10.1007/s00774-013-0550-x>
- Baig MS et al (2015) NOS1-derived nitric oxide promotes NF-kappaB transcriptional activity through inhibition of suppressor of cytokine signaling-1. *J Exp Med* 212:1725–1738. <https://doi.org/10.1084/jem.20140654>
- Baker K, Beales PL (2009) Making sense of cilia in disease: the human ciliopathies. *Am J Med Genet C: Semin Med Genet* 151C:281–295. <https://doi.org/10.1002/ajmg.c.30231>
- Bogdan C (2001) Nitric oxide and the immune response. *Nat Immunol* 2:907–916. <https://doi.org/10.1038/ni1001-907>
- Brodie A, Azaria JR, Ofra Y (2016) How far from the SNP may the causative genes be? *Nucleic Acids Res* 44:6046–6054. <https://doi.org/10.1093/nar/gkw500>
- Cupples LA, Heard-Costa N, Lee M, Atwood LD (2009) Genetics analysis workshop 16 problem 2: the Framingham Heart Study data. *BMC Proc* 3 Suppl 7:S3
- Dai Z, Chung SK, Miao D, Lau KS, Chan AW, Kung AW (2011) Sodium/myo-inositol cotransporter 1 and myo-inositol are essential for osteogenesis and bone formation. *J Bone Miner Res* 26:582–590. <https://doi.org/10.1002/jbmr.240>
- Das S et al (2016) Next-generation genotype imputation service and methods. *Nat Genet* 48:1284–1287. <https://doi.org/10.1038/ng.3656>

- Davies JMS et al (2017) The Oxygen Paradox, the French Paradox, and age-related diseases. *GeroScience* 39:499–550. <https://doi.org/10.1007/s11357-017-0002-y>
- Delaneau O, Marchini J, Zagury JF (2011) A linear complexity phasing method for thousands of genomes. *Nat Methods* 9: 179–181. <https://doi.org/10.1038/nmeth.1785>
- Finch CE (2018) The biology of human longevity: Inflammation, nutrition, and aging in the evolution of lifespans. Elsevier, Findlay DM, Atkins GJ (2014) Osteoblast-chondrocyte interactions in osteoarthritis. *Curr Osteoporos Rep* 12:127–134. <https://doi.org/10.1007/s11914-014-0192-5>
- Franceschi C, Garagnani P (2016) Suggestions from geroscience for the genetics of age-related diseases. *PLoS Genet* 12: e1006399. <https://doi.org/10.1371/journal.pgen.1006399>
- Franco OH, Karnik K, Osborne G, Ordovas JM, Catt M, van der Ouderaa F (2009) Changing course in ageing research: the healthy ageing phenotype. *Maturitas* 63:13–19. <https://doi.org/10.1016/j.maturitas.2009.02.006>
- Fried LP, Guralnik JM (1997) Disability in older adults: evidence regarding significance, etiology, and risk. *J Am Geriatr Soc* 45:92–100
- Fried LP et al (1991) The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1:263–276
- Fried LP et al (2001) Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 56:M146–M156
- Fries JF (1980) Aging, natural death, and the compression of morbidity. *N Engl J Med* 303:130–135
- Garatachea N, Lucia A (2013) Genes and the ageing muscle: a review on genetic association studies. *Age (Dordr)* 35:207–233. <https://doi.org/10.1007/s11357-011-9327-0>
- Goldring MB (2012) Chondrogenesis, chondrocyte differentiation, and articular cartilage metabolism in health and osteoarthritis. *Ther Adv Musculoskelet Dis* 4:269–285. <https://doi.org/10.1177/1759720X12448454>
- Guarente L (2011) Franklin H. Epstein lecture: sirtuins, aging, and medicine. *N Engl J Med* 364:2235–2244. <https://doi.org/10.1056/NEJMr1100831>
- Guralnik JM, LaCroix AZ, Abbott RD, Berkman LF, Satterfield S, Evans DA, Wallace RB (1993) Maintaining mobility in late life. I. Demographic characteristics and chronic conditions. *Am J Epidemiol* 137:845–857
- Harris JL, Yeh HW, Swerdlow RH, Choi IY, Lee P, Brooks WM (2014) High-field proton magnetic resonance spectroscopy reveals metabolic effects of normal brain aging. *Neurobiol Aging* 35:1686–1694. <https://doi.org/10.1016/j.neurobiolaging.2014.01.018>
- Haycraft CJ, Serra R (2008) Cilia involvement in patterning and maintenance of the skeleton. *Curr Top Dev Biol* 85:303–332. [https://doi.org/10.1016/S0070-2153\(08\)00811-9](https://doi.org/10.1016/S0070-2153(08)00811-9)
- Hayes JD, McLellan LI (1999) Glutathione and glutathione-dependent enzymes represent a co-ordinately regulated defence against oxidative stress. *Free Radic Res* 31:273–300
- Heckerman D, Traynor BJ, Picca A, Calvani R, Marzetti E, Hernandez D, Nalls M, Arepali S, Ferrucci L, Landi F (2017) Genetic variants associated with physical performance and anthropometry in old age: a genome-wide association study in the iLSIRENTE cohort. *Sci Rep* 7:15879. <https://doi.org/10.1038/s41598-017-13475-0>
- Hinrichs AS et al (2006) The UCSC Genome Browser Database: update 2006. *Nucleic Acids Res* 34:D590–D598. <https://doi.org/10.1093/nar/gkj144>
- Jitapunkul S, Kunanusont C, Phoolcharoen W, Suriyawongpaisal P, Ebrahim S (2003) Disability-free life expectancy of elderly people in a population undergoing demographic and epidemiologic transition. *Age Ageing* 32:401–405
- Juster FT, Suzman R (1995) An overview of the health and retirement study. *J Hum Resour* 30:S7–S56
- Kaeberlein M, Rabinovitch PS, Martin GM (2015) Healthy aging: the ultimate preventative medicine. *Science* 350:1191–1193. <https://doi.org/10.1126/science.aad3267>
- Kang EH, Lee YJ, Kim TK, Chang CB, Chung JH, Shin K, Lee EY, Lee EB, Song YW (2010) Adiponectin is a potential catabolic mediator in osteoarthritis cartilage. *Arthritis Res Ther* 12:R231. <https://doi.org/10.1186/ar3218>
- Katz S, Akpom CA (1976) 12. Index of ADL. *Med Care* 14:116–118
- Khanshour AM et al (2018) Genome-wide meta-analysis and replication studies in multiple ethnicities identify novel adolescent idiopathic scoliosis susceptibility loci. *Hum Mol Genet* 27:3986–3998. <https://doi.org/10.1093/hmg/ddy306>
- Kulminski A, Yashin A, Ukraintseva S, Akushevich I, Arbeeve K, Land K, Manton K (2006) Accumulation of health disorders as a systemic measure of aging: findings from the NLTCs data. *Mech Ageing Dev* 127:840–848
- Kulminski AM et al (2016) Pleiotropic associations of allelic variants in a 2q22 region with risks of major human diseases and mortality. *PLoS Genet* 12:e1006314. <https://doi.org/10.1371/journal.pgen.1006314>
- Kulminski AM, Loika Y, Huang J, Arbeeve KG, Bagley O, Ukraintseva S, Yashin AI, Kulminskaya I (2019) Pleiotropic meta-analysis of age-related phenotypes addressing evolutionary uncertainty in their molecular mechanisms. *Front Genet* 10:433. <https://doi.org/10.3389/fgene.2019.00433>
- Lewis R, Gomez Alvarez CB, Rayman M, Lanham-New S, Woolf A, Mobasher A (2019) Strategies for optimising musculoskeletal health in the 21(st) century. *BMC Musculoskelet Disord* 20:164. <https://doi.org/10.1186/s12891-019-2510-7>
- Liguori I et al (2018) Oxidative stress, aging, and diseases. *Clin Interv Aging* 13:757–772. <https://doi.org/10.2147/CIA.S158513>
- Manichaikul A et al (2012) Analysis of family- and population-based samples in cohort genome-wide association studies. *Hum Genet* 131:275–287. <https://doi.org/10.1007/s00439-011-1071-0>
- Manton KG (1982) Changing concepts of morbidity and mortality in the elderly population. *Milbank Mem Fund Q Health Soc* 60:183–244
- Manton KG, Gu X, Lamb VL (2006) Change in chronic disability from 1982 to 2004/2005 as measured by long-term changes in function and health in the U.S. elderly population. *Proc Natl Acad Sci U S A* 103:18374–18379. <https://doi.org/10.1073/pnas.0608483103>
- Martin GM (2007) Modalities of gene action predicted by the classical evolutionary biological theory of aging. *Ann N Y Acad Sci* 1100:14–20. <https://doi.org/10.1196/annals.1395.002>
- Martin GM, Austad SN, Johnson TE (1996) Genetic analysis of ageing: role of oxidative damage and environmental stresses. *Nat Genet* 13:25–34. <https://doi.org/10.1038/ng0596-25>
- Meulenbelt I, Min JL, van Duijn CM, Kloppenburg M, Breedveld FC, Slagboom PE (2006) Strong linkage on 2q33.3 to

- familial early-onset generalized osteoarthritis and a consideration of two positional candidate genes. *Eur J Hum Genet* 14: 1280–1287. <https://doi.org/10.1038/sj.ejhg.5201704>
- Nishioka K et al (2008) Trps1 deficiency enlarges the proliferative zone of growth plate cartilage by upregulation of Pthrp. *Bone* 43:64–71. <https://doi.org/10.1016/j.bone.2008.03.009>
- Ohyama Y et al (2012) Modulation of matrix mineralization by Vwc2-like protein and its novel splicing isoforms. *Biochem Biophys Res Commun* 418:12–16. <https://doi.org/10.1016/j.bbrc.2011.12.075>
- Okoro CA, Hollis ND, Cyrus AC, Griffin-Blake S (2018) Prevalence of disabilities and health care access by disability status and type among adults - United States, 2016. *MMWR* 67:882–887. <https://doi.org/10.15585/mmwr.mm6732a3>
- Olshansky SJ, Perry D, Miller RA, Butler RN (2007) Pursuing the longevity dividend: scientific goals for an aging world. *Ann N Y Acad Sci* 1114:11–13. <https://doi.org/10.1196/annals.1396.050>
- Panda D, Goltzman D, Juppner H, Karaplis AC (2009) TIP39/parathyroid hormone type 2 receptor signaling is a potent inhibitor of chondrocyte proliferation and differentiation. *Am J Physiol Endocrinol Metab* 297:E1125–E1136. <https://doi.org/10.1152/ajpendo.00254.2009>
- Pham-Huy LA, He H, Pham-Huy C (2008) Free radicals, antioxidants in disease and health. *Int J Biomed Sci* 4:89–96
- Pickrell JK, Berisa T, Liu JZ, Segurel L, Tung JY, Hinds DA (2016) Detection and interpretation of shared genetic influences on 42 human traits. *Nat Genet* 48:709–717. <https://doi.org/10.1038/ng.3570>
- Piscopo DM, Johansen EB, Derynck R (2009) Identification of the GATA factor TRPS1 as a repressor of the osteocalcin promoter. *J Biol Chem* 284:31690–31703. <https://doi.org/10.1074/jbc.M109.052316>
- Pope AM, Tarlov AR (1991) Disability in America : toward a national agenda for prevention. National Academy Press, Washington, D.C.
- Purcell S et al (2007) PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 81:559–575. <https://doi.org/10.1086/519795>
- Qu XW, Wang H, De Plaen IG, Rozenfeld RA, Hsueh W (2001) Neuronal nitric oxide synthase (NOS) regulates the expression of inducible NOS in rat small intestine via modulation of nuclear factor kappa B. *FASEB J* 15:439–446. <https://doi.org/10.1096/fj.99-0343com>
- Rahmati M, Nalesso G, Mobasheri A, Mozafari M (2017) Aging and osteoarthritis: central role of the extracellular matrix. *Ageing Res Rev* 40:20–30. <https://doi.org/10.1016/j.arr.2017.07.004>
- Robine J-M (2003) Determining health expectancies. Wiley, Chichester
- Rockwood K, Mitnitski A (2011) Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clin Geriatr Med* 27:17–26. <https://doi.org/10.1016/j.cger.2010.08.008>
- Sabatier L, Miosge N, Hubmacher D, Lin G, Davis EC, Reinhardt DP (2011) Fibrillin-3 expression in human development. *Matrix Biol* 30:43–52. <https://doi.org/10.1016/j.matbio.2010.10.003>
- Sierra F, Hadley E, Suzman R, Hodes R (2008) Prospects for life span extension. *Annu Rev Med*. <https://doi.org/10.1146/annurev.med.60.061607.220533>
- Stallard E (2016) Compression of morbidity and mortality: new perspectives. *N Am Actuar J* 20:341–354. <https://doi.org/10.1080/10920277.2016.1227269>
- Stallard E (2019) Interactions of LTC morbidity and mortality. In: Dupourqué E, Planchet F, Sator N (eds) *Actuarial Aspects of Long Term Care*. Springer, Cham, pp 3–16
- Stuck AE, Walthert JM, Nikolaus T, Bula CJ, Hohmann C, Beck JC (1999) Risk factors for functional status decline in community-living elderly people: a systematic literature review. *Soc Sci Med* (1982) 48:445–469
- Sun MM, Beier F (2014) Chondrocyte hypertrophy in skeletal development, growth, and disease. *Birth Defects Res C Embryo Today* 102:74–82. <https://doi.org/10.1002/bdrc.21062>
- Sun J et al (2017) Glutaredoxin 1 (GRX1) inhibits oxidative stress and apoptosis of chondrocytes by regulating CREB/HO-1 in osteoarthritis. *Mol Immunol* 90:211–218. <https://doi.org/10.1016/j.molimm.2017.08.006>
- The Women's Health Initiative Study Group (1998) Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials* 19:61–109
- Theis KA, Steinweg A, Helmick CG, Courtney-Long E, Bolen JA, Lee R (2019) Which one? What kind? How many? Types, causes, and prevalence of disability among U.S. adults. *Disabil Health J* \:411–421. doi:<https://doi.org/10.1016/j.dhjo.2019.03.001>
- Trupin L, Rice DP, Max W (1995) Medical expenditures for people with disabilities in the United States, 1987. U.S. Dept. of Education, Office of Special Education and Rehabilitative Services, National Institute on Disability and Rehabilitation Research : Office of Educational Research and Improvement, Educational Resources Information Center., [Washington, DC]
- Uldry M, Ibberson M, Horisberger JD, Chatton JY, Riederer BM, Thorens B (2001) Identification of a mammalian H(+)-myo-inositol symporter expressed predominantly in the brain. *EMBO J* 20:4467–4477. <https://doi.org/10.1093/emboj/20.16.4467>
- Veland IR, Awan A, Pedersen LB, Yoder BK, Christensen ST (2009) Primary cilia and signaling pathways in mammalian development, health and disease. *Nephron Physiol* 111:39–53. <https://doi.org/10.1159/000208212>
- Visscher PM, Yang J (2016) A plethora of pleiotropy across complex traits. *Nat Genet* 48:707–708. <https://doi.org/10.1038/ng.3604>
- Whewy G, Nazlamova L, Hancock JT (2018) Signaling through the primary cilium. *Front Cell Dev Biol* 6:8. <https://doi.org/10.3389/fcell.2018.00008>
- Willer CJ, Li Y, Abecasis GR (2010) METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* 26:2190–2191. <https://doi.org/10.1093/bioinformatics/btq340>
- Wink DA, Hines HB, Cheng RY, Switzer CH, Flores-Santana W, Vitek MP, Ridnour LA, Colton CA (2011) Nitric oxide and

- redox mechanisms in the immune response. *J Leukoc Biol* 89:873–891. <https://doi.org/10.1189/jlb.1010550>
- Wuelling M, Kaiser FJ, Buelens LA, Braunholz D, Shivdasani RA, Depping R, Vortkamp A (2009) Trps1, a regulator of chondrocyte proliferation and differentiation, interacts with the activator form of Gli3. *Dev Biol* 328:40–53. <https://doi.org/10.1016/j.ydbio.2009.01.012>
- Wuelling M, Pasdziernik M, Moll CN, Thiesen AM, Schneider S, Johannes C, Vortkamp A (2013) The multi zinc-finger protein Trps1 acts as a regulator of histone deacetylation during mitosis. *Cell Cycle* 12:2219–2232. <https://doi.org/10.4161/cc.25267>
- Xiong Y, Uys JD, Tew KD, Townsend DM (2011) S-glutathionylation: from molecular mechanisms to health outcomes. *Antioxid Redox Signal* 15:233–270. <https://doi.org/10.1089/ars.2010.3540>
- Yelin E, Weinstein S, King T (2016) The burden of musculoskeletal diseases in the United States. *Semin Arthritis Rheum* 46: 259–260. <https://doi.org/10.1016/j.semarthrit.2016.07.013>
- Zhavoronkov A, Moskalev A (2016) Editorial: should we treat aging as a disease? Academic, Pharmaceutical, Healthcare Policy, and Pension Fund Perspectives. *Front Genet* 7. <https://doi.org/10.3389/fgene.2016.00017>
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