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ORIGINAL ARTICLE

Association of vitamin D receptor gene polymorphisms with disc degeneration

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Abstract

Purpose Numerous candidate genes and single-nucleotide polymorphisms (SNPs) have been identified in the background of lumbar disc degeneration (LDD). However, in most of these underpowered studies, definitions of LDD are inconsistent; moreover, many of the findings have not been replicated and are contradictory. Our aim was to characterize LDD by well-defined phenotypes and possible endophenotypes and analyse the association between these and candidate vitamin D receptor (VDR) gene polymorphisms on a large ($N = 1426$) dataset.

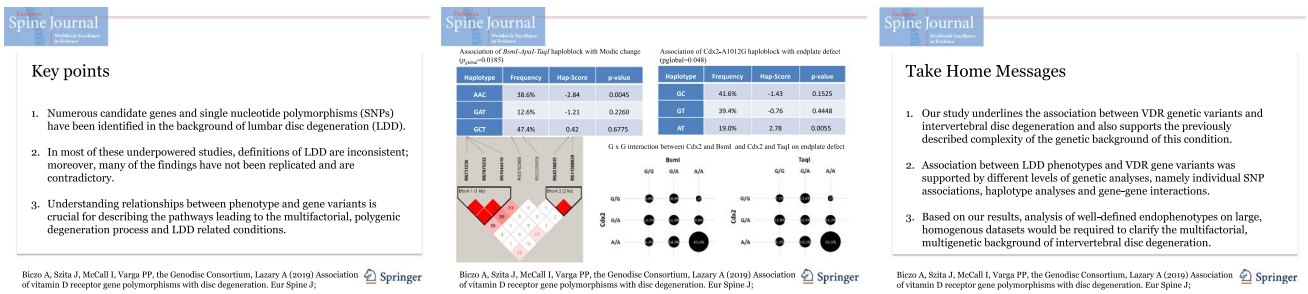
Methods Seven candidate VDR SNPs were genotyped. Individual association, haplotype and gene–gene interaction analyses were performed. All degenerative endophenotypes were significantly associated with one or more candidate VDR gene variants.

Results Haplotype analyses confirmed the association between the 3′-end VDR variants (*BsmI, ApaI, TaqI*) and Modic changes as well as the relationship of 5′-end variants (*Cdx2, A1012G*) with endplate defects. We also found significant interactions between the 3′- and 5′-end regulatory regions and endplate defects. Based on our results, VDR and its gene variants are highly associated with specific degenerative LDD endophenotypes.

Conclusion Understanding relationships between phenotype and gene variants is crucial for describing the pathways leading to the multifactorial, polygenic degeneration process and LDD-related conditions.

Graphic abstract

These slides can be retrieved under Electronic Supplementary Material.



Keywords VDR · Lumbar disc degeneration · Single-nucleotide polymorphism · Haplotype · Endophenotype

Introduction

Low back pain (LBP) is one of the most significant healthcare problems worldwide [1] and imposes a heavy burden on the national health systems in the industrialized countries. Low back pain is thought to be associated with various spinal pathologies (such as disc herniation, spinal stenosis,

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segmental instability) arising from lumbar intervertebral disc degeneration (LDD). The pathomechanism leading to LDD is still unclear. Twin studies showed that up to 70% of LDD could be genetically determined [2]. Candidate gene and genome-wide association studies have identified numerous genes and single-nucleotide polymorphisms (SNPs) in the background of LDD [3]. Vitamin D receptor gene (VDR) has been reported to be one of the first [4] and since then one of the most studied [5] candidate genes. However, studies of the possible role of VDR genetic variants have led to contradictory results with only few findings replicated. Videman et al. [4] in a Finnish population found that "tt" genotype of *TaqI* polymorphism was associated with the most severe degenerative MRI phenotype, yet, also in Finnish populations, Noponen-Hietala et al. [6] and Kelempisioti [6, 7] found no association with disc degeneration and *FokI* and *TaqI* variants. On the other hand, in a Japanese population, Kawaguchi et al. [8], in agreement with Videman et al. [4], found that *TaqI* VDR variant was associated with severe degeneration based on Schneiderman score, though here the risk genotype was "Tt" [8].

Some of the contradictions in the literature could be related to differences in the definition of the LDD phenotype. Rajasekaran et al. [9] critically reviewed the LDD-related genetic studies and examined gene associations with LDD-related morphological phenotypes such as degree of disc degeneration, disc bulging, Modic change, endplate defects and Schmorl's node on a large cohort. They highlighted the importance of standardizing the description of disc degeneration for studies of this topic. The contradictions could also arise from underpowered studies, with only small numbers of subjects examined (e.g. Noponen-Hietala compared only 29 subjects with 56 controls; Kawaguchi's study population consisted of 205 young adults; Toktas compared 75 subjects with 25 controls).

Hence, in the present study, well-defined phenotypes within a homogenous dataset of a large, international cohort were analysed in association with the candidate VDR single-nucleotide gene variants and haplotypes to clarify the possible significance of VDR in LDD. These results point to the existence of endophenotypes in the process of disc degeneration, viz. specific phenotypes (Pfirrmann score, endplate defect, Modic changes, disc prolapse) each with a clear distinct genetic connection underpinning a biological pathway.

Materials and methods

Study population

An international database (Genodisc cohort) containing the clinical, radiological, demographic and genetic data of 2635 low back pain patients from spine hospitals in three European countries (Hungary, Italy, UK) was used [10–14]. All subjects were hospitalized and surgically treated for degenerative lumbar spine pathology. Subjects were involved in the study after signing a written informed consent with the approval of the competent ethical committee. The original dataset of the present study is available upon request.

Phenotype measurements

A set of degenerative phenotypes was qualitatively determined on lumbar spine MRIs by the same radiologist (IM). Four different phenotypes (Pfirrmann grade, Modic change, disc prolapse, endplate defect) were used in the present analysis. All the phenotypes were assessed at five lumbar segments. In the subsequent analysis, we determined the genetic association with the phenotypes at any lumbar levels, at also at L4/5 and L5/S1 levels separately. Pfirrmann grading system was used to determine the level of overall disc degeneration. Mean *Pfirrmann grade* and dichotomous derivate were analysed statistically. In the latter case, as suggested by others [7, 15], discs were scored as "normal" (Pfirrmann 1–2) and "pathologic" (Pfirrmann 3–5) (Fig. 1). Degenerative endplate changes, such as Modic I and Modic II changes, were grouped together into the dichotomous *Modic change* phenotype. *Disc prolapse* was defined as the presence of disc bulging or herniation at the given spinal segment. *Endplate defect* was determined as bony defect at either the upper or the lower endplate (e.g. Schmorl's node). The distribution of the prevalence of the degenerative phenotypes in the Genodisc cohort was the following: 1858 patients had Modic change, 2586 patients had pathologic Pfirrmann grade, 1225 patients had endplate defect and 2541 patients had disc prolapse. The distribution of the studied phenotypes in the final study population is given in Table 1.

Genotyping

DNA was extracted from venous blood or saliva samples using commercial kits. Seven candidate VDR SNPs were genotyped at the Technology Centre, Institute for Molecular Medicine Finland (FIMM), University of Helsinki, using a Sequenom MassArray technology and the iPLEX Gold reagents (Sequenom Inc., San Diego, USA). Allelic and genotype distributions, Hardy–Weinberg equilibrium, minor allele frequency (MAF) as well as associations between genetic variants and degenerative phenotypes were determined and analysed using the "SNPassoc" and "haplo.stats" R software packages [16]. Individual genotype–phenotype associations and gene–gene interactions were studied in generalized linear models, while haplotype–phenotype association was analysed applying haplo.score tests. In haplo.score analysis, a global test of association as well as individual haplotype-specific tests was

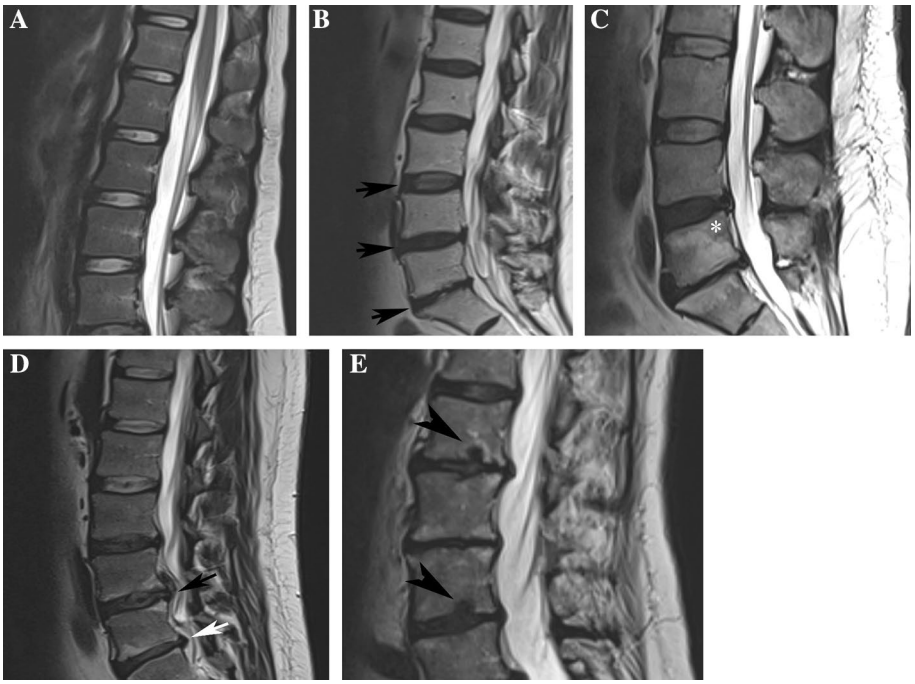

Fig. 1 Degenerative phenotypes. **a** Healthy discs (T2-weighted sagittal MR image); **b** black arrows show degenerated discs, from top to bottom Pfirrmann grades III, IV and V; **c** white star indicates type I Modic change at the lower endplate of the L.V and at the upper endplate of S.I; **d** black arrow indicates posterior disc herniation; white arrow shows posterior disc bulging; **e** black arrowheads show endplate defects

Table 1 Prevalence of the degenerative phenotypes in the study population

	Any	L4/5	L5/S1	L.4/S1
Modic	873	447	529	782
Pathologic Pfirrmann	1402	1185	1186	1385
Endplate	460	140	40	168
Disc prolapse	1364	1038	1013	1335

carried out using a score function. Significant covariates (age, gender, weight and height, and smoking status) were determined for each phenotype, and a p value less than 0.05 was considered significant. The genetic association analysis was also approved by the Scientific and Research Ethics Committee of the Medical Research Council of Hungary (431/PI/2007).

Results

Descriptive statistics

A total of 1426 Caucasian subjects with a complete dataset were involved in this study (Supplementary Figure 1). Mean age was 49.2 years with a range from 18 to 87 years. The male/female distribution was 46% and 54%. Mean height was 170.6 cm (SD 10.5) and mean weight was 79.7 kg (SD 16.6) in the cohort. In the study population, we had no data about the smoking habits of 128 subjects, while 593 subjects were never-smoker and 705 patients were ever-smoker. Table 2 shows the result of the genotyping process. Genotyping success rate was more than 95% for all variants. All the seven candidate SNPs were in Hardy–Weinberg equilibrium (HWE). A haploblock constructed by three candidate SNPs, *BsmI, ApaI* and *TaqI* (rs1544410, rs7975232, rs731236), was identified at the 3′-end of the gene, and another haploblock

Table 2 Studied VDR SNPs and descriptive statistics of genotyping

rs number	Traditional name	Alleles	Region	Success rate (%)	MAF	HWp
rs11568820	*Cdx2*	G/A	Promoter	95.7	0.190	0.659
rs4516035	*A1012G*	T/C	Promoter	99.3	0.415	0.661
rs2228570	*FokI*	C/T	Exon 2	98.2	0.405	0.867
rs3782905	*DdeI*	C/G	Intron 2	98.9	0.295	0.522
rs1544410	*BsmI*	G/A	Intron 8	99.3	0.397	0.505
rs7975232	*ApaI*	A/C	Exon 9	99.5	0.480	0.456
rs731236	*TaqI*	T/C	Exon 9	99.6	0.388	0.434

MAF minor allele frequency, *HWp p* value of Hardy–Weinberg equilibrium

constructed by two SNPs, *Cdx2* and *A1012G* (rs11568820, rs4516035), was found at the 5′-end of the gene (Fig. 2).

Individual genetic associations

Pfirrmann grade

Ddel (rs3782905), *FokI* (rs2228570), and *ApaI* (rs7975232) polymorphisms were found to be associated with Pfirrmann grade (Supplementary Table 1). "G/G" genotype of *Ddel* was significantly associated with the presence of disc degeneration at level L4–5 (ref = C/C; C/G: OR 0.75, 95% CI 0.55–1.03; G/G: OR 2.01, 95% CI 1.00–4.05; $p = 0.0064$ in codominant model) (Fig. 3a). At L5–S1 level, "C/C" genotype of *ApaI* was significantly related to the risk of severe degeneration (ref = A/A–C/A; C/C, OR 1.46, 95% CI 1.01–2.13, $p = 0.0408$).

Disc prolapse

ApaI was associated with disc prolapse (Supplementary Table 2). Homozygous subjects had a higher frequency of disc prolapse at any spinal level ($p = 0.0458$). At L5/S1 region, "C/C" carriers showed the highest risk of disc prolapse (ref = A/A–C/A; C/C: OR 1.39, 95% CI 1.03–1.88; $p = 0.0271$, in recessive model) (Fig. 3b).

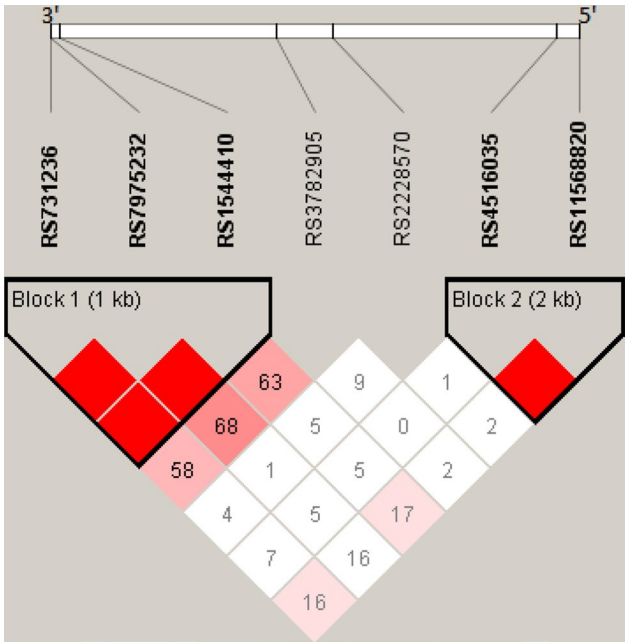

Fig. 2 Linkage disequilibrium (LD) map of the seven candidate SNPs squares that are coloured darker if the $|D'|$ value is high, that is, LD is strong. Empty dark squares mean $|D'| = 1$, that is, complete LD between two single-nucleotide polymorphisms

Modic change

"A/A" genotype of *BsmI* (rs1544410) was associated with a lower frequency of Modic change at any spinal level (ref = G/G–G/A; A/A, OR 0.67, 95% CI 0.49–0.91, $p = 0.01$, recessive model) and at L4–5 (ref = G/G–G/A; A/A, OR 0.65, 95% CI 0.47–0.91, $p = 0.0103$ in recessive model) (Fig. 3c) (Supplementary Table 3). C/C genotype of *TaqI* (rs731236) polymorphism had also a protective effect against Modic change at any level (ref = T/T–C/T; C/C, OR 0.62, 95% CI 0.45–0.86, $p = 0.0032$) and at L4/5 segment (ref = T/T–C/T; C/C, OR 0.61, 95% CI 0.43–0.86, $p = 0.0034$). *FokI* (rs2228570) polymorphism was found to have an association with Modic change in codominant genetic model at level L4/5 (ref = C/C; T/C, OR 1.27, 95% CI 0.98–1.64, T/T, OR 0.83, 95% CI 0.58–1.20, $p = 0.0302$).

Endplate defect

"G" allele of *Ddel* (rs3782905) polymorphism was associated with endplate defect at any lumbar level (ref = C/C; C/G–G/G, OR 1.38, 95% CI 1.09–1.74, $p = 0.0064$, in dominant model) (Fig. 3d) (Supplementary Table 4). "A/A" genotype of *Cdx2* (rs11568820) variant was related to the higher risk of having an endplate defect at L4/5 level (ref = G/G–A/G; A/A, OR 2.32, 95% CI 1.08–4.9, $p = 0.0444$, in the recessive model).

Haplotype analyses

Three haplotypes with more than 1% frequency were identified inside the VDR haploblock located at the 3′-end of the gene (*BsmI–ApaI–TaqI*). The haploblock was significantly associated with the Modic change at L4/5 level ($p_{global} = 0.0185$ in recessive model) where the second most common "AAC" haplotype was associated with lower risk of Modic change ($p = 0.0045$) (Table 3A). Another haploblock with three different haplotypes was identified at the 5′-end (*Cdx2–A1012G*). It was related to the endplate defect at L4/5 level ($p_{blobal} = 0.048$ in additive model), where the rarest "AT" haplotype was associated with the highest risk of endplate defect ($p = 0.0055$) (Table 3B).

Gene–gene interaction analysis

Significant GxG interactions were found between *Cdx2* and *BsmI* ($p_{interaction} = 0.0206$) and between *Cdx2* and *TaqI* ($p_{interaction} = 0.0062$) on endplate defect at L4/5 level (Fig. 4).

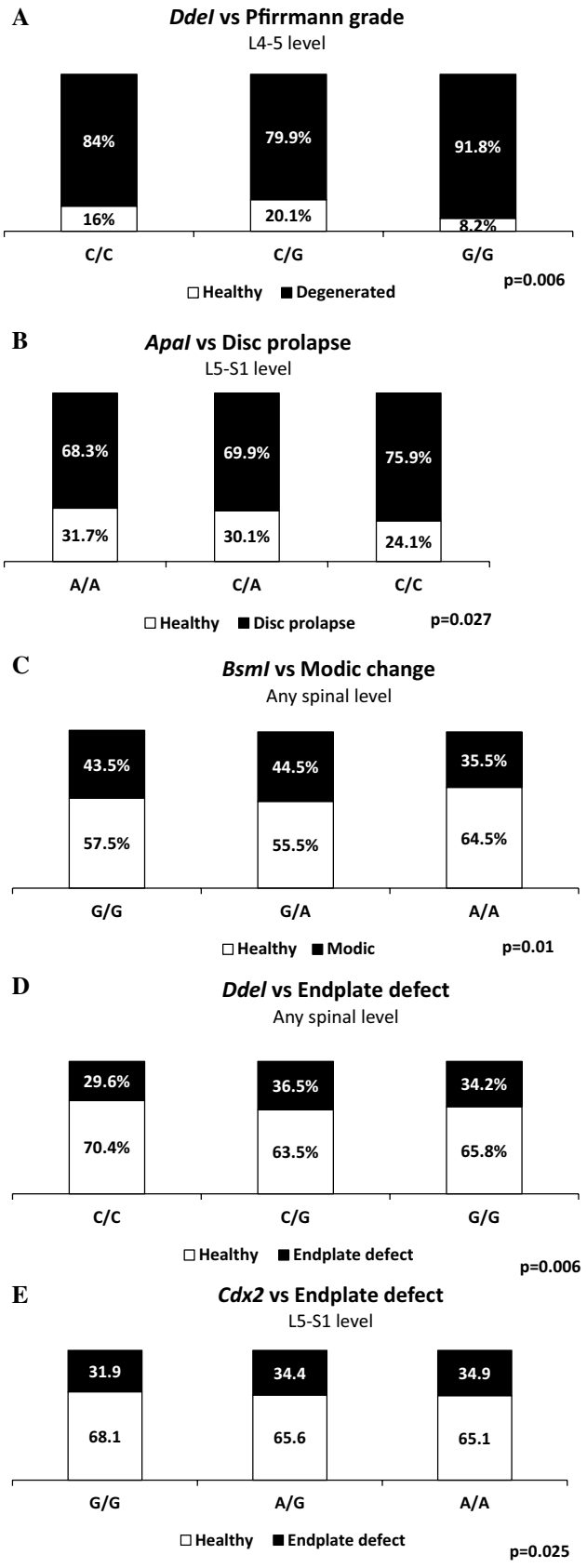

Fig. 3 Association of *DdeI* with Pfirrmann grade (**a**), *ApaI* with disc prolapse (**b**), *BsmI* with Modic change (**c**) and *DdeI* and *Cdx2* with endplate defect (**d**, **e**) distribution of healthy and pathologic endophenotype is represented by genotypes

Discussion

Our study underlines the association between VDR genetic variants and intervertebral disc degeneration and also supports the previously described complexity of the genetic background of this condition. In this study, we analysed the genetic and imaging data of a large homogenous sample ($N = 1426$) of subjects treated because of LDD. We determined and analysed associations between VDR genetic variants and distinct degenerative disc MRI phenotypes Pfirrmann grade, disc prolapse, Modic change and endplate defect. Association between LDD phenotypes and VDR gene variants was supported by different levels of genetic analyses, namely individual SNP associations, haplotype analyses and gene–gene interactions. We found that each of the specific disc degeneration-linked phenotypes was differently associated with VDR polymorphisms; Pfirrmann grade was associated with *DdeI*, *FokI* and *ApaI*; disc prolapse was associated with *ApaI*; Modic change was associated with *BsmI*, *TaqI*, *FokI* SNPs and the *BsmI–ApaI–TaqI* haploblock; endplate defect was associated with *DdeI, Cdx2* SNPs and the *Cdx2–A1012G* haploblock. Significant VDR gene–gene interactions were also found to be associated with endplate defects.

VDR is one of the most intensely studied candidate genes in musculoskeletal and extra skeletal conditions. Its influence has already been shown in osteoporosis [17], muscle function [11] and increased fracture risk [18], but studies on the role of the VDR polymorphisms in the development of LDD have shown conflicting results [8, 19–24] as discussed by three recent meta-analyses about the association of VDR genotypes and LDD [5, 25, 26]. These papers have underlined the importance of large-scale, well-designed international studies to overcome the contradictory research results related to the heterogeneous phenotype definitions as well as gender and ethnic differences.

The direct biological effect of VDR genomic variants is not known in LDD process, some in vitro data can support the genetic results. In a previous cell line study, it was shown that the 3′UTR haploblock's (*BsmI–ApaI–TaqI)* "GCT" haplotype resulted in 15% less mRNA and has 30% increased decay rate than "AAC" haplotype [27]. This alteration likely causes a decreased quantity of VDR protein in target cells for vitamin D giving such cells an impaired response to vitamin D. The 3′UTR "GCT" haplotype was published in association with increased fracture risk [20] and weaker hand grip strength [11]. On the other hand, polymorphisms in the VDR promoter can also influence the genetic function.

Table 3 (A) Association of *BsmI–ApaI–TaqI* haploblock with Modic change (p_{global} = 0.0185) and (B) association of *Cdx2–A1012G* haploblock with endplate defect (p_{global} = 0.048)

Haplotype	Frequency (%)	Hap-Score	*p* value
(*A*)			
AAC	38.6	− 2.84	0.0045
GAT	12.6	− 1.21	0.2260
GCT	47.4	0.42	0.6775
(*B*)			
GC	41.6	− 1.43	0.1525
GT	39.4	− 0.76	0.4448
AT	19.0	2.78	0.0055

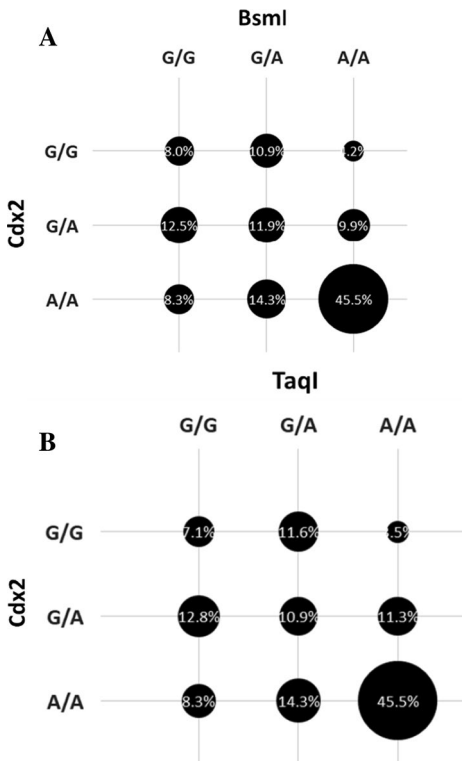

Fig. 4 GxG interaction between *Cdx2* and *BsmI* (**a**) and *Cdx2* and *TaqI* (**b**) on endplate defect (bubbles represent the percentage of subjects with endplate defect at L4/5 in different genotype combinations)

Transcriptional activity of the VDR promoter is 30% less in case of *Cdx2* "G" allele compared to "A" allele [28]. The "A" to "G" transition in A1012G SNP negatively modifies the GATA-3 transcription factor-binding ability of the VDR promoter [29]. "A" allele ("T" in our paper) results in an increased promoter activity proved by Fang et al. [27] using luciferase activity measurements. These in vitro results thus support the role of various possible biological roles for VDR variants in the processes of disc degeneration.

As our results indicate the distinct phenotypes are differently associated with VDR genetic variants, we introduce the use of the "endophenotype" term in LDD genetic association research, which has been already applied in psychiatric genetic association studies. Endophenotype is a quantitative biological trait that is reliable in reflecting the function of a discrete biological system and is reasonably heritable, and as such is more closely related to the root cause of the disease than the broad clinical phenotype [30].

A Modic change is an excellent example of an endophenotype in LDD as it can be present before any visible damage on the intervertebral disc itself [31] even though the pathomechanism of a Modic change is not known. Some authors suggest that it is caused by mechanical stress while others suppose that it is related to ongoing inflammation in the degeneration process [32]. The mechanical stress model is based on biomechanical studies which found that increased shear force on endplates adjacent to degenerated discs resulted in microtrauma in the endplates with consequential bone marrow oedema similar to that seen on MRI for Modic I changes [31]. An alternative pathway via elevated levels of proinflammatory mediators such as IL-6 and prostaglandin E2 has been suggested in a study where surgically removed disc tissue from patients undergoing fusion because of LBP was compared to tissue from patients undergoing discectomy for sciatica [33]. An inflammatory pathway for Modic changes has been also suggested in a study which found higher expression of tumour necrosis factor (TNF), an increase in ingrowth of immunoreactive nerve fibres and elevated cytokine levels in surgically extracted disc tissue of patients with Modic I change [34]. VDR SNPs appear linked to elevated susceptibility to inflammatory diseases; the prevalence of *TaqI* is a relative risk of chronic periodontitis [35], the frequency of the "C" allele of a *TaqI* polymorphism is higher in chronic extremity osteomyelitis [36], the "A" allele of *BsmI* seems to be protective against rheumatoid arthritis [37], and the "C/C" genotype of *FokI* has a positive correlation with rheumatoid arthritis [37]. Considering the above-mentioned correlations, it is not impossible that the VDR gene polymorphisms can play a role in the emergence of Modic change through modulation of inflammation in the bone marrow.

In our study, risk of Modic change was significantly lower in carriers of 3′-end "AAC" haplotype, while the promoter haplotype was associated with the presence of structural endplate defects. These two endplate-related phenotypes were also associated with VDR genetic variants in individual SNP analyses. Since VDR is known to have an effect on different bone tissue-related physiological processes (e.g. remodelling, immune response) [19–22, 24] and VDR SNPs have an effect on fracture risk and bone density [27], it is plausible that through these mechanisms the endplates of a

vertebrae could be genetically more susceptible to mechanical injuries (fractures, Schmorl's nodes) [38] too.

Besides the endplate changes in degenerative spinal disorders, we examined the degenerative changes in the intervertebral disc itself, namely disc prolapse and also loss of signal intensity and disc height, classified by the Pfirrmann grade [39]. The intervertebral disc is made of two independent anatomical structures, the outer annulus fibrosus and the inner nucleus pulposus. The nucleus pulposus cells produce extracellular matrix components such as type II collagen or aggrecan which govern the disc's biomechanical behaviour [40]. In human degenerative discs, the resident cells also produce inflammatory cytokines (TNF-α, IL-1β) which result in an "inflammation-like" state [41, 42] and which stimulate expression of enzymes able to degrade the matrix (ADAMTS, MMPs), resulting in loss of aggrecan leading to consequent dehydration to a weakened resistance against mechanical loading and fall in disc height [43–45]. This inflammatory state can be modified by VDR as discussed above [22, 24, 32]. We found some associations between VDR gene variants and these disc-related endophenotypes; however, they were not supported by haplotype and gene–gene interaction analysis, possibly because of the complexity of the disc degeneration process.

Degeneration not only has a multigenetic background, where several gene and gene variants play small, but significant, roles, but it is also influenced by external factors. The influence of environment could explain the findings that genetic influence on the degeneration process differs at different spinal levels (where loading and other biomechanical factors are also different). Hence, although the exact pathomechanism is unknown, degeneration appears to arise as a consequence of the influences of ageing and environmental factors such as mechanical loading on a strong genetic background [46].

There are some important limitations of the present study. We could not take into account possibly relevant environmental effects such as physical loading history or diet. Also, there could be an overlapping between the phenotypes even with the use of the endophenotype approach. We did not apply any correction of the alpha level during the genetic association testing process. We followed this method because we used a hypothesis-driven approach where effect of candidate SNPs on a phenotype was calculated. Moreover, genetic associations were tested on different levels with different statistical models (individual SNP association, haplotype analysis, gene–gene interaction) to confirm the associations of the study even if the type I error rate was not conservatively reduced. Moreover, some of our results showed a different association with that reported in previous papers; whether this arises from differences in study population phenotype definitions or even selection bias cannot be ascertained. These limitations above can influence the reliability of our findings; therefore, independent replications of the study on different populations are strongly recommended.

In conclusion, we state that VDR gene variants are associated with different disc degeneration-related endophenotypes. The most plausible explanation of these associations is related to the influence of vitamin D on modulating inflammation and the immune response, but this assumption needs more in vitro and in vivo studies to confirm it. Based on our results, analysis of well-defined endophenotypes on large, homogenous datasets would be required to clarify the multifactorial, multigenetic background of intervertebral disc degeneration.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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