**Supplemental Note**

The OMGenSV pipeline uses single molecules for genotyping because of observations that the Bionano *de novo* assembly pipeline is highly error-prone at loci with segmental duplications. To quantify the difference between single-molecule-based genotyping and *de novo* assembled contigs, we used the 16p12 locus as a testbed and counted the configurations present in the assembled contigs from our 154-sample dataset (Figure S1). We detected configurations in the contigs by extracting local contigs from each sample and using them as input to the OMGenSV pipeline, treating the contigs as through they were molecules and following the approach described in Methods.

The analysis showed striking differences in configuration prevalence between results obtained with single molecules and with contigs, despite using the same set of samples for both (Figure S1). In particular, configurations G1-3 and G3-3, which corresponded to the hg38 structure and, in the latter case, the S3 structure as well, were overrepresented in the contigs >10-fold compared to the single molecules. The low single-molecule-based prevalence for these configurations (2-3%) is more concordant with previous publications, as the hg38 reference configuration was not observed in a FISH analysis of 20 chromosomes (Antonacci *et al.* 2010); the FISH results would be highly unlikely if the contig-based prevalence of 38% were correct (*p* < 3x10-4, Fisher’s exact test). It should be noted that the genome reference is not used to guide the *de novo* assembly process, and it is unclear which factors bias the assembly algorithm towards certain configurations over others.

Antonacci F., J. M. Kidd, T. Marques-Bonet, B. Teague, M. Ventura, *et al.*, 2010 A large and complex structural polymorphism at 16p12.1 underlies microdeletion disease risk. Nat. Genet. 42: 745–750. https://doi.org/10.1038/ng.643