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Does Disrupted-in-Schizophrenia (DISC1) Generate Fusion Transcripts?

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A balanced chromosome (1; 11)(q42.1; q14.3) translocation was found to segregate (maximum LOD=7.1) with schizophrenia, bipolar disorder and major depression in a large Scottish family (1). Subsequent molecular studies identified two genes, DISC1 and DISC2, that were disrupted by the translocation breakpoint in chromosome 1q42.1. The potential contribution of the DISC1/2 and a nearby TRAX genes to the pathogenesis of schizophrenia was subsequently supported by a number of, but not all, genetic association studies in general population with different ethic genetic background (). However, the odds ratios are modest for DISC1 as a susceptibility gene without functional mutations identified. In contrast, the t(1; 11) translocation in the Scottish family appears to be the causal genetic lesion with 70% penetrance for major mental illness. The identification of the truncated DISC1 from the translocation prompted many intriguing studies in recent years to elucidate the biological functions of DISC1 and its molecular pathways relevant to schizophrenia and related psychiatric disorders (). Therefore, the understanding of the precise genetic lesion in the Scottish family will be valuable for molecular biologists to unravel the underlying molecular mechanism for the diseases.

The breakpoint from the t(1; 11) translocation was localized between exons 8 and 9 of the DISC1 gene where the DISC2 gene was transcribed as a single large exon overlapping with exon 9 of the DISC1 gene in an anti-sense orientation (2,3). The function of the DISC2 was presumed to be involved in the regulation of DISC1 expression (2,3). Nevertheless, no gene was found to be disrupted at the breakpoint in chromosome 11q14.3 (2,4). Therefore, either haploinsufficiency or the dominant negative form, or both, of the truncated DISC1 has been suggested to contribute to the pathogenesis of schizophrenia and related affective disorders (4,5,). Although many molecular studies have been conducted to investigate the functions of the truncated DISC1 proteins in both *in vitro* cultured neuronal cells and *in vivo* transgenic mice, it remains unknown where the translation of the truncated DISC1 proteins stops. If there is no gene being disrupted by the translocation in chromosome 11q14.3, we assume that the stop codon for the truncated DISC1 will likely come from cryptic splicing from chromosome 11q14.3. Therefore, we re-examined the breakpoint of the balanced translocation in chromosome 11q14.3. The breakpoint was reported to be localized in the BAC clone AP000684, and the sequences of the two junction fragments were published (2,6). After searching for candidate genes, we surprisingly found that two internal exons from CK 000409 (EST) are localized in the AP000684 BAC clone. Apparently, the CK 000409 gene encompasses a much larger genomic locus than the BAC clone. We therefore performed the gene alignment with the cDNA sequence from the CK 000409 gene against a large contig NT_008984.17 which contains the AP000684 BAC clone. Seven exons for the CK 000409 gene were identified to encompass more than a 660 kb genomic locus in chromosome 11q14.3 (Figure 1A). Further DNA sequence alignment revealed perfect splicing donors and acceptors

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for all seven exons (Table 1). It is likely that exon 1 is still an internal exon because the first 9 nucleotides of the CK 000409 gene do not belong to exon 1. Alternative splicing may occur at this locus in the generation of another transcript (BU599486, Figure 1A). The translocation breakpoint is localized in the intron between exons 3 and 4 of the CK 000409 gene in chromosome 11q14.3. No deletion was found at the two breakpoints for the balanced translocation (2). Therefore, two types of candidate fusion transcripts might be formed between DISC1 and the CK 000409 genes (Figure 1B). The first type of fusion transcript(s), driven by the endogenous DISC1 promoter, will consist of exons 1 to 8 from the DISC 1 gene and exons 4 to 7 from the CK 000409 gene. It is difficult to predict what fusion transcript(s) may be generated because of alternative splicing at this locus. However, additional amino acid residues will be added to the truncated DISC1 C-terminal. The second type of fusion transcript(s), driven by the promoter of the CK 000409 gene, may contain some of the first 3 exons from the CK 000409 gene and exons 9 to 13 from the DISC1 gene. Putative truncated DISC1 C-terminal proteins could be formed from some of the fusion transcript(s). Therefore, the effect for the translocation (disrupted-in-schizophrenia) may be much more complicated than just the truncation of DISC1 gene. The duplication of a 16 Mb DNA segment, containing the CK000409 gene, in chromosome 11q14 has recently been found to segregate with all four major depression patients in a three-generation family pedigree (7). Unfortunately, the nucleotide sequences of either CK 000409 or BU599486 genes do not provide much information about their potential functions as they do not seem to encode any protein larger than 100 amino acid residues. It is likely that they are non-coding RNAs, although a definitive conclusion cannot be made until the full-length cDNAs for both transcripts are cloned. Many non-coding RNAs have been recently discovered to play critical roles in the regulation of gene expression (microRNAs), chromatin inactivation (Xist) and imprinting (H19) (8).

Taken together, the functions for both CK 000409 and BU599486 genes need to be investigated, and the putative fusion transcripts need to be confirmed to fully understand the underlying molecular mechanism for the influence of the translocation on schizophrenia and related affective disorders.

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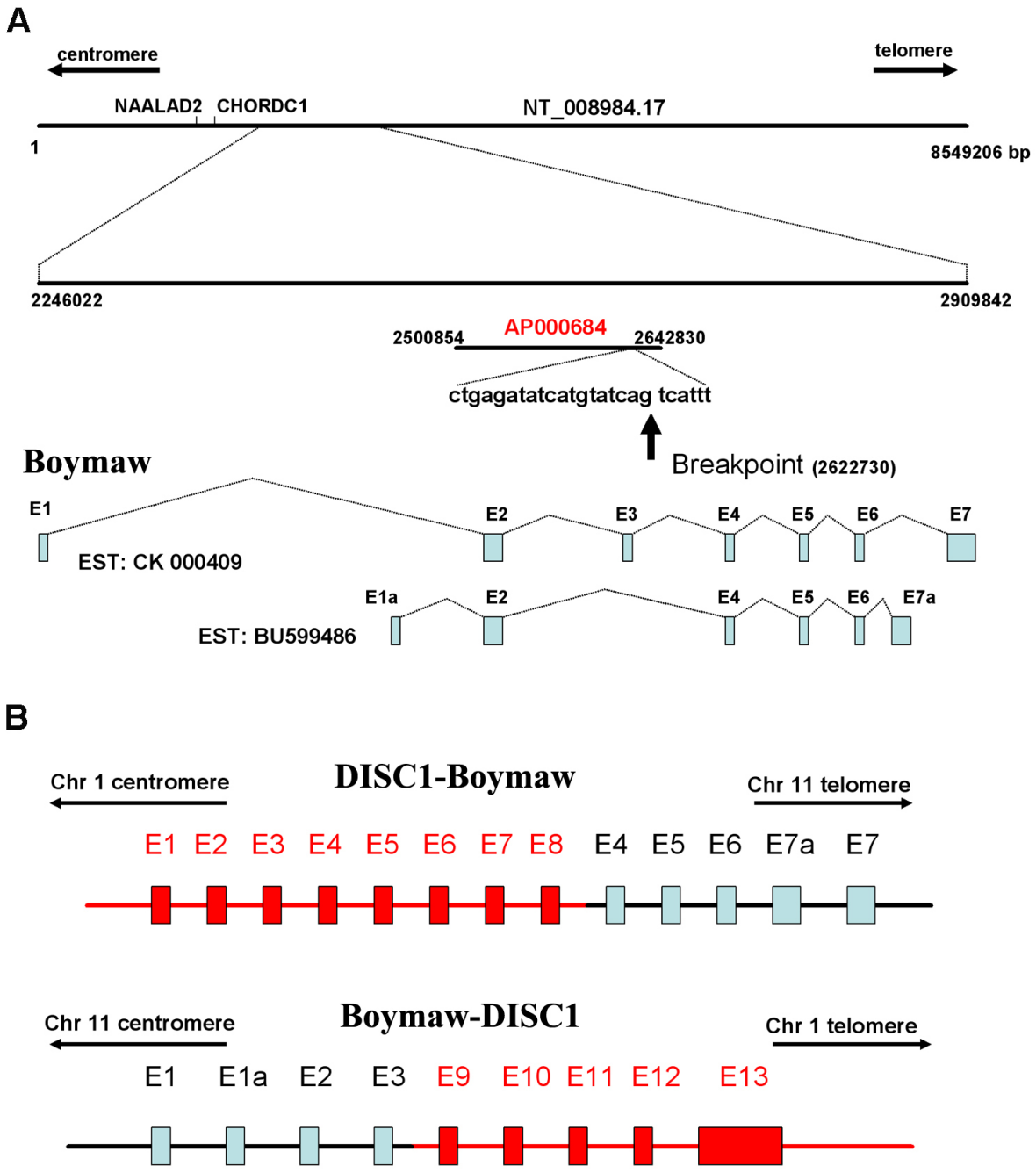

Figure 1.

Genomic locus for CK 000409 gene in Chromosome 11q14.3. **(A)** The positions of BAC clone and the breakpoint were marked relative to the contig NT_008984.17 sequence. Seven exons from the CK 000409 gene encompass more than 660 kb genomic locus, and the translocation breakpoint was mapped in the intron between exon 3 and 4. BU599486 transcripts could come from the alternative splicing of the same gene as CK 000409. **(B)** The formation of two putative fusion transcripts between DISC1 and CK 000409 and BU599486 genes. Exons marked with red letters are from DISC1 gene, and exons marked with black letters are from CK 000409 and BU599486 genes.

Table 1

The Splicing Site Sequences for ESTs CK 000409 and BU599486

Exon	Exon size (bp)	Exon Position	Splice Acceptor	Splice Donor
1	84	10–93	tggtaaagAAGTGC	CAGAACTgtgagtt
1a	42	(6–47)	ttctccttgCCTTCCA	TGGAACTgtaagtc
2	142	94–235	tttcacagGCATTT	CCTCAAGgtaaaaa
3	104	236–339	tttttcagGGGTTTC	GGAACTgtaagtcc
4	97	340–436	tgaccagGTACCA	TCTTAGGgtgagta
5	70	437–506	cccacagTTTCAG	CAAAAGgtgggca
6	92	507–598	ttctctagAATATT	TTTTCTGgtaagat
7a	247	(457–703)	caaacagAAGATGG	Unknown
7	183	599–781	ccacttagGACAAA	N/A