Positional cloning of the causative mutation for bovine dilated cardiomyopathy (BDCMP)

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Introduction

Bovine dilated cardiomyopathy (BDCMP) is a severe and terminal disease of the heart muscle. It was first observed in the late 1970s in Switzerland, Japan and Canada. Three different types of cardiomyopathy have been reported in cattle, whereas BDCMP affects exclusively animals of Canadian Holstein origin.

The disease is characterized by a global heart enlargement, chamber dilatation, reduction of wall thickness and myocardiofibrosis in all parts of myocardium. Characteristic clinical symptoms include edema of the brisket, congested jugular veins, abduction of the forelegs and tachycardia with gallop rhythm (Figure 1). Typical age at onset of the disease is between 2 and 4 years, nevertheless younger calves and older cows have also been diagnosed with BDCMP.

A hereditary nature of BDCMP is strongly suggested by the pedigree analysis of reported cases, which allowed to trace back to the common ancestral bull “ABC Reflection Sovereign”. Subsequently an autosomal recessive mode of inheritance was proposed and the disease-causing locus was mapped to the interval of 6.7 Mb on bovine chromosome 18 (BTA18).

Present studies are focused on further fine mapping of the interval of interest in order to identify the causative mutation for BDCMP.

Methods

- Isolation of BTA18 BAC clones and construction of BAC contig.
- Genotyping of microsatellite and single nucleotide polymorphism (SNP) markers around the interval of interest.
- Re-sequencing of the critical region as well as putative candidate genes.

Results and conclusions

- The BAC clones allowed to establish and confirm the order of microsatellites and genes surrounding the region of interest on BTA18 (Figure 2).
- Microsatellite markers and SNPs enabled us to narrow down the interval in question to 218 kb (Figure 3).
- Re-sequencing of the crucial chromosomal region requires the amplification of 35 PCR products, which are 3-11 kb long.
- Mutations in the genes located in the reduced interval have not been previously reported as causative mutations for dilated cardiomyopathy in human patients.

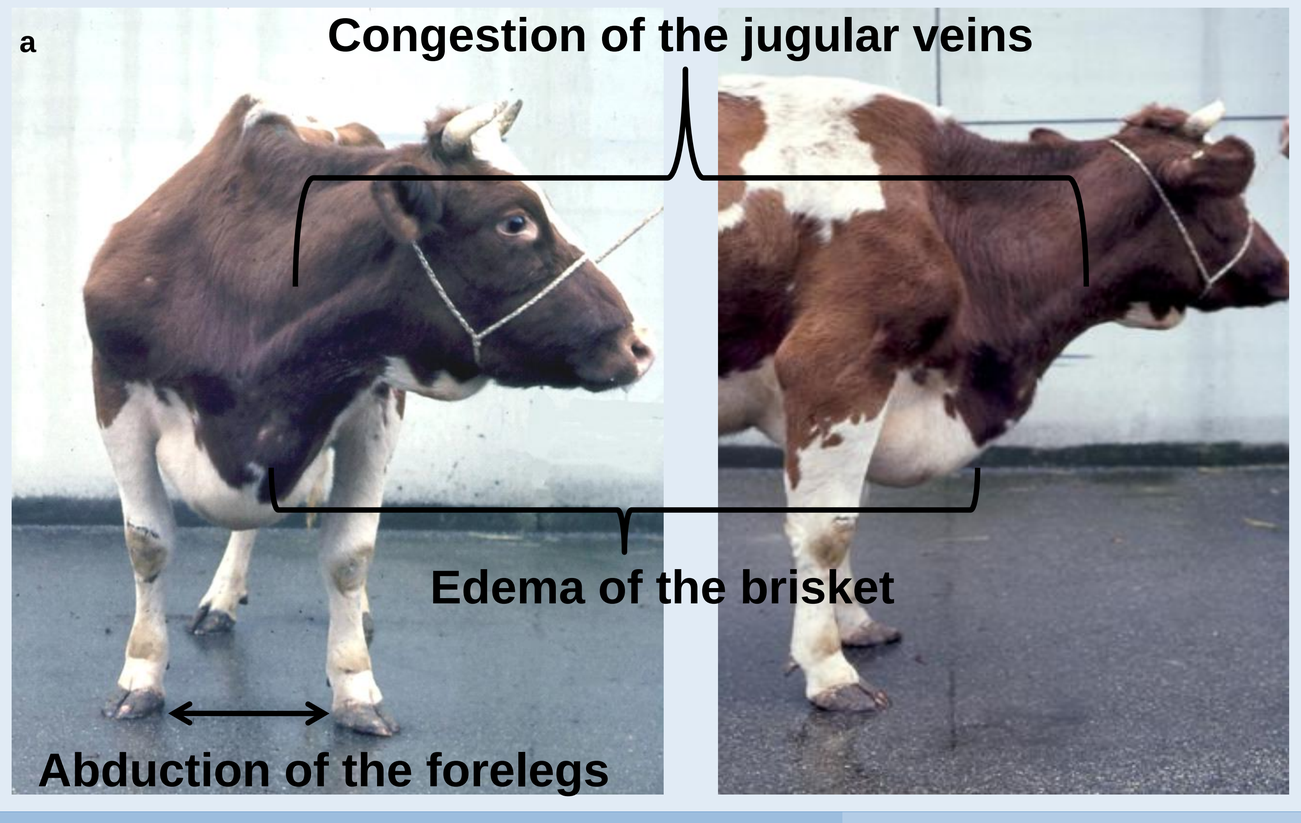

Figure 1. Symptoms of BDCMP
a) characteristic clinical symptoms, b) cardiomegaly and chamber dilatation, c) progressive myocardiofibrosis (blue), d) congested kidneys

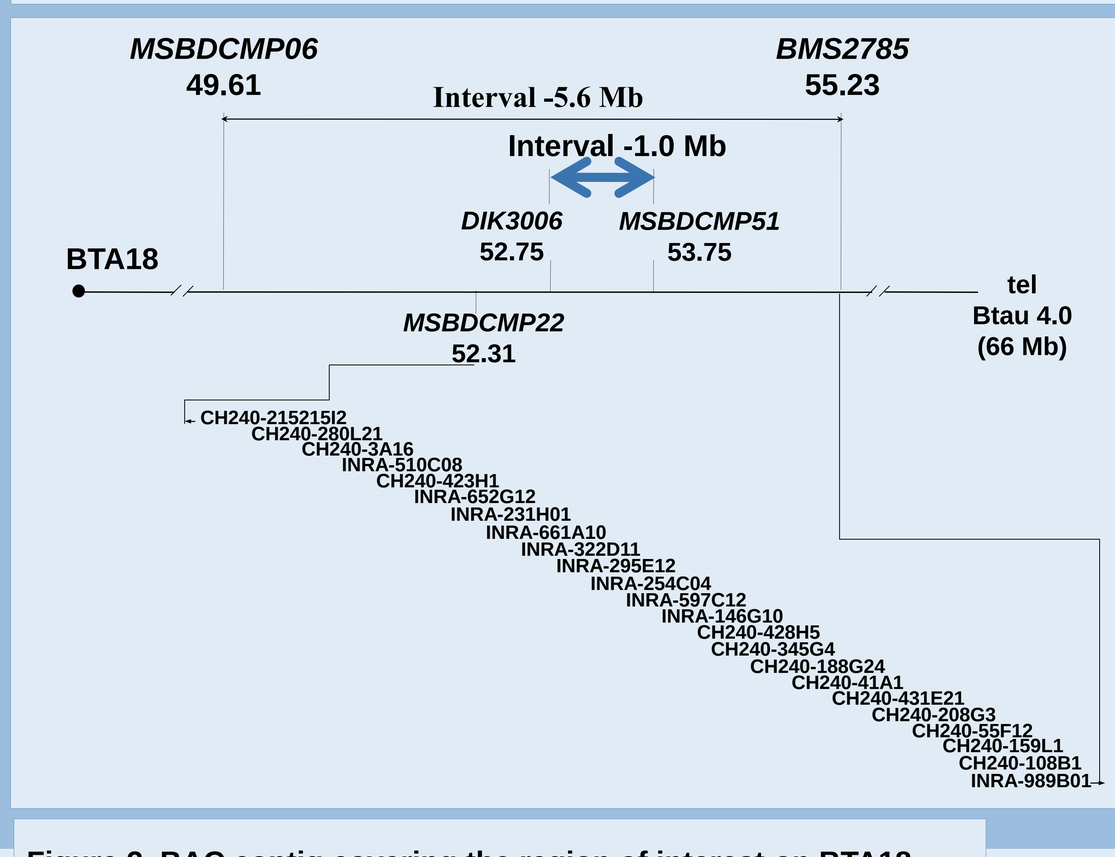

Figure 2. BAC contig covering the region of interest on BTA18.

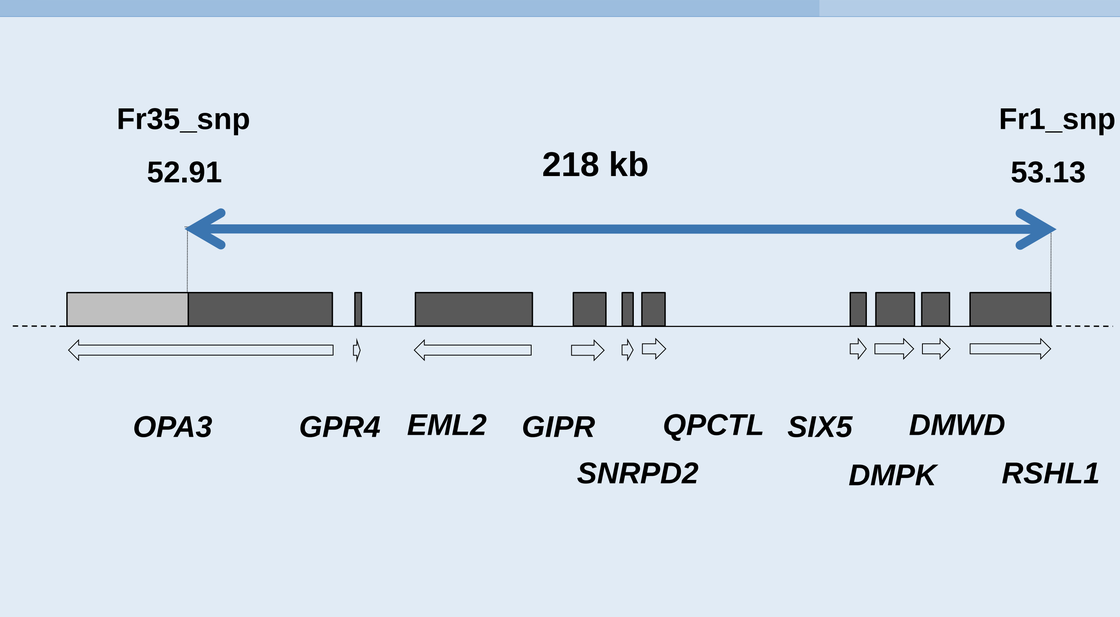

Figure 3. Critical interval with the BDCMP locus is reduced to 218 kb. The narrowed down region on BTA18 contains ten genes (abbreviations of these genes are presented below).