Elastin (ELN) gene point mutation in patients with inguinal hernia

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Abstract

Groin hernias emerge at the myopectineal orifice of Fruchaud which is closed off by the fascia transversalis. Our previous studies showed structural and quantitative changes of the fascia transversalis elastic fibers of inguinal hernia patients and elderly people. The present study used single-strand conformation polymorphism (SSCP) elastin analysis to investigate the 34 exons of the ELN gene of 49 inguinal hernia patients (7 females, 42 males aged 58.7 ± 19.82 years) and 75 non-herniated controls (35 females, 40 males aged 46.2 ± 14.32 years). We found that 47 patients and 24 controls had an abnormal exon 20 pattern caused by a g28197A > G missense mutation leading to an S422G amino acid substitution in the elastin hydrophobic domain. The g28197A > G allele frequency was 0.71 ± 0.045 in hernia patients and 0.21 ± 0.030 in controls and 23 patients and 7 controls were g28197A > G homozygous and 24 patients and 17 controls were heterozygous. This point-mutation showed a statistically significant association with inguinal hernia, chi-squared being 46.89 (p < 0.001) and the odds ratio 49.93 (95% confidence interval of 11 to 223). These results indicate that the g28197A > G mutation is involved in the genesis of inguinal hernia (possibly due to abnormal elastic fiber production) and explains impaired fascia transversalis function.

Key words: fascia transversalis, extracellular matrix, elastic fibers, elastin gene, inguinal hernia.

Received: October 13, 2004; Accepted: July 26, 2005.
for ELN gene mutations using single-strand conformation polymorphism (SSCP) analysis (Orita et al., 1989). Each of the 34 exons of the ELN gene was amplified using intronic primers as previously described by Tassabehji et al. (1997) and the PCR products separated by overnight electrophoreses on non-denaturing 10% (w/v) polyacrylamide gels (49:1 acrylamide:N, N’ bisacrylamide) at 4 °C and a constant 550 V, the products being detected by silver staining. Whenever an abnormal banding pattern was observed the relevant exon was directly sequenced using an ABI Prism 377 sequencer (Perkin Elmer). Sequences were aligned by using the basic local alignment search tool (BLAST) (Altschul et al., 1999) using the nucleotide sequence data deposited in GenBank under access number NT007758.10.

Our initial SSCP analysis examined the 34 ELN f gene exons of 19 inguinal hernia patients and 16 non-herniated controls and detected abnormal banding mobility in exon 20 of all the 19 patients and 11 of the controls. Sequence analysis revealed an exon 20 missense mutation consisting of a single g28197A > G nucleotide substitution corresponding to a S422G substitution at the protein level (NP_000492). These results prompted us to sequence the ELN exon 20 from an additional group of 30 inguinal hernia patients and 59 non-herniated controls. In all, the g28197A > G missense mutation was present in 47 out of 49 herniated patients and 24 out of 75 non-herniated controls. In all, the g28197A > G missense mutation was present in 47 out of 49 herniated patients and 24 out of 75 non-herniated controls and this led to an S422G amino acid substitution in the elastin hydrophobic domain. This point-mutation showed a statistically significant association with inguinal hernia, chi-squared being 46.89 (p < 0.001) and the odds ratio being 11.74 with a 95% confidence interval of 1.00 to 12.86. This mutation is present at a significantly higher frequency in inguinal hernia patients and 0.21 ± 0.030 in the controls. The mutant allele frequency was 0.71 ± 0.045 in hernia patients and 0.21 ± 0.030 in the controls.

The ELN f gene exon 20 g28197A > G missense point mutation is present at a significantly higher frequency in inguinal hernia patients than in non-herniated controls. Normal tropoelastin is rich in non-polar amino acids which produce the hydrophobic domain required for the elastic property of the fiber but the g28197A > G missense mutation changes non-polar amino acids to charged ones resulting in hydrophobic changes in the tropoelastin. Variability in the amino acid sequence may change the tropoelastin conformation and produced defective elastin fibers, abnormal fibrillogenesis or an altered response to enzymatic degradation (Parks and Deak, 1990). It appears that the accumulation of damaged elastic fibers which occurs in the fascia transversalis of elderly people and patients with inguinal hernia may be a consequence of mutations in ELN gene. Tassabehji et al. (1998) detected a frameshift mutation in exon 32 of the ELN gene of a patient affected by dominant autosomal cutis laxa, this mutation produced a defective tropoelastin protein which altered the architecture of elastic fibers and produced skin with a prematurely aged appearance.

Our results favor the hypothesis that the ELN f gene exon 20 g28197A > G missense mutation leads to the production of abnormal elastic fibers and the loss of fascia transversalis function and thus plays a role in the genesis of inguinal hernia.

References


Associate Editor: Angela M. Vianna-Morgante