Article ID: WMC003202 ISSN 2046-1690

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

Corresponding Author:
Dr. Jian M Chen,
Genetics, INSERM U1078 and EFS-Bretagne, 29218 - France

Submitting Author:
Dr. Jian-min Chen,
Genetics, INSERM U1078 and EFS-Bretagne, 29218 - France

Article ID: WMC003202

Article Type: Research articles

Submitted on:28-Mar-2012, 08:31:19 PM GMT **Published on:** 29-Mar-2012, 03:59:06 PM GMT

Article URL: http://www.webmedcentral.com/article_view/3202

Subject Categories:BLOOD TRANSFUSION

Keywords:PRDM9-binding motif, Homologous recombination hotspot, FUT2, Gene conversion, Nonallelic homologous recombination, NAHR

How to cite the article: Chen JM, Cooper DN, Férec C. Identification of a Putative PRDM9-Binding Motif within the Homologous Recombination Hotspot in the SEC1 and FUT2 Genes . WebmedCentral BLOOD TRANSFUSION 2012;3(3):WMC003202

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

Author(s): Chen JM, Cooper DN, Férec C

Introduction

The *FUT2* gene (OMIM #182100) encodes ?(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, CCNCCNTNNCCNC.[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.

References

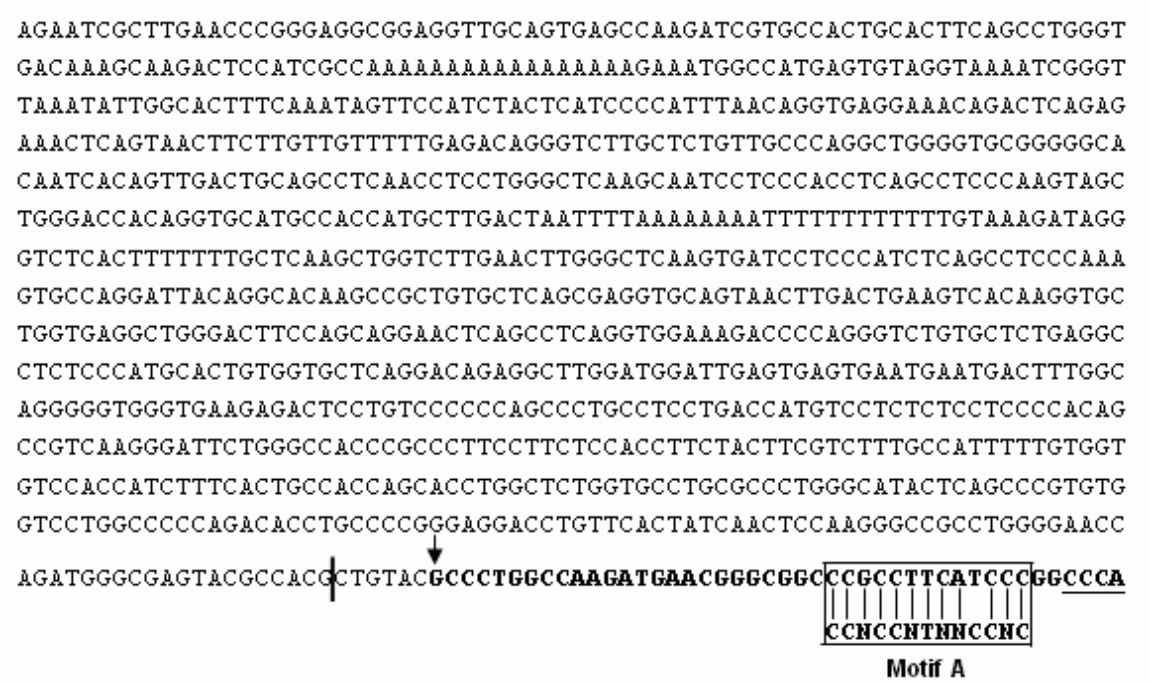
1. Koda Y, Soejima M, Liu Y, Kimura H. Molecular basis for secretor type ?(1,2)-fucosyltransferase gene deficiency in a Japanese population: a fusion gene generated by unequal crossover responsible for the enzyme deficiency. Am J Hum Genet 1996;59:343-50.
2. Soejima M, Fujihara J, Takeshita H, Koda Y. Sec1-FUT2-Sec1 hybrid allele generated by interlocus gene conversion. Transfusion 2008;48:488-92.
3. Chen JM, Cooper DN, Chuzhanova N, Férec C,

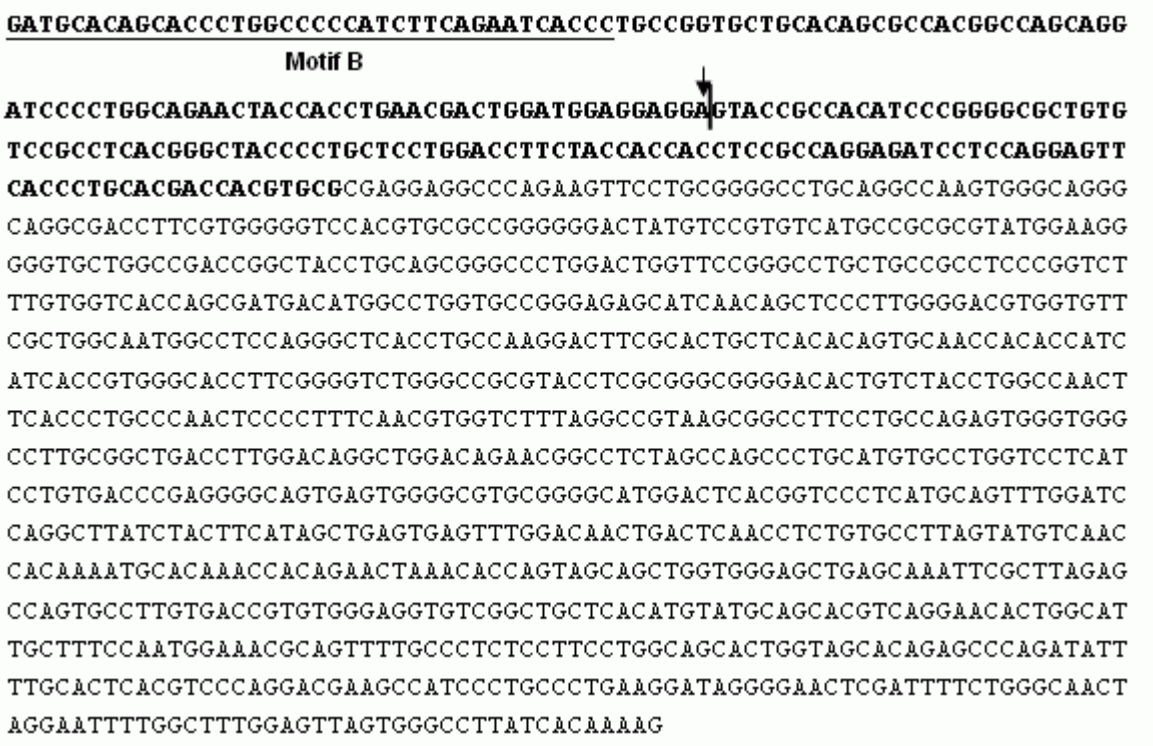
Patrinos GP. Gene conversion: mechanisms, evolution and human disease. Nat Rev Genet 2007;8:762-75.
4. Chen JM, Férec C. Role of non-B DNA conformations in initiating the nonallelic homologous recombination-derived Sefus allele and the interlocus gene conversion-derived Sec1-FUT2-Sec1 hybrid allele. Transfusion 2008;48:1522-3.
5. Cooper DN, Bacolla A, Férec C, Vasquez KM, Kehrer-Sawatzki H, Chen JM. On the sequence-directed nature of human gene mutation: the role of genomic architecture and the local DNA sequence environment in mediating gene mutations underlying human inherited disease. Hum Mutat 2011;32:1075-99.
6. Baudat F, Buard J, Grey C, Fledel-Alon A, Ober C, Przeworski M, Coop G, de Massy B. PRDM9 is a major determinant of meiotic recombination hotspots in humans and mice. Science 2010;327:836-40.
7. Berg IL, Neumann R, Lam KW, Sarbajna S, Odenthal-Hesse L, May CA, Jeffreys AJ. PRDM9 variation strongly influences recombination hot-spot activity and meiotic instability in humans. Nat Genet 2010;42:859-63.
8. Myers S, Bowden R, Tumian A, Bontrop RE, Freeman C, MacFie TS, McVean G, Donnelly P. Drive against hotspot motifs in primates implicates the PRDM9 gene in meiotic recombination. Science 2010;327:876-9.
9. Parvanov ED, Petkov PM, Paigen K. Prdm9 controls activation of mammalian recombination hotspots. Science 2010;327:835.
10. Kong A, Thorleifsson G, Gudbjartsson DF, Masson G, Sigurdsson A, Jonasdottir A, Walters GB, Jonasdottir A, Gylfason A, Kristinsson KT, Gudjonsson SA, Frigge ML, Helgason A, Thorsteinsdottir U, Stefansson K. Fine-scale recombination rate differences between sexes, populations and individuals. Nature 2010;467:1099-103.
11. Hinch AG, Tandon A, Patterson N, Song Y, Rohland N, Palmer CD, Chen GK, Wang K, Buxbaum SG, Akylbekova EL, Aldrich MC, Ambrosone CB, Amos C, Bandera EV, Berndt SI, Bernstein L, Blot WJ, Bock CH, Boerwinkle E, Cai Q, Caporaso N, Casey G, Cupples LA, Deming SL, Diver WR, Divers J, Fornage M, Gillanders EM, Glessner J, Harris CC, Hu JJ, Ingles SA, Isaacs W, John EM, Kao WH, Keating B, Kittles RA, Kolonel LN, Larkin E, Le Marchand L, McNeill LH, Millikan RC, Murphy A, Musani S, Neslund-Dudas C, Nyante S, Papanicolaou GJ, Press MF, Psaty BM, Reiner AP, Rich SS, Rodriguez-Gil JL, Rotter JI, Rybicki BA, Schwartz AG, Signorello LB, Spitz M, Strom SS, Thun MJ, Tucker MA, Wang Z, Wiencke JK, Witte JS, Wrensch M, Wu X, Yamamura Y, Zanetti KA, Zheng W, Ziegler RG, Zhu X, Redline S, Hirschhorn JN, Henderson BE, Taylor HA Jr, Price AL, Hakonarson H, Chanock SJ, Haiman CA, Wilson JG, Reich D, Myers SR. The landscape of recombination in African Americans. Nature 2011;476:170-5.
12. Berg IL, Neumann R, Sarbajna S, Odenthal-Hesse L, Butler NJ, Jeffreys AJ. Variants of the protein PRDM9 differentially regulate a set of human meiotic recombination hotspots highly active in African populations. Proc Natl Acad Sci USA 2011;108:12378-83.
13. Grey C, Barthès P, Chauveau-Le Friec G, Langa F, Baudat F, de Massy B. Mouse PRDM9 DNA-binding specificity determines sites of histone H3 lysine 4 trimethylation for initiation of meiotic recombination. PLoS Biol 2011;9:e1001176.
14. Ségurel L, Leffler EM, Przeworski M. The case of the fickle fingers: how the PRDM9 zinc finger protein specifies meiotic recombination hotspots in humans. PLoS Biol 2011;9:e1001211.
15. Myers S, Freeman C, Auton A, Donnelly P, McVean G. A common sequence motif associated with recombination hot spots and genome instability in humans. Nat Genet 2008;40:1124-9.
16. Sarbajna S, Denniff M, Jeffreys AJ, Neumann R, Soler Artigas M, Veselis A, May CA. A major recombination hotspot in the XqYq pseudoautosomal region gives new insight into processing of human gene conversion events. Hum Mol Genet 2012 Feb 8. [Epub ahead of print]

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.





Disclaimer