nature REVIEWS DISEASE PRIMERS

SUPPLEMENTARY INFORMATION

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Low back pain

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Supplementary Table 1. Genetic associations studies of back pain-related phenotypes.

Year	N	Population	Phenotype	Gene	Variant	Refs
2004	131	Finnish (at risk for back pain)	Risk of back pain Pain intensity Disability	*IL1B* *IL1RN* *IL1A*	rs1143634 IL1RN-1812 IL1A-T889	1
2010	151	Caucasians (with back pain)	Risk of back pain	*KCNS1*	**rs734784**, rs13043825	2
2011	370	Chinese (154 Patients with discogenic back pain, 216 controls)	Risk of back pain	*CASP9*	rs4645978	3
2012	516	European-Caucasian (258 patients with LDD and sciatic pain, 258 controls)	Risk of back pain Pain intensity Disability	*COMT*	rs4680	4
2012	1004	Australians (adolescents from the Western Australian Pregnancy Cohort)	Risk of back pain	*ADRB2*	rs2053044	5
2013	406	Croatian war veterans (102 with PTSD and back pain, 108 with PTSD only, 99 with back pain only, 97 controls)	Risk of back pain Pain intensity	*IL1B*	rs1143634	6
2013	892	Chinese male soldiers (305 with back pain, 587 without back pain)	Risk of back pain	*CASP9* *GDF5*	rs4645978 rs143383	7
2017	60	Italians (athletes, 24 with back pain, 36 without)	Risk of back pain	*VDR*	rs2228570	8
2005	334	Finnish (155 with IDD-related sciatica, 179 controls)	LDD	*IL6*	rs1800797, **rs1800796**, rs1800795, rs13306435	9
2007	387	Japanese (217 with osteophyte formation with disc height narrowing, 99 with osteophyte formation without disc height narrowing, 71 controls without osteophyte formation)	LDD	*ADH2*	rs1229984	10
2010	462	Chinese (178 with LDD, 284 controls)	LDD	*MMP3* *VDR*	rs3025058 rs7975232	11
2011	100	Turkish (Cases with LDD, controls without it)*	LDD	*ACAN*	Short allele	12
2011	179	Spanish (50 with LDH, 129 controls)	LDD	*IL1B*	rs1143634	13
2012	146	Norwegians (with back pain and disc degeneration)	LDD	*IL18R1* *IL18RAP*	rs2287037 rs1420100	14
2013	241	Koreans (102 with LDD, 139 controls)	LDD	*VEGFA*	**rs699947**, **rs2010963**, **rs1570360**, rs3025039	15
2013	93	Norwegians (with back pain for >1 year and LDD)	LDD Pain intensity Disability	*IL18RAP* *IL18R1* *IL1A* *MMP3*	rs1420100, rs917997, rs1420106 rs2287037 rs2071375 rs3025058	16
2013	4680	330 participants of the Framingham Heart Study 192 Dutch from the GARP study	LDD	*PARK2* *LOC100130207; LRRN1*	rs926849 rs17034687	17

		3414 Dutch from the Rotterdam study 744 Caucasian twins from UK		*MHCII*	rs2187689, rs7767277	
2014	40	Disc specimens from individuals with degenerative disc disease and back pain	LDD	*COMT* *THBS2*	rs165656, rs4633 rs2095019, rs470859	18
2014	1047	Chinese Han (489 with LDD, 558 controls)	LDD	*ADAMTS5*	rs151058, rs229052, rs162502	19
2014	144	Egyptians (84 with LDD, 60 controls)	LDD	*MMP3* *VDR*	rs731236 rs35068180	20
2016	978	Chinese Han (482 with LDD, 496 controls)	LDD	*ADAMTS4*	rs4233367	21
2016	285	European (with back pain)	LDD	*IL18RAP* *MMP9*	rs1420106, rs917997 rs20544	22
2016	809	Indians (with back pain or sciatica)	LDD	*CILP* *ADAMTS5* *IGF1R* *VDR* *MMP20* *MMP10* *CALM1* *FN1*	rs11856834, rs2019185, rs2073711 rs2249350 rs11247361 rs2228570 rs17099008, rs1784438, rs1784430 rs11225422 rs2300496, rs3213718 rs1250247	23
2017	51	Finnish (2 families with history of LDD and sciatica)	LDD	*HSPG2* *MAML1*	c.4829_4831delAGCinsCACTGTG rs61753465	24
2017	106	Sri Lankan females (with chronic back pain)	LDD	*IL1A* *ADAMTS4* *ADAMTS5* *TIMP3*	rs2856836, rs1304037, rs17561, rs1800587 rs41270041, rs34884997 rs226794, rs55933916 rs9862	25
2017	106	Sri Lankans (with back pain)	LDD	*ACAN*	rs2272023, rs35430524, rs2882676, rs1042630, rs2351491, rs938609, rs3825994, rs698621	26
2017	24386	Meta-analysis of 74 studies (10,250 with LDD, 14,136 controls)	LDD	*IL6* *MMP9*	rs1800797, rs1800795, rs17576	27
2006	168	Caucasian (who underwent surgical discectomy for persistent lumbar root pain caused by intervertebral disc herniation)	Pain intensity	*GCH1*	rs8007267, rs3783641, rs8007201, **rs4411417**, rs752688	28
2010	69	Caucasians (who underwent surgical	Pain	*GCH1*	rs10483639,	29

		treatment for LDD)	intensity Disability		rs7142517, rs752688, **rs4411417**, rs8007201, **rs9671371**, rs7492600, rs12147422, rs998259, rs7147286, rs3783641, rs2183080, **rs2878172**, rs8007267	
2010	195 179	Finnish (with sciatica symptoms) Caucasians (with lumbar root pain)	Pain intensity	*SCN9A*	rs6746030	[30]
2010	115	Dutch (78 with back pain, 37 controls)	Pain intensity	*COMT* *BDNF*	rs4680 **rs6265**	[31]
2012	258	European-Caucasian (with lumbar disc herniation and sciatic pain)	Pain intensity Disability	*OPRM1*	**rs1799971**	[32]
2012	93	Norwegians (93 with back pain for >1 year and LDD)	Pain intensity	*COMT*	rs4633, rs4680	[33]
2013	138	White (75 with back pain, 63 controls)	Pain intensity	*KCNJ6*	rs1543754, rs858035, rs2835925, rs2211843, rs1787337, rs2835930, rs9981629, rs928723	[34]
2013	74	Italians (with back pain)	Pain intensity	*COMT*	rs4680	[35]
2013	260	European-white (with LDH and sciatic pain)	Pain intensity Disability	*MMP1*	rs1799750	[36]
2013	192	Koreans (with degenerative spondylolisthesis)	Pain intensity	*ESR1*	rs9340799, rs2234693	[37]
2014	258	Norwegians (258 with lumbar radicular pain due to disc herniation)	Pain intensity Disability	*IL1A* *IL1RN*	rs1800587 rs2234677	[38]
2014	176	Caucasian (176 with LDH and subjected to lumbar discectomy)	Pain intensity	*COMT*	rs6269, rs4633, **rs4818**, rs4680	[39]
2014	121	European-white (121 with lumbar radicular pain due to LDH)	Pain intensity	*IL1A*	rs1800587	[40]
2015	371	European (with back pain)	Pain intensity Disability	*COMT*	**rs4818**, rs4680, rs6269, rs4633, rs2075507	[41]
2017	296	Norwegians (with back pain)	Pain intensity	*VDR* *MMP9* *OPRM1*	rs731236 rs17576 **rs1799971**	[42]
2017	176	Caucasians (with LDH and leg or back pain who underwent lumbar discectomy)	Pain intensity	*SCN9A*	rs6746030	[43]
2018	104	(84 with back pain, 20 controls)	Pain intensity Disability	*FAAH*	rs324420, rs932816, rs4141964	[44]
2007	290	Members of the Maine Lumbar Spine Study (with acute sciatica)	Disability	*GABRB1*	rs4694846, rs17461905, rs13107066,	[45]

					rs6813436, rs7439087, rs6290	
2008	153	Finnish (with sciatica)	Disability	*IL6*	rs1800797, **rs1800796**, rs1800795, rs13306435	46
2010	69	Caucasians (who underwent surgical treatment for LDD)	Disability	*COMT*	rs6269, rs4633, **rs4818**, rs4680	47

Footnotes: N=sample size; LDD=lumbar disc disease; LDH= lumbar disc herniation; *ACAN*= aggrecan; *ADAMTS4*= ADAM metallopeptidase with thrombospondin type 1 motif 4; *ADAMTS5*= ADAM metallopeptidase with thrombospondin type 1 motif 5; *ADH2*= alcohol dehydrogenase 2; *ADRB2*= adrenoceptor beta 2; *BDNF*= brain derived neurotrophic factor; *CALM1*= calmodulin 1; *CASP9*= caspase 9; *CILP*= cartilage intermediate layer protein; *COMT*= catechol-O-methyltransferase; *ESR1*= estrogen receptor 1; *FAAH*= fatty acid amide hydrolase; *FN1*=fibronectin 1; *GABRB1*= gamma-aminobutyric acid type A receptor beta1 subunit; *GCH1*= GTP cyclohydrolase 1; *GDF5*= growth differentiation factor 5; *HSPG2*= heparan sulfate proteoglycan 2; *IGF1R*= insulin like growth factor 1 receptor; *IL1B*= interleukin 1 beta; *IL1A*= interleukin 1 alpha; *IL18R1*= interleukin 18 receptor 1; *IL18RAP*= interleukin 18 receptor accessory protein; *IL1RNA*= interleukin 1 receptor antagonist; *IL6*= interleukin 6; *KCNJ6*= potassium inwardly-rectifying channel, subfamily J, member 6; *KCNS1*= potassium voltage-gated channel modifier subfamily S member; *LRRN1*= leucine rich repeat neuronal 1; *MAML1*= mastermind like transcriptional coactivator 1; *MHCII*= major histocompatibility complex class II region; *MMP1*= matrix metallopeptidase 1; *MMP10*= matrix metallopeptidase 10; *MMP20*= matrix metallopeptidase 20; *MMP3*= matrix metallopeptidase 3; *MMP9*= matrix metallopeptidase 9; *OPRM1*= opioid receptor mu 1; *PARK2*= parkin RBR E3 ubiquitin protein ligase; *SCN9A*= sodium voltage-gated channel alpha subunit 9; *THBS2*= thrombospondin 2; *TIMP3*= TIMP metallopeptidase inhibitor 3; *VDR*= vitamin D receptor; *VEGFA*= vascular endothelial growth factor A; **Bolded variants highlight those that have been associated with a pain phenotype and subsequently replicated in an independent study of multiple pain conditions, including low back pain**[48].

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