INTRODUCTION

Pre-mRNA splicing is an essential process in gene expression. During this process, introns are looped and cut away from exons and exons are then joined together to form a mature transcript (Adams *et al*., 1996). As diagnoses are often based on changes in amino acid sequences, the importance of pre-mRNA splicing and its regulation was underestimated for a long time. Now it is clear that mutations that alter the splicing process are often connected with pathological conditions. In fact, 15-50% of splicing mutations can cause human hereditary diseases, including several types of cancer and some inflammatory diseases (Venables, 2006; Cacéres *et al*., 2002; Häsler *et al*., 2011).

The recognition of exon-intron boundaries is necessary for detemining the appropriate course of the splicing process. Three consensus intronic sequences are needed for this recognition: 5‘ splicing site, 3‘ splicing site, and polypyrimidine tract. Pre-mRNA splicing is regulated by *cis* elements located in both introns and exons, which can increase or decrease the probability of the recognition of splicing sites. These elements are called exonic/intronic splicing enhancers (ESE/ISE) and exonic/intronic splicing silencers (ESS/ISS). These elements are binding sites for *trans* factors such as serine/arginine rich proteins (SR proteins) and heterogeneous nuclear ribonucleoproteins (hnRNPs) (Adams *et al*., 1996; Ward & Cooper, 2010).

This study is focused on splicing regulators of the *SERPING1* gene which codes for the C1-inhibitor (C1INH). C1INH belongs to a superfamily of serpin-type protease inhibitors in plasma. Quantitative or qualitative C1INH deficiency leads to hereditary angioedema (HAE). HAE is an autosomal dominant disease that manifests as acute attacks of subcutaneous and submucosal swelling in the body. The most severe condition is edema of the upper airways, which can lead to suffocation. Due to C1INH deficiency, a kinin cascade is deregulated, an excessive amount of bradykinin is produced, blood vessels become more permeable, and the tissues are filled with liquid (Cugno *et al*., 2003; Cugno *et al*., 2009).

SERPING1 is located on chromosome 11 (11q11-q13.1); it is about 17 kb long (Theriault *et al.*, 1990) and is composed of 8 exons and 7 introns (Carter *et al.,* 1988). Although hundreds of mutations have been detected (Kalmár *et al*., 2005; Pappalardo *et al.*, 2008), little is known about the exact effect of the mutations on the regulation of *SERPING1* gene expression. A cell-specific alternative splicing of *SERPING1* (full variant and exon 3 skipped variant) was recently described (Cruz *et al.*, 2011). Regulatory elements of exon 3 *SERPING1* were mapped in this study. Our hypothesis was that exon 3 (as an alternative exon and a very long exon) is regulated by more regulatory elements that make it more prone to splicing aberrations caused by its mutations. The results of this study should help understand the molecular basis of the pathogenesis of HAE and contribute to the knowledge of splicing regulation in general.