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ARTICLE ADDENDUM

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The interaction of schizophrenia-related proteins DISC1 and NDEL1, in light of the newly identified domain structure of DISC1

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ABSTRACT

DISC1 and NDEL1 are both key proteins in cortical neurodevelopment, which are each also implicated in the pathogenesis of mental illness. That the two proteins interact with each other in a functionally important manner is well established, but two distinct binding domains for NDEL1 on DISC1 have been proposed. A partial domain structure for DISC1 has recently been described, consisting of 4 structured regions referred to as "D," "I," "S" and "C" respectively, with one of the NDEL1 binding sites lying in the "C" region of DISC1. In light of this domain structure, it can be deduced that this site is the likely location at which NDEL1 binds, although the other proposed site (which lies in the DISC1 "I" and "S" regions) may indirectly impact on DISC1-NDEL1 interactions through determination of the oligomeric state of DISC1.

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Disrupted in Schizophrenia 1 (DISC1) is a critical scaffolding protein, which regulates many distinct signaling pathways in cortical and hippocampal neurodevelopment, as a result of its diverse array of protein interaction partners (reviewed in ref. 1). Among the most prominent of these binding proteins is Nuclear Distribution Element-Like 1 (NDEL1, also known as Nudel), which, along with its close paralog NDE1/NudE, is a prominent neurodevelopmental protein in its own right (reviewed in ref. 2). The roles of NDEL1 are diverse, but are particularly associated with cortical development through modulation of the motor protein dynein, and the associated protein Lissencephaly 1 (LIS1, encoded by *PAFAH1B1*).

The critical amino acid residues of NDEL1 for binding to DISC1 are well established[3] and are found in a predicted α-helical region that is involved in binding to multiple proteins (reviewed in ref. 4). In contrast, two distinct and seemingly contradictory binding sites of NDEL1 on DISC1 have been described (Fig. 1A). The first, suggested by Morris et al.,[5] arose because NDEL1 had been seen to bind to a C-terminal section of DISC1, corresponding to amino acids (AA) 598–854 of the 854 AA full length human DISC1, but was incapable of interacting with a DISC1 construct containing only AA 697–854 (Fig. 1B). The authors therefore postulated that NDEL1 must bind within AA 598–696 of DISC1. In contrast, Kamiya et al.[6] later showed that while NDEL1 could bind to a nearly full length DISC1 construct containing AA 1–835, it was incapable of binding to a slightly more truncated version comprising AA 1–801 (Fig. 1C). They therefore concluded the existence of an extreme C-terminal binding region on DISC1 between AA 802–835. This latter result was in broad agreement with a prior result by Brandon et al.,[3] showing that deletion of AA 807–828 of DISC1 weakened its ability to interact with NDEL1 (Fig. 1D).

Recently, we have studied the domain structure of DISC1 through high throughput expression of fragments of DISC1 in *E. coli*, and testing the solubility and stability of the ensuing recombinant proteins.[7] This technique, known as ESPRIT for Expression of Soluble Proteins by Random Incremental Truncation, has been developed and successfully used to identify distinct folded domains within proteins for which domain structures cannot easily be predicted by homology.[8] Using recombinant protein fragments expressed from almost 30,000 truncated DISC1 vectors, the 31 seemingly most highly expressing

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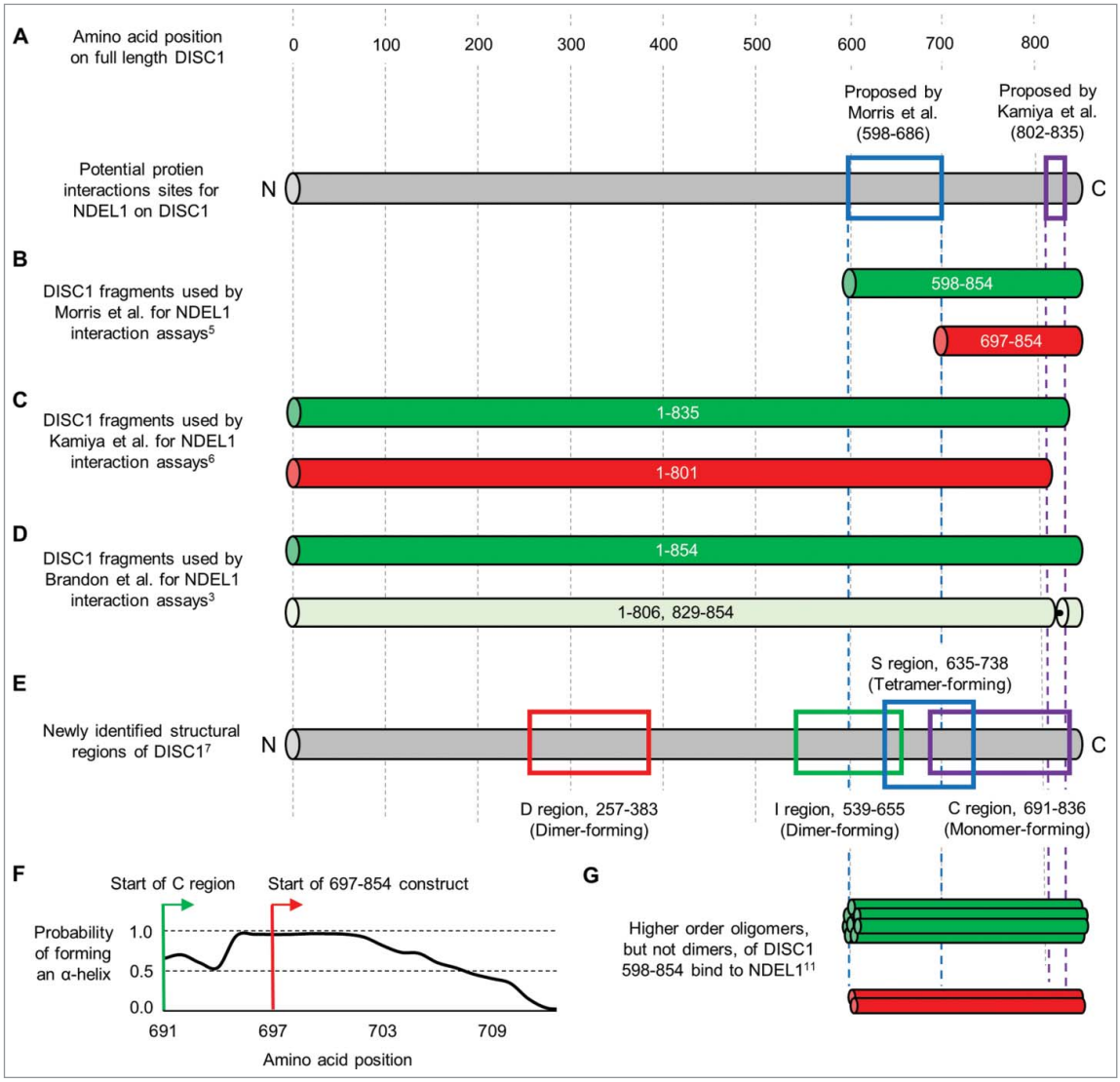

Figure 1. Domain structure of the DISC1 protein and its proposed NDEL1-binding domains in one-dimension, to scale. All numbers in the figure refer to amino acid position in full length (854 amino acid) human DISC1. (A) Location of the 2 proposed binding domains of NDEL1 on DISC1. (B) Constructs used by Morris et al. to suggest a NDEL1 binding domain at amino acids 598–696[5]. Dark green indicates NDEL1 interaction, red indicates failure to interact with NDEL1. (C) Equivalent images of constructs used by Kamiya et al. to suggest a NDEL1 binding domain at amino acids 802–835[6]. (D) Equivalent constructs used by Brandon et al. to show that deletion of amino acids 807–828 leads to reduced interaction with NDEL1 (pale green). (E) The 4 overlapping structured regions of DISC1 identified by Yerabham et al. via high-throughput solubility screening of recombinant proteins.[7] (F) Predicted α-helix forming potential of the first the N-terminal end of the DISC1 "C" region (amino acids 691–835), as determined using PSIPRED.[9] The start of the amino acid 697–854 construct used by Morris et al.[5] is seen to delete part of a highly predicted α-helix. (G) As shown by Leliveld et al., higher order oligomers (most likely tetramers of octomers) of DISC1 amino acids 598–854 interact with NDEL1, while dimers do not.

and soluble clones were chosen over multiple selection steps, and then further investigated, to confirm whether they truly represented stable folded proteins. These would be predicted to represent discrete folded regions or domains within the full length DISC1 protein. In this way, DISC1 was found to include at least 4 folded regions, which we labeled as "D," "I," "S" and "C," that have been mapped to AA 257–383, 539–655, 635–738 and 691–836 respectively of the full length 854 AA DISC1 protein (Fig. 1E). The extreme C-terminal NDEL1 binding site of Kamiya et al. therefore lies wholly within the "C" region, while the more central binding site of Morris et al. is found in the "I" and/or "S" regions.

This new model of the domain structure of DISC1 allows for 2 potential, mutually compatible, explanations for the two NDEL1-binding domain results, both of which imply that the proposed interaction site within the "C" region is the location on DISC1 to which NDEL1

physically binds. The first of these derives from the ESPRIT screening process performed, in which only two stable fragments of DISC1 were identified that contained the NDEL1 binding domain of Kamiya et al. These consisted of DISC1 AA 684–836 and AA 691–836, leading to an outer boundary for the highly stable, α-helical "C" region.[7] The lack of shorter constructs may therefore imply that AA 691–836 represents, or is close to, the minimum number of amino acids needed to encode the folded "C" region. These boundaries are superficially similar to the AA 697–854 construct of Morris et al. which did not interact with NDEL1,[5] however this latter construct is further truncated at the N-terminus, lacking 6 amino acids which are predicted by PSIPRED (Fig. 1F) to be part of an α-helix.[9] It may therefore be that the incomplete "C" terminal region encoded by AA 697–854 does not properly fold (as was the case when the "C" region was truncated from the C-terminus[7]), and loses its ability to bind to NDEL1 for this reason, rather than exclusion of the NDEL1 binding site.

A second partial possibility arises from the oligomeric states of DISC1 and NDEL1. Full length recombinant DISC1 has been shown to form both octamers and dimers.[10] Two oligomeric states are also seen for recombinant fragments containing the C-terminal sections of DISC1 (AA 598 or 640 to the C-terminus[11,12]). This oligomerization is believed to occur principally through the "S" region, which forms tetramers when expressed in isolation.[7] NDEL1 also exists in multiple oligomeric states,[13] including a monomer with an endopeptidase activity,[14] a dimer which binds to its key interaction functional interaction partners LIS1[15] and dynein (implied by analogy to NDE1[16]), and a tetramer of uncertain function. Of these oligomeric states, the full length DISC1 octamer binds to the NDEL1 tetramer in a 1:1 ratio,[10] while NDEL1 similarly interacts exclusively with the higher-order oligomer, as opposed to the dimer, of DISC1 AA 598–854[11] (Fig. 1G). Given the dependence on higher oligomeric states of full length DISC1 for interaction with NDEL1 and the role of the "I" and "S" regions in oligomer formation, it is therefore probable that these regions are indirectly required for successful binding of NDEL1 to full length or larger fragments of DISC1. (The possibility that very short fragments, such as the "C" domain in isolation, can bind to NDEL1 without oligomerization exists, however.) This argument would imply that the AA 598–696 site proposed by Morris et al.[5] would be important for DISC1-NDEL1 interaction through facilitating correct DISC1 oligomerization, without binding to NDEL1 directly.

Interactions of DISC1 with NDE1, the paralog of NDEL1, have not been studied in as much detail; however, NDE1 forms the same set of oligomeric states and has the same general structure as NDEL1,[13] as well as sharing the binding domain in the "C" region of DISC1.[17] It therefore appears likely that the mechanisms of interaction of DISC1 with NDE1 are directly analogous to those with NDEL1.

Our recently described domain structure for DISC1 therefore implies that NDEL1 (and NDE1) are most likely to interact with AA 801–835 of DISC1, within the highly stable "C" region, and requiring this region to be complete and correctly folded. For full length DISC1, or longer recombinant fragments, the oligomeric state of DISC1 is important, and it is therefore likely that the "I" and "S" regions (which overlapped the proposed AA 598–696 binding domain) have an indirect effect of modulating DISC1-NDEL1 interactions through their requirement for DISC1 oligomerization.

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Abbreviations

AA	Amino acid
DISC1	Disrupted in Schizophrenia 1
ESPRIT	Expression of Soluble Proteins by Random Incremental Truncation
LIS1	Lissencephaly 1 (encoded by *PAFAH1B1*)
NDE1	Nuclear Distribution Element 1 (also known as NudE)
NDEL1	Nuclear Distribution Element-Like 1 (also known as Nudel)

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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