Genetic Predisposition to Symptomatic Lumbar Disk Herniation in Pediatric and Young Adult Patients.

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Study Design

Case-control whole-genome sequencing analysis of a highly select, young cohort with symptomatic lumbar disk herniation (LDH) compared with the standard variation in a large reference population.

Objective

To assess genetic influences predisposing pediatric and young adult patients to symptomatic LDH.

Figure 1

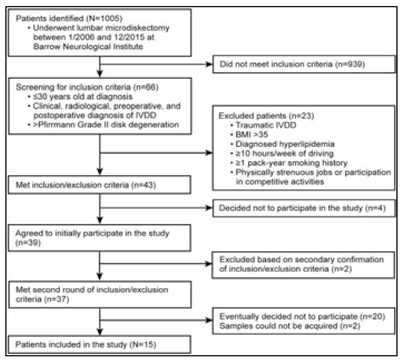

Figure 2

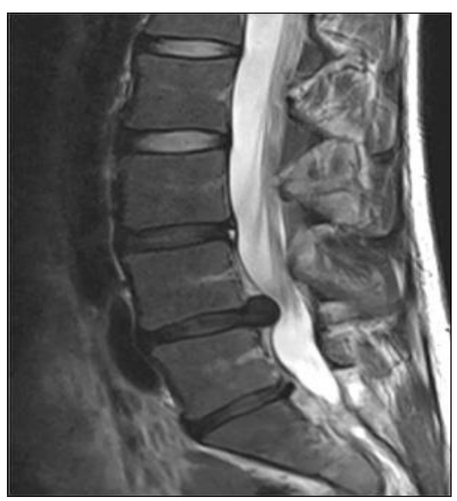

Table 3

Gene Symbol	Patients With at Least 1 Mutation, No. (%)	Patients With Multiple Mutations, No. (%)
CHD7	6 (40)	0
HLA-DPA1	6 (40)	0
HLA-DQB1	6 (40)	0
HSPG2	6 (40)	0
PARP4	6 (40)	0
BTNL2	6 (40)	6 (40)
GGT1	9 (60)	2 (13)
HLA-C	9 (60)	4 (27)
HLA-DRB1	10 (67)	0
PRH1	10 (67)	0
FRG1	10 (67)	4 (27)
HLA-B	10 (67)	10 (67)
ANKLE1	11 (73)	11 (73)
ACAN	13 (87)	3 (20)
HLA-DQB2	13 (87)	0
FCRL3	2 (13)	2 (13)
MMP19	2 (13)	2 (13)
MST1	2 (13)	2 (13)
PTPN22	2 (13)	2 (13)
NEB	2 (13)	2 (13)

See Table 1 for definitions of gene symbols.

Table 4

Patient	Genes With Missense Variation
1	*MMP19 (2), WRNIP1, TRIM6, COL6A, COL24A*
2	*FTH1, MMP17, MMP25, COL6A*
3	*TIM6, COL12A*
4	*COL9A, COL17A, OR51M1, UBQLNL, MMP7*
5	*TRIM6*
6	*EPN3, TNFAIP6, NOTCH, COL6A, COL8A, COL17A*
7	*ACAN, COL14A*
8	*COL1A1, COL4A, COL9A, COL16A, COL28A*
9	*COL9A2, UBQLNL, MMP7, COL24A*
10	*DUOX1, MMP7, COL6A (2)*
11	*COL11A1 (2), IL1RL1, COL18A, COL28A*
12	*ADAM17, MMP1, NOTCH, COL12A (2), COL14A, COL18A*
13	*TRIM6, WRNIP1, COL9A, COL14A, COL23A*
14	*MMP19 (2), ACAN*
15	*NR2F6*

Genes were filtered with a database of human nonsynonymous SNPs (dbNSFP); dbNSFP-predicted damaging variations were compared with the original compiled list of contributory genes.
See Table 1 for definitions of gene symbols.

Table 5

Gene Symbol	RSN	Type of Mutation	Haplotype	LDH Allele Frequency	Reference Allele Frequency[a]	Odds Ratio (95% CI)	GWAS *P* Value
COL1A1	rs112626388	Insertion	Heterozygous	0.43	0.69	0.34 (0.16–0.72)[b]	0.00467
	Novel[c]: g.1040delA	Deletion	Heterozygous	0.033	Unknown[d]	NA	NA
COL9A2	rs140041506	Missense	Heterozygous	0.067	0.01	7.07 (1.48–33.78)[b]	0.045
COL9A3	Novel: g.1625C>G	Missense	Heterozygous	0.033	Unknown	NA	NA
COL11A1	rs140954784	Missense	Heterozygous	0.033[§]	0.00005	NS	0.029
	rs144562769	Missense	Heterozygous	0.033[§]	0.00002	NS	0.029
	rs36076089	Splice	Heterozygous	0.1	0.01	11 (2.86–42.25)[b]	0.00524
	rs143875783	Transition	Heterozygous	0.033	0.00 (very rare)	NA	NA
MMP3	rs679620	Missense	Heterozygous	0.37	0.68	0.27 (0.13–0.58)[b]	0.0006
VDR	rs371312471	Transversion	Heterozygous	0.067[¶]	Unknown	NA	NA
	Novel: g.2100A>T	Transversion	Heterozygous	0.067[¶]	Unknown	NA	NA
IGF1R	rs58523117	Deletion	Heterozygous	0.47	0.85	0.15 (0.07–0.32)[b]	0.000196
	rs375097523	Transition	Heterozygous	0.033	Unknown[d]	NA	NA
	rs3051365	Insertion	Heterozygous	0.067	0.01	7.07 (1.48–33.78)[b]	0.045
	Novel: g.2291C>A	Transversion	Heterozygous	0.033	Unknown	NA	NA
	Novel: g.5771delA	Deletion	Heterozygous	0.033	Unknown	NA	NA
	Novel: g.3443G>A	Transition	Heterozygous	0.033	Unknown	NA	NA
	Novel: g.5741insC	Insertion	Heterozygous	0.033	Unknown	NA	NA
ACAN	rs117116488	Missense	Heterozygous	0.067	0.005	14.21 (2.64–76.44)[b]	0.016
	rs3817428	Missense	Heterozygous	0.23	0.87	0.05 (0.02–0.11)[b]	1.55×10^{-14}
	rs12899191	Novel	Heterozygous	0.33	Unknown	NA	NA
	rs181736584	Missense	Heterozygous	0.067	0.001	71.36 (6.28–810.26)[b]	0.00242
	rs11638262	Missense	Heterozygous	0.033	0.49	0.04 (0–0.26)[b]	7.84×10^{-81}
THBS2	Novel: g.761T>G	Transversion	Heterozygous	0.033	Unknown	NA	NA
	Novel: g.3355T>C	Missense	Heterozygous	0.033	Unknown	NA	NA

[a] *Reference population from the 1000 Genomes Project.*[73]
[b] *SNPs with $P<0.05$ are presented; $P<1\times10^{-7}$ is statistically significant. The frequency of novel SNPs in the LDH cohort is also presented.*
[c] *Allele frequency not available for novel variants.*
[d] *Same patient.*
[¶] *Same group of patients.*
[§] *Previously reported variant, but allele frequency not available in reference population.*
CI indicates confidence interval; LDH, lumbar disk herniation; GWAS, genome-wide association study; NA, not available; NS, not significant; RSN, reference serial number; SNP, single-nucleotide polymorphism. See Table 1 for definitions of gene symbols.

Results

Among the 61 candidate genes flagged, 20 had missense mutations in 2 or more LDH cases. Missense mutations in collagen-encoding genes were observed in 12 of 15 patients (80%).

A potential association with clinical presentation was indicated by odds ratios of key single-nucleotide polymorphism (SNP) variants in genes that encode collagen. Relative to the reference population, the LDH cohort demonstrated two statistically significant SNP variants in the gene encoding for aggrecan, a protein that facilitates load-bearing properties in the cartilaginous end plate.

Aggrecan genes SNPs rs3817428 and rs11638262 were significantly associated with decreased odds of symptomatic LDH: odds ratio 0.05 (0.02–0.11) and 0.04 (0–0.26), respectively ($P<1\times10–7$ for both).

Conclusion

These results suggest that collagen-encoding variants may be a genetic risk factor for LDH. They also shed new light on the role of variants that impact aggrecan, which sustains the cartilaginous end plate.

Genetic predisposition to LDH may therefore be related to a multimodal combination of mutations that affect the nucleus pulposus, annulus fibrosus, and the cartilaginous end plates.

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