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ARTICLE

Clinical Research

# The association between vitamin D receptor polymorphisms and tissue-specific insulin resistance in human obesity

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## Abstract

**Background/objectives** To investigate (1) the association of four VDR polymorphisms (TaqI/rs731236, ApaI/rs7975232, FokI/rs10735810, and BsmI/rs1544410) with markers of adiposity and tissue-specific insulin resistance at baseline, after weight loss and weight maintenance; (2) the effect of the VDR polymorphisms in the SAT transcriptome in overweight/obese Caucasians of the DiOGenes cohort.

**Methods** We included 553 adult obese individuals (mean BMI 34.8 kg/m$^2$), men ($n = 197$) and women ($n = 356$) at baseline, following an 8-week weight loss intervention and 26 weeks weight maintenance. Genotyping was performed using an Illumina 660W-Quad SNP chip on the Illumina iScan Genotyping System. Tissue-specific IR was determined using Hepatic Insulin Resistance Index (HIRI), Muscle Insulin Sensitivity Index (MISI), and Adipose Tissue Insulin Resistance Index (Adipo-IR). Expression quantitative trait loci (eQTL) analysis was performed to determine the effect of SNPs on SAT gene expression.

**Results** None of the VDR polymorphisms were associated with HIRI or MISI. Interestingly, carriers of the G allele of VDR FokI showed higher Adipo-IR (GG + GA 7.8 ± 0.4 vs. AA 5.6 ± 0.5, $P = 0.010$) and higher systemic FFA (GG + GA: 637.8 ± 13.4 vs. AA: 547.9 ± 24.7 µmol/L, $P = 0.011$), even after adjustment with age, sex, center, and FM. However, eQTL analysis showed minor to no effect of these genotypes on the transcriptional level in SAT. Also, VDR polymorphisms were not related to changes in body weight and IR as result of dietary intervention ($P > 0.05$ for all parameters).

**Conclusions** The VDR FokI variant is associated with elevated circulating FFA and Adipo-IR at baseline. Nevertheless, minor to no effect of VDR SNPs on the transcriptional level in SAT, indicating that putative mechanisms of action remain to be determined. Finally, VDR SNPs did not affect dietary intervention outcome in the present cohort.

## Introduction

The prevalence of obesity has increased dramatically reaching epidemic proportions worldwide [1]. Overweight and obesity have been shown as major risk factors for the development of insulin resistance, type 2 diabetes mellitus (T2D), and cardiovascular diseases (CVDs) [2]. Next to economic, social, and physical environment, genetic factors play an important role in obesity development and its comorbidities [3]. Previous studies have shown that human obesity is often characterized by vitamin D deficiency (circulating vitamin 25-hydroxyvitamin $D_3$/25OHD < 50 nmol/L) [4] and increased vitamin D receptor (VDR) expression within subcutaneous adipose tissue (SAT) [5]. Interestingly, adipose tissue overexpression of human VDR in mice leads to an increased fat mass (FM), a decreased glucose tolerance, and energy expenditure [6]. In line, our recent data indicated that VDR mRNA expression in SAT was positively related with body mass index (BMI) [7] and

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adipose tissue insulin resistance derived from a hyperinsulinemic euglycemic clamp [7], indicating a possible role for VDR in regulating adipose tissue function. The VDR gene is a polygenetic gene, and several known single nucleotide polymorphisms (SNPs) might affect the expression and function of VDR within these insulin sensitive tissues [8].

Genetic variations (SNPs) of VDR (ApaI, TaqI, BsmI, and FokI) have previously been related with measures of adiposity and insulin resistance. Some studies have shown that the ApaI, TaqI, BsmI, and FokI VDR variants are associated with markers of adiposity [9–11]. In contrast, others reported a lack of association between VDR variants and adiposity [12, 13]. Thus, evidence for the relationship between VDR genetic variants and obesity remains inconclusive. Of note, the majority of these studies determined adiposity based only on BMI [9–12], and therefore did not take a more precise determination of body composition into account.

Furthermore, it has been shown that VDR genetic variants may be associated with whole body insulin resistance [14–16] and the development of T2D [17]. Interestingly, it has been shown that the effects of vitamin D supplementation on insulin sensitivity (i.e., HOMA-IR) are affected by VDR genetic variation [18, 19]. The latter may suggest that metabolic effects of vitamin D and intervention outcome, particularly insulin sensitivity, may also be influenced by genetic variation in the VDR. However, studies investigate the relationship between VDR polymorphisms, adiposity, and (tissue-specific) insulin sensitivity (including muscle, liver and adipose tissue) are currently lacking. Also, it is currently unknown whether these VDR variants may affect human SAT at the transcriptional level. Therefore, we aimed to investigate the possible association of the VDR TaqI, ApaI, BsmI, and FokI polymorphisms with markers of adiposity including body composition and tissue-specific insulin resistance in the adult Caucasian obese/overweight population of the DiOGenes study. In addition, we investigated in the DiOGenes study whether these polymorphisms affected body weight loss as well as change in (tissue-specific) insulin sensitivity after an 8-week weight loss intervention followed by 26 weeks weight maintenance. To gain mechanistic insight, we also determined whether these VDR variants affect abdominal SAT at the transcriptional level.

## Materials/subjects and methods

### Study design

The DiOGenes study is a Pan-European multicenter, randomized, controlled dietary intervention study, designed to assess the efficacy of moderate fat diets that vary in protein content and glycemic index for preventing weight regain and obesity-related risk factors after weight loss (for details see Larsen et al. [20]). The study involved eight European countries (eight centers: Denmark, Netherlands, UK, Germany, Spain, Bulgaria, Czech Republic, and Greece). In total, 938 overweight or obese, nondiabetic adults free of CVD [age 18–65 years, BMI 27–45 kg/m$^2$] were recruited. More details on recruitment, inclusion and exclusion criteria, and study design are described elsewhere [20].

The analyses described here mainly focuses baseline data of 553 participants (men = 197 and women = 356), prior to any intervention, for whom VDR polymorphisms (TaqI/rs731236, ApaI/rs7975232, FokI/rs10735810, and Bsml/rs1544410) and detailed information of body composition, such as BMI, waist circumference (WC), and FM, as well as glucose and insulin concentrations during an oral glucose tolerance test (OGTT) were available. Subsequently, we analyzed how the indicated VDR polymorphisms related to changes in body weight and (tissue-specific) insulin sensitivity during a weight loss and subsequent weight maintenance period.

For this, after the first clinical investigation day (pre low-calorie diet) with baseline measurements (CID1), eligible adults followed an 8-week low-calorie diet (Modifast, Nutrition et Sante', France) consisting of 800 kcal/d. Adults who achieved a weight loss of ≥8% after 8 weeks underwent the second clinical investigation day (post low-calorie diet), was randomized to ad libitum diets for 26 weeks of weight maintenance [20]. After weight loss and weight maintenance the clinical investigation day was repeated (CID2 and CID3, respectively) The Medical Ethical Committees of the respective countries approved the study protocol. All participants gave written informed consent and the study was conducted in accordance with the principle of the Declaration of the Helsinki II.

### Body composition and blood sampling

Body composition was determined and blood samples were collected after an overnight fast. We included the following baseline anthropometric parameters: body weight, BMI, WC, and FM. BMI was calculated by dividing the mass in kg by squared height. Body composition was determined by Dual energy X-ray Absorptiometry (DXA) (Lunar Radiation, Madison, WI, USA) or bioelectrical impedance analysis/BIA (QuadScan 4000; Bodystat, Douglas, Isle of Man, British Isles). Bodystat is unique since it uses their own specifically developed and validated algorithm to calculate fat free mass, rather than using the 73.2% water assumption more commonly used in BIA devices [20]. In addition, glucose, free fatty acids (FFA) (automatic spectrophotometric enzymatic techniques) and insulin (radioimmunoassay) were measured from fasting blood samples [20].

## Estimates of insulin resistance indexes

Participants underwent a standard 5-point OGTT at baseline. Briefly, after an overnight fast, venous blood was collected before (t0) and after a 75 g glucose load was ingested. Blood samples were taken at 0, 30, 60, 90, and 120 min to determine glucose and insulin concentrations [20]. Muscle insulin sensitivity index (MISI) and hepatic insulin resistance index (HIRI) were estimated using the methods of Abdul-Ghani et al. [21].

The MISI was calculated according to the following formula: MISI = (dG/dt)/mean plasma insulin concentrations during the OGTT. Here, dG/dt is the rate of decay of plasma glucose concentrations during the OGTT, calculated as the slope of the least square fit to the decline in plasma glucose concentration from peak to nadir [21]. The decline in plasma glucose concentration after 60 min primarily reflects glucose uptake by peripheral tissue mainly skeletal muscle.

The HIRI was calculated using the square root of the product of the area under curves (AUCs) for glucose and insulin during the first 30 min of the OGTT. The formula of HIRI's calculation was SQRT ($glucose_{0–30}$ [AUC in mg/d × h] × $insulin_{0–30}$ [AUC in μU/mL × h]). This index has been developed and validated against the product of fasting plasma insulin and endogenous glucose production in hyperinsulinemic euglycemic clamp studies in a Mexican-American population (non-Caucasian) [21].

The Adipose tissue insulin resistance index (Adipo-IR) was calculated for 485 participants (FFA data available) using the method of Søndergaard et al. [22]. The Adipo-IR was calculated using fasting insulin and fasting FFA concentrations (fasting insulin [μIU/mL] × fasting FFA [μmol/L]/1000). This formula has been strongly associated with suppression of lipolysis derived from palmitate flux ($IC_{50}$) as measured by the multistep pancreatic clamp technique [22].

## SNP selection and genotyping

Buffy coats were collected for DNA extraction and genetic SNPs analysis. The four VDR SNPs: TaqI(rs731236), ApaI(rs7975232), BsmI(rs1544410), and FokI(rs10735810; rs10735810 was merged into rs2228570; https://www.ncbi.nlm.nih.gov/snp/?term=rs2228570) were evaluated by allelic discrimination real-time PCR using an Illumina 660W-Quad SNP chip on the Illumina iScan Genotyping System (Illumina, San Diego, CA, USA).

## Abdominal SAT RNA-seq analysis

Total RNA was extracted from abdominal SAT biopsies as described before [23]. Gene expression was examined by using 100-nucelutide long paired-end RNA sequencing with an Illumina HiSeq 2000 of libraries prepared by using the Illumina TruSeq kit following the manufacturer's standard protocols. Sequencing was performed using baseline SAT prior to any weight loss intervention. For each sample, the number of reads mapping onto genes was retrieved by using Genomic Alignments as previously described [24].

## Statistical analysis

All continuous variables were checked for normal distribution. Variables with a skewed distribution were natural logarithmically transformed (BMI, WC, FM, MISI, HIRI, and Adipo-IR) to satisfy the condition of normality. The data were back-transformed and presented as mean ± SE.

Allele frequency and Hardy-Weinberg Equilibrium (HWE) were calculated for all VDR SNPs. The non-random association of alleles at different loci of VDR polymorphisms (pairwise linkage disequilibrium (LD)) analysis was analyzed using SNPStat [25] (available online at https://www.snpstats.net/start.htm). Coefficient D′ was used to describe pairwise LD, where a D′ value close to 1 indicated high LD and D′ value close to 0 suggested weak LD.

Analysis of covariance (ANCOVA) was performed to examine the differences in body composition (BMI, waist, and FM) between the genotypes adjusted for age, sex, and center. The changes in body weight between genotypes following weight loss intervention were adjusted for initial body weight, while the differences in body weight between genotypes following weight maintenance were corrected for weight loss during LCD and mean body weight pre and post LCD. Furthermore, ANCOVA was also conducted to analyze the differences in tissue-specific insulin resistance index (MISI, HIRI, and Adipo-IR) between the genotypes adjusted for age, sex, center, and FM at baseline. The changes in MISI, HIRI, and Adipo-IR between the genotypes following weight loss intervention were adjusted for MISI, HIRI, and Adipo-IR at baseline, respectively. The changes in MISI, HIRI, and Adipo-IR between the genotypes following weight maintenance were adjusted for the changes MISI, HIRI, and Adipo-IR during LCD and mean of MISI, HIRI, Adipo-IR pre and post LCD, respectively. In addition, dominant, recessive, over, and co-dominant models were selected. Briefly, a dominant model compares homozygote dominant versus heterozygote–homozygote recessive, whereas the recessive model compares heterozygote–homozygote dominant versus homozygote recessive. An overdominant model compares homozygote dominant–recessive vs. heterozygote where this model assumes the heterozygote has the strongest impact on the outcome. On the other hand, co-dominant models hypothesize that each genotype may be associated with the outcomes [26].

Expression quantitative trait loci (eQTL) analysis [27] was conducted to analyze the association between the VDR gene variants and abdominal SAT tissue gene expression

**Table 1** Participants' demographic, anthropometric, and clinical characteristics.

| | Baseline (CID1) ($N = 553$) | | After weight loss (CID2) ($N = 491$) | | After weight maintenance (regain) (CID3) ($N = 356$) | |
|---|---|---|---|---|---|---|
| Variable | Mean ± SE | Range | Mean ± SE | Range | Mean ± SE | Range |
| Age (years) | 41.5 ± 0.3 | 24–63 | 41.7 ± 0.3 | 24–63 | 42.5 ± 0.3 | 24–63 |
| Sex (M/F) | 197/356 | | 178/313 | | 120/236 | |
| Weight (kg) | 100.6 ± 0.8 | 66.6–168.6 | 89.4 ± 0.9 | 59–150 | 89.7 ± 0.7 | 57–154 |
| BMI (kg/m$^2$) | 34.8 ± 0.2 | 26.7–52.0 | 30.9 ± 0.2 | 22.2–45.7 | 30.9 ± 0.2 | 21.8–43.9 |
| WC (cm) | 109 ± 0.6 | 64.0–155.0 | 98.8 ± 0.7 | 70.0–133.0 | 99.3 ± 0.6 | 71.0–138.0 |
| FM (kg) | 40.8 ± 0.5 | 15.6–82.6 | 32.2 ± 0.6 | 9.9–58.8 | 33.2 ± 0.5 | 11.9–68.7 |
| Fasting glucose (mmol/L) | 5.2 ± 0.1 | 3.4–8.7 | 4.9 ± 0.0 | 4.0–8.0 | 5.0 ± 0.0 | 4.0–7.0 |
| Fasting insulin μIU/mL | 11.9 ± 0.4 | 2.0–134.0 | 8.3 ± 0.3 | 2.0–87.0 | 9.3 ± 0.5 | 2.0–100.0 |
| Fasting FFA (μmol/L) | 627 ± 12[a] | 162–2226 | 712 ± 11[b] | 153–1727 | 555 ± 12[c] | 109–1419 |
| HIRI | 33.4 ± 0.5[d] | 11.9–94.3 | 26.4 ± 0.7[e] | 7.4–73.3 | 32.0 ± 0.9[f] | 6.5–89.6 |
| MISI | 0.06 ± 0.00[g] | 0.01–0.53 | 0.06 ± 0.00[h] | 0.01–0.30 | 0.07 ± 0.00[i] | 0.01–0.36 |
| Adipo-IR | 7.0 ± 0.2[a] | 1.0–39.3 | 5.8 ± 0.3[b] | 0.7–43.9 | 5.1 ± 0.3[c] | 0.4–58.5 |

*Adipo-IR* adipose tissue insulin resistance index, *BMI* body mass index, *F* female, *FM* fat mass, *FFA* free fatty acid, *HIRI* hepatic insulin resistance index, *HOMA-IR* homeostatic model assessment for insulin resistance, *M* male, *MISI* muscle insulin sensitivity index.

[a]$N = 485$.

[b]$N = 420$.

[c]$N = 281$.

[d]$N = 539$.

[e]$N = 383$.

[f]$N = 303$.

[g]$N = 519$.

[h]$N = 383$.

[i]$N = 300$.

(RNA-seq). We considered three sets of genes for the eQTL analysis: (1) the VDR gene (*cis*), (2) all VDR target genes (*trans*) and (3) all genes in *cis*, defined as any gene within 1 Mb upstream or downstream of the genomic location of the respective SNP. To test for eQTL associations, we first recoded the genotype of each SNP to the alternative allele dosage (i.e., 0, 1, or 2 copies). To construct the set of VDR target genes, we manually performed a search using PubMed (search criteria combined with Boolean operators AND/OR: Vitamin D, VDR, target genes, obesity). From the list of articles retrieved [6, 28–42], abstracts were scanned, and only those that reported vitamin D, gene name and obesity and/or insulin resistance were further analyzed resulting in a list of VDR target genes. Next, for each gene in a set, a linear additive model was created with gene expression as the dependent variable and the alternative allele dosage as the independent variable, while correcting for age, sex, and center. Correction for multiple testing was performed by means of a Bonferroni correction and for eQTL analysis we performed the false discovery rate (FDR) correction. All analyses were performed in the statistical programming language R (version 3.3.1) [43].

## Results

The main demographic, anthropometric, and clinical characteristics of participants are presented in Table 1. In our population genotypes of TaqI rs731236, ApaI rs7975232, BsmI rs1544410, and FokI rs10735810 were predominantly heterozygous and all SNPs were compatible with HWE as shown in Supplementary Table S1.

### VDR variants and anthropometry measurements at baseline

Variants in VDR TaqI in the dominant model (AA *versus* AG + GG) were related to BMI, WC, and FM ($P = 0.007$; $P = 0.08$; $P = 0.006$, respectively) (Table 2). Furthermore, variants in VDR TaqI were associated with BMI, WC, and FM ($P = 0.009$, $P = 0.013$, $P = 0.006$, respectively) in the overdominant model (AA + GG vs. AG). Overall, G allele (39.51%) carriers (AG + GG) of the VDR TaqI had higher BMI, WC, and FM as compared to non-carriers (AA) (Table 2).

**Table 2** The relationship between VDR polymorphisms and body composition.

| | | BMI | ($kg/m^2$) | | | Waist(cm) | | | Fat mass(kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Genotype | *N* | Mean | SE | *P* value | Mean | SE | *P* value | Mean | SE | *P* value |
| TaqI rs731236 | | | | | | | | | | | |
| Co-dominant | AA | 209 | 34.1 | 0.3 | 0.017 | 107 | 0.9 | 0.045 | 39.1 | 0.7 | 0.012 |
| | AG | 251 | 35.4 | 0.3 | | 110 | 0.9 | | 42.1 | 0.8 | |
| | GG | 93 | 34.9 | 0.5 | | 107 | 1.4 | | 41.1 | 1.2 | |
| Dominant | AA | 209 | 34.1 | 0.3 | 0.007 | 107 | 0.9 | 0.08 | 39.1 | 0.7 | 0.006 |
| | AG + GG | 344 | 35.3 | 0.3 | | 109 | 0.7 | | 41.8 | 0.7 | |
| Recessive | AA + AG | 460 | 34.8 | 0.2 | 0.99 | 109 | 0.6 | 0.17 | 40.8 | 0.5 | 0.74 |
| | GG | 93 | 34.9 | 0.5 | | 107 | 1.4 | | 41.1 | 1.2 | |
| Overdominant | AA + GG | 302 | 34.3 | 0.3 | 0.009 | 107 | 0.7 | 0.013 | 39.7 | 0.6 | 0.006 |
| | AG | 251 | 35.4 | 0.3 | | 110 | 0.9 | | 42.1 | 0.8 | |
| ApaI rs7975232 | | | | | | | | | | | |
| Co-dominant | CC | 206 | 34.1 | 0.3 | 0.033 | 107 | 0.9 | 0.11 | 39.4 | 0.7 | 0.026 |
| | CA | 250 | 35.4 | 0.3 | | 110 | 0.9 | | 42.1 | 0.8 | |
| | AA | 97 | 34.8 | 0.5 | | 106 | 1.3 | | 40.5 | 1.2 | |
| Dominant | CC | 206 | 34.1 | 0.3 | 0.023 | 107 | 0.9 | 0.36 | 39.4 | 0.7 | 0.028 |
| | CA + AA | 347 | 35.3 | 0.3 | | 109 | 0.8 | | 41.7 | 0.6 | |
| Recessive | CC + CA | 456 | 34.9 | 0.2 | 0.56 | 109 | 0.6 | 0.15 | 40.9 | 0.5 | 0.38 |
| | AA | 97 | 34.8 | 0.5 | | 106 | 1.3 | | 40.5 | 1.2 | |
| Overdominant | CC + AA | 303 | 34.3 | 0.3 | 0.012 | 107 | 0.7 | 0.056 | 39.8 | 0.6 | 0.008 |
| | CA | 250 | 35.4 | 0.3 | | 110 | 0.9 | | 42.1 | 0.8 | |
| BsmI rs1544410 | | | | | | | | | | | |
| | TT | 166 | 34.9 | 0.4 | 0.18 | 108 | 1.0 | 0.40 | 41.1 | 0.9 | 0.44 |
| Co-dominant | TC | 263 | 35.1 | 0.3 | | 110 | 0.9 | | 41.2 | 0.7 | |
| | CC | 124 | 34.1 | 0.4 | | 108 | 1.1 | | 39.6 | 1.0 | |
| Dominant | TT | 166 | 34.9 | 0.4 | 0.78 | 108 | 1.0 | 0.43 | 41.1 | 0.9 | 0.87 |
| | TC + CC | 387 | 34.8 | 0.3 | | 109 | 0.7 | | 40.7 | 0.6 | |
| Recessive | TT + TC | 429 | 35.1 | 0.2 | 0.07 | 109 | 0.7 | 0.45 | 41.2 | 0.6 | 0.21 |
| | CC | 124 | 34.1 | 0.4 | | 108 | 1.1 | | 39.6 | 1.0 | |
| Overdominant | TT + CC | 290 | 34.6 | 0.3 | 0.21 | 108 | 0.8 | 0.18 | 40.5 | 0.7 | 0.37 |
| | TC | 263 | 35.1 | 0.3 | | 110 | 0.9 | | 41.2 | 0.7 | |
| FokI rs10735810 | | | | | | | | | | | |
| Co-dominant | GG | 227 | 34.9 | 0.3 | 0.94 | 109 | 0.9 | 0.85 | 40.5 | 0.8 | 0.14 |
| | GA | 259 | 34.9 | 0.3 | | 109 | 0.8 | | 41.6 | 0.7 | |
| | AA | 67 | 34.8 | 0.6 | | 108 | 1.5 | | 39.2 | 1.4 | |
| Dominant | GG | 227 | 34.9 | 0.3 | 0.96 | 109 | 0.9 | 0.76 | 40.5 | 0.8 | 0.57 |
| | GA + AA | 326 | 34.8 | 0.3 | | 109 | 0.7 | | 41.1 | 0.6 | |
| Recessive | GG-GA | 486 | 34.9 | 0.2 | 0.76 | 109 | 0.6 | 0.73 | 41.1 | 0.5 | 0.10 |
| | AA | 67 | 34.8 | 0.6 | | 108 | 1.5 | | 39.2 | 1.4 | |
| Overdominant | GG + AA | 294 | 34.8 | 0.3 | 0.80 | 109 | 0.8 | 0.59 | 40.2 | 0.7 | 0.11 |
| | GA | 259 | 34.9 | 0.3 | | 109 | 0.8 | | 41.6 | 0.7 | |

*P* value was corrected for age, sex, and center.

*BMI* body mass index, *FM* fat mass, *WC* waist circumference.

In the dominant model VDR ApaI (CC vs. CA + AA) was associated with higher BMI and FM ($P = 0.023$; $P = 0.028$, respectively) (Table 2). Further analysis in the overdominant model showed that CC + AA variants in VDR ApaI were related to BMI and FM ($P = 0.012$; $P = 0.008$, respectively) as compared to the CA variant. Overall,

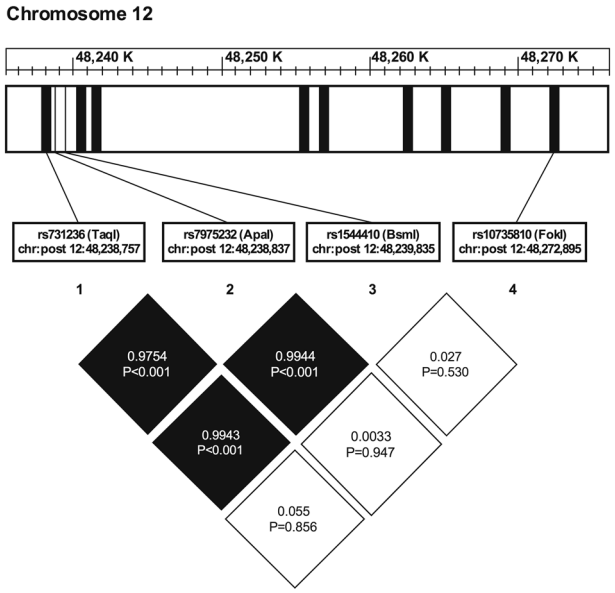


**Fig. 1 The VDR gene on chromosome 12 and LD analysis.** The VDR gene on chromosome 12. The approximate locations of the observed polymorphisms are indicated by arrows. The blocks represented pairwise linkage disequilibrium (LD) pattern. Each square described the D′ values and the p values between the pairs of VDR polymorphisms. The black blocks are proportional to D′ values which indicates high LD between polymorphisms. The white blocks indicate low LD between polymorphisms.

A allele (40.15%) carriers (CA + AA) of VDR ApaI had higher BMI and FM compared to non-carriers (CC). However, neither VDR BsmI nor FokI were related to BMI, WC, and FM in this cohort ($P > 0.05$ for all parameters).

### Linkage disequilibrium of VDR variants and haplotype analysis

Pairwise LD between SNPs was assessed, and LD analysis revealed strong LD between VDR TaqI, ApaI, and BsmI ($D' = 0.9754$, $D' = 0.9944$, $D' = 0.9943$, respectively see Fig. 1). In contrast, weak LD (D′ values close to 0, see Fig. 1) was observed between these variants (TaqI, ApaI, BsmI) and FokI. However, subsequent haplotype analysis revealed no significant associations between different haplotypes and BMI, WC, and FM, even after adjustment for age, sex, and center (except uncommon haplotypes (frequency < 1%) (Supplementary Table S2). Further haplotype analysis showed no association with HIRI, MISI, or Adipo-IR (data not shown).

### VDR variants and tissue-specific insulin resistance index

The analysis of tissue-specific insulin resistance according to VDR genotypes as described in Table 3, shows no significant associations between VDR variants, HIRI and MISI ($P > 0.05$ for all). Of interest, G allele (64.84%) carriers of VDR FokI showed higher Adipo-IR (GG + GA $7.8 \pm 0.4$ vs. AA $5.6 \pm 0.5$, $P = 0.010$) even after adjustment for age, sex, center, and FM. Moreover, circulating FFA but not fasting insulin, were significantly higher in G allele (64.84%) carriers of VDR FokI as compared to non-carriers (GG + GA: $637.8 \pm 13.4$ (μmol/L) vs. AA: $547.9 \pm 24.7$, $P = 0.011$) (Supplementary Table S3).

### Association between VDR polymorphisms and SAT gene transcription level

eQTL analysis was conducted to analyze the association between the VDR gene variants and abdominal SAT tissue gene expression. Hoverer, *cis* and *trans* eQTL analysis showed that VDR gene expression did not significantly differ between genotypes of any of the VDR SNPs (TaqI, ApaI, BsmI, and FokI). We observed no significance difference of the VDR SNPs with gene expression of VDR target genes in *cis* and *trans* after FDR correction ($P > 0.05$) (Supplementary Tables S4 and S5).

### VDR polymorphisms and change of body weight, change of tissue-specific IR following weight loss and maintenance

No effects of VDR genetic variants on the change of body weight following weight loss and weight maintenance were observed (Supplementary Table S6). Furthermore, there were no effects of VDR polymorphisms on the change of tissue-specific insulin resistance indexes (HIRI, MISI, and Adipo-IR) following weight loss intervention and weight maintenance (regain) (Supplementary Tables S7 and S8).

## Discussion

In this study, we showed that variants in VDR TaqI and ApaI are associated with elevated BMI (contributing 0.9 kg/m2 per risk allele), WC (3 cm per risk allele), or FM at baseline (2 kg per risk allele) at baseline. Secondly, variants in FokI VDR were associated with Adipo-IR as well as elevated circulating FFA at baseline (79 μmol/L per risk allele). Thirdly, *cis* and *trans* eQTL analysis demonstrated no major effects of these VDR polymorphisms on the SAT transcriptome at baseline. Finally, there was no relationship between VDR polymorphisms and changes in body weight and tissue-specific insulin resistance during weight loss and weight maintenance.

In the present study, we found that BMI, WC, and FM were significantly higher in individuals that carried the VDR TaqI G allele (AG and GG genotype) compared to non-carriers (AA genotype). In addition, BMI and FM of VDR ApaI A allele carriers were considerably higher than those of non-carriers

**Table 3** The association between VDR polymorphisms and tissue-specific insulin resistance index.

| | | HIRI[a] | | | | MISI[b] | | | | Adipo-IR[c] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Genotype | *N* | Mean | SE | *P* value | N | Mean | SE | *P* value | *N* | Mean | SE | *P* value |
| TaqI rs731236 | | | | | | | | | | | | | |
| Co-dominant | AA | 205 | 32.6 | 0.7 | 0.89 | 200 | 0.05 | 0.0 | 0.54 | 183 | 6.7 | 0.3 | 0.81 |
| | GA | 243 | 33.8 | 0.7 | | 233 | 0.06 | 0.0 | | 225 | 8.1 | 0.5 | |
| | GG | 91 | 34.1 | 1.5 | | 86 | 0.05 | 0.0 | | 77 | 7.7 | 1.2 | |
| Dominant | AA | 205 | 32.6 | 0.7 | 0.64 | 200 | 0.05 | 0.0 | 0.31 | 183 | 6.7 | 0.3 | 0.63 |
| | GA + GG | 334 | 33.9 | 0.7 | | 319 | 0.06 | 0.0 | | 302 | 8.0 | 0.5 | |
| Recessive | AA + GA | 448 | 33.3 | 0.5 | 0.90 | 433 | 0.06 | 0.0 | 0.44 | 408 | 7.5 | 0.3 | 0.80 |
| | GG | 91 | 34.1 | 1.5 | | 86 | 0.05 | 0.0 | | 77 | 7.7 | 1.2 | |
| Overdominant | AA + GG | 296 | 33.1 | 0.7 | 0.72 | 286 | 0.05 | 0.0 | 0.68 | 260 | 6.9 | 0.4 | 0.52 |
| | GA | 243 | 33.8 | 0.7 | | 233 | 0.06 | 0.0 | | 225 | 8.1 | 0.5 | |
| ApaI rs7975232 | | | | | | | | | | | | | |
| Co-dominant | CC | 201 | 32.6 | 0.7 | 0.71 | 200 | 0.05 | 0.0 | 0.73 | 181 | 6.7 | 0.4 | 0.83 |
| | CA | 243 | 33.7 | 0.7 | | 233 | 0.06 | 0.0 | | 223 | 8.0 | 0.5 | |
| | AA | 95 | 34.2 | 1.4 | | 86 | 0.05 | 0.0 | | 81 | 7.8 | 1.1 | |
| Dominant | CC | 201 | 32.6 | 0.7 | 0.41 | 200 | 0.05 | 0.0 | 0.42 | 181 | 6.7 | 0.4 | 0.56 |
| | CA + AA | 338 | 33.9 | 0.7 | | 319 | 0.06 | 0.0 | | 304 | 7.9 | 0.5 | |
| Recessive | CC + CA | 444 | 33.2 | 0.5 | 0.65 | 433 | 0.06 | 0.0 | 0.76 | 404 | 7.4 | 0.3 | 0.71 |
| | AA | 95 | 34.2 | 1.4 | | 86 | 0.05 | 0.0 | | 81 | 7.8 | 1.1 | |
| Overdominant | CC + AA | 296 | 33.1 | 0.7 | 0.43 | 286 | 0.05 | 0.0 | 0.58 | 262 | 7.1 | 0.4 | 0.77 |
| | CA | 243 | 33.7 | 0.7 | | 233 | 0.06 | 0.0 | | 223 | 8.0 | 0.5 | |
| BsmI rs1544410 | | | | | | | | | | | | | |
| Co-dominant | TT | 163 | 34.3 | 1.1 | 0.59 | 154 | 0.05 | 0.0 | 0.52 | 141 | 8.5 | 0.9 | 0.59 |
| | TC | 255 | 33.2 | 0.7 | | 246 | 0.06 | 0.0 | | 236 | 7.2 | 0.3 | |
| | CC | 121 | 32.6 | 0.9 | | 119 | 0.06 | 0.0 | | 108 | 6.8 | 0.5 | |
| Dominant | TT | 163 | 34.3 | 1.1 | 0.37 | 154 | 0.05 | 0.0 | 0.41 | 141 | 8.5 | 0.9 | 0.32 |
| | TC + CC | 376 | 33.0 | 0.6 | | 365 | 0.06 | 0.0 | | 344 | 7.1 | 0.3 | |
| Recessive | TT + TC | 418 | 33.6 | 0.6 | 0.43 | 400 | 0.06 | 0.0 | 0.30 | 377 | 7.7 | 0.4 | 0.56 |
| | CC | 121 | 32.6 | 0.9 | | 119 | 0.06 | 0.0 | | 108 | 6.9 | 0.5 | |
| Overdominant | TT + CC | 284 | 33.6 | 0.7 | 0.87 | 273 | 0.06 | 0.0 | 0.90 | 249 | 7.8 | 0.6 | 0.67 |
| | TC | 255 | 33.2 | 0.7 | | 246 | 0.06 | 0.0 | | 236 | 7.2 | 0.3 | |
| FokI rs10735810 | | | | | | | | | | | | | |
| Co-dominant | GG | 219 | 33.8 | 0.8 | 0.54 | 213 | 0.06 | 0.0 | 0.60 | 202 | 7.7 | 0.5 | 0.038 |
| | GA | 254 | 33.5 | 0.7 | | 244 | 0.06 | 0.0 | | 225 | 7.8 | 0.5 | |
| | AA | 66 | 31.8 | 1.4 | | 62 | 0.07 | 0.01 | | 58 | 5.6 | 0.5 | |
| Dominant | GG | 219 | 33.8 | 0.8 | 0.64 | 213 | 0.06 | 0.0 | 0.49 | 202 | 7.7 | 0.5 | 0.69 |
| | GA + AA | 320 | 33.2 | 0.7 | | 306 | 0.06 | 0.0 | | 283 | 7.4 | 0.4 | |
| Recessive | GG + GA | 473 | 33.6 | 0.5 | 0.27 | 457 | 0.06 | 0.0 | 0.36 | 427 | 7.8 | 0.4 | 0.010 |
| | AA | 66 | 31.8 | 1.4 | | 62 | 0.07 | 0.01 | | 58 | 5.6 | 0.5 | |
| Overdominant | GG + AA | 285 | 33.3 | 0.7 | 0.80 | 275 | 0.06 | 0.0 | 0.92 | 260 | 7.2 | 0.4 | 0.29 |
| | GA | 254 | 33.5 | 0.7 | | 244 | 0.06 | 0.0 | | 225 | 7.8 | 0.5 | |

*P* value was corrected for age, sex, center, and fat mass.

*Adipo-IR* adipose tissue insulin resistance index, *HIRI* hepatic insulin resistance index, *MISI* muscle insulin sensitivity index.

[a]$N = 539$.

[b]$N = 519$.

[c]$N = 485$.

(CC genotype). In line with this, Al-Daghri et al. showed that TaqI (G allele) and ApaI (A allele) were associated with higher BMI in a dark-pigmented Caucasian population [9]. In addition, the TaqI polymorphism was also associated with higher BMI in a Greek population [10]. In contrast, Vimaleswaran et al. and Walsh et al. showed no association between variants in VDR TaqI, BMI [44] and FM [45] in male and female, lean/overweight and obese Caucasians. Regarding BsmI and FokI, we did not find any association with BMI, WC, or FM, which is in line with a previous finding by Dorjgochoo et al. and Walsh et al. showing no relationship between BsmI and FokI variants and markers of body composition (BMI [46] or FM [45]) in a Caucasian population.

Furthermore, pairwise LD analysis showed strong LD between TaqI, ApaI, and BsmI in our obese/overweight Caucasian population. However, haplotype analysis revealed no significantly associations with BMI, FM, and tissue-specific insulin resistance, even after adjustment for age, sex, and center. These results, are in contrast with Al-Daghri et al. showing that in Dark-pigmented Caucasian individuals carriers of both G allele (TaqI) and A allele (ApaI) had significantly higher BMI independent from age and sex [9]. Differences in study populations (i.e., broader BMI vs. overweight/obese BMI) and ethnic-pigmentation (Dark-pigmented versus White-pigmented Caucasian) might partly explain this discrepancy [14], which still needs further investigation.

With respect to tissue-specific insulin resistance, we did not find any associations between VDR polymorphisms (TaqI, ApaI, BsmI, and FokI), HIRI or MISI estimated from 5 time-points OGTT. Of interest, G allele Carriers of VDR FokI showed a significant higher Adipo-IR and elevated fasting FFA concentrations, independent of age and sex. Moreover, recent studies in Asian populations with dyslipidemia suggested an association between FokI variants elevated triglyceride (TG) [47] and low-density lipoprotein [48]. These findings may indicate that VDR FokI variants are merely related to dyslipidemia and an impaired liver lipid metabolism [49], which needs to be investigated in more detail. Furthermore, the FokI polymorphism is located on the exon in the coding region of the VDR gene, resulting in different translation initiation sites and giving rise to a full-length VDR protein or a three amino acid shorter VDR protein variant [50], having higher transcriptional activity [51, 52]. Therefore, we studied whether variants in VDR FokI were associated with changes in the abdominal SAT transcriptome (targeted gene expression related to adipose tissue glucose, and lipid metabolism as well as inflammation). However, our *cis* and *trans* eQTL analysis suggested no effect of VDR FokI variants on SAT gene transcription, suggesting a minor contribution of VDR polymorphisms on adipose tissue function in overweight/obese men and women.

Further analysis, showed no effect of TaqI, ApaI, and FokI VDR genetic variants on the change of body weight and tissue-specific insulin resistance following weight loss and weight regain. Thus although these polymorphisms significantly contribute to adiposity and Adipo-IR in a cross-sectional analysis they are apparently of less importance in determining dietary intervention outcome. This seems to be in contrast to another study in a T2D Saudi population showing that VDR genetic variants (i.e., TaqI and BsmI) affect intervention outcome (i.e., insulin sensitivity measured by HOMA-IR) following vitamin D supplementation [19].

In conclusion, our findings indicate that variants in VDR TaqI and ApaI are associated with markers of adiposity. In addition, the VDR FokI G allele is associated with elevated circulating FFA and Adipo-IR in overweight/obese Caucasians. These VDR SNPs were not related changes in body weight and insulin sensitivity as result of dietary intervention. Nevertheless, these VDR SNPs had no effect on the transcriptional level, at least in abdominal SAT, indicating that the putative mechanisms of action remain to be determined.

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**Author contributions** WHMS and AA designed the DiOGenes clinical study. AP, JWJ, and EEB designed the study. AP performed data analyses and wrote the manuscript. JWEJ and MEA supervised adipose tissue transcriptome data analysis. All authors contributed to revising the article critically and gave their final approval of the version to be published. EEB is the guarantor of this study.

## Compliance with ethical standards

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

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