



Supplementary Figure 2:

Location of rare coding missense variants in the SET domain of human SETD1B, alongside missense variants identified in the gnomAD cohort.

(a) All three *de novo* missense variants described here (black text) are predicted to lie within the histone binding pocket of the SET domain. The histone 3 tail is displayed in red ribbon, with electron densities for Arg1885 in green, Arg1902 in purple and Phe1945 in pink. Remainder of modelled domain is in grey. Dimethylated lysine residue 4 of H3 is depicted in ball-and-stick format.

(b, c, d) Wire diagrams of SET domain missense variants identified in the gnomAD cohort. The side chains of these residues (marked with green text) are predicted to lie outside of the histone-binding pocket of this domain (various views).