

Hypotheses and Emerging Facts: the Vitamin D Receptor Capacitor, Rheumatoid Arthritis and Beyond

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ABSTRACT

As System-IN Failing, complex diseases such as autoimmune diseases (ADs) like rheumatic arthritis (RA), and the associated cancers remain as a challenge to thoroughly understand, though their common underlying mechanisms emerge. In this visionary article, we summarize some recent hypothesis-generating discussions on the Vitamin D and its receptor (VDR) capacitor for autoimmune diseases (ADs) and associated cancers, then update bioinformatics evidence along with latest progress in RA. We could conclude this may provide one unique angle to view the controversies surrounding the beneficial effects of Vitamin D supplementation.

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Key words: Rheumatoid arthritis; Autoimmune diseases; Vitamin D receptor capacitor; Cancer; Prevention

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INTRODUCTION

Complex diseases such as autoimmune diseases (ADs) like rheumatoid arthritis (RA), ankylosing spondylitis (AS) and the associated cancers such as lung cancer and breast cancer are related to a reduction of mobility. Generally, RA is an autoimmune disease in which the body's own immune system mistakenly attacks patients' healthy tissue. This often causes pain, loss of joint shape and alignment, and consequently loss of movement. Currently, no single cause for RA has been assigned, but patients seem to be genetically predisposed to the disease. AS is a chronic, progressive inflammatory disease involving primarily the sacroiliac joints and the axial skeleton. Understanding the causes behind these diseases and then addressing them properly may allow patients to live a more active life.

Beyond bone health, basically, although we are still lacking convincing data [namely, if any, but very few facts and mainly bioinformatics dry evidence], in order to better understand their pathophysiology, the Vitamin D and its receptor (VDR) capacitor hypothesis for ADs and associated cancers has been developed. Vitamin D might only improve diseases status of patients with marginally insufficiency, for which high doses as 400-1,000 IU daily might be required. Beyond certain points, there would be not any beneficial effect with vitamin D supplementation. It does not mean that the vitamin D is sufficient in those individuals and/or generally no beneficial effect for vitamin D supplementation. For decades, it remains debatable for beneficial effects and even definition of sufficiency of vitamin D. Rather than to resolve all these issues, this hypothesis may provide one viewpoint/interpretation for such controversy. Such capacitor (like the electronic device) has preventive effects and only slight side-effects at a rational range along with supplementation. Human beings are speculatively good at surviving the challenges of genetic variations and environmental factors, and rely on the robustness of complex genetic regulatory networks, possibly including the VDR as a capacitor, similar to its homologue DAF-12 in *Caenorhabditis elegans*. Besides, decoding the genetics of the complex diseases associated with the aging process with which that DAF-12 contribution was proven is critical in understanding the controversies surrounding the beneficial effects of

Vitamin D supplementation. In this visionary article, we summarize some recent hypothesis-generating discussion as well as analyze latest bioinformatic indirect evidence from RA. In turn, this increased understanding has also heightened our awareness of current gaps in our knowledge. We conclude it by considering possible explanations, and suggesting future lines of experiments.

MAIN POINTS OF THE HYPOTHESIS

(1) This hypothesis is distilled from the comparative advantages of different model systems, data from genome-wide association studies (GWAS), and chromatin immunoprecipitation (ChIP)-seq/ChIP-chip studies^[1-6] (Table 1).

(2) It hypothesizes that the evolutionarily conserved roles of Vitamin D and the VDR may shed light on the important role of human VDR^[1-9].

(3) Similar to DAF-21/HSP90VDR may buffer disease-causing genetic mutations and/or variations, the diseased phenotype may occur with polygenic genetic mutations and/or variations plus a deficiency of Vitamin D and a lack of UVB. In these circumstances, mal-functional DAF-12/VDR loses of its buffering ability as a capacitor^[1-9].

(4) Environmental factor-induced malfunctioning DAF-12/VDR may be postulated to cause the dys-regulation of expression of an array of its target genes; supposedly, the citrullination of such dys-regulated genes might be tightly mediated by VDR-orchestrated processes and consequently end with autoimmunity^[4].

(5) Human VDR studies^[1-4] show VDR binding loci to be enriched near AD-associated genes^[2,4] (Table 1) and to overlap many conserved targets of the homologous DAF-12/VDR in *C. elegans*^[5]. VDR ChIP-seq assays in primary CD4+ cells have related serum 25-hydroxyvitamin D levels to ADs^[6].

(6) Regarding the signalling pathways, when VDR function is down-regulated due to genetic defects or by Vitamin D unavailability, it may remodel many different processes and make adjustments to multiple signal transducers, thereby simultaneously disturbing several developmental pathways. If DAF-12/VDR loses its buffering capability, ADs and associated cancers may arise in patients^[4].

(7) At a systems biology level, the age-related genetic regulatory network (GRN) of VDR, the human homologue of DAF-12 in *C. elegans*, may play a central role as being the common basis preventing some ADs and associated cancers. In fact, the GRN of DAF-12/VDR combines microRNA regulations, autophagy, longevity and cellular reprogramming, and forward or feedback loops. Our recent ChIP-chip screening for DAF-12/VDR target genes^[5,7,8], along with NCBI Aceview, may reveal many translatable targets that overlap with validated homologues identified in human VDR studies that are significantly enriched near genes that are pathologically associated with ADs^[4,9], including phospholipase C-like 1 (PLCL1), B lymphoid tyrosine kinase (BLK) (i.e. *pll-1* and *src-1* respectively; Table 1). Vitamin D3 regulates matrix metalloproteinase (MMP3) in cultured human cells^[10].

(8) Hypothesis: some of targets of vitamin D and VDR-associated "loci" identified by GWAS for ADs and associated cancers collectively have significance for gene function. Namely, some of them may contribute to producing self-antigens or the machinery of producing of autoantibodies; others may responsible for the quantity of either self-antigens, auto-antibodies and/or immune machinery capacitor^[1-9,19].

(9) Different genetic backgrounds would create personalized Vitamin D insufficiencies and necessities of personalized Vitamin D supplementation.

(10). A Vitamin D deficiency status of a "system robustness failure" may lead to a "one-way" street and thus be irreversible for ADs, including RA. Vitamin D insufficiency might lead to a "system in failing"^[4].

EXPERIMENTAL AND/OR CLINICAL OBSERVATIONS

One GWAS reveals that, strikingly, an allelic VDR variant may link to clinical autoimmune antibodies including the anti-p150 (TIF-1 γ)/p140 (TIF-1 α)^[11] and TIF-1 γ/α genes' *C. elegans* homologues, *flt-1* and *nhl-2*, which are also direct targets of DAF-12/VDR (Table 1)^[5].

One of our recent experiences is as follows: when the new key regulators for ADs were published online, we predicted that they would be putative target candidates of Vitamin D-VDR signalling (and DAF-12/VDR signalling); amazingly, for most, if not all, this turned out to be the case. For instance, the key regulator fibrillin-1/FBN1, which is responsible for fibrosis and autoimmunity in mouse models of scleroderma, turns out to be the homologue of *fbl-1* in *C. elegans*, the putative target of DAF-12/VDR^[12].

Another GWAS identified genetic variants for joint damage progression in autoantibody-positive RA^[13], where three key genes (sperm-associated antigen 16 (*SPAG16*), and matrix metalloproteinase 1 and 3 (*MMP1* and *MMP3*) are among human homologue candidates of DAF-12/VDR target genes^[7,5,14-16]. Vitamin D regulates matrix MMP3 in cultured human cells^[10]. The latest case is *POLR3A* gene/*rpc-1*, which is responsible for both scleroderma and cancer^[17]. Moreover, Miller FW *et al*^[18] reporting on a GWAS of dermatomyositis (DM), revealed a genetic overlap with other ADs, the first identification of genetic predispositions towards ADs shared with DM. Likely, a malfunction of VDR could affect the pathogenesis of RA and associated cancers^[9,19,20] and expand to many other ADs, paraneoplastic neurological diseases and DM^[18,21-23] (Table 1). Further patterns of genetic overlap across ADs have emerged^[18,24]. A malfunction in VDR could thus affect the pathogenesis of RA and possibly associated cancers^[9,19]. Importantly, MMP3 contributes to this process^[3,7,25]. In closing, the pathophysiology of ADs (or at least a subgroup of ADs) may share the common underlying mechanism of the GRN of VDR.

To seek for novel support of this emerging concept, we have extended these observations by looking into GWAS-identified AS (in preparation), such as *endoplasmic reticulum aminopeptidase 1/ERAP-1* for AS mapping to the *pam-1*, one *C. elegans* DAF-12/VDR target genes), particularly RA risk loci as follows:

A recent study^[26] reported the discovery of 42 novel rheumatoid arthritis (RA) risk loci, providing insights into RA biology, contributing to drug discovery. Indeed, Vitamin D-VDR signalling (VITAMIN D-VDR) may act as a upstream master of the risk gene candidates found in RA and VITAMIN D-VDR studies over the last few decades^[1,2,4,5,25,27-31].

As VITAMIN D-VDR targets, some RA risk genes (e.g. *PTPN22*) may alter adaptive immunity and initiate abnormal responses. VITAMIN D-VDR studies relate 25-hydroxyvitamin D levels to ADs. Given that ~80% of the novel risk locus-associated candidate genes in Okada *et al*^[26] are VD3/VDR targets (Table 1) and one-third of them have homologous putative DAF-12/VDR targets^[5] (Table 1), about 80% (273/377, regardless of species^[1,4-5,7,27-31]) of 377 genes included in 101 loci^[26] (~1/3 (127/377) of their rat homologues^[27]) merge with VITAMIN D-VDR targets^[26] (Table 2), as do all (29/29) the highlighted RA drug target genes^[1,5,26,30,31]. This suggests that VITAMIN D-VDR may play a central role in RA pathogenesis^[2]. Further, multilayered regulatory networks benefit us in preventing RA

alongside using protein–protein interactions, including those applied for identifying RA drug target genes^[26] and complexes between VDR and its targets (e.g. MED1).

Innate immunity is important in RA pathogenesis. However, stating that there is no overlap in innate immunity^[26] may convey a biased message. Several innate immunity participants are actually among the latest highlighted 98 genes in a recent study^[26] (e.g. interleukin-1 receptor-associated kinase 1/*IRAK1*^[1], *CD40*^[4], colony stimulating factor 2/*CSF2*^[30], *complement component 5/C5* and interferon regulatory factor 8/*IRF8*^[4]). Some drugs targeting innate immunity may be repurposed for RA. Since DAF-12/VDR and its targets are required for innate immunity in *C. elegans*, other innate immunity-related genes within 101 risk loci with a biological score of <2^[26] highlighted in that study^[26] but which overlap DAF-12/VDR targets (such as *rpn-3/PSMD3* and *MAK-2/MAPKAPK5*^[5,32]) may be investigated for drug discovery. Indeed, GLPG0259, an inhibitor of MAPKAPK5, is a new target for treating RA that is undergoing trial^[33]. Lastly, half (34/66) of the VITAMIN D-VDR targets with a biological score of 1^[26] (e.g. *rhotein 2/RTKN2*)^[34] may be possibly re-designated as risk genes because of their role in certain ADs.

As mentioned previously, the VITAMIN D-VDR capacitor is an extension from its homologous DAF-12/VDR development “capacitor”^[5], similar to the HSP90 capacitor^[35], likely masking minor genetic variations, mutations and environmental insults^[2,7]. If UVB and Vitamin D are insufficient or if mutations in VDR occur, this feature could become overtaxed, leading to RA^[2,4,35]. Many VITAMIN D-VDR (DAF-12/VDR) targets, such as *POLY3A/rpc-1*, may encode self-antigens that possibly elicit autoantibodies^[2,17] (Table 1).

Further investigation is needed for improving our understanding of RA, genetics and the role of Vitamin D. A fraction of ~1500 VITAMIN D-VDR targets^[4] may switch to context-dependent RA risk genes at certain points and democratically contribute to “system failure” RA. Vitamin D supplementation may prevent ADs by its buffering capability; outside these contexts, disease status becomes independent of it^[35], entering a “one-way street”.

In closing, VITAMIN D-VDR regulation is critical for identifying RA risk genes and drug discovery. For healthcare, RA prevention with personalized Vitamin D optimization rather than disease reversal could be pursued, since therapies targeting a single RA risk gene may have a limited effect, e.g. RA therapy fails with the anti- TNF (a VITAMIN D-VDR target) alone^[25,26]; better inhibition of human Th17-mediated synovial inflammation is achieved by combining it with Vitamin D^[25].

Therefore, we may draw the following conclusions. (1) The preventive effects of Vitamin D supplementation on such complex diseases may well need to be considered and we should avoid Vitamin D insufficiency in patients; (2) We predict that combination therapy with Vitamin D will likely benefit the treatment of ADs such as RA and AS.

METHODS

Analysis of Vitamin D/VDR context-dependent targets is based on data from several recent studies including microarray, ChIP-chip/ChIP-seq publications and some references therein^[1,25,27,31,42]. NCBI Aceview is used to identify homologues of VDR downstream ADs-related target gene candidates alongside published DAF-12/VDR binding sites^[7]. For comprehensive identification of gene candidates, both sides of the DAF-12/VDR binding sites are considered, as some ADs-related gene homologues may be missed (the original online supplementary material may describe their neighbouring genes only). For BlastP, the $P < 10^{-04}$ is defined as the cut-off for the identification

of significant homologue candidates; otherwise, they are considered “exceptional”.

Table 1 Association of the downstream targets of Vitamin D and its receptor VDR in “novel” RA risk loci.

I					
ADs	Human/Mouse Genes	VD/VDR target	<i>C. elegans</i> DAF-12/VDR target	BlastP for <i>C. elegans</i>	
Dermatomyositis & RA	BLK	+ =	<i>src-1</i>	e=2 10 ⁻³⁴	
Scleroderma (SSC)	FBN1	+ =	<i>fbl-1</i>	e=2 10 ⁻⁴⁷	
SSC	TOP1	+ =	<i>top1</i>	e=10 ⁻²⁵	
SSC & cancer	POLR3A	+	<i>rpc-1</i>	e=6 10 ⁻⁵¹	
RA	SPAG16	N.D.	<i>wdr-5.1</i>	e=4 10 ⁻²⁶	
RA	MMP3	+ =	<i>H36L18.1</i>	e=10 ⁻³⁸	
RA	ATG5	+	<i>Atg-5</i>	e=4 10 ⁻¹²	
II					
RA	Chr	Human genes	VD/VDR target	<i>C. elegans</i> DAF-12/VDR target	BlastP
rs227163	1	TNFRSF9	+	N.D.	
rs2105325	1	LOC100506023/	+		
	2	PRDX6			
rs10175798	2	LBH	+		
rs6732565	2	ACOXL	+		
rs6715284	2	CFLAR	+		
rs6715284	3	CASP8	+ √ =		
rs3806624	6	EOMES	+ √	N.D.	
rs9378815	6	IRF4	+		
rs2234067	6	ETV7	+		
rs9373594	7	PPIL4	+		
rs67250450	8	JAZF1	+		
rs678347	8	GRHL2	+		
rs1516971	10	PVT1	+		
rs12413578	10	10p14	+		
rs726288	11	SFTPD	+	N.D.	
chr11:107967350	13	ATM	+ =		
rs9603616	14	COG6	+ =		
rs3783782	17	PRKCH	+ =		
rs72634030	17	CIQBP	+ =		
rs1877030	18	MED1	+		
rs2469434	19	CD226	+		
chr19:10771941	21	ILF3	+ =		
rs73194058	22	IFNGR2	+ =		
rs11089637	22	UBE2L3	+ =		
rs11089637	22	YDJC	+		
rs909685	16	SYNGR1	+ √		
chrX:78464616		P2RY10	+		
III					
RA			VD3/VDR target	<i>C. elegans</i> DAF-12/VDR	BlastP
rs28411352	1	<i>MTF1</i>	+ =	<i>tra-1</i>	e=3 10 ⁻²³
rs28411352	1	<i>INPP5b</i>	+	<i>ocr1-1/C48B4.1 [*C48B4.3]</i>	e=5 10 ⁻¹²
rs2664035	4	<i>TEC</i>	=	<i>kin-22/src-2/ F49B2.5[*F49B2.6]</i>	e=10 ⁻²⁵
rs4272	7	<i>CDK6</i>	+ =	<i>cdk-5</i>	e=9 10 ⁻⁶⁷
rs998731	8	<i>TPD52</i>	+ =	<i>F13E6.1</i>	e=3 10 ⁻⁹
rs793108	10	<i>ZNF438</i>	+	<i>acd-3/C27C12.5[*egrh-1/C27C12.2]</i>	e=2 10 ⁻⁷
rs4452313	3	<i>PLCL2</i>	+ =	<i>pll-1[*gei-4]</i>	e=0.0
rs968567	11	<i>FADS1</i>	+ √ =	<i>fat-3</i>	e=10 ⁻¹¹
rs968567	11	<i>FADS2</i>	+	<i>fat-4</i>	e=3 10 ⁻²²
rs968567	11	<i>FADS3</i>	+	<i>fat-3</i>	e=10 ⁻⁹
rs73013527	11	<i>ETS1</i>	+ =	<i>ets-5</i>	e=9 10 ⁻³¹
rs773125	12	<i>CDK2</i>	+ =	<i>cdk-1/ncc-1/ T05G5.3[*T05G5.5]</i>	e=6 10 ⁻⁷⁰
rs10774624	12	<i>SH2B3</i>	+ =	<i>csk-1/ Y48G1C.5[*Y48G1C.8]</i>	e=7 10 ⁻⁶
rs10774624	12	<i>PTPN11</i>	=	<i>anc-1/Zk973.6[*scpl-3/ Y47D9A.2]</i>	e=3 10 ⁻⁴
rs1950897	14	<i>RAD51B</i>	+ =	<i>rad-51</i>	e=2 10 ⁻²²
rs4780401	16	<i>TXNDC11</i>	+	<i>pdi-3/H06O01</i>	e=0.001

Note: (1) adapted from table 1 in Okada *et al*^[26]; (2) +, √, =: yes; N.D.: not determined; further, +: Human; √: mouse; =: rat. Not exhaustive manual inspections. (3) *: listed in original table in the publication 5.

Table 2 Overlapping of VD-VDR targets and Biological scores of the genes in the RA risk loci.

RA risk SNP (cytoband)	Gene(VD-VDR target, yellow(human+/-rat); yellowish green for rat only)	Rat	Co-relate Autoimmune diseases	References
chr1:2523811 (1p36)	LOC115110	0		31
chr1:2523811 (1p36)	TNFRSF14	4	1	1,27,29,31
chr1:2523811 (1p36)	LOC100133445	0		
chr1:2523811 (1p36)	MMEL1	1		36
chr1:2523811 (1p36)	FAM213B	0		
chr1:2523811 (1p36)	TTC34	0		
rs227163 (1p36)	TNFRSF9	2		30
rs2301888 (1p36)	PADI4	2		31
rs28411352 (1p34)	EPHA10	0		30
rs28411352 (1p34)	MANEAL	1		
rs28411352 (1p34)	YRDC	1		30,37
rs28411352 (1p34)	C1orf122	0		
rs28411352 (1p34)	MTF1	1	1	1,27
rs28411352 (1p34)	INPP5B	1	1	27,31
rs12140275 (1p34)	LOC339442	0		31
rs2476601 (1p13)	RSBN1	0		1
rs2476601 (1p13)	PTPN22	5		1
rs624988 (1p13)	CD2	2		nd
rs2228145 (1q21)	IL6R	5	1	27
rs2228145 (1q21)	SHE	1		28
rs2228145 (1q21)	TDRD10	0		28
rs2317230 (1q23)	FCRL4	2		
rs2317230 (1q23)	FCRL3	3		
rs2317230 (1q23)	FCRL2	1	1	38
rs2317230 (1q23)	FCRL1	1	1	38
chr1:161644258 (1q23)	SLAMF7	2		31
rs4656942 (1q23)	LY9	3		31
rs4656942 (1q23)	CD244	1	1	1
rs4656942 (1q23)	ITLN1	0		31
chr1:161644258 (1q23)	ITLN2	0		31
chr1:161644258 (1q23)	F11R	0	1	27,31
chr1:161644258 (1q23)	TSTD1	1		
chr1:161644258 (1q23)	USF1	0	1	27
chr1:161644258 (1q23)	ARHGAP30	0		1
chr1:161644258 (1q23)	PVRL4	0		
chr1:161644258 (1q23)	KLHDC9	1		31
chr1:161644258 (1q23)	PFDN2	0		
chr1:161644258 (1q23)	NIT1	0	1	27,30
chr1:161644258 (1q23)	DEDD	2	1	27,30
chr1:161644258 (1q23)	UCF1	0	1	27,31
chr1:161644258 (1q23)	USP21	0		1
chr1:161644258 (1q23)	PPOX	0		1
chr1:161644258 (1q23)	B4GALT3	0	1	27,31
chr1:161644258 (1q23)	ADAMTS4	0	1	27
chr1:161644258 (1q23)	NDUFS2	0		
chr1:161644258 (1q23)	FCER1G	2		1,30
chr1:161644258 (1q23)	APOA2	0	1	27,31
chr1:161644258 (1q23)	TOMM40L	0		1
chr1:161644258 (1q23)	NR1I3	0		
chr1:161644258 (1q23)	MPZ	1	1	1,31
chr1:161644258 (1q23)	SDHC	1	1	27,30
chr1:161644258 (1q23)	C1orf192	0		
rs72717009 (1q23)	FCGR2A	3		1,30,31
rs72717009 (1q23)	HSPA6	2		31
rs72717009 (1q23)	FCGR3A	1	1	27
chr1:161644258 (1q23)	FCGR3B	1	1	1
chr1:161644258 (1q23)	FCGR2B	5	1	27,30
chr1:161644258 (1q23)	RPL31P11	0		
chr1:161644258 (1q23)	FCRLA	2		27
chr1:161644258 (1q23)	FCRLB	1	1	1
chr1:161644258 (1q23)	DUSP12	0	1	27,31
chr1:161644258 (1q23)	ATF6	0		31
rs2105325 (1q25)	LOC100506023	0		
rs17668708 (1q31)	PTPRC	6	1	27,30
rs10175798 (2p23)	LBH	0		30
rs34695944 (2p16-p15)	FL16341	0		
rs34695944 (2p16-p15)	REL	4	1	27,31
rs34695944 (2p16-p15)	PEX13	0	1	1,27
rs34695944 (2p16-p15)	KIAA1841	0		30,31
rs34695944 (2p16-p15)	LOC339803	0		
rs34695944 (2p16-p15)	C2orf74	0		

Table 2 Overlapping of VD-VDR targets and Biological scores of the genes in the RA risk loci.

RA risk SNP (cytoband)	Gene(VD-VDR target, yellow(human+/-rat); yellowish green for rat only)	Rat	Co-relate Autoimmune diseases	References
rs34695944 (2p16-p15)	AHSA2	1	1	27,31
rs34695944 (2p16-p15)	USP34	0		30,31
rs34695944 (2p16-p15)	SNORA70B	0		
rs34695944 (2p16-p15)	XPO1	2	1	27,31
rs13385025 (2p15)	MIR5192	0		
rs13385025 (2p15)	B3GNT2	1	1	1,31
rs1858037 (2p14)	SPRED2	0	1	1,27,31,38
rs9653442 (2q11)	AFF3	4		30
rs9653442 (2q11)	LONRF2	0		30
rs6732565 (2q13)	ACOXL	0		31,38
rs11889341 (2q32)	STAT4	3	1	27,31
rs6715284 (2q33)	CFLAR	3	1	27,30
rs6715284 (2q33)	CFLAR-AS1	0		
rs6715284 (2q33)	CASP10	2		1,38
rs6715284 (2q33)	CASP8	2	1	27,30,31
rs6715284 (2q33)	ALS2CR12	1	1	27
rs6715284 (2q33)	TRAK2	0		1
rs6715284 (2q33)	STRADB	0		30,31
rs6715284 (2q33)	ALS2CR11	0		
rs1980422 (2q33)	CD28	4		31,38
rs3087243 (2q33)	CTLA4	4	1	27,31
rs4452313 (3p24)	PLCL2	1	1	27,30,31
rs4452313 (3p24)	MIR3714	0		
rs3806624 (3p24)	EOMES	1	1	30,31
rs73081554 (3p14)	FLNB	0	1	27,30
rs73081554 (3p14)	DNASE1L3	1	1	27,30,31
rs73081554 (3p14)	ABHD6	1	1	27,30
rs73081554 (3p14)	RPP14	0	1	27,30,31
rs73081554 (3p14)	PXK	1	1	27,31
rs73081554 (3p14)	PDHB	0	1	27,31
rs73081554 (3p14)	KCTD6	0	1	27,31
rs9826828 (3q22)	PCCB	0	1	27,30
rs9826828 (3q22)	STAG1	1	1	27,30,31
rs9826828 (3q22)	SLC35G2	0		
rs9826828 (3q22)	NCK1	1	1	27,30,31
rs9826828 (3q22)	IL20RB	3		31
rs13142500 (4p16)	CLNK	1	1	27
rs11933540 (4p15)	C4orf52	0		29
rs2664035 (4p12-p11)	TEC	2	1	27
rs10028001 (4q21)	ANXA3	1	1	27,30,31
rs10028001 (4q21)	LOC100505702	0		
rs45475795 (4q26-q27)	KIAA1109	0		31
rs45475795 (4q26-q27)	ADAD1	1	1	1
rs45475795 (4q26-q27)	IL2	5		29
rs45475795 (4q26-q27)	IL21	3		31
rs7731626 (5q11)	ANKRD55	2		1
rs2561477 (5q21)	C5orf30	0		1,30
rs657075 (5q31)	CD42SE2	0		1
rs657075 (5q31)	RAPGEF6	1		
rs657075 (5q31)	FNIP1	1		1,38
rs657075 (5q31)	ACSL6	2		28,30,31
rs657075 (5q31)	IL3	4		31
rs657075 (5q31)	CSF2	4	1	27,31
rs657075 (5q31)	P4HA2	0	1	27
rs657075 (5q31)	PDLIM4	0	1	27,28,31
rs657075 (5q31)	SLC22A4	1	1	30,37
rs657075 (5q31)	MIR3936	0		
rs657075 (5q31)	LOC553103	0		
rs657075 (5q31)	SLC22A5	0	1	27,31
rs657075 (5q31)	C5orf56	0		29
rs9378815 (6p25)	IRF4	3	1	1,27,31
chr6:14103212 (6p23)	CD83	3	1	27,31
rs2234067 (6p21)	ETV7	1		30,39
rs2234067 (6p21)	PXT1	0		
rs2233424 (6p21)	HSP90AB1	2		1,38
rs2233424 (6p21)	MIR4647	0		
rs2233424 (6p21)	SLC35B2	0	1	27
rs2233424 (6p21)	NFKBIE	4		1
rs2233424 (6p21)	TMEM151B	0		
rs2233424 (6p21)	TCFE1	2	1	30
rs2233424 (6p21)	AARS2	1	1	27

Table 2 Overlapping of VD-VDR targets and Biological scores of the genes in the RA risk loci.

RA risk SNP (cytoband)	Gene(VD-VDR target, yellow(human+/-rat); yellowish green for rat only)	Rat	Co-relate Autoimmune diseases	References
rs9372120 (6q21)	ATG5	1	1	1,30
rs17264332 (6q23)	LOC100130476	0		
rs7752903 (6q23)	TNFAIP3	6		1,38
rs9373594 (6q25)	PPIL4	0		30
rs9373594 (6q25)	GINM1	0		
rs2451258 (6q25)	TAGAP	2		1,30
rs1571878 (6q27)	FGFR10P	1	1	1,30
rs1571878 (6q27)	CCR6	2	1	27
rs67250450 (7p15)	JAZF1	1	1	30
rs4272 (7q21)	FAM133B	0		
rs4272 (7q21)	FAM133DP	0		
rs4272 (7q21)	CDK6	4	1	27,30,31,38
chr7:128580042 (7q32)	IRF5	4	1	27,30,38
chr7:128580042 (7q32)	TNPO3	1	1	27,31
rs2736337 (8p23)	FAM167A	0		
rs2736337 (8p23)	BLK	3		27,31
rs998731 (8q21)	TPD52	0	1	27,30,31
rs678347 (8q22)	GRHL2	0	1	29
rs1516971 (8q24)	MIR1208	0		29
rs11574914 (9p13)	CCL19	2		31
rs11574914 (9p13)	CCL21	2		30
rs11574914 (9p13)	FAM205A	0		
rs10985070 (9q33)	LOC253039	0		
rs10985070 (9q33)	PHF19	1	1	1,30
rs10985070 (9q33)	TRAF1	4		30,31
rs10985070 (9q33)	C5	4		27,30,38
rs706778 (10p15)	IL2RA	5	1	27,31
rs947474 (10p15)	LOC399715	0	1	
rs3824660 (10p14)	GATA3-AS1	0		
rs3824660 (10p14)	GATA3	2		31
rs793108 (10p11)	ZNF438	0		1,30
rs2671692 (10q11)	WDFY4	2		30
rs2671692 (10q11)	LRRC18	0		30
rs71508903 (10q21)	ARID5B	2		27,30,31
rs6479800 (10q21)	RTKN2	1	1	27,30,31
rs726288 (10q22)	MBL1P	1	1	30
rs726288 (10q22)	LOC100288974	0		
rs726288 (10q22)	SFTPD	2		31
rs331463 (11p12)	PRR5L	0		27,30,31
rs331463 (11p12)	TRAF6	4	1	27,31
rs331463 (11p12)	RAG1	4	1	27,31
rs331463 (11p12)	RAG2	3	1	31
rs331463 (11p12)	C11orf74	0		
rs508970 (11q12)	CD5	4	1	27,31
rs508970 (11q12)	VPS37C	0		1,30
rs968567 (11q12)	MYRF	0		
rs968567 (11q12)	TMEM258	0		
rs968567 (11q12)	MIR611	0		
rs968567 (11q12)	FEN1	1	1	30
rs968567 (11q12)	FADS1	3	1	27,30,31
rs968567 (11q12)	MIR1908	0		
rs968567 (11q12)	FADS2	3	1	27,30,31
rs11605042 (11q13)	ARAP1	0		30
rs4409785 (11q21)	FAM76B	0		
chr11:107967350 (11q22)	CUL5	1	1	27,30,31
chr11:107967350 (11q22)	ACAT1	0	1	27,31
chr11:107967350 (11q22)	NPAT	0	1	27,30,31
chr11:107967350 (11q22)	ATM	4	1	27,31
chr11:107967350 (11q22)	C11orf65	1		30
chr11:107967350 (11q22)	KDELC2	0		30
rs10790268 (11q23)	DDX6	1	1	27,31
rs10790268 (11q23)	CXCR5	2		30
rs73013527 (11q24)	ETS1	2	1	27,31
rs773125 (12q13)	CDK2	3	1	27,30,31
rs773125 (12q13)	RAB5B	0	1	27,31
rs773125 (12q13)	SUOX	2	1	27,30,31
rs773125 (12q13)	IKZF4	0		1
rs773125 (12q13)	RPS26	1	1	27,31
rs773125 (12q13)	ERBB3	2		40
rs1633360 (12q13-q14)	ARHGGEF25	0		
rs1633360 (12q13-q14)	SLC26A10	0		

Table 2 Overlapping of VD-VDR targets and Biological scores of the genes in the RA risk loci.

RA risk SNP (cytoband)	Gene(VD-VDR target, yellow(human+/-rat); yellowish green for rat only)	Rat	Co-relate Autoimmune diseases	References
rs1633360 (12q13-q14)	B4GALNT1	1	1	27
rs1633360 (12q13-q14)	OS9	0		30
rs1633360 (12q13-q14)	AGAP2	0		30
rs1633360 (12q13-q14)	LOC100130776	0		
rs1633360 (12q13-q14)	TSPAN31	1	1	36
rs1633360 (12q13-q14)	CDK4	3	1	27,30
rs1633360 (12q13-q14)	CYP27B1	2		30,31
rs1633360 (12q13-q14)	METTL1	0		1,30
rs1633360 (12q13-q14)	METTL21B	1	1	30
rs1633360 (12q13-q14)	TSFM	0		1
rs1633360 (12q13-q14)	AVIL	0		30
rs10774624 (12q24)	CORO1C	0	1	27,30
rs10774624 (12q24)	SSH1	0		1,30,38
rs10774624 (12q24)	DAO	0	1	27,31
rs10774624 (12q24)	SVOP	0		
rs10774624 (12q24)	USP30	0	1	27,31
rs10774624 (12q24)	USP30-AS1	0		
rs10774624 (12q24)	ALKBH2	0	1	27,31
rs10774624 (12q24)	UNG	2	1	27,30,31
rs10774624 (12q24)	ACACB	0		1,30
rs10774624 (12q24)	FOXN4	0		
rs10774624 (12q24)	MYO1H	0		
rs10774624 (12q24)	KCTD10	0		1,31
rs10774624 (12q24)	MMAB	0		1
rs10774624 (12q24)	MVK	2		31
rs10774624 (12q24)	FAM222A	0		
rs10774624 (12q24)	FAM222A-AS1	0		
rs10774624 (12q24)	TRPV4	1	1	1
rs10774624 (12q24)	MIR4497	0		
rs10774624 (12q24)	GLTP	0		1,30
rs10774624 (12q24)	TCHP	0		
rs10774624 (12q24)	GIT2	1	1	27
rs10774624 (12q24)	ANKRD13A	0	1	27,30
rs10774624 (12q24)	C12orf76	0		1
rs10774624 (12q24)	IFT81	0		30
rs10774624 (12q24)	ATP2A2	0	1	27,31
rs10774624 (12q24)	ANAPC7	0	1	27,31
rs10774624 (12q24)	ARPC3	0	1	27,31
rs10774624 (12q24)	GPN3	1		30,38
rs10774624 (12q24)	FAM216A	0		
rs10774624 (12q24)	VPS29	0	1	27,31
rs10774624 (12q24)	RAD9B	0	1	27,30,31
rs10774624 (12q24)	PPTC7	0		1
rs10774624 (12q24)	TCNT1	0		30
rs10774624 (12q24)	HVCN1	0		30
rs10774624 (12q24)	PPP1CC	0		31
rs10774624 (12q24)	CCDC63	1		
rs10774624 (12q24)	MYL2	0		31
rs10774624 (12q24)	LOC100131138	0		
rs10774624 (12q24)	CUX2	1		1
rs10774624 (12q24)	FAM109A	0		1,28
rs10774624 (12q24)	SH2B3	5		n.d.
rs10774624 (12q24)	ATXN2	0		1
rs10774624 (12q24)	BRAP	0		31
rs10774624 (12q24)	ACAD10	0		
rs10774624 (12q24)	ALDH2	1	1	30
rs10774624 (12q24)	MAPKAPK5	1	1	1
rs10774624 (12q24)	MAPKAPK5-AS1	0		
rs10774624 (12q24)	ADAMIA	0	1	27
rs10774624 (12q24)	TMEM116	0		
rs10774624 (12q24)	ERP29	0	1	27,30
rs10774624 (12q24)	NAA25	0		
rs10774624 (12q24)	TRAFD1	2		1
rs10774624 (12q24)	HECTD4	0		
rs10774624 (12q24)	RPL6	1	1	27
rs10774624 (12q24)	PTPN11	3	1	27
rs9603616 (13q14)	COG6	1	1	1
rs9603616 (13q14)	MIR4305	0		27
rs3783782 (14q23)	PRKCH	2	1	27,28,30
rs1950897 (14q24)	RAD51B	0	1	27
rs2582532 (14q32)	PLD4	1	1	28,30

Table 2 Overlapping of VD-VDR targets and Biological scores of the genes in the RA risk loci.

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rs2582532 (14q32)	AHNAK2	1		1,30
rs8032939 (15q14)	RASGRP1	2	1	27,31
rs8026898 (15q23)	LOC145837	0		31
rs4780401 (16p13)	SNN	0		1
rs4780401 (16p13)	TXNDC11	1		28,31
rs4780401 (16p13)	ZC3H7A	0		1
rs13330176 (16q24)	IRF8	3		30,36-38
rs72634030 (17p13)	DHX232	0		1
rs72634030 (17p13)	USP6	0	1	27,31
rs72634030 (17p13)	ZNF594	2		1
rs72634030 (17p13)	SCIMP	0		
rs72634030 (17p13)	LOC100130950	0		
rs72634030 (17p13)	RABEP1	1	1	27,31
rs72634030 (17p13)	NUP88	1	1	27,30,31
rs72634030 (17p13)	C1QB	2	1	27,30,31
rs72634030 (17p13)	DHX33	0		1
rs1877030 (17q12)	FBXL20	2	1	27,31
rs1877030 (17q12)	MED1	2		41
rs1877030 (17q12)	CDK12	0		1
rs1877030 (17q12)	NEUROD2	0		
rs1877030 (17q12)	PPP1R1B	1	1	27,31
rs1877030 (17q12)	STARD3	2		27,31
chr17:38031857 (17q12-q21)	IKZF3	4		42
chr17:38031857 (17q12-q21)	ZBP2	2	1	27,31
chr17:38031857 (17q12-q21)	GSDMB	2		1
chr17:38031857 (17q12-q21)	ORMDL3	2		1
chr17:38031857 (17q12-q21)	LRRC3C	0		27,31
chr17:38031857 (17q12-q21)	GSDMA	1	1	nd
chr17:38031857 (17q12-q21)	PSMD3	0	1	27,31
chr17:38031857 (17q12-q21)	CSF3	4	1	27
chr17:38031857 (17q12-q21)	MED24	1		
rs8083786 (18p11)	PTPN2	3	1	27,31,38
rs2469434 (18q22)	DOK6	0		
rs2469434 (18q22)	CD226	3	1	27,30,31,38
rs34536443 (19p13)	ICAM1	4	1	27,30,38
rs34536443 (19p13)	ICAM4	0	1	27,31
rs34536443 (19p13)	ICAM5	0	1	27,31
rs34536443 (19p13)	ZGLP1	0		
rs34536443 (19p13)	FDX1L	0		
rs34536443 (19p13)	RAVER1	0		31
rs34536443 (19p13)	ICAM3	2		43
rs34536443 (19p13)	TYK2	6	1	27,30,31
chr19:10771941 (19p13)	AP1M2	0		31
chr19:10771941 (19p13)	SLC44A2	0		1,30
chr19:10771941 (19p13)	ILF3-AS1	0		
chr19:10771941 (19p13)	ILF3	1	1	27,31
rs4239702 (20q13)	SLC12A5	1		
rs4239702 (20q13)	NCOA5	0		1
rs4239702 (20q13)	CD40	6		30
rs73194058 (21q22)	IFNGR2	6	1	1,27-31
rs73194058 (21q22)	TMEM50B	1		1
rs73194058 (21q22)	DNAJC28	0		1,30
rs73194058 (21q22)	GART	0	1	27,30
chr21:35928240 (21q22)	RCANI	1	1	1
rs8133843 (21q22)	LOC100506403	0		
rs1893592 (21q22)	UBASH3A	2		30
rs2236668 (21q22)	ICOSLG	5		30
rs2236668 (21q22)	DNMT3L	0	1	27,31
rs2236668 (21q22)	AIRE	4		30,31
rs11089637 (22q11)	UBE2L3	0	1	27,31
rs11089637 (22q11)	YDJC	1		1,37
rs11089637 (22q11)	CCDC116	0		

Table 2 Overlapping of VD-VDR targets and Biological scores of the genes in the RA risk loci.

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rs11089637 (22q11)	SDF2L1	0	1	27,30,31
rs3218251 (22q12)	IL2RB	3		38
rs909685 (22q13)	RPL3	1	1	27
rs909685 (22q13)	SNORD83B	1		
rs909685 (22q13)	SNORD83A	1		
rs909685 (22q13)	RNU86	1		
rs909685 (22q13)	SNORD43	1		
rs909685 (22q13)	SYNGR1	1	1	27,31
chrX:78464616 (Xq21)	MIR4328	0		
chrX:78464616 (Xq21)	P2RY10	0		31
chrX:78464616 (Xq21)	GPR174	0		
rs5987194 (Xq28)	ARHGAP4	0		31
rs5987194 (Xq28)	NAA10	0		1
rs5987194 (Xq28)	RENBP	0	1	27,30,31
rs5987194 (Xq28)	HCFC1	0		1,28-30
rs5987194 (Xq28)	MIR3202-2	0		
rs5987194 (Xq28)	MIR3202-1	0		
rs5987194 (Xq28)	TMEM187	0		
rs5987194 (Xq28)	IRAK1	3		30,31
rs5987194 (Xq28)	MIR718	0		
rs5987194 (Xq28)	MECP2	0	1	27,30

Adapted from Supplementary Table 5^[26].

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

- Seuter S, Heikkinen S, Carlberg C. Chromatin acetylation at transcription start sites and vitamin D receptor binding regions relates to effects of 1alpha,25-dihydroxyvitamin D3 and histone deacetylase inhibitors on gene expression. *Nucleic acids research* 2013; **41**: 110-124
- Zhang Y. Synthetic and Systems Biology :Toward Achieving Impossible Missions and Deciphering Human Complex Disease Genetics. *Curr Synthetic Sys Biol* 2013; **1**: e102
- Noyola-Martinez N, Díaz L, Avila E, Halhali A, Larrea F, Barrera D. Calcitriol downregulates TNF-alpha and IL-6 expression in cultured placental cells from preeclamptic women. *Cytokine* 2013; **61**: 245-250
- Zhang, Y Emerging Vitamin D Receptor-Centered Patterns of Genetic Overlap across Some Autoimmune Diseases and Associated Cancers. *J Genet Syndr Gene Ther* 2013; **4(11)**: 1000e123
- Hochbaum D, Zhang Y, Stuckenholtz C, Labhart P, Alexiadis V, Martin R, Knölker HJ, Fisher AL. DAF-12 regulates a connected network of genes to ensure robust developmental decisions. *PLoS genetics* 2011; **7**: e1002179
- Handel AE, Sandve GK, Disanto G, Berlanga-Taylor AJ, Gallone G, Hanwell H, Drablos F, Giovannoni G, Ebers GC, Ramagopalan SV. Vitamin D receptor ChIP-seq in primary CD4+ cells: relationship to serum 25-hydroxyvitamin D levels and autoimmune disease. *BMC medicine* 2013; **11**: 163
- Sanghi D, Mishra A, Sharma AC, Singh A, Natu SM, Agarwal S, Srivastava RN. Does vitamin D improve osteoarthritis of the knee: a randomized controlled pilot trial. *Clinical orthopaedics and related research* 2013; **471**: 3556-3562
- Antebi A, Yeh WH, Tait D, Hedgecock EM, Riddle DL. daf-12 encodes a nuclear receptor that regulates the dauer diapause and developmental age in *C. elegans*. *Genes & development* 2000; **14**: 1512-1527
- Zhang Y. Gaps! Transgenesis, model organisms, and human diseases *J Cloning and transgenesis* 2013; **2**: e103

- 10 Schmitz JP, Schwartz Z, Sylvia VL, Dean DD, Calderon F, Boyan BD. Vitamin D3 regulation of stromelysin-1 (MMP-3) in chondrocyte cultures is mediated by protein kinase C. *Journal of cellular physiology* 1996; **168**: 570-579
- 11 Kapoor S, Cooper, Robert G, Chinoy, Hector, et al. The Relationship Between the Vitamin D Receptor Gene and Anti-155/140 Antibodies in UK Caucasians with Idiopathic Inflammatory Myositis. *Arthritis Rheum* 2009; **60**: 805
- 12 Gerber EE, Gallo EM, Fontana SC, Davis EC, Wigley FM, Huso DL, Dietz HC. Integrin-modulating therapy prevents fibrosis and autoimmunity in mouse models of scleroderma. *Nature* 2013;
- 13 Knevel R, Klein K, Somers K, Ospelt C, Houwing-Duistermaat JJ, van Nies JA, de Rooy DP, de Bock L, Kurreeman FA, Schonkeren J, Stoeken-Rijsbergen G, Helmer Q, van der Linden MP, Kern M, Manjarrez-Orduno N, Rodriguez-Rodriguez L, Stinissen P, Huizinga TW, Toes RE, Gay S, Gregersen PK, Somers V, van der Helm-van Mil AH. Identification of a genetic variant for joint damage progression in autoantibody-positive rheumatoid arthritis. *Annals of the rheumatic diseases* 2013;
- 14 Motola DL, Cummins CL, Rottiers V, Sharma KK, Li T, Li Y, Suino-Powell K, Xu HE, Auchus RJ, Antebi A, Mangelsdorf DJ. Identification of ligands for DAF-12 that govern dauer formation and reproduction in *C. elegans*. *Cell* 2006; **124**: 1209-1223
- 15 Yang CY, Leung PS, Adamopoulos IE, Gershwin ME. The Implication of Vitamin D and Autoimmunity: a Comprehensive Review. *Clinical reviews in allergy & immunology* 2013;
- 16 Greer EL, Maures TJ, Hauswirth AG, Green EM, Leeman DS, Maro GS, Han S, Banko MR, Gozani O, Brunet A. Members of the H3K4 trimethylation complex regulate lifespan in a germline-dependent manner in *C. elegans*. *Nature* 2010; **466**: 383-387
- 17 Joseph CG, Darrah E, Shah AA, Skora AD, Casciola-Rosen LA, Wigley FM, Boin F, Fava A, Thoburn C, Kinde I, Jiao Y, Papadopoulos N, Kinzler KW, Vogelstein B, Rosen A. Association of the Autoimmune Disease Scleroderma with an Immunologic Response to Cancer. *Science* 2013;
- 18 Miller FW, Cooper RG, Vencovský J, Rider LG, Danko K, Wedderburn LR, Lundberg IE, Pachman LM, Reed AM, Ytterberg SR, Padyukov L, Selva-O'Callaghan A, Radstake TR, Isenberg DA, Chinoy H, Ollier WE, O'Hanlon TP, Peng B, Lee A, Lamb JA, Chen W, Amos CI, Gregersen PK, Myositis Genetics Consortium. Genome-wide association study of dermatomyositis reveals genetic overlap with other autoimmune disorders. *Arthritis and rheumatism* 2013;
- 19 Zhang, Y. Genetic basis of DAF-12/vitamin D receptor (VDR) in autoimmune immunity, autoimmune diseases and associated cancers. *J Cloning and transgenesis* 2013; **2**: e105
- 20 Larman HB1, Zhao Z, Laserson U, Li MZ, Ciccia A, Gakidis MA, Church GM, Kesari S, Leproust EM, Solimini NL, Elledge SJ. Autoantigen discovery with a synthetic human peptidome. *Nature biotechnology* 2011; **29**: 535-541
- 21 Fiorentino D, Casciola-Rosen L. Autoantibodies to transcription intermediary factor 1 in dermatomyositis shed insight into the cancer-myositis connection. *Arthritis and rheumatism* 2012; **64**: 346-349
- 22 Shah AA, Rosen A, Hummers L, Wigley F, Casciola-Rosen L. Close temporal relationship between onset of cancer and scleroderma in patients with RNA polymerase I/III antibodies. *Arthritis and rheumatism* 2010; **62**: 2787-2795
- 23 Shah AA, Rosen A. Cancer and systemic sclerosis: novel insights into pathogenesis and clinical implications. *Current opinion in rheumatology* 2011; **23**: 530-535
- 24 Richard-Miceli C, Criswell LA. Emerging patterns of genetic overlap across autoimmune disorders. *Genome medicine* 2012; **4**: 6
- 25 van Hamburg JP, Asmawidjaja PS, Davelaar N, Mus AM, Cornelissen F, van Leeuwen JP, Hazes JM, Dolhain RJ, Bakx PA, Colin EM, Lubberts E. TNF blockade requires 1,25(OH)2D3 to control human Th17-mediated synovial inflammation. *Annals of the rheumatic diseases* 2012; **71**: 606-612
- 26 Okada Y, Wu D2, Trynka G1, Raj T3, Terao C4, Ikari K5, Kochi Y6, Ohmura K7, Suzuki A6, Yoshida S5, Graham RR8, Manoharan A8, Ortmann W8, Bhangale T8, Denny JC9, Carroll RJ10, Eyler AE11, Greenberg JD12, Kremer JM13, Pappas DA14, Jiang L15, Yin J15, Ye L15, Su DF16, Yang J17, Xie G18, Keystone E19, Westra HJ20, Esko T21, Metspalu A22, Zhou X23, Gupta N24, Mirel D24, Stahl EA25, Diogo D1, Cui J1, Liao K1, Guo MH26, Myouzen K6, Kawaguchi T27, Coenen MJ28, van Riel PL29, van de Laar MA30, Guchelaar HJ31, Huizinga TW32, Dieudé P33, Mariette X34, Bridges SL Jr35, Zernakova A36, Toes RE32, Tak PP37, Miceli-Richard C34, Bang SY38, Lee HS38, Martin J39, Gonzalez-Gay MA40, Rodriguez-Rodriguez L41, Rantapää-Dahlqvist S42, Arlestig L42, Choi HK43, Kamatani Y44, Galan P45, Lathrop M46; RACI consortium; GAR-NET consortium, Eyre S47, Bowes J47, Barton A48, de Vries N49, Moreland LW50, Criswell LA51, Karlson EW52, Taniguchi A5, Yamada R53, Kubo M54, Liu JS55, Bae SC38, Worthington J47, Padyukov L56, Klareskog L56, Gregersen PK57, Raychaudhuri S58, Stranger BE59, De Jager PL3, Franke L20, Visscher PM17, Brown MA60, Yamanaka H5, Mimori T7, Takahashi A61, Xu H15, Behrens TW8, Siminovitch KA18, Momohara S5, Matsuda F62, Yamamoto K63, Plenge RM1. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature* 2013;
- 27 Ding N, Yu RT, Subramaniam N, Sherman MH, Wilson C, Rao R, Leblanc M, Coulter S, He M, Scott C, Lau SL, Atkins AR, Barish GD, Gunton JE, Liddle C, Downes M, Evans RM. A vitamin D receptor/SMAD genomic circuit gates hepatic fibrotic response. *Cell* 2013; **153**: 601-613
- 28 Heikkinen S, Väisänen S, Pehkonen P, Seuter S, Benes V, Carlberg C. Nuclear hormone 1 α ,25-dihydroxyvitamin D3 elicits a genome-wide shift in the locations of VDR chromatin occupancy. *Nucleic acids research* 2011; **39**: 9181-9193
- 29 Seuter S, Pehkonen P, Heikkinen S, Carlberg C. Dynamics of 1 α ,25-dihydroxyvitamin D3-dependent chromatin accessibility of early vitamin D receptor target genes. *Biochimica et biophysica acta* 2013; **1829**: 1266-1275
- 30 Verway M, Bouttier M, Wang TT, Carrier M, Calderon M, An BS, Devemy E, McIntosh F, Divangahi M, Behr MA, White JH. Vitamin D induces interleukin-1 β expression: paracrine macrophage epithelial signaling controls M. tuberculosis infection. *PLoS pathogens* 2013; **9**: e1003407
- 31 Wang TT, Tavera-Mendoza LE, Laperriere D, Libby E, MacLeod NB, Nagai Y, Bourdeau V, Konstorum A, Lallemand B, Zhang R, Mader S, White JH. Large-scale in silico and microarray-based identification of direct 1,25-dihydroxyvitamin D3 target genes. *Molecular endocrinology* 2005; **19**: 2685-2695
- 32 Alper S, Laws R, Lackford B, Boyd WA, Dunlap P, Freedman JH, Schwartz DA. Identification of innate immunity genes and pathways using a comparative genomics approach. *Proceedings of the National Academy of Sciences of the United States of America* 2008; **105**: 7016-7021
- 33 Westhovens R, Keyser FD, Rekalov D, Nasonov EL, Beetsens J, Van der Aa A, Wigerinck P, Namour F, Vanhoutte F, Durez P. Oral administration of GLPG0259, an inhibitor of MAPKAPK5, a new target for the treatment of rheumatoid arthritis: a phase II, randomised, double-blind, placebo-controlled, multicentre trial. *Annals of the rheumatic diseases* 2013; **72**: 741-744
- 34 Myouzen K, Kochi Y, Okada Y, Terao C, Suzuki A, Ikari K, Tsunoda T, Takahashi A, Kubo M, Taniguchi A, Matsuda F, Ohmura K, Momohara S, Mimori T, Yamanaka H, Kamatani N, Yamada R, Nakamura Y, Yamamoto K. Functional variants in NFKBIE and RTKN2 involved in activation of the NF-kappaB pathway are associated with rheumatoid arthritis in Japanese. *PLoS genetics* 2012; **8**: e1002949
- 35 Rohner N, Jarosz DF, Kowalko JE, Yoshizawa M, Jeffery WR,

- Borowsky RL, Lindquist S, Tabin CJ. Cryptic variation in morphological evolution: HSP90 as a capacitor for loss of eyes in cavefish. *Science* 2013; **342**: 1372-1375
- 36 Disanto G, Sandve GK, Berlanga-Taylor AJ, Ragnedda G, Morahan JM, Watson CT, Giovannoni G, Ebers GC, Ramagopalan SV. Vitamin D receptor binding, chromatin states and association with multiple sclerosis. *Human molecular genetics* 2012; **21**: 3575-3586
- 37 Hossein-nezhad A, Spira A, Holick MF. Influence of vitamin D status and vitamin D3 supplementation on genome wide expression of white blood cells: a randomized double-blind clinical trial. *PLoS one* 2013; **8**: e58725
- 38 Satoh J, Tabunoki H. Molecular network of chromatin immunoprecipitation followed by deep sequencing-based vitamin D receptor target genes. *Multiple sclerosis* 2013; **19**: 1035-1045
- 39 Kawagoe H, Potter M, Ellis J, Grosveld GC. TEL2, an ETS factor expressed in human leukemia, regulates monocytic differentiation of U937 Cells and blocks the inhibitory effect of TEL1 on ras-induced cellular transformation. *Cancer research* 2004; **64**: 6091-6100
- 40 Upadhyay SK, Verone A, Shoemaker S, Qin M, Liu S, Campbell M, Hershberger PA. 1,25-Dihydroxyvitamin D3 (1,25(OH)2D3) Signaling Capacity and the Epithelial-Mesenchymal Transition in Non-Small Cell Lung Cancer (NSCLC): Implications for Use of 1,25(OH)2D3 in NSCLC Treatment. *Cancers* 2013; **5**: 1504-1521
- 41 Tuohimaa P, Wang JH, Khan S, Kuuslahti M, Qian K, Manninen T, Auvinen P, Vihinen M, Lou YR. Gene expression profiles in human and mouse primary cells provide new insights into the differential actions of vitamin D3 metabolites. *PLoS one* 2013; **8**: e75338
- 42 Yarwood A, Martin P, Bowes J, Lunt M, Worthington J, Barton A, Eyre S. Enrichment of vitamin D response elements in RA-associated loci supports a role for vitamin D in the pathogenesis of RA. *Genes and immunity* 2013; **14**: 325-329
- 43 Babina M, Krautheim M, Grutzkau A, Henz BM. Human leukemic (HMC-1) mast cells are responsive to 1 α , 25-dihydroxyvitamin D(3): selective promotion of ICAM-3 expression and constitutive presence of vitamin D(3) receptor. *Biochemical and biophysical research communications* 2000; **273**: 1104-1110

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