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Common inversion polymorphisms and rare microdeletions at 15q13.3

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Sharp *et al*[1] recently described microdeletions at 15q13.3 associated with mental retardation and seizures. These deletions are between Prader–Willi/Angelman break points BP4 and BP5 and include the nicotinic acetylcholine α7 receptor gene (*CHRNA7*). The authors also report a common inversion polymorphism in this region, one orientation of which they suggest might predispose to the microdeletions by non-allelic homologous recombination (NAHR).

15q11–q14 has many segmental duplications, which we have extensively characterised in the human sequence database (Build 36) mainly from one individual.[2] Duplicons of around 300 kb associated with *CHRNA7* and its partial duplication *CHRFAM7A* are in opposite orientation (Figure 1a, black arrows), as are a pair of adjacent

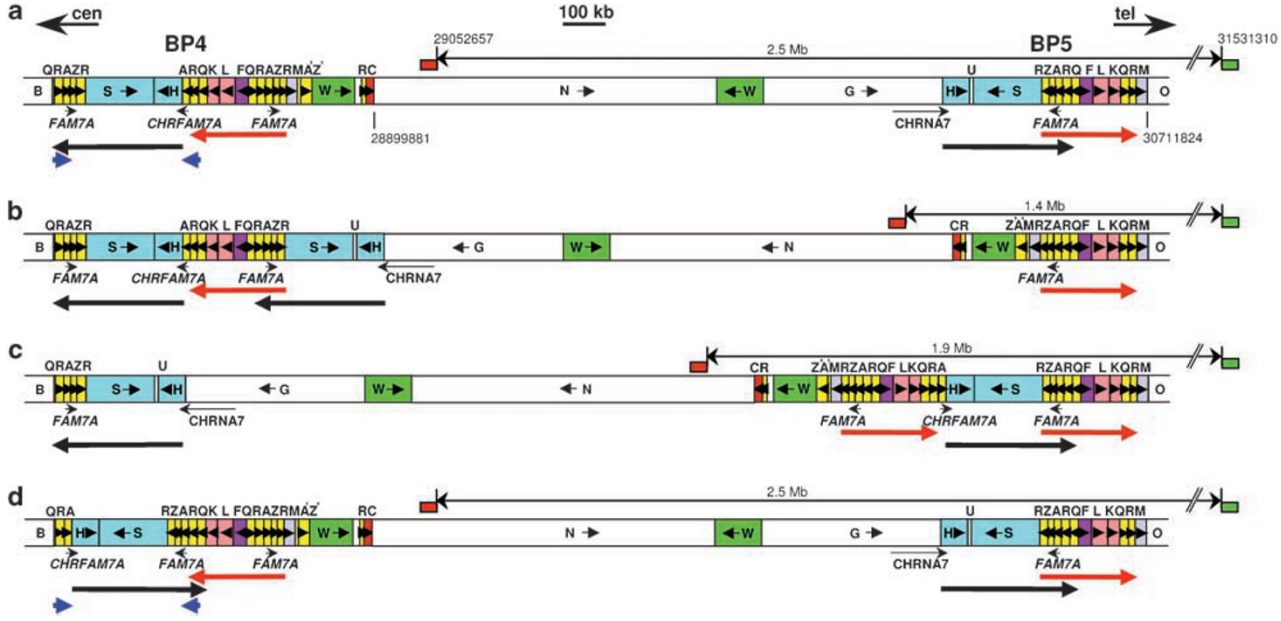

Figure 1 Potential and actual inversion polymorphisms affecting *CHRNA7*. Duplicated segments are shown in the same colour and letter, and unique segments in white, as used previously[5]. (**a**) Database structure from BP4-BP5, showing three pairs of inverted repeats (red, black and blue arrows). (**b**, **c**) Predicted structures for inversion due to NAHR between red (**b**) or black (**c**) arrows. (**d**) Likely structure for confirmed inversion due to NAHR between blue arrows. ▬ Positions of metaphase FISH probes, which are closer together after inversion reported by Sharp *et al*[1]. Coordinates on chromosome 15 build 36 are shown for the above probes[1] and nearby segment junctions.[5]

duplicons of around 200 kb (red arrows). Both pairs of inverted repeats are almost certainly responsible for supernumerary marker chromosomes (SMCs) involving BP4 and BP5.[2,3] They are probably also responsible for inversions, as NAHR between inverted repeats produce SMCs when between chromatids, and inversions when within a chromatid.[4] Predicted inversions involving either pair of duplicons probably explain the common inversion observed by Sharp *et al*,[1] which was assayed by two metaphase FISH signals moving closer together (Figure 1b, c). However, neither would predispose to the observed microdeletions, as NAHR between duplicons in the same orientation (panel b, black arrows; panel c, red arrows) would produce a small deletion removing *CHRFAM7A*, but leaving *CHRNA7* and most of BP4-BP5 intact.

We recently reported another common polymorphic inversion (Figure 1d),[5] which is not detectable by the FISH assay used in the above-mentioned study.[1] This structure is most likely to be ancestral to the database structure (Figure 1a), probably by NAHR between the blue arrows.[5] NAHR between duplicons in direct orientation (panel d, black arrows) would produce BP4-5 deletions, including *CHRNA7*. This inversion is therefore much more likely to predispose to the observed microdeletions of 15q13.3. There appear, therefore, to be several common genomic structures for the BP4-5 region, and probably many uncommon structures, some of which may play a role in psychosis.

Note added in proof

While this letter was in review, two papers were published that independently reported similar microdeletions at 15q13.3.[6,7] Both studies showed that these microdeletions are significantly associated with schizophrenia, which therefore indicates that the inversion structure shown in Figure 1d may predispose to schizophrenia.

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