Supplementary Figure 1. An illustration showing several scenarios as examples for the combination of CNV events in father (F), mother (M) and offspring (O). The grey box indicates the predicted CNV regions. For the first row, there is no boundary discordance between individuals in the family, so a simple Bayesian approach can be used to validate the 125 combinatorial possibilities to determine the most likely *a posterior* trio states. For the second and third row, there are boundary discordances, so we section the combined CNV regions into discrete blocks, then make CNV calls jointly for the trio for each block via Viterbi algorithm (see Supplementary Figure 8 for more detail).

Supplementary Figure 2. Histograms showing the CNV size distribution (in base pair unit) in the European population (CEU), the African population (YRI) and the Asian population (CHB+JPT). The CNVs were detected by PennCNV on HapMap founders (parents in CEU and YRI population and all individuals in the CHB+JPT population) without the use of family information.

Supplementary Figure 3. Histograms showing the CNV size distribution (in base pair unit) for each copy number state. The CNVs were detected by PennCNV on HapMap founders (parents in CEU and YRI population and all individuals in the CHB+JPT population) without the use of family information.

Supplementary Figure 4. A karyotype map showing the genome location and relative frequency of all CNVs detected in HapMap founders (parents in the CEU and YRI population and all individuals in the CHB+JPT population) by PennCNV without the use of family information. Several regions in chromosome 6, 11 and 19 have especially high frequency of CNVs.

Supplementary Figure 5. Histograms showing the size distribution (in base pair unit) of CNV-NDPs (CNVs detected in offspring but not in parents) in HapMap CEU+YRI offspring with and without the use of family information in the PennCNV algorithm. After application of family information, CNVs with smaller sizes are less likely to be detected as CNV-NDPs, resulting in skewed distribution in the histogram.

Supplementary Figure 6. Examples showing LRR and BAF patterns for normal female chrX (A), and chrX with increasingly stronger evidence of heterosomic chromosome deletions (B, C and D) in cell line samples for four females. Deletion of chrX in some cells in a cell culture will cause the AB genotype cluster to split to reflect the allelic imbalance caused by unequal average copy number of two alleles, and this trend will continue to increase when higher fraction of cells lose one copy of chrX. On the other hand, the signal intensity values of LRR generally slightly decrease. In this figure, the

average LRR for chrX in the four individuals are 0.25, 0.17, 0.087 and -0.024, respectively, reflect the lower average copy number of chrX in cell culture. (Note that unlike autosomes, the expected LRR values for a normal chrX in female individuals should be around 0.25, rather than around zero). Our analysis indicates that genotype analysis on cell-line samples should be performed with caution due to heterosomic chromosome aberrations.

Supplementary Figure 7. Examples showing LRR and BAF patterns for heterosomic aberrations in chr2 (A), chr12 (B), chr9 (C) and chr12 (D) in four cell line samples that we have encountered. These phenomena usually occur in the entire chromosome or the entire chromosome arm, and can be easily spotted by non-canonical clustering of BAF values or non-canonical changes in LRR values.

Supplementary Figure 8. A simplified illustration of the trio-based HMM model for CNV boundary mapping and discordance reconciliation. The PennCNV algorithm is applied on each individual in a trio separately, and a deletion CNV (state=2) is found in both father and child but with different boundaries. To use pedigree information to determine where the most likely boundaries are, we section the combined CNV region from the trio into 3 blocks, and treat each block as one node in a HMM model (SNPs within each block is assumed to be in the same CNV state for each individual). For transition probability in HMM model, we used the CNV inheritance matrices to model the CNV transmission status from parents to offspring with one exception: to reduce biases caused by ignoring parental phase and recombination, we arbitrarily treat an offspring block as *de novo* CNV if the parental copy numbers remain constant between consecutive blocks but offspring copy number changes. Six representative trio-based state transition paths are shown in the lower panel, and a standard Viterbi algorithm can be used to test which path is the most likely path to generate the observed data.

Supplementary Table 1. Mode of B Allele Frequency distribution at different copy number states.

Copy number state	Total copy number	Mode of B Allele Frequency distribution
1	0	$\mu_{1,1}=0.5$
2	1	$\mu_{2,1}=0$, $\mu_{2,2}=1$
3	2	$\mu_{3,1}=0$, $\mu_{3,2}=0.5$, $\mu_{3,3}=1$
4	2	$\mu_{4,1}=0$, $\mu_{4,2}=1$
5	3	$\mu_{5,1}=0$, $\mu_{5,2}=0.33$, $\mu_{5,3}=0.66$, $\mu_{5,4}=1$
6	4	$\mu_{6,1}=0$, $\mu_{6,2}=0.25$, $\mu_{6,3}=0.5$, $\mu_{6,4}=0.75$, $\mu_{6,5}=1$

Supplementary Table 2. An example illustrating that after identification of a CNV-NMI (50 SNPs, 97kb), the inheritance patterns for 12 informative SNP markers (highlighted in bold font) can be further used to determine that a *de novo* event occurs at the paternal chromosome.

	Father			Mother			Offspring		
SNP	**genotype**	**SNP BAF**	**SNP LRR**	**genotype**	**SNP BAF**	**SNP LRR**	**genotype**	**SNP BAF**	**SNP LRR**
rs11716390	AB	0.491	0.209	BB	0.978	0.092	BB	0.982	-0.428
rs17038848	AB	0.489	-0.004	AA	0.000	0.256	AA	0.013	-1.110
rs1039260	AB	0.501	0.077	BB	0.986	0.222	BB	1.000	-0.350
rs2588357	BB	1.000	-0.358	BB	1.000	-0.094	BB	0.963	-0.634
rs1243812	BB	1.000	0.049	BB	1.000	0.041	BB	1.000	-0.449
rs9845164	AB	0.587	-0.212	AB	0.472	-0.063	BB	0.948	-0.533
rs9850111	BB	0.999	0.017	BB	0.998	-0.040	BB	1.000	-0.315
rs317565	AB	0.537	-0.099	BB	1.000	-0.017	BB	1.000	-0.563
rs12630208	BB	0.966	0.020	BB	1.000	0.089	BB	0.975	-0.868
rs9311220	AA	0.000	0.131	AA	0.000	0.227	AA	0.007	-0.468
rs11129844	BB	1.000	-0.056	BB	1.000	-0.047	BB	1.000	-0.317
rs12630241	BB	0.997	0.029	BB	1.000	-0.067	BB	1.000	-0.401
rs17039519	AA	0.004	0.023	AA	0.000	0.229	AA	0.025	-1.129
rs17039568	AA	0.003	0.015	AA	0.003	0.151	AA	0.010	-0.895
rs17039576	AB	0.575	-0.091	AA	0.002	-0.159	AA	0.000	-0.981
rs9862263	**AA**	**0.011**	**-0.035**	**AB**	**0.585**	**-0.225**	**BB**	**1.000**	**-0.549**
rs1562080	AB	0.473	0.052	AA	0.004	0.124	AA	0.009	-0.588
rs1074650	BB	1.000	-0.166	BB	1.000	-0.056	BB	0.997	-0.356
rs12492239	BB	1.000	0.070	BB	0.988	0.189	BB	1.000	-0.454
rs1087894	AA	0.001	0.041	AA	0.003	-0.050	AA	0.012	-0.623
rs1110797	AA	0.006	-0.025	AB	0.579	0.150	AA	0.030	-0.970
rs9848430	BB	1.000	0.109	BB	0.994	0.060	BB	0.989	-0.447
rs1111441	**AA**	**0.000**	**0.208**	**AB**	**0.517**	**-0.018**	**BB**	**0.981**	**-0.618**

rs4685724	AA	0.008	0.030	AA	0.013	-0.007	AA	0.031	-1.084
rs12152235	**AA**	**0.007**	**-0.135**	**AB**	**0.578**	**-0.038**	**BB**	**1.000**	**0.070**
rs7615618	**AA**	**0.000**	**0.033**	**AB**	**0.495**	**-0.047**	**BB**	**1.000**	**-0.284**
rs317588	**BB**	**1.000**	**-0.023**	**AA**	**0.008**	**-0.064**	**AA**	**0.014**	**-1.101**
rs12490386	AA	0.009	0.236	AA	0.003	0.335	AA	0.021	-0.810
rs167601	**BB**	**0.999**	**0.017**	**AB**	**0.540**	**-0.013**	**AA**	**0.005**	**-0.432**
rs317593	**AA**	**0.005**	**0.076**	**BB**	**1.000**	**-0.020**	**BB**	**1.000**	**-0.366**
rs317599	**AA**	**0.010**	**0.180**	**AB**	**0.575**	**0.071**	**BB**	**0.995**	**-0.668**
rs317613	**BB**	**1.000**	**0.082**	**AB**	**0.597**	**-0.014**	**AA**	**0.000**	**-1.042**
rs317616	AB	0.478	0.169	AA	0.006	0.352	AA	0.011	-0.509
rs13099728	AA	0.003	-0.049	AB	0.548	-0.141	AA	0.029	-0.905
rs317623	**BB**	**1.000**	**0.116**	**AB**	**0.555**	**-0.046**	**AA**	**0.016**	**-0.906**
rs6806504	AB	0.518	-0.190	AB	0.521	-0.113	AA	0.064	-0.962
rs6806903	AB	0.470	0.064	AB	0.516	0.012	AA	0.018	-0.660
rs1092733	AB	0.530	-0.053	AB	0.524	-0.051	BB	0.977	-0.523
rs317605	AB	0.499	0.016	AA	0.001	0.121	AA	0.016	-0.906
rs10865894	AB	0.533	-0.204	AB	0.505	-0.114	AA	0.003	-0.926
rs317606	AB	0.471	0.101	AA	0.002	0.296	AA	0.012	-0.572
rs7624815	BB	1.000	0.003	BB	0.998	-0.088	BB	0.990	-0.580
rs1987888	AB	0.493	-0.016	AB	0.515	-0.171	AA	0.005	-0.797
rs1087817	**BB**	**0.999**	**0.045**	**AB**	**0.521**	**-0.187**	**AA**	**0.000**	**-0.483**
rs9877622	AA	0.000	0.062	AA	0.004	-0.015	AA	0.003	-0.313
rs11917349	**BB**	**1.000**	**0.033**	**AB**	**0.536**	**-0.150**	**AA**	**0.062**	**-0.545**
rs17039739	AA	0.010	-0.235	AA	0.013	-0.158	AA	0.011	-0.813
rs317530	AB	0.557	-0.009	BB	1.000	-0.064	BB	1.000	-0.392
rs317528	**BB**	**1.000**	**0.016**	**AB**	**0.594**	**-0.054**	**AA**	**0.015**	**-0.755**
rs17039742	BB	0.995	0.030	BB	0.994	-0.010	BB	1.000	-0.372

Supplementary Table 3. An autosome-specific CNV inheritance matrix that species the conditional probability of copy number in offspring (O0-O4 represent 0 to 4 copies in offspring), given parental copy number (F0-F4 represent 0 to 4 copies in father, and M0-M4 represent 0 to 4 copies in mother, respectively). The parameter e refers to the probability of genome-wide de novo events, and it is treated as a constant for all states.

CNV inheritance matrix for autosomes	F0		F1		F2		F3		F4	
M0	**O0**	1-e	**O0**	0.5*(1-e)	**O0**	0.25*e	**O0**	0.3333*e	**O0**	0.5*e
	O1	0.25*e	**O1**	0.5*(1-e)	**O1**	1-e	**O1**	0.5*(1-e)	**O1**	0.25*(1-e)
	O2	0.25*e	**O2**	0.3333*e	**O2**	0.25*e	**O2**	0.5*(1-e)	**O2**	0.5*(1-e)
	O3	0.25*e	**O3**	0.3333*e	**O3**	0.25*e	**O3**	0.3333*e	**O3**	0.25*(1-e)
	O4	0.25*e	**O4**	0.3333*e	**O4**	0.25*e	**O4**	0.3333*e	**O4**	0.5*e
M1	**O0**	0.5*(1-e)	**O0**	0.25*(1-e)	**O0**	0.3333*e	**O0**	0.5*e	**O0**	e
	O1	0.5*(1-e)	**O1**	0.5*(1-e)	**O1**	0.5*(1-e)	**O1**	0.25*(1-e)	**O1**	0.125*(1-e)
	O2	0.3333*e	**O2**	0.25*(1-e)	**O2**	0.5*(1-e)	**O2**	0.5*(1-e)	**O2**	0.375*(1-e)
	O3	0.3333*e	**O3**	0.5*e	**O3**	0.3333*e	**O3**	0.25*(1-e)	**O3**	0.375*(1-e)
	O4	0.3333*e	**O4**	0.5*e	**O4**	0.3333*e	**O4**	0.5*e	**O4**	0.125*(1-e)
M2	**O0**	0.25*e	**O0**	0.3333*e	**O0**	0.25*e	**O0**	0.3333*e	**O0**	0.5*e
	O1	1-e	**O1**	0.5*(1-e)	**O1**	0.25*e	**O1**	0.3333*e	**O1**	0.5*e
	O2	0.25*e	**O2**	0.5*(1-e)	**O2**	1-e	**O2**	0.5*(1-e)	**O2**	0.25*(1-e)
	O3	0.25*e	**O3**	0.3333*e	**O3**	0.25*e	**O3**	0.5*(1-e)	**O3**	0.5*(1-e)
	O4	0.25*e	**O4**	0.3333*e	**O4**	0.25*e	**O4**	0.3333*e	**O4**	0.25*(1-e)
M3	**O0**	0.3333*e	**O0**	0.5*e	**O0**	0.3333*e	**O0**	0.5*e	**O0**	0.5*e
	O1	0.5*(1-e)	**O1**	0.25*(1-e)	**O1**	0.3333*e	**O1**	0.5*e	**O1**	0.5*e
	O2	0.5*(1-e)	**O2**	0.5*(1-e)	**O2**	0.5*(1-e)	**O2**	0.25*(1-e)	**O2**	0.125*(1-e)
	O3	0.3333*e	**O3**	0.25*(1-e)	**O3**	0.5*(1-e)	**O3**	0.5*(1-e)	**O3**	0.375*(1-e)
	O4	0.3333*e	**O4**	0.5*e	**O4**	0.3333*e	**O4**	0.25*(1-e)	**O4**	0.5*(1-e)
M4	**O0**	0.5*e	**O0**	e	**O0**	0.5*e	**O0**	0.5*e	**O0**	0.5*e
	O1	0.25*(1-e)	**O1**	0.125*(1-e)	**O1**	0.5*e	**O1**	0.5*e	**O1**	0.5*e
	O2	0.5*(1-e)	**O2**	0.375*(1-e)	**O2**	0.25*(1-e)	**O2**	0.125*(1-e)	**O2**	0.0625*(1-e)
	O3	0.25*(1-e)	**O3**	0.375*(1-e)	**O3**	0.5*(1-e)	**O3**	0.375*(1-e)	**O3**	0.25*(1-e)
	O4	0.5*e	**O4**	0.125*(1-e)	**O4**	0.25*(1-e)	**O4**	0.5*(1-e)	**O4**	0.6875*(1-e)

Supplementary Table 4. A male chromosome X specific CNV inheritance matrix that species the conditional probability of copy number in male offspring (O0-O4 represent 0 to 4 copies in offspring), given parental copy number (F0-F4 represent 0 to 4 copies in father, and M0-M4 represent 0 to 4 copies in mother, respectively). The parameter e refers to the probability of genome-wide de novo events, and it is treated as a constant for all states.

CNV inheritance matrix for male offspring chrX	F0		F1		F2		F3		F4	
M0	**O0**	1-e	**O0**	0.25*e	**O0**	0.25*e	**O0**	0.25*e	**O0**	0.25*e
	O1	0.25*e	**O1**	1-e	**O1**	0.25*e	**O1**	0.25*e	**O1**	0.25*e
	O2	0.25*e	**O2**	0.25*e	**O2**	1-e	**O2**	0.25*e	**O2**	0.25*e
	O3	0.25*e	**O3**	0.25*e	**O3**	0.25*e	**O3**	1-e	**O3**	0.25*e
	O4	0.25*e	**O4**	0.25*e	**O4**	0.25*e	**O4**	0.25*e	**O4**	1-e
M1	**O0**	0.5*(1-e)	**O0**	0.3333*e	**O0**	0.3333*e	**O0**	0.3333*e	**O0**	0.25*e
	O1	0.5*(1-e)	**O1**	0.5*(1-e)	**O1**	0.3333*e	**O1**	0.3333*e	**O1**	0.25*e
	O2	0.3333*e	**O2**	0.5*(1-e)	**O2**	0.5*(1-e)	**O2**	0.3333*e	**O2**	0.25*e
	O3	0.3333*e	**O3**	0.3333*e	**O3**	0.5*(1-e)	**O3**	0.5*(1-e)	**O3**	0.25*e
	O4	0.3333*e	**O4**	0.3333*e	**O4**	0.3333*e	**O4**	0.5*(1-e)	**O4**	1-e
M2	**O0**	0.25*e	**O0**	0.25*e	**O0**	0.25*e	**O0**	0.25*e	**O0**	0.25*e
	O1	1-e	**O1**	0.25*e	**O1**	0.25*e	**O1**	0.25*e	**O1**	0.25*e
	O2	0.25*e	**O2**	1-e	**O2**	0.25*e	**O2**	0.25*e	**O2**	0.25*e
	O3	0.25*e	**O3**	0.25*e	**O3**	1-e	**O3**	0.25*e	**O3**	0.25*e
	O4	0.25*e	**O4**	0.25*e	**O4**	0.25*e	**O4**	1-e	**O4**	1-e
M3	**O0**	0.3333*e	**O0**	0.3333*e	**O0**	0.3333*e	**O0**	0.25*e	**O0**	0.25*e
	O1	0.5*(1-e)	**O1**	0.3333*e	**O1**	0.3333*e	**O1**	0.25*e	**O1**	0.25*e
	O2	0.5*(1-e)	**O2**	0.5*(1-e)	**O2**	0.3333*e	**O2**	0.25*e	**O2**	0.25*e
	O3	0.3333*e	**O3**	0.5*(1-e)	**O3**	0.5*(1-e)	**O3**	0.25*e	**O3**	0.25*e
	O4	0.3333*e	**O4**	0.3333*e	**O4**	0.5*(1-e)	**O4**	1-e	**O4**	1-e
M4	**O0**	0.5*e	**O0**	0.5*e	**O0**	0.3333*e	**O0**	0.25*e	**O0**	0.25*e
	O1	0.25*(1-e)	**O1**	0.5*e	**O1**	0.3333*e	**O1**	0.25*e	**O1**	0.25*e
	O2	0.5*(1-e)	**O2**	0.25*(1-e)	**O2**	0.3333*e	**O2**	0.25*e	**O2**	0.25*e
	O3	0.25*(1-e)	**O3**	0.5*(1-e)	**O3**	0.25*(1-e)	**O3**	0.25*e	**O3**	0.25*e
	O4	0.5*e	**O4**	0.25*(1-e)	**O4**	0.75*(1-e)	**O4**	1-e	**O4**	1-e

Supplementary Table 5. An female chromosome X specific CNV inheritance matrix that species the conditional probability of copy number in female offspring (O0-O4 represent 0 to 4 copies in offspring), given parental copy number (F0-F4 represent 0 to 4 copies in father, and M0-M4 represent 0 to 4 copies in mother, respectively). The parameter e refers to the probability of genome-wide de novo events, and it is treated as a constant for all states.

CNV inheritance matrix for female offspring chrX	F0		F1		F2		F3		F4	
M0	**O0**	1-e	**O0**	1-e	**O0**	1-e	**O0**	1-e	**O0**	1-e
	O1	0.25*e	**O1**	0.25*e	**O1**	0.25*e	**O1**	0.25*e	**O1**	0.25*e
	O2	0.25*e	**O2**	0.25*e	**O2**	0.25*e	**O2**	0.25*e	**O2**	0.25*e
	O3	0.25*e	**O3**	0.25*e	**O3**	0.25*e	**O3**	0.25*e	**O3**	0.25*e
	O4	0.25*e	**O4**	0.25*e	**O4**	0.25*e	**O4**	0.25*e	**O4**	0.25*e
M1	**O0**	0.5*(1-e)	**O0**	0.5*(1-e)	**O0**	0.5*(1-e)	**O0**	0.5*(1-e)	**O0**	0.5*(1-e)
	O1	0.5*(1-e)	**O1**	0.5*(1-e)	**O1**	0.5*(1-e)	**O1**	0.5*(1-e)	**O1**	0.5*(1-e)
	O2	0.3333*e	**O2**	0.3333*e	**O2**	0.3333*e	**O2**	0.3333*e	**O2**	0.3333*e
	O3	0.3333*e	**O3**	0.3333*e	**O3**	0.3333*e	**O3**	0.3333*e	**O3**	0.3333*e
	O4	0.3333*e	**O4**	0.3333*e	**O4**	0.3333*e	**O4**	0.3333*e	**O4**	0.3333*e
M2	**O0**	0.25*e	**O0**	0.25*e	**O0**	0.25*e	**O0**	0.25*e	**O0**	0.25*e
	O1	1-e	**O1**	1-e	**O1**	1-e	**O1**	1-e	**O1**	1-e
	O2	0.25*e	**O2**	0.25*e	**O2**	0.25*e	**O2**	0.25*e	**O2**	0.25*e
	O3	0.25*e	**O3**	0.25*e	**O3**	0.25*e	**O3**	0.25*e	**O3**	0.25*e
	O4	0.25*e	**O4**	0.25*e	**O4**	0.25*e	**O4**	0.25*e	**O4**	0.25*e
M3	**O0**	0.3333*e	**O0**	0.3333*e	**O0**	0.3333*e	**O0**	0.3333*e	**O0**	0.3333*e
	O1	0.5*(1-e)	**O1**	0.5*(1-e)	**O1**	0.5*(1-e)	**O1**	0.5*(1-e)	**O1**	0.5*(1-e)
	O2	0.5*(1-e)	**O2**	0.5*(1-e)	**O2**	0.5*(1-e)	**O2**	0.5*(1-e)	**O2**	0.5*(1-e)
	O3	0.3333*e	**O3**	0.3333*e	**O3**	0.3333*e	**O3**	0.3333*e	**O3**	0.3333*e
	O4	0.3333*e	**O4**	0.3333*e	**O4**	0.3333*e	**O4**	0.3333*e	**O4**	0.3333*e
M4	**O0**	0.5*e	**O0**	0.5*e	**O0**	0.5*e	**O0**	0.5*e	**O0**	0.5*e
	O1	0.25*(1-e)	**O1**	0.25*(1-e)	**O1**	0.25*(1-e)	**O1**	0.25*(1-e)	**O1**	0.25*(1-e)
	O2	0.5*(1-e)	**O2**	0.5*(1-e)	**O2**	0.5*(1-e)	**O2**	0.5*(1-e)	**O2**	0.5*(1-e)
	O3	0.25*(1-e)	**O3**	0.25*(1-e)	**O3**	0.25*(1-e)	**O3**	0.25*(1-e)	**O3**	0.25*(1-e)
	O4	0.5*e	**O4**	0.5*e	**O4**	0.5*e	**O4**	0.5*e	**O4**	0.5*e