Original Paper

Impact of Vitamin D Receptor VDR rs2228570 Polymorphism in Oldest Old

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Key Words

Ageing • Gene variant • Vitamin D • Calcitriol • Osteoporosis • Transitoric ischemic attacks • Hypertension • Allergy • Depression

Abstract

Background: Calcitriol, a key player in the regulation of mineral metabolism, influences, directly or by increasing plasma Ca^{2+} and phosphate levels, a multitude of physiological functions, such as bone mineralization, cell proliferation, immune response, carbohydrate metabolism, blood pressure, platelet reactivity, gastric acid secretion, cognitive function and mood. Calcitriol is mainly effective by stimulation of the Vitamin D receptor VDR. The responsiveness of VDR may be affected by gene variants, such as the FokI polymorphism (rs2228570). The GG gene variant is expected to be more active than the GA or AA gene variant. The present study explored the impact of VDR rs2228570 on survival and health of oldest old individuals (> 90 years). **Methods:** 101 individuals > 90 years were examined and genotyped. As a result, the prevalence of GG, GA & AA was 36 (10 ♂, 26 ♀), 52 (24 ♂, 28 ♀) and 13 (4 ♂, 9 ♀), respectively, a prevalence not significantly different from the frequency in public available dbSNP and a population (n = 208) of young volunteers (average age 49 years). **Results:** As compared to carriers of GG, carriers of AA and/or GA displayed significantly ($p < 0.05$) lower diastolic blood pressure (significant only in ♂), higher instrumental activity of daily life (IADL) score and more frequent hospital visits (significant only in ♂), significantly lower prevalence of depression (significant in ♀+♂), renal disease (significant only in ♀), allergy, peptic ulcer and urolithiasis (significant only in ♂), as well as significantly higher prevalence of transitoric ischemic attacks. In a younger population a German version of the NEO-FFI, allowing reliable and valid assessment of personality, revealed decreased neuroticism (significant only in ♂) and increased extraversion in AA carriers. **Conclusion:** The Vitamin D receptor gene variant VDR rs2228570 has only little impact on life span but may affect a variety of pathophysiologically relevant functions including mood.

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Introduction

Physiologically active 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}_3$) [1], is produced in kidney [2], B cells [3] as well as activated DCs and macrophages [4, 5]. The hormone is a powerful regulator of cellular and systemic Ca^{2+} and phosphate metabolism as well as bone mineralization [1]. Moreover, $1,25(\text{OH})_2\text{D}_3$ is a potent regulator of the immune response [6-8], of glucose metabolism [9], and of behavior [10, 11]. Vitamin D deficiency thus predisposes not only to osteomalacia [12], but as well to diseases seemingly unrelated to Ca^{2+} phosphate metabolism including diabetes mellitus, hypertension, infections, asthma and cancer (for review see [13, 14]) as well as several psychiatric disorders, such as depression, bipolar disorder and schizophrenia [15-17]. Vitamin D intake may counteract multiple sclerosis [18] and fibromyalgia [19]. Vitamin D receptor (VDR) and metabolizing enzymes are expressed in a wide variety of tissues [20, 21] including prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus, and substantia nigra of the brain [22].

Polymorphisms of VDR have been reported to be associated with bone mineral density [23] diabetes mellitus [24, 25], hypertension [26], asthma [27, 28], periodontitis [29, 30], risk of multiple sclerosis [31, 32] and malignancy [33-38]. On the other hand, several studies failed to report an impact of VDR polymorphisms on multiple sclerosis [39], inflammatory bowel disease [40], coronary artery disease [41] or malignancy [42-44].

The present study explored, whether the FokI VDR polymorphism (rs2228570) impacts on life span and on health history of an elderly population (age > 90 years). The A variant (f allele) of the FokI restriction fragment polymorphism [45] results in the generation of a longer VDR protein [46] with less activity [47]. The G (or guanosine) variant (F allele) is 1.7-fold more active [48-50]. Carriers of the GG VDR gene variant are thus expected to have more VDR activity than carriers of the GA or AA gene variant. To date, the FokI polymorphism is the only known VDR gene polymorphism that results in the generation of an altered protein [45].

Materials and Methods

A total of 101 volunteers (38♂, 63♀) with an age over 90 years were recruited, all of whom were unrelated individuals of German descent (Caucasians). For comparison, a group of 208 volunteers younger than 90 years (123♂, 85♀) were included. Those individuals previously participated in a study on tinnitus [51]. No association was found between tinnitus and the polymorphism and the distribution of the polymorphism was similar in this population and the oldest old. The younger population completed the German version of the NEO-FFI [52], which consists of 60 items and allows reliable and valid assessment of personality along the dimensions *neuroticism*, *extraversion*, *openness to experiences*, *agreeableness* and *conscientiousness* [53]. The study was approved by the local ethics committee. After detailed information about the study, written informed consent was obtained by all study participants.

The study explored the occurrence of the FokI polymorphism (rs2228570) and its association with physical exams like body weight and blood pressure as well as selected disease entities reported by a face-to-face interview based on history data.

Leukocyte DNA was isolated using standard procedures (QIAamp DNA Blood Mini Kit, Qiagen, Hilden, Germany). Genotyping for rs2228570 was performed by a 5' nuclease assay using the predesigned TaqMan assay (Assay ID: C_12060045_20). Detection was performed by the ABI Prism 7900 Sequence Detection System (Applied Biosystems, Foster City, CA). Laboratory staff was blinded to the case status of the study participants during the entire genotyping process.

Data are provided as means $\pm$ SEM. Data were analyzed by parametric or nonparametric methods, depending on whether data distribution was normal or not. For statistical analysis, the Student's t-test, the

Table 1. Prevalence of FokI-Polymorphisms. Numbers or percentages of individuals carrying the polymorphism in the group with age >90 (>90), the group of individuals with

FokI Polymorphism (rs2228570)	Oldest old (>90 yrs)		Controls (< 90 yrs)		HapMap-CEU*	
Total number of individuals	101	%	208	%	113	%
G allele frequency	124	61.4	252	60.6		58.8
A allele frequency	78	38.6	164	39.4		41.2
GG frequency	36	35.6	75	36.1		37.2
AA frequency	13	12.9	31	14.9		19.5
GA frequency	52	51.5	102	49.0		43.4

*Data derived from the public available dbSNP for subjects only with European origin (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=2228570)

age <90 (<90) normal individual group and in common population (per dbSNP = Single Nucleotide Polymorphism database; CEPH-Col = Centre d'Étude du Polymorphisme Humain-Collection; HapMap = haplotype map; CEU = Utah residents with ancestry from northern and western Europe)

χ^2 -Test and the Mann-Whitney U-test were used as appropriate. All statistical tests were used two-tailed and a *p*-value of ≤ 0.05 was defined as statistically significant. For all calculations the JMP IN software package version 5.1.2 was used (SAS institute Inc., Cary, NC, USA). A *p* value of $p < 0.05$ was considered significant. Correction for multiple testing was not performed since our study was explorative and not confirmatory.

Results

To explore the impact of the FokI polymorphism (rs2228570) on life span, the prevalence of the polymorphism in the elderly population (mean age 92) was compared to the prevalence in individuals younger than 90 years (mean age 49 years) and to the prevalence in the publicly available databases per dbSNP (Single Nucleotide Polymorphism database), CEPH-Col = Centre d'Étude du Polymorphisme Humain-Collection) HapMap (haplotype map) and CEU (Utah residents with ancestry from northern and western Europe) (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=2228570). As listed in table 1, in the oldest old population the prevalence of the GG genotype (10♂, 26♀) was higher than the prevalence of AA (4♂, 9♀). Half of the population showed heterozygosity (GA, 24♂, 28♀). The frequency of genotypes was in Hardy-Weinberg equilibrium. A similar distribution of genotypes was found in the control group (GG 36.1%, AA 14.9% and GA 49.0%) which was not significantly different to the frequency distribution of the public available HapMap-CEU cohort (GG: 37.2%; AA: 19.5% and GA: 43.4%, table 1). The distribution of the rs2228570 polymorphism was similar in all three cohorts, if males and females were grouped together. The percentage of males tended to be lower in oldest old carriers of either AA and GG than in heterozygote individuals, a difference significant ($p < 0.05$) for the GG carriers.

Additionally physical exam for selected parameters like blood pressure and well established geriatric assessment scores (i.e. Mini-Mental State Examination [MMSE], Instrumental Activities of Daily Living scale (IADL) were performed as listed in table 2. Blood pressure tended to be lower in the AA carriers and GA carriers than in GG carriers, a difference, however, reaching statistical significance only for diastolic blood pressure in male AA carriers. The prevalence of hypertension tended again to be lower in the AA carriers and GA carriers than in the GG carriers, a difference, however, not reaching statistical significance.

No significant differences between male or female genotypes were observed for size and body mass index (table 2). If both, female and male individuals were grouped together, body weight was significantly higher in GA- and GA&AA carriers than in GG carriers, a difference at least in part due to the higher percentage of males in the GA- and GA&AA carriers. Moreover, the MMSE-Score yielded similar mean values in all three groups. AG- and AA&AG carriers

Table 2. Association between measured variables (MMSE = Mini-Mental-State Examination; IADL = Instrumental activity of daily life) in oldest old (> 90 years) and the VDR rs2228570 polymorphism

Genotype (VDR rs2228570)	GG	AA	GA & AA	GA
Number	36 (26♀,10♂)	13 (9♀,4♂)	65 (37♀,28♂)	52 (28♀,24♂)
Age	93.44 ± 0.62	91.69 ± 0.64	92.43 ± 0.31	92.62 ± 0.35
♀	93.81 ± 0.81	92.33 ± 0.85	92.73 ± 0.42	92.86 ± 0.48
♂	92.50 ± 0.73	90.25 ± 0.25	92.04 ± 0.45	92.33 ± 0.50
Size	164.23 ± 1.34	168.09 ± 2.79	166.81 ± 1.16	166.50 ± 1.28
♀	161.36 ± 1.21	164.57 ± 2.42	161.16 ± 1.08	160.16 ± 1.16
♂	172.13 ± 1.94	174.25 ± 5.57	174.04 ± 1.15	174.00 ± 1.00
Weight kg	60.48 ± 2.07	64.10 ± 2.52	65.70 ± 1.36*	66.04 ± 1.57*
♀	57.23 ± 2.07	60.00 ± 2.68	59.97 ± 1.39	59.96 ± 1.63
♂	68.44 ± 4.08	70.25 ± 2.95	72.80 ± 1.65	73.29 ± 1.89
systolic blood pressure	161.50 ± 4.44	152.69 ± 6.26	153.98 ± 3.48	154.31 ± 4.09
♀	162.65 ± 5.49	160.00 ± 7.18	159.81 ± 4.71	159.75 ± 5.84
♂	158.50 ± 7.55	136.25 ± 8.39	146.29 ± 4.89	147.96 ± 5.52
diastolic blood pressure	85.03 ± 1.92	80.38 ± 3.69	79.97 ± 1.69	79.87 ± 1.92
♀	85.85 ± 2.39	85.00 ± 4.48	83.51 ± 2.23	83.04 ± 2.62
♂	82.90 ± 3.10	70.00 ± 2.12*	75.29 ± 2.35	76.17 ± 2.69
Blood pressure amplitude	76.47 ± 3.66	72.31 ± 3.77	74.02 ± 2.93	74.44 ± 3.55
♀	76.81 ± 4.56	75.00 ± 4.33	76.30 ± 4.05	76.71 ± 5.21
♂	75.60 ± 6.07	66.25 ± 7.38	71.00 ± 4.20	71.79 ± 4.77
Body mass index	22.42 ± 0.75	22.64 ± 0.60	23.58 ± 0.42	23.79 ± 0.50
♀	22.03 ± 0.81	22.27 ± 0.86	23.18 ± 0.62	23.40 ± 0.74
♂	23.49 ± 1.74	23.19 ± 0.83	24.07 ± 0.57	24.24 ± 0.66
MMSE score	27.14 ± 0.93	28.38 ± 0.56	27.95 ± 0.31	27.84 ± 0.37
♀	27.00 ± 1.21	27.89 ± 0.73	27.57 ± 0.44	27.46 ± 0.53
♂	27.50 ± 1.34	29.50 ± 0.50	28.50 ± 0.42	28.32 ± 0.49
IADL-score	5.56 ± 0.44	6.69 ± 0.56	6.66 ± 0.24*	6.65 ± 0.27*
♀	5.50 ± 0.50	6.67 ± 0.65	6.38 ± 0.32	6.29 ± 0.37
♂	5.70 ± 0.94	6.75 ± 1.25	7.04 ± 0.36	7.08 ± 0.38
Hospital visits	4.34 ± 0.84	4.15 ± 0.72	4.43 ± 0.36	4.50 ± 0.42
♀	4.40 ± 1.16	2.89 ± 0.61	3.51 ± 0.34	3.71 ± 0.41
♂	4.20 ± 0.59	7.00 ± 0.82*	5.64 ± 0.64	5.42 ± 0.73

Data are provided as means ± SEM

did, however, score significantly higher than GG carriers in IADL-score. The frequency of hospital visits was significantly higher in male AA carriers than in GG carriers, but tended to be lower in female AA carriers than in female GG carriers. Taken together, the frequency of hospital visits was not significantly different between GG carriers and AA carriers. No significant differences between GG carriers and the other genotypes (AA carriers, GA carriers or GA&AA) was observed in the prevalences of osteoporosis, myocardial infarction, stroke, obesity, type II diabetes, gout and tumors without detailed specification (table 3).

The prevalence of renal disease tended to be lower in AA or GA carriers than in GG carriers, a difference statistically significant only for female GA&AA carriers. Individuals carrying AA had significantly more frequent transitory ischemic attacks (TIA) than GG carriers, a difference again significant for the female population (table 3).

The prevalence of allergy was significantly lower in GA or GA&AA carriers than in GG carriers, a difference significant again for the female GA&AA population. Moreover, in contrast to the other genotypes, none of the AA carriers suffered from peptic ulcers. The difference to the prevalence of peptic ulcers in GG carriers was statistically significant. The prevalence of urolithiasis was lower in AA carriers and GA carriers than in GG carriers, a difference reaching statistical significance for the male GA or male GA&AA population (table 3).

Table 3. Association between selected diseases in oldest olds and the VDR rs2228570 polymorphism

Genotype (VDR_rs2228570)	GG		AA		GA & AA		GA	
	n	%	n	%	n	%	n	%
Renal disease	10	27.8	2	15.4	10	15.4	8	15.4
♀	6	23.1	0	0	3	8.1*	3	10.7
♂	4	40.0	2	50.0	7	25.0	5	20.8
Hypertension	22	61.1	7	53.9	31	47.7	24	46.2
♀	16	61.5	5	55.6	19	51.4	14	50.0
♂	6	60.0	2	50.0	12	42.9	10	41.7
Myocardial infarction	3	8.3	1	7.7	5	7.7	4	7.7
♀	2	7.7	0	0	1	2.7	1	3.6
♂	1	10.0	1	25.0	4	14.3	3	12.5
Stroke	2	5.6	2	15.4	7	10.8	5	9.6
♀	1	3.9	0	0	1	2.7	1	3.6
♂	1	10.0	2	50.0	6	21.4	4	16.7
TIA	1	2.8	3	23.1*	8	12.3	5	9.6
♀	1	3.9	3	33.3**	6	16.2	3	10.7
♂	0	0	0	0	2	7.1	2	8.3
Type II Diabetes	4	11.1	2	15.4	8	12.3	6	11.5
♀	3	11.5	0	0	2	5.4	2	7.1
♂	1	10.0	2	50.0*	6	21.4	4	16.7
Obesity	4	11.1	1	7.7	8	12.3	7	13.5
♀	2	7.7	0	0	3	8.1	3	10.7
♂	2	20.0	1	25.0	5	17.9	4	16.7
Allergy	12	33.3	2	15.4	10	15.4*	8	15.4*
♀	10	38.5	1	11.1	5	13.5*	4	14.3
♂	2	20.0	1	25.0	5	17.9	4	16.7
Peptic Ulcer	7	19.4	0	0*	12	18.5	12	23.1
♀	2	7.7	0	0	3	8.1	3	10.7
♂	5	50.0	0	0*	9	32.1	9	37.5
Urolithiasis	6	16.7	0	0	5	7.7	5	9.6
♀	2	7.7	0	0	2	5.4	2	7.1
♂	4	40.0	0	0	3	10.7*	3	12.5*
Gout	3	8.3	2	15.4	6	9.2	4	7.7
♀	0	0	0	0	0	0	0	0
♂	3	30.0	2	50.0	6	21.4	4	16.7
Tumors (not specified)	13	36.1	5	38.5	25	38.5	20	38.5
♀	9	34.6	4	44.4	9	24.3	5	17.9
♂	4	40.0	1	25.0	16	57.1	15	62.5
Depression	8	22.2	1	7.7	4	6.2**	3	5.8*
♀	4	15.4	0	0	1	2.7*	1	3.6
♂	4	40.0	1	25.0	3	10.7*	2	8.3*
Osteoporosis	1	2.8	2	15.4	8	12.3	6	11.5
♀	1	3.9	1	1.1	4	10.8	3	10.7
♂	0	0	1	25.0	4	14.3	3	12.5

*(p<0.05), **(p<0.01) indicates significantly different from GG. (TIA=Transitory Ischemic attack; (#)= positive given number)

The prevalence of depression was markedly lower in AA and GA carriers than in GG carriers, a difference reaching statistical significance for the GA&AA population of either gender, for ♀&♂ GA carriers and for male GA carriers. As a matter of fact as many as 40% of the male GG carriers and 15% of the female GG carriers suffered from depression. The prevalence of depression was less than 10% in the GA or the GA&AA population. To

Table 4. Association between measured variables in subjects < 90 years and the VDR rs2228570 polymorphism

Genotype (VDR_rs2228570)	GG	AA	GA & AA	GA
Number	75 (35♀,40♂)	31 (11♀,20♂)	133 (50♀,83♂)	102 (39♀,63♂)
Age	48.09 ± 1.80	49.16 ± 2.73	49.65 ± 1.16	49.79 ± 1.27
♀	46.03 ± 2.65	44.55 ± 4.11	46.78 ± 1.79	47.41 ± 2.00
♂	49.90 ± 2.46	51.70 ± 3.51	51.37 ± 1.49	51.27 ± 1.63
Size	172.81 ± 0.95	171.77 ± 1.59	173.33 ± 0.77	173.81 ± 0.89
♀	166.77 ± 0.99	168.09 ± 2.81	166.00 ± 0.95	165.41 ± 0.94
♂	178.10 ± 0.95	173.80 ± 1.81*	177.80 ± 0.76	179.10 ± 0.75
Weight	72.64 ± 1.45	72.94 ± 1.98	75.44 ± 1.12	76.21 ± 1.33
♀	65.49 ± 1.94	65.45 ± 1.86	66.92 ± 1.55	67.33 ± 1.92
♂	78.90 ± 1.56	77.05 ± 2.47	80.63 ± 1.23	81.79 ± 1.39
systolic blood pressure	134.53 ± 2.30	138.10 ± 3.81	134.85 ± 1.84	133.78 ± 2.09
♀	132.00 ± 3.33	131.18 ± 7.69	127.17 ± 3.03	125.91 ± 3.21
♂	137.22 ± 3.14	142.11 ± 3.94	139.56 ± 2.15	138.70 ± 2.55
diastolic blood pressure	86.48 ± 1.80	85.73 ± 2.06	84.55 ± 0.93	84.16 ± 1.04
♀	86.91 ± 2.91	82.36 ± 3.13	81.46 ± 1.54	81.17 ± 1.79
♂	86.03 ± 2.11	87.68 ± 2.66	86.45 ± 1.13	86.04 ± 1.23
Blood pressure amplitude	48.05 ± 1.81	52.37 ± 2.94	50.30 ± 1.36	49.62 ± 1.53
♀	45.09 ± 2.09	48.82 ± 6.06	45.72 ± 2.33	44.74 ± 2.44
♂	51.19 ± 2.92	54.42 ± 3.08	53.11 ± 1.59	52.66 ± 1.86
Body mass index	24.23 ± 0.38	24.68 ± 0.54	25.06 ± 0.32	25.17 ± 0.38
♀	23.45 ± 0.58	23.39 ± 1.09	24.38 ± 0.63	24.65 ± 0.74
♂	24.90 ± 0.49	25.39 ± 0.55	25.47 ± 0.33	25.50 ± 0.41
NEO_FFI_N	2.80 ± 0.07	2.52 ± 0.14	2.68 ± 0.06	2.73 ± 0.07
♀	2.91 ± 0.10	2.91 ± 0.26	2.92 ± 0.11	2.93 ± 0.13
♂	2.70 ± 0.10	2.33 ± 0.14*	2.54 ± 0.07	2.61 ± 0.08
NEO_FFI_E	3.14 ± 0.07	3.38 ± 0.08*	3.25 ± 0.04	3.21 ± 0.05
♀	3.19 ± 0.09	3.46 ± 0.11	3.26 ± 0.08	3.21 ± 0.09
♂	3.09 ± 0.10	3.34 ± 0.10	3.24 ± 0.05	3.21 ± 0.06
NEO_FFI_O	3.50 ± 0.06	3.53 ± 0.09	3.55 ± 0.04	3.56 ± 0.05
♀	3.55 ± 0.08	3.68 ± 0.15	3.69 ± 0.06	3.69 ± 0.06
♂	3.45 ± 0.08	3.46 ± 0.11	3.47 ± 0.05	3.47 ± 0.06
NEO_FFI_V	3.62 ± 0.05	3.44 ± 0.09	3.53 ± 0.04	3.56 ± 0.04
♀	3.62 ± 0.06	3.56 ± 0.13	3.62 ± 0.06	3.64 ± 0.06
♂	3.61 ± 0.07	3.38 ± 0.12	3.48 ± 0.05	3.51 ± 0.05
NEO_FFI_G	3.80 ± 0.06	3.90 ± 0.09	3.85 ± 0.05	3.84 ± 0.06
♀	3.73 ± 0.06	3.78 ± 0.17	3.80 ± 0.08	3.81 ± 0.09
♂	3.87 ± 0.11	3.97 ± 0.11	3.88 ± 0.07	3.86 ± 0.08

*(p<0.05) indicates significantly different from GG

further test the impact of the FokI polymorphism on mood a German version of the NEO-FFI, allowing reliable and valid assessment of personality traits, was employed to evaluate the younger population. As illustrated in table 4, NEO-FFI_N score reflecting neuroticism tended to be lower in AA and GA carriers than in GG carriers, a difference reaching statistical significance for male AA carriers. Conversely, the NEO-FFI_E score reflecting extraversion was significantly higher in AA carriers than in GG carriers.

Discussion

The present observations reveal an impact of the FokI vitamin D receptor VDR (rs2228570) polymorphism in an oldest old population on instrumental activity of daily life (IADL)-score, diastolic blood pressure, (male) hospital visits, prevalence of (female) renal

disease, allergy, peptic ulcer, (male) urolithiasis, transitoric ischemic attacks and depression. The present statistical analysis did not include Bonferroni correction and is limited by lack of a replication cohort. The observations thus allow suggestions rather than firm conclusions. Nevertheless, several observations were made in both, female and male individuals. Moreover, the personality traits apparent from NEO-FFI in younger (age 49 years) individuals supported a role of vitamin D receptor VDR in neuroticism and extraversion.

Variants of the vitamin D receptor gene have previously been shown to be associated with the susceptibility to age-related changes in cognitive function and depressive symptoms [54]. The functional impact of VDR may mimic the functional consequences of vitamin D deficiency or excess and/or deranged formation of $1,25(\text{OH})_2\text{D}_3$. A VDR polymorphism with reduced function such as the FokI gene variant AA were expected to have a similar functional impact as Vitamin D deficiency, the opposite of what has been observed. In an earlier study [55], we could show an association between $1,25(\text{OH})_2\text{D}_3$ serum concentration and personality traits, i.e. increased $1,25(\text{OH})_2\text{D}_3$ concentrations were associated with higher scores in the personality dimensions of extraversion and openness. Extraversion is negatively correlated with social phobia, cluster C personality disorders and suicide risk, which are more prevalent in depressive patients than in the general population [16, 56]. Along those lines, the seasonal variations of sun exposure and thus $1,25(\text{OH})_2\text{D}_3$ formation have been associated with seasonal affective disorders [57-59]. In animals, vitamin D deficiency leads to increased anxiety, less explorative behavior, aberrant grooming, submissive social behavior, maternal cannibalism and social neglect [60-62]. $1,25(\text{OH})_2\text{D}_3$ may in mice further lead to altered emotional/anxiety states [17]. The desynchronisation in seasonal affective disorders has thus been suggested to result from vitamin D_3 deficiency [63]. Moreover, depression may be associated with decreased serum $25(\text{OH})\text{D}_3$ levels [64, 65]. Conversely, vitamin D supplementation may counteract depressive symptoms [57-59]. Vitamin D deficiency during development of the brain has been considered a risk factor for schizophrenia, a condition associated with higher levels of neuroticism and lower levels of extraversion [66]. Conversely high vitamin D consumption decreases the risk to develop psychotic-like symptoms [15]. Several mechanisms could contribute to the effect of $1,25(\text{OH})_2\text{D}_3$ on the brain, including antioxidant and anti-inflammatory defenses against vascular injury, stimulation of neurotrophins and improvement of metabolic and cardiovascular function [10]. Behavioral alterations in response to vitamin D deficiency may result from alterations in cellular development, dopamine metabolism, and brain morphology [67]. Moreover, $1,25(\text{OH})_2\text{D}_3$ may, at least in theory, affect neuronal function by influencing cellular Ca^{2+} entry and/or exit [1, 68, 69]. Earlier studies suggested a cross-talk between vitamin D_3 and glucocorticoids, which in turn impact on major depression [70]. Input nuclei to the pineal gland express $1,25(\text{OH})_2\text{D}_3$ dependent calcium binding protein [71].

The present study does not allow safe conclusions as to the causes for the seeming contrast between the impact of the FokI VDR polymorphism observed in this study and Vitamin D availability or $1,25(\text{OH})_2\text{D}_3$ plasma levels reported earlier. It is noteworthy, however, that VDR stimulates Klotho and FGF23 expression, which in turn inhibit $1,25(\text{OH})_2\text{D}_3$ formation [72]. Thus, a negative feedback may be expected to blunt the functional impact of VDR polymorphisms. Moreover, the tight regulation of $1,25(\text{OH})_2\text{D}_3$ formation dampens the impact of dietary vitamin D [72]. It were even feasible that a loss of function VDR polymorphism enhances the formation of $1,25(\text{OH})_2\text{D}_3$ with up-regulation of VDR independent $1,25(\text{OH})_2\text{D}_3$ effects. Clearly, additional experimental observations are necessary to either confirm or disprove the presently observed association of the FokI VDR gene variants with mood and its relation to vitamin D supplementation and $1,25(\text{OH})_2\text{D}_3$ plasma concentrations.

The VDR rs2228570 polymorphism is expected to impact on further functional consequences and/or disorders. The FokI VDR polymorphism is associated with bone density [73] and is expected to impact on osteoporosis given the known effect of the VDR in mineralization of bone [23]. In the present study AA/GA carriers tended to suffer more frequently from osteoporosis, a difference, however, not reaching statistical significance. VDR rs2228570 polymorphisms have further been shown to impact on blood pressure and

prevalence of hypertension [26]. Vitamin D deficiency may limit mobility in community dwelling older adults [74], which may impact on instrumental activity of daily life (IADL)-score. In theory, the influence on the prevalence of peptic ulcers may be secondary to stimulation of intestinal Ca^{2+} absorption with subsequent increase of extracellular Ca^{2+} and stimulation of gastric H^+ secretion by the Ca^{2+} sensing receptor [75, 76]. The known influence of VDR on the immune response [6-8] may have contributed to or even accounted for the impact of the VDR rs2228570 polymorphism on allergy. Previous observations revealed an influence of the FokI VDR polymorphism on prevalence and/or clinical course of asthma [27, 28], immune type 1 diabetes [77], multiple sclerosis [31], systemic lupus erythematosus [78], graft rejection [79], ulcerative colitis [40], aggressive periodontitis [30] and dengue hemorrhagic fever [80].

Our study did not show a consistent impact of VDR polymorphisms on cardiac infarction, diabetes mellitus and tumor growth. Several earlier studies similarly failed to reveal an impact of VDR polymorphisms on coronary artery disease [41] or malignancy [42-45]. Other studies, however, did show an impact of VDR polymorphisms on the prevalence of diabetes mellitus [24, 25], diabetic nephropathy [24] and malignancy [33-38, 45, 81]. Specifically, FokI VDR polymorphisms have been reported to impact on breast, prostate, skin, colorectum, ovary and bladder cancer with strongest impact on breast cancer, prostate cancer and malignant melanoma [45]. Increased blood vitamin D levels are associated with reduced occurrence of and reduced mortality from malignancy [81] and vitamin D deficiency worsens the prognosis of some cancers [82]. However, vitamin D supplementation did not improve the prognosis of prostate cancer patients [82]. Despite the impact of the VDR FokI polymorphism on several pathophysiologically relevant functions, the prevalence of the polymorphism is not significantly different between the young and the oldest old population or between the oldest old and the common population. In view of the limited number of individuals tested, the present study does not exclude an influence of the polymorphism on life span. Moreover, the different gender distribution in homozygote and heterozygote carriers of the FokI polymorphism may point to gender differences in the impact of the genotype on survival. Beyond that the impact of the polymorphism on health risk and survival may depend on the age of the individual. Interestingly, the polymorphism was associated with the life span of the parents (not shown). Possibly, life span before or beyond the age of the individuals studied is affected by the polymorphism.

Conclusions

Besides a potential influence of the FokI VDR polymorphism on instrumental activity of daily life (IADL)-score and diastolic blood pressure, as well as prevalence of renal disease, transitory ischemic attacks, allergy, urolithiasis and peptic ulcer, the present observations suggest that FokI VDR polymorphism impacts on the prevalence of depression, an observation highlighting the role of $1,25(\text{OH})_2\text{D}_3$ in the regulation of neuronal function.

Conflicts of Interest

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

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