normalized Hi-C counts, TADs, directionality index (DI), CTCF occupancy (Dixon et al., 2012; ENCODE Project Consortium, 2012), and the orientation of CBSs of a Chr12 genomic region are shown as an example. Note that all boundary regions of neighboring TADs (number 1-6) have CBS pairs in the reverse-forward orientation, except boundary number 5, which only has one close CBS in the forward orientation.

Figure S5. CTCF/cohesin-mediated Directional DNA Looping in the Human *β-globin* Gene Cluster, Related to Figure 5

(A) Diagram of the human *β-globin* cluster (yellow) and the flanking olfactory receptor (*OR*) clusters (gray). The *HS5* within *LCR* and *3'HS1* are indicated. Predicted looping interactions and topological domains, based on location and orientation of CBSs as well as both CTCF and cohesin (SMC3) co-occupancy in K562 cells, are also shown.

(B) The predicted interactions, in the control, CBS4-knockout (D3, D7, and D19), or CBS4/5 double-knockout (C2, C4, and C14) subcloned CRISPR cell lines, are confirmed by 4C with CBS3(5'HS5) as an anchor. The average log2 ratios of interactions are indicated between the profiles. **P* < 0.05 and ***P* <0.01.

(C) The predicted interactions in the CBS4-knockout or CBS4/5 double-knockout cell lines are also confirmed by 4C with CBS8 as an anchor. **P* <0.05 and ***P* <0.01.

SUPPLEMENTAL TABLES

Table S1. CBSs and Their Orientations in K562 and MCF-7 Cells, Related to Figure 4

Coordinates are based on the genome assembly of hg19. CBSs and their orientations were obtained from the CTCF ChIP-seq datasets of K562 and MCF-7 cells.

Table S2. Positions and Sequences of CBS Pairs in K562, E14, and MCF-7 Cells, Related to Figure 4

The sequences of CBS pairs were obtained by analyzing the CTCF ChIA-PET datasets of K562, E14 pluripotent, and MCF-7 cells.

Table S3. Positions and Sequences of CBS Pairs at Different Chromatin-looping Strengths in K562 Cells, Related to Figure 4

The sequences of CBS pairs were obtained by analyzing the CTCF ChIA-PET dataset of the ENCODE Project. The sequences of CBS pairs were obtained by analyzing the CTCF ChIA-PET dataset of the ENCODE Project. Positions

and sequences of CBS pairs at chromatin-looping strengths of 200, 300, 400, 500, and ≥ 600 in K562 cells were shown.

Table S4. A Role of Cohesin in the Organization of Genome-wide CCDs in K562 and MCF-7 Cells, Related to Figure 4

Shown are lists of genome-wide CTCF/cohesin co-occupied CBSs, CBS pairs of CTCF/cohesin co-occupancy from ChIA-PET dataset, CCDs merged from overlapping loops of CTCF/cohesin co-occupied CBS pairs, and orientation configuration of CBS pairs at CCD boundaries.

Table S5. Human CCDs Based on the Orientations of Tethered CBS Pairs and their CTCF Occupancy in K562 and MCF-7 Cells, Related to Figure 4

The CCDs were obtained by analyzing the CTCF ChIA-PET datasets of K562 and MCF-7 cells from the ENCODE Project.

Table S6. Distribution of Orientation Configurations of CTCF-occupied CBS Pairs in the Boundaries Separating Neighboring CCDs in the Human Genome, Related to Figure 4

The orientation configurations of boundary CBS pairs were obtained by analyzing the CTCF ChIA-PET datasets of K562 and MCF-7 cells from the ENCODE Project.

Table S7. Primer Sets Used in This Study, Related to Experimental Procedures