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Identification of a Putative PRDM9-Binding Motif within the Homologous Recombination Hotspot in the SEC1 and FUT2 Genes

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Introduction

The *FUT2* gene (OMIM #182100) encodes α (1,2)fucosyltransferase which regulates the expression of the ABO and Lewis histo-blood group antigens via the synthesis of H antigen on epithelial cells. *FUT2* and its homologous pseudogene, *SEC1*, are separated by 23 kb on chromosome 19q13.3. To date, two alleles derived from homologous recombination between these two genes have been reported: whereas the *Se^{fus}* allele was generated by nonallelic homologous recombination (NAHR),^[1] the *SEC1-FUT2-SEC1* allele originated via interlocus gene conversion.^[2] The highly unusual overlap between the crossover region of the NAHR event and the maximal converted tract (MaxCT^[3]) of the interlocus gene event^[4] could be held to imply the existence of a novel homologous recombination hotspot in the human genome.

It has been increasingly appreciated that local DNA sequence features contribute to the formation of recombination hotspots.^[5] In particular, PRDM9, a meiosis-specific histone H3 methyltransferase, has recently been identified as a major determinant of meiotic recombination hotspots in humans and mice.^[6-14] PRDM9 activates recombination hotspots via chromatin remodeling by binding to a degenerate 13-mer motif, CCNCCNTNCCNC.^[15] We wondered whether PRDM9 might also drive the *SEC1/FUT2* homologous recombination hotspot and we therefore searched the hotspot region and its flanking 1-kb sequences on both sides for the possible presence of the 13-mer motif.

Results and Discussion

Having allowed for one mismatch,^[16] we identified a single putative PRDM9-binding site (termed motif A): it is located not only within the aforementioned overlapping region (of only 158-bp) but also only 2-bp 5' to our previously identified non-B DNA-forming motif (termed motif B) (Illustration 1). In the Figure, the *SEC1* sequence was used for illustration because

SEC1 represents the "acceptor" in the interlocus gene conversion event involving *SEC1* and *FUT2*.^[2] This means that the double-strand break that initiated the interlocus gene conversion event must have occurred within the *SEC1* sequence. Nonetheless, both motif A and motif B are present within the overlapping region (indicated by two downward pointing arrows) that are shared by the crossover region (delimited by vertical bars) of the NAHR event^[1] and the MaxCT of the interlocus gene conversion event;^[2] no paralogous sequence variants exist in this region between the two genes. In other words, use of either *SEC1* sequence or *FUT2* sequence for illustration does not affect our observation.

The co-localization of this putative PRDM9-binding site and the non-B DNA-forming motif prompted us to speculate that the two distinct motifs could have interacted synergistically to initiate homologous recombination between the *SEC1* and *FUT2* loci in the following way: the binding of PRDM9 to motif A (i) would serve to modify the local chromatin structure, thereby facilitating the formation (ii) of a non-B DNA structure (motif B) which is susceptible to double-strand breaks (iii) which then initiate homologous recombination (iv).

To the best of our knowledge, this is the first time that the co-localization of a putative PRDM9-binding motif and a non-B DNA-forming motif has been explicitly invoked to explain the activity of a homologous recombination hotspot. Our finding may however find wide application as additional NAHR and interlocus gene conversion hotspots are characterized at the nucleotide sequence level.

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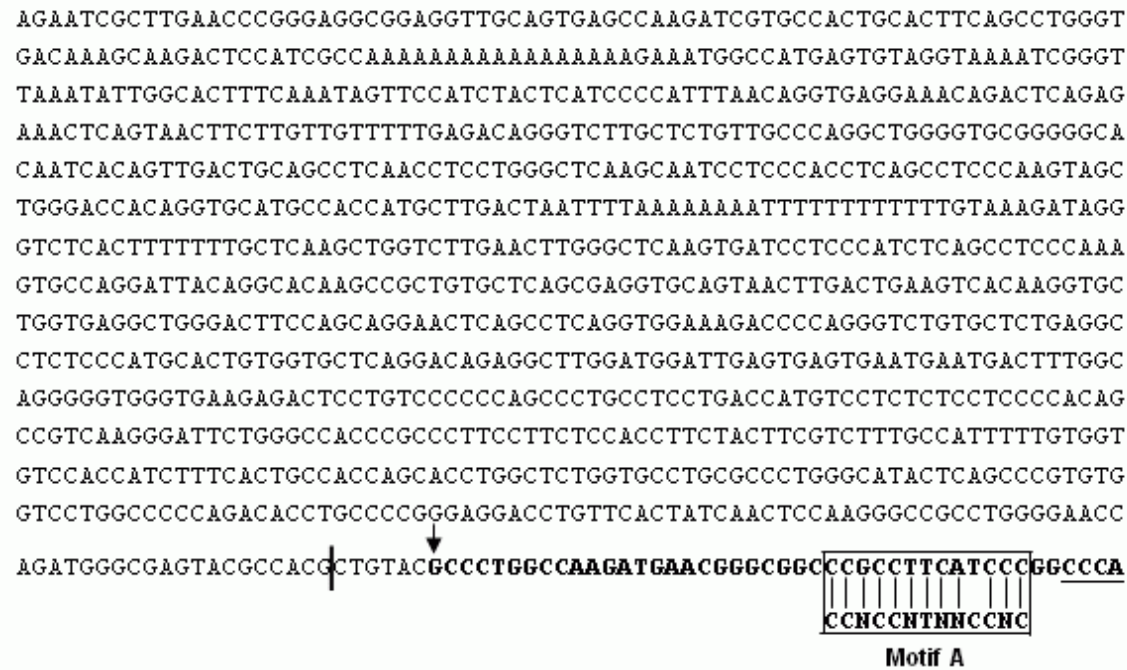
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Illustrations

Illustration 1

Identification of a putative PRDM9-binding motif within the homologous recombination hotspot in the SEC1 and FUT2 genes. See text for details. The sequences illustrated in the Figure correspond to nucleotide positions 21450730-21453010 of GenBank NT_011109.16.



GATGCACAGCACCCCTGGCCCCATCTTCAGAATCACCCCTGCCGGTGCTGCACAGCGCCACGGCCAGCAGG

Motif B

**ATCCCCTGGCAGAACTACCACCTGAACGACTGGATGGAGGAGGAGTACCGCCACATCCCGGGGCGCTGTG
TCCGCCTCACGGGCTACCCCTGCTCCTGGACCTTCTACCACCACCTCCGCCAGGAGATCCTCCAGGAGTT
CACCCCTGCACGACCACGTGCGCGAGGAGGCCCCAGAAAGTTCTGCGGGGCTGCAGGCCAAGTGGGCAGGG
CAGGGCACCCTTCGTGGGGGTCCACGTGCGCCGGGGGGACTATGTCCGTGTTCATGCCGCGGTATGGAAGG
GGGTGCTGGCCGACCGGCTACCTGCAGCGGGCCCTGGACTGGTTCCGGGCTGCTGCCGCTCCCGGTCT
TTGTGGTCAACCAGCGATGACATGGCCTGGTGCCGGGAGAGCATCAACAGCTCCCTTGGGGACGTGGTGT
CGCTGGCAATGGCCTCCAGGGCTCACCTGCCAAGGACTTCGCACTGCTCACACAGTGCAACCACACCATC
ATCACCGTGGGCACCTTCGGGGTCTGGGCCGCGTACCTCGCGGGCGGGGACACTGTCTACCTGGCCAACT
TCACCCTGCCCAACTCCCTTTCAACGTGGTCTTTAGGCCGTAAGCGGCCTTCTGCCAGAGTGGGTGGG
CCTTGCGGCTGACCTTGGACAGGCTGGACAGAACGGCCTCTAGCCAGCCCTGCATGTGCCTGGTCTCAT
CCTGTGACCCGAGGGGCAGTGAGTGGGGCGTGCGGGGCATGGACTCACGGTCCCTCATGCAGTTTGGATC
CAGGCTTATCTACTTCATAGCTGAGTGAGTTTGGACAACTGACTCAACCTCTGTGCCTTAGTATGTCAAC
CACAAAATGCACAAAACACAGAACTAAACACCAGTAGCAGCTGGTGGGAGCTGAGCAAAATTCGCTTAGAG
CCAGTGCCCTTGTGACCGTGTGGGAGGTGTGGCTGCTCACATGTATGCAGCACGTCAGGAACACTGGCAT
TGCTTTCCAAATGGAAAACGCAGTTTTTGCCTCTCCTTCCCTGGCAGCACTGGTAGCACAGAGCCCAGATATT
TTGCACTCACGTCCCAGGACGAAGCCATCCCTGCCCTGAAGGATAGGGGAACCTCGATTTTCTGGGCAACT
AGGAATTTTGGCTTTGGAGTTAGTGGGCCTTATCACAAAAG**

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