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Occupational and Genetic Risk Factors Associated With Intervertebral Disc Disease

Iita M. Virtanen, BM,* Jaro Karppinen, MD, DMSc,†‡§ Simo Taimela, DMSc,‖ Jürg Ott, PhD,¶ Sandra Barral, MSc,¶ Kaisu Kaikkonen, MSc,# Olli Heikkilä, BM,# Pertti Mutanen, PhD,‡ Noora Noponen, MD,* Minna Männikkö, PhD,* Osmo Tervonen, DMSc,** Antero Natri, DMSc,†† and Leena Ala-Kokko, DMSc,*‡‡

Study Design. Cross-sectional epidemiologic study.

Objective. To evaluate the interaction between known genetic risk factors and whole-body vibration for symptomatic intervertebral disc disease (IDD) in an occupational sample.

Summary of Background Data. Risk factors of IDD include, among others, whole-body vibration and heredity. In this study, the importance of a set of known genetic risk factors and whole-body vibration was evaluated in an occupational sample of train engineers and sedentary controls.

Methods. Eleven variations in 8 genes (*COL9A2, COL9A3, COL11A2, IL1A, IL1B, IL6, MMP-3*, and *VDR*) were genotyped in 150 male train engineers with an average of 21-year exposure to whole-body vibration and 61 male paper mill workers with no exposure to vibration. Subjects were classified into IDD-phenotype and asymptomatic groups, based on the latent class analysis.

Results. The number of individuals belonging to the IDD-phenotype was significantly higher among train engineers (42% of train engineers *vs.* 17.5% of sedentary workers; $P = 0.005$). IL1A −889T allele represented a significant risk factor for the IDD-phenotype both in the single marker allelic association test ($P = 0.043$) and in the logistic regression analysis ($P = 0.01$). None of the other allele markers was significantly associated with symptoms when analyzed independently. However, for all the SNP markers considered, whole-body vibration represents a nominally significant risk factor.

Conclusion. The results suggest that whole-body vibration is a risk factor for symptomatic IDD. Moreover, whole-body vibration had an additive effect with genetic risk factors increasing the likelihood of belonging to the IDD-phenotype group. Of the independent genetic markers, IL1A −889T allele had strongest association with IDD-phenotype.

Key words: intervertebral disc disease, sciatica, genetics, interleukin 1A, whole-body vibration. **Spine 2007;32: 1129–1134**

Intervertebral disc disease (IDD), characterized by intervertebral disc herniation and/or sciatic pain, is a common musculoskeletal disorder, affecting about 5% of Finnish adults.[1] Risk factors include environmental and constitutional factors such as occupational load, occupational driving, mental stress, smoking, height, and weight.[2–7] Even though the contribution of environmental risk factors to IDD is well established, more recent epidemiologic studies suggest that genetic factors may primarily explain disc degeneration.[8–10] Several predisposing genetic factors have been identified.[11]

One of the best-known environmental risk factors for IDD is vibration in occupational driving.[2] In a meta-analysis, the risk of sciatica was shown to be 2-fold on exposure to whole-body vibration. This was also associated with a higher risk of intervertebral disc herniations.[12] However, the role of whole-body vibration in the pathogenesis of IDD has also been questioned.[13,14]

Genetic variations in the genes coding for certain structural components of the intervertebral disc have been identified to associate with low back disorders, *i.e.*, symptomatic IDD with or without sciatica, disc degeneration and low back pain (LBP). Two mutations in collagen IX, Gln326Trp in the α2 chain and Arg103Trp in the α3 chain, have been shown to be associated with disc disease in Finnish patients with sciatica,[15–17] and 2 polymorphisms in the vitamin D receptor gene, *VDR*,[18–21] and 1 single nucleotide insertion/deletion in the matrix metalloproteinase-3 gene, *MMP-3*,[22] have been linked with intervertebral disc degeneration. A sequence variation in *COL11A2* (IVS6-4 A>T) has recently been identified that is associated with ossification of the posterior lumbar ligament[23] and lumbar spinal stenosis.[24]

The pathogenesis of IDD also involves an inflammatory component, and it is possible that inflammatory mediators are at least partially responsible for LBP and sci-

From the *Collagen Research Unit, Biocenter and Department of Medical Biochemistry and Molecular Biology, University of Oulu, Oulu, Finland; †Department of Physical Medicine and Rehabilitation, University of Oulu, Oulu, Finland; ‡Finnish Institute of Occupational Health, Helsinki, Finland; §Orton Orthopaedic Hospital, Helsinki, Finland; ‖Department of Public Health, University of Helsinki, Helsinki, Finland; ¶Laboratory of Statistical Genetics, Rockefeller University, New York, NY; #Oulu Deaconess Institute, Oulu, Finland; **Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland; ††University of Tampere, Section of Orthopedics, Department of Surgery, Tampere University Hospital, Tampere, Finland; and ‡‡Connective Tissue Gene Tests, Allentown, PA.

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Address correspondence and reprint requests to Leena Ala-Kokko, DMSc, Department of Medical Biochemistry and Molecular Biology, University of Oulu, Aapistie 7, 90220 Oulu, Finland; E-mail: leena.ala-kokko@oulu.fi

Table 1. Description of Variables Used in the Clustering

Variable	Description	Range of Values	Cutoff Value for Dichotomization
LBP week	Have you had LBP during the past week	0–1	0 *vs.* 1
LBP episodes	No. of cumulative LBP episodes (≥14 days); continuous	0–200	0–1 *vs.* ≥2
Sciatica episodes	No. of cumulative sciatica episodes (≥14 days); continuous	0–100	0–1 *vs.* ≥2
LBP duration	LBP duration during the past year (0, 1 = 1–7 days; 2 = 8–30 days; 3 = >30 but not daily; 4 = daily)	0–4	0–2 *vs.* ≥3
Sciatica duration	Duration of sciatica during the past 3 mo (0, 1 = 1–7 days; 2 = 8–30 days; 3 = >30 but not daily; 4 = daily)	0–4	0–1 *vs.* ≥2
Disabling sciatica	Bothersomeness of sciatica during the past 3 mo (0, 1 = 1–7 days; 2 = 8–30 days; 3 = >30 but not daily; 4 = daily)	0–4	0–1 *vs.* ≥2
LBP intensity	LBP intensity within the past 3 mo (10-cm visual analog scale); continuous	0–9	0–2 *vs.* ≥3
Sciatic pain intensity	Intensity of sciatic pain within the past 3 mo (10-cm visual analog scale); continuous	0–9	0 *vs.* ≥1

LBP indicates low back pain.

atica.[25–27] In support of this, recent studies suggest an association between LBP and polymorphisms in the genes coding for interleukins 1α and 1β, more precisely C-889T in *IL1A* and C3954T in *IL-1B*.[28] A significant association has similarly been demonstrated between variations in interleukin-6 gene, *IL-6* (G-597A, G-174C, T15A in exon 5) and IDD.[29]

It is possible, however, that environmental and constitutional risk factors together with alterations in the matrix components may result in structural weakness of a disc, thereby increasing the risk of IDD. It has been shown, for instance, that persistent obesity and genetic risk factors have a synergistic effect in this respect.[30]

The purpose of the current study is to examine whether one of the best-known occupational risk factors, whole-body vibration, in conjunction with known genetic risk factors is associated with symptomatic IDD.

■ Subjects and Methods

Subjects. The subjects consisted of 150 train engineers working for the Finnish state railways, with an average of 21 years (range, 5–31 years) of exposure to whole-body vibration. They all were full-time train drivers with about 5-hour daily exposure to whole-body vibration. The vibration composed of both vertical and horizontal components. All the train engineers were male and were 38 to 56 years of age at the time of enrollment. Moreover, they were all from the same part of Finland, which ensures that they had been operating the same kinds of locomotives and had similar exposure to vibration.

The occupational control group consisted of 61 male paper mill workers with sedentary jobs and no occupational exposure to vibration. They were similar to the train engineers in age distribution and educational background. All the subjects were Finnish and unrelated to each other.

The protocol was approved by Oulu University Ethics Committee, and signed informed consent was obtained from all the subjects.

Clinical Assessments. A medical history, including possible low back symptoms, was obtained from each subject. If a subject reported previous LBP, he was asked further about the intensity, duration, and frequency of the symptoms, including the intensity of low back and leg pain during the past week and past 3 months (10-cm Visual Analogue Scale; 0 = no pain, 10 = worst pain), duration of LBP within the last year (1 = no pain within the last year, 5 = daily pain), the bothersomeness of the pain within the last year (1 = no pain, 5 = bothersome daily), and the number of previous LBP and sciatica episodes (of at least 14 days' duration).

Clustering of study subjects according to their symptoms was based on the latent class analysis (LCA),[31] which was performed blinded to the genetic data. LCA represents a special case of mixture cluster modeling, where the latent classes explain the observed dependent variables similar to factor analysis.[32] In contrast to factor analysis, however, LCA provides classification of individuals. M-Plus software (version 3.13) was used in the analysis.[33] Latent class models are fitted successively, starting with a 2-cluster model and then adding another cluster for each successive model. Different summary measures (Lo-Mendel-Rubin adjusted likelihood ratio test for n-1 *vs.* n clusters),[34] Akaike's Information Criterion (AIC), adjusted Bayes information criterion (adjusted BIC) and entropy) were used in the estimation of optimum number of clusters.[33] In the classification of individuals questions related to subjective symptoms were originally binary or were dichotomized (0/1). Different combinations of variables and different cutoff values for categorical and continuous variables were explored. The best model was obtained with a combination of following variables; presence of LBP during the past week, number of previous LBP and sciatica episodes, LBP duration during the past year, sciatica duration and bothersomeness during the past 3 months, and LBP and sciatic pain intensity within the past 3 months (Table 1). In the current analysis, optimum number of clusters was 4 (low *P* value with a leveling of AIC decrease; Table 2). With 6 clusters *versus* 5 the *P* value was low but the software warned of parameter estimate problems (nonpositive matrix). The clustering was made first for the 201 individuals with complete

Table 2. Summary Measures of Clustering of Study Population With Latent Class Analysis

No. Clusters	Lo-Mendel-Rubin Likelihood Ratio Test* (*P*)	Akaike's Information Criterion
2	<0.0001	1707.1
3	0.07	1677.9
4	0.07	1659.84
5	0.46	1653.4
6	<0.01	1648.5†
7	0.46	1654.7
8	0.56	1656.6

*For n − 1 *versus* n clusters.
†Estimate problems!

Table 3. Genetic Variations Analyzed

Gene	Region	SNP	Predicted Consequence	Detection Method	Reference
COL9A2	Exon 19	C22T	Arg326Trp	Sequencing	Annunen *et al*, 1999
COL9A3	Exon 5	C52T	Gln103Trp	Sequencing	Paassilta *et al*, 2001
COL11A2	Intron 6	IVS6–4A>T	Alternative splicing	*Bsm*FI digestion	Noponen-Hietala *et al*, 2003
IL1A	Promoter	C-889*T	NK	*Nco*I digestion	Solovieva *et al*, 2004
IL1B	Exon 5	C3954T	NK	*Taq*I digestion	Solovieva *et al*, 2004
IL6	Promoter	G-597*A	NK	Sequencing	Noponen-Hietala *et al*, 2004
	Promoter	G-174*C	NK	Sequencing	
	Exon 5	T15A	Asp162Glu	Sequencing	
MMP-3	Promoter	−1171*Δa	NK	Sequencing	Takahashi *et al*, 2001
VDR	Exon 2	T2C	Met2Thr	*Fok*I digestion	Videman *et al*, 1998, 2001
	Exon 9	T352C	NK	*Taq*I digestion	Kawaguchi *et al*, 2002

*From the start of translation.
NK indicates not known.

data set. Individuals (n = 27) with missing data were then evaluated manually in order to fit them into the right cluster. Finally, for each extreme group (clusters 1 and 4), only those individuals with a posterior probability value higher than 0.55 were included.

Genetic Analysis. Previously identified genetic risk factors were analyzed in genomic DNA extracted by conventional techniques from 20 mL of venous blood collected from each subject (Table 3). This DNA was used as a template for polymerase chain reaction (PCR). The PCR amplifications were typically performed using 20 ng of genomic DNA, 0.25 μmol/L of forward and reverse primers, 1.5 μmol/L $MgCl_2$, 0.2 mmol/L dNTPs, and 1 U of *Taq*I polymerase (AmpliTaq Gold; Applied Biosystems). The PCR conditions included an initial denaturation for 10 minutes at 95 C, 35 cycles at 95 C for 30 seconds, 58 to 64 C for 30 seconds, and 72 C for 30 seconds, followed by 1 cycle at 72 C for 10 minutes.

Two polymorphisms leading to tryptophan changes in *COL9A2* (Trp2) and *COL9A3* (Trp3) were analyzed by sequencing with the BigDye Terminator Sequencing Kit and ABI PRISM 3100 sequencer (Applied Biosystems).

Two intragenic polymorphisms in the *VDR* gene, T to C in exon 9 and T to C in the translation initiation codon (ATG/ACG), were analyzed by restriction enzyme digestion. The former was detected by *Taq*I and the latter by *Fok*I restriction enzyme digestion. An intronic change, A to T in *COL11A2*, was detected by *Bsm*FI digestion. Two polymorphisms in *IL1* were also analyzed by restriction enzyme digestion: C-889T in *IL1A* by *Nco*I and C3954T in exon 5 of *IL1B* by *Taq*I.

A 179- or 180-bp region of the *MMP-3* promoter containing a 5a/6a polymorphism was analyzed by sequencing, and sequence variations in the *IL6* gene (G-597A, G-174C, and T15A in exon 5) were similarly determined by sequencing.

Statistical Analysis. Possible differences in genotype and allele frequencies between the *symptomatic (IDD-phenotype)* and *"asymptomatic"* individuals were tested with the χ^2 statistic being computed with SYSTAT from 3 × 2 (3 possible genotypes in 2 different groups) and 2 × 2 (2 possible alleles in 2 different groups) tables for each of the single nucleotide polymorphism (SNP) markers. False discovery rate correction in the genotypic and allelic association tests was applied. For each single SNP marker, a logistic regression analysis was carried out, where the outcome variable is IDD-phenotype and occupation and genotypes at each variant as independent dummy coded variables.

■ Results

Division of Subjects Into IDD-Phenotype and "Asymptomatic" Groups

Of total 201 individuals of LCA analysis, 90.6% had a posterior probability value of more than 0.7 of belonging to its "own" group. Table 4 shows the dichotomized mean values of the symptom variables in the 4 clusters

Table 4. Mean Dichotomized Values of the Patients' Subjective Symptoms in the 4 Clusters According to the Occupational Group*

	Cluster 1		Cluster 2		Cluster 3		Cluster 4	
Variable	Train Engineers (n = 53)	Sedentary Controls (n = 33)	Train Engineers (n = 27)	Sedentary Controls (n = 16)	Train Engineers (n = 41)	Sedentary Controls (n = 13)	Train Engineers (n = 38)	Sedentary Controls (n = 7)
LBP week	0.13	0.03	0.50	0.40	0.34	0.08	1.00	0.86
LBP episodes	0.02	0.11	0.67	0.60	0.31	0.31	0.73	0.71
Sciatica episodes	0.00	0.00	0.58	0.53	0.06	0.15	0.61	0.71
LBP duration	0.02	0.00	0.32	0.33	0.45	0.15	0.89	1.00
Sciatica duration	0.00	0.00	0.21	0.20	0.54	0.46	0.74	0.50
Disabling sciatica	0.06	0.10	0.54	0.40	0.73	0.69	1.00	1.00
LBP intensity	0.00	0.00	0.08	0.06	0.59	0.77	1.00	1.00
Sciatic pain intensity	0.11	0.03	0.23	0.00	0.83	0.85	1.00	1.00

*Mean dichotomized values refer to Table 2, *e.g.*, a mean value of 1.00 for LBP episodes would mean that all members in the respective cluster have at least 2 previous LBP episodes, whereas a value 0 would mean that all members have at most one previous LBP episode.

Table 5. Allelic Association Analysis of Variants With IDD-Phenotype Patients

Gene	SNP	LR χ^2	*df*	*P*
COL9A2	E19 + 22	0.844	1	0.358
COL9A3	E5 + 52	1.534	1	0.215
COL11A2	IVS6-4	0.046	1	0.830
IL1A	−889	4.088	1	0.043*
IL1B	3954	2.472	1	0.116
IL6	−597	3.129	1	0.077
IL6	−174	2.555	1	0.110
IL6	E5 + 15	0.223	1	0.636
MMP-3	−1174	0.196	1	0.658
VDR	2	0.214	1	0.643
VDR	352	0.816	1	0.366

*Point-wise significant after correcting for multiple testing with the FDR test.

according to occupation for the whole study population (including the manually sorted ones). Cluster "1" represents clearly the "asymptomatic" group with no or minimal symptoms (Table 4). Majority of the subjects in the cluster "4" reach the cutoff limits of the selected symptoms, *e.g.*, 61% of train engineers and 71% of sedentary controls in the cluster "4" have 2 or more previous sciatica episodes. Hereafter, cluster "4" is called IDD-phenotype. Clusters "2" and "3" represent those in-between these 2 extreme clusters.

Comparison of Occupational Groups

A total of 42% (38 of 91) of train engineers *versus* 17.5% (7 of 40) of sedentary workers had IDD-phenotype (cluster "4"). Train engineers belonged significantly more often to IDD-phenotype ($P = 0.005$).

Genetic Analysis

At the initial phase, train engineers and office workers groups were pooled for the genetic analysis and IDD-phenotype (n = 45) was compared with the "asymptomatic" group (n = 86; Table 5).

No significant differences were found in the genotype frequencies between IDD-phenotype and "asymptomatic" individuals, *i.e.*, none of the genotypes appears to be associated with the symptoms. However, IL1A −889T allele frequency showed formally significant differences when IDD-phenotype and "asymptomatic" clusters were compared ($P = 0.043$). After correcting for multiple testing (false discovery rate ≤5%), none of the other SNP markers appeared to be significantly associated with the IDD-phenotype.

Logistic regression analysis pointed out whole-body vibration as a nominally significant risk factor for IDD-phenotype (*P* values range from 0.005 to 0.014 at SNP markers IL1A −889 and VDR +352 respectively; data not shown). The result reflects again the previously reported different proportion of affected individuals between train engineers and office workers.

Among the selected SNP markers, only TT genotype at IL1A represents a significant risk factor for IDD-phenotype ($P = 0.01$). Moreover, the overall significance of both independent variables (IL1A genotypes and occupation) remains statistically significant at the 5% level after the Bonferroni correction (Table 6).

■ Discussion

The results of the present study further support the role of whole-body vibration in symptomatic IDD. In addition, logistic regression analysis revealed that whole-body vibration has significant interactions with all the SNPs analyzed suggesting an additive effect of vibration and genetic risk factors for IDD-phenotype.

The definition of IDD varies from 1 study to another. Mostly, however, IDD is defined on basis of symptomatic disease.[29] The classification of the present study was based on clustering method identifying the variables that discriminate individuals according to their affection status. This classification relies on symptomatic disease, moreover identifying the individuals with recurrent symptoms.

The role of whole-body vibration and occupational motor vehicle driving in increasing the risk of IDD has been demonstrated repeatedly, and it has been suggested that occupational exposure to vibration causes damage to the intervertebral disc, resulting in disc degeneration and herniation.[12] The role of whole-body vibration has been also questioned. A recent study of the effects of occupational driving in Finnish male monozygotic twin pairs by Battié *et al*[14] suggested that, although driving may worsen back symptoms, it does not damage the disc itself because disc degeneration did not differ between the occupational drivers and their twin brothers. There was no overall tendency for greater degeneration or more serious pathology in the occupational drivers.

The present results, however, identify greater risk of symptomatic IDD among the train engineers who had been exposed to vibration for several years; 42% of the train engineers belonged to the IDD-phenotype group, whereas the corresponding rate for sedentary workers was only 17.5%. Although the synergistic effect of *COL9A3* polymorphism and persistent obesity has been reported to increase the risk for intervertebral disc degeneration,[30] there are not many studies on

Table 6. Logistic Regression Analysis

Variable	Coefficient	SE	t Ratio	*P*	OR	95% CI	Overall *P*
IL1A −889							0.001
TT/CC	2.062	0.797	2.587	0.010	7.87	37.54–1.65	
TC/CC	0.267	0.410	0.651	0.515	1.31	2.92–0.58	
Occupation	−1.412	0.503	−2.807	0.005	0.24	0.65–0.09	

gene-environment interactions in low back disorders. The present study further supports the interaction of genetic and environmental risk factors, as the exposure to whole-body vibration had additive effect with all included genetic markers in an occupational cluster representing symptomatic IDD-phenotype. The genetic markers were selected strictly on basis of previous association studies in low back disorders.

On the contrary to the previous studies, the results indicated that only 1 of the single polymorphisms, IL1A −889, was significantly associated with the disease status (IDD-phenotype *vs*. "asymptomatic" group) independently ($P = 0.01$). Moreover, it had highly significant ($P = 0.001$) interaction with whole-body vibration. The lack of association regarding rest of the analyzed SNPs independently may be due to the design of the present study. The study population consisted of an occupational sample of males in contrast to the previous studies where the cases had been derived from selected, "enriched" patient populations.[29]

In case of *IL1A*, the TT genotype (−889) has been shown to significantly increase the transcriptional activity of the *IL1A* gene[35] and IL-1β protein levels.[36] IL-1 synthesized by native disc cells induces an imbalance between catabolic and anabolic events, and is therefore thought to play an important role in the pathogenesis of intervertebral disc degeneration.[37] The present finding is interesting since the *IL1A* polymorphism has been previously reported to have a role in low back disorders in the Finnish population.[28,38]

There is strong evidence that manual material handling, bending/twisting of the trunk, and whole-body vibration can increase the risk of LBP,[39] and this is further supported by the present study by showing increased risk for symptomatic IDD in individuals with long-term exposure to whole-body vibration. One of the tested SNPs was significantly associated with IDD-phenotype. The results also suggested a synergistic effect between whole-body vibration and previously identified genetic risk factors, suggesting that several factors jointly increase the likelihood of IDD. Even though all the so far identified genetic risk factors for low back disorders were analyzed in the present study, the genetic pattern behind IDD has not been identified yet.

■ Key Points

- Eleven known genetic risk factors for intervertebral disc disease (IDD) were genotyped in 150 male train engineers with an average of 21-year exposure to whole-body vibration and 61 male paper mill workers with no exposure to vibration.
- Greater risk of IDD-phenotype was observed among the train engineers compared with sedentary controls.
- The results indicated that one of the single polymorphisms analyzed, IL1A −889T, significantly associated with the disease status (IDD-phenotype vs. "asymptomatics") in the whole study population.
- An additive effect of vibration and genetic risk factors for IDD was observed.

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