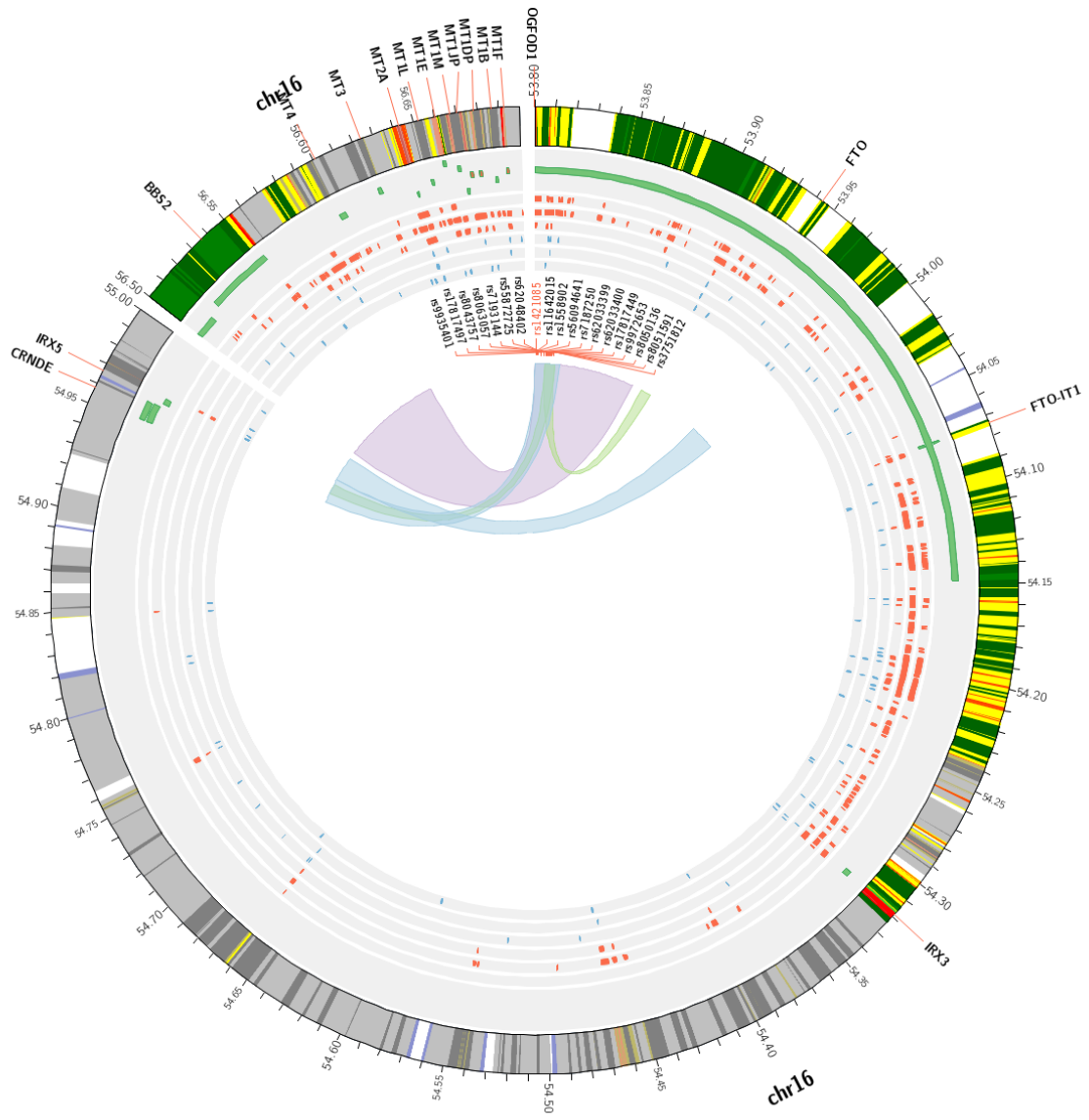


S1 Text. Validation of the 3DSNP locus prioritization pipeline testing *FTO* variants rs9930506 (GWAS proxy) and rs1421085 (causal)

To validate the performance of our 3DSNP prioritization pipeline, we showed that the established causal variant (rs1421085) at *FTO* could be detected using the known tagging variant (rs9930506), as previously reported by Claussnitzer *et al.* (1)

Using 3DSNP, we began by assessing the GWAS-detected *FTO* proxy variant rs9930506 and the reported causal SNP, rs1421085, reported by Claussnitzer *et al.* (1), for functionality and topological interactions. While rs9930506 had a functionality score of 1.05, rs1421085 had a score 15 times higher (14.96). Notably, the Circos plot of rs1421085 (causal), revealed distal interactions with *IRX5* (see figure below for rs1421085), a recently discovered downstream target of rs1421085 (50), while rs9930506 (proxy) demonstrated no such interactions (see figure below for rs9930506). Furthermore, using 3DSNP we were able to identify a number of variants with considerably higher functionality scores compared to rs1421085 and in high LD with rs9930506, suggesting that there might be other causal variants with potentially greater potency in terms of regulatory impact.

rs1421085:



References

1. Claussnitzer M, Dankel SN, Kim KH, Quon G, Meuleman W, Haugen C, et al. *FTO Obesity Variant Circuitry and Adipocyte Browning in Humans*. The New England journal of medicine. 2015;373(10):895-907.