Method article

PeakCNV: A multi-feature ranking algorithm-based tool for genome-wide copy number variation-association study

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Abstract

Copy Number Variation (CNV) refers to a type of structural genomic alteration in which a segment of chromosome is duplicated or deleted. To date, many CNVs have been identified as causative genetic elements for several diseases and phenotypes. However, performing a CNV-based genome-wide association study is challenging due to inconsistency in length and occurrence of CNVs across different individuals under investigation. One of the most efficient strategies to address this issue is building CNV regions (genomic regions in which CNVs are overlapping - CNVRs). However, this approach is susceptible to a high false positive rate due to overlapping and co-occurring of confounding CNVRs with true positive CNVs.

Here, we develop PeakCNV that differentiates false-positive CNVRs from true positives by calculating a new metric, independence ranking score, (IR-score) via a feature ranking approach. We compared the performance of PeakCNV with other current existing tools by carrying out two case studies one using the CNV genotype data for individuals with prostate cancer (194 cases and 2,392 healthy individuals) and the second one for individuals with neurodevelopmental disorders (19,642 cases and 6,451 healthy individuals). Crucially, our benchmarking analyses on prostate cancer cohort indicated that PeakCNV identifies a fewer risk candidate CNVRs with shorter lengths compared to other tools.

1. Introduction

A copy number variation (CNV) is a type of structural change in the genome in which a segment of the genome is amplified or deleted [1]. To date, many CNVs have been reported in association with several phenotypes, traits, and diseases such as different types of cancers and neurodevelopmental disorders (NDD) [2,3]. For instance, duplication of the APP gene caused by a CNV has been shown to be associated with increasing the risk of developing Alzheimer’s disease [4]. The CNV deletion or duplication at 15q11-q13 is linked to the development of Prader-Willi and Angelman syndromes [5]. A CNV deletion at 1q21.1 locus found to be linked with the development of intellectual disability and autism [6]. Another example is a CNV deletion at 2p24.3 locus [7] which is...
associated with increasing the risk for progressive prostate cancer. It has been also reported that the CNV duplication at 14q32.33 genomic region resulting in duplication of IGHG3 gene contributes to high prevalence and mortality of prostate cancer [8].

Identifying risk CNVs can be used as a handle to improve the diagnosis and potentially disease management. To identify risk CNVs, a genome-wide association study needs to be performed on the genomic regions that harbor CNVs. However, one of the major obstacles in a CNV-based genome-wide association study occurs when categorizing CNVs across all cases (individuals with the phenotype of interest) and controls (healthy individuals), which is challenging because CNVs are inconsistent in sequence, size, and genomic coordinates across individuals [9]. To address this issue, one effective approach is to build CNVRs (genomic regions where CNVs are overlapping - CNVRs) prior to identifying those CNVRs statistically associated with the phenotype of interest. There are few tools currently available that utilize the above-mentioned strategy as the cornerstone of their analytic pipelines. The CNVRuler tool [10] provides three different strategies including reciprocal overlap, overlapping regions and segmentation at CNV boundaries to define CNVRs and then estimates the association of each defined CNVR with the phenotype of interest. CNVRuler also offers logistic regression, linear regression, chi-squared, and fisher exact test to perform the association test. PLINK [11] performs a permutation-based one-sided overrepresentation test to carry out a CNVR-phenotype association study and determine the empirical p value for each CNVR. To determine the associated CNVRs with small size in length, Single Nucleotide Association Test CNV (SNATCNV) [12] was proposed. This tool firstly identifies genomic regions in which more often deleted/duplicated among cases than healthy individuals at a single base pair resolution using one-tailed Fisher’s exact test following series of permutations. Then SNATCNV merges the resultant significantly associated base pairs if they are in close proximity to generate associated CNVRs with the phenotype under investigation. CoNVAQ [13] defines CNVRs by segmentation of genomic regions that CNVs overlapping. Then, it determines the statistically significant CNVRs with using a fisher’s exact test.

Nevertheless, these existing approaches are susceptible to high false positive rates due to CNVRs which overlap or co-occur with true positive CNVRs. We here proposed a novel Artificial Intelligence (AI) based tool, PeakCNV, to correct this bias by distinguishing independent CNVR associations from that of confounding CNVRs within the same loci, resulting in identifying more accurate and biological meaningful list of CNVRs associated with phenotype of interest via a genome-wide CNV-phenotype association study.

2. Methods

PeakCNV first builds deletion and duplication CNVR maps for case and control individuals separately. Then to perform the CNV-phenotype association study with the single nucleotide resolution, it assesses the association of each base pair within deletion and duplication CNVR maps and identifies the nucleotides with deletion or duplication that are significantly over-represented for cases over controls. Then, PeakCNV identifies groups of CNVRs which have a similar association significance with their respective phenotype. Next to differentiate false positive CNVRs from true positives within each group (cluster), PeakCNV calculates a new metric, which we termed independence ranking score (IR-score) via a feature ranking algorithm. This score identifies a true positive CNVR when its significance of association is independent of any other overlapping or co-occurring CNVRs within that cluster (independent CNVRs). Lastly, PeakCNV identifies the true positive CNVRs with the highest IR-scores within each cluster as cluster representative CNVRs. The final output of the PeakCNV is a list of CNVRs with a greater probability of being true positives.

2.1. CNVR map building

PeakCNV builds deletion and duplication CNVR maps for cases and controls by mapping the genomic coordinates of deletion and duplication CNVs, respectively (Fig. 1A1). Then, PeakCNV estimates the probability of either deletion or duplication in cases versus controls for each base pair within these maps using a one-tailed fisher’s exact test. This provides every nucleotide (base pair) that are significantly more frequently deleted or duplicated in cases than controls (p value < 0.05 - Fig. 1A2). Then, it merges significant nucleotides where they are in near proximity (within one base pair distance) to identify significant CNVRs. PeakCNV performs this process for the nucleotides that are significantly deleted or duplicated in cases versus controls, separately.

2.2. Clustering process

PeakCNV uses the DBSCAN [15] clustering algorithm to identify groups of CNVRs containing CNVRs with a similar association significance with their respective phenotype. A number of clustering algorithms including hierarchical clustering gap, hierarchical clustering with Silhouette, spectral clustering, model-based clustering, and DBSCAN were tested using the Dunn Index method to determine the best performing clustering algorithm for grouping CNVRs with the similar CNV-phenotype association significance level. We performed the above-mentioned clustering algorithms for grouping CNVRs on chromosome 10 which are significantly (p value < 0.05) associated with PC. We then assessed the efficiency of each clustering algorithm using the Dunn Index method. The results indicated that DBSCAN had the highest efficiency (Supplementary Table 1). DBSCAN requires two hyperparameters including MinPts and ε. MinPts determines the minimum number of CNVRs required to form a cluster. Since, it has been reported that for two dimensional data, DBSCAN performs most efficiently when the hyperparameter MinPts specified to four [14], we used the same value for MinPts hyperparameter. The hyperparameter ε determines the maximum pairwise distance for a set of CNVRs within a given cluster. We identified the optimised value of ε for analysing CNVRs in each chromosome using k-distance plot [14]. The k-distance plot for each chromosome was generated by performing a k-nearest neighbours as the k specified to the same value, we used for MinPts. Two features (CNVR uniqueness and the genomic distance between CNVRs) obtained from paired wise comparison of CNVRs are used as inputs for the clustering step (Fig. 1B and Fig. 2). Uniqueness value refers to the number of case samples covered by a given CNVR after subtracting the common case samples between each pair of CNVRs. This value is obtained through Equation (1).

\[ \text{Uniqueness}(R_i) = S_{R_i} - S_{R_i}\cap R_j \]

where \( R_i \) and \( R_j \) are the two CNVRs, and \( S_{R_i} \) shows the number of similar case samples covered by \( R_i \) and \( R_j \).
2.3. Selection process

In the selection process, PeakCNV identifies the most independent CNVRs within each cluster using the IR-score. Independent CNVRs are those detected in the greatest number of cases while having a minimum co-occurrence of other CNVRs (Fig. 1C1). PeakCNV estimates the IR-score for CNVRs by performing a feature ranking algorithm with two objectives (Equation (2)): summation and correlation of the uniqueness values of CNVRs within a cluster. The first objective indicates the absolute case sample coverage rate by a given CNVR compared to other CNVRs within a cluster, and the second objective indicates the co-occurrence (co-duplication or co-deletion) of a given CNVR with other CNVRs within a cluster. PeakCNV computes IR-score through Equation (2) for any given CNVR within each cluster to determine the most independent CNVRs within each cluster.

\[
IR - Score(R_i) = \sum_{R \in C} \left( \frac{Uniqueness(R_i)}{S_{R_i}} \right) - \sum_{R_i \neq R_j \in C} Corr(Uniqueness(R_i, R_j))
\] (2)

Fig. 1. The schematic workflow of PeakCNV. PeakCNV consists of three main steps; (A) CNVR Map Building, (B) Clustering and (C) Selection Processes. In the CNVR map building step, PeakCNV builds deletion and duplication CNVR maps for case and control individuals by merging the genomic coordinates of deletion and duplication CNVs, respectively (A1). Then, PeakCNV estimates the probability of either deletion or duplication in case over control for each nucleotide within these maps using a one-tailed Fisher's exact test. This provides CNVRs that are significantly (p value < 0.05) more frequently occurring in case than control individuals (A2). In the clustering step, PeakCNV groups CNVRs which have a similar association significance with the phenotype of interest using two features obtained from paired wise comparison of CNVRs: CNVR uniqueness and the genomic distance between CNVRs (B1 and 2). In the selection, PeakCNV differentiates false positive CNVRs from true positives within each cluster by calculating an independence ranking score (IR-score) for each CNVR (C1). Then, PeakCNV merges CNVRs with the highest IR-score in each cluster if they are in near proximity. The final output of the PeakCNV is a list of CNVRs with a greater probability of being true positives (D). CNV and CNVR stand for copy number variation and copy number variation region, respectively.
where C is the number of CNVRs in each cluster, \(R_l\) and \(R_r\) are the two randomly chosen CNVRs from the same cluster for pairwise comparison. \(S_0\) is the total number of samples for \(R_l\) and \(Corr(Uniqueness(R_l, R_r))\) denotes the correlation between the uniqueness values of CNVRs within each cluster, that is calculated by a Kendall’s rank correlation test \[16\].

Lastly, PeakCNV sorts CNVRs within each cluster by IR-score and merges regions with the highest IR-score if they are in proximity (default value is 1000 bp). A pseudo code of the clustering step is presented in Fig. 3.

| Algorithm1. Clustering Process |
|-------------------------------|
| **Input**                    |
| CNV: The significant CNV list |
| \(\text{eps} \): Distance threshold |
| \(\text{Minpts} \): The minimum number of points required to form a cluster (default value is 5) |
| **Output**                   |
| Result: Clustered matrix     |
| 1: Begin algorithm           |
| 2: For each chromosome       |
| 3: Compute Uniqueness matrix contains the number of samples after removing the common samples between each two regions |
| 4: Compute distance matrix between each two regions |
| 5: Combine distance matrix and Uniqueness matrix as the input matrix |
| 6: End for                   |
| 7: For each input in each chr |
| 8: For each unvisited point \(p\) in \(\text{input}_{\text{chr}}\) |
| 9: Mark \(p\) as visited     |
| 10: If \(\text{length}(\text{NeighborPts}) < \text{Minpts}\) |
| 11: Mark \(p\) as Noise      |
| 12: Else                     |
| 13: \(C = \) next cluster    |
| 14: Add \(p\) to cluster \(C\) |
| 15: For each point \(p’\) in \(\text{NeighborPts}\) |
| 16: If \(p’\) is not visited |
| 17: Mark \(p’\) as visited   |
| 18: \(\text{NeighborPts’} = \) find the neighboring points of \(p’\) |
| 19: If \(\text{length}(\text{NeighborPts’}) > = \text{Minpts}\) |
| 20: \(\text{NeighborPts} = \) \(\text{NeighborPts’} \cup \text{NeighborPts}\) |
| 21: End if                   |
| 22: End if                   |
| 23: If \(p’\) is not yet member of any cluster |
| 24: Add \(p’\) to cluster \(C\) |
| 25: End if                   |
| 26: End                      |
| 27: End                      |
| 28: End                      |
| 29: End                      |
| 30: Return clustered matrix as the result |
| 31: End                      |
| 32: End algorithm            |

### Algorithm2. Selection Process

| **Input** | Result: CNVs with their clusters |
|-----------|---------------------------------|
| Threshold: maximum distance for merging CNVRs (default value:1000 bp) |
| **Output** | Final list: Selected CNV regions |
| 1: Begin algorithm |
| 2: For each chromosome |
| 3: \(C = \) number of clusters for each chromosome |
| 4: For each \(c_i\) in \(C\) |
| 5: For each region, in \(c_i\) |
| 6: Calculate score for each region using Equation (2). |
| 7: End for |
| 8: End for |
| 9: Sort regions based on the score |
| 10: Best region = region with maximum score |
| 11: For each region in \(C\) |
| 12: If \(\text{distance}(\text{Bestregion}, \text{region}) < \text{Threshold}\) |
| 13: \(\text{Start}_{\text{CNV}} = \text{Start}_{\text{Bestregion}}\) |
| 14: \(\text{End}_{\text{CNV}} = \text{End}_{\text{region}}\) |
| 15: End If |
| 16: End for |
| 17: End for |
| 18: Return Best region for each \(C_i\) |
| 19: End For |
| 20: End algorithm |

### 3. Results and discussion

We validated the capability of PeakCNV in identifying more accurate and biological meaningful pathogenic CNVRs by performing three case studies. In the first case study, we assessed the performance of PeakCNV by analyzing a simulated ground truth CNV genotype data. We also compared the performance of PeakCNV in identifying pathogenic CNVRs for PC (case study-two) and NDD (case study-three) to that of other currently available tools; SNATCNV, PLINK, CoNVaQ and CNVRuler. SNATCNV was executed with the default parameters of “indvbased” mode, which returns significant CNVRs using a one-tailed Fisher’s exact test. PLINK v1.9 was performed with “mperm” mode which identifies statistically significant CNVRs by providing empirical \(p\) values based on 50,000 null permutations. The CoNVaQ was executed in “statistical model” mode which uses a Fisher’s exact test to identify significant CNVRs. The CNVRuler was carried out with “CNVR method” and “logistic regression” settings. To discriminate the significantly associated CNVRs with their respective phenotype, a \(p\) value < 0.05 was used as the threshold for statistical significance for the output of all above mentioned tools.

To interrogate and compare the biological relevance of identified risk CNVRs by our newly developed tool and other available tools, we identified genes which overlapped with identified CNVRs (CNVgenes). The reference gene list that we used here is the combination of FANTOM5 \[17\], Ensembl \[18\] and GENCODE \[19\] gene annotation files for hg19 genome assembly to curate a comprehensive reference gene list. The FANTOM5 gene annotation file was
used as the backbone of our reference gene list, but when the gene annotation was absent from FANTOM5 these were acquired from Ensembl and GENCODE. The final reference gene list contained 82,539 genes including 58,000, 24,501 and 38 genes from FANTOM5, Ensembl and GENCODE, respectively (Supplementary Table 1).

Then to identify the list of CNV genes, we search for CNVRs and genes with overlapping genomic coordinates using bedtools v2.30.0 [20].

3.1. Case study-one: Simulated CNV genotype dataset

The ground truth simulated dataset contains the genotype data (genomic coordinate) of 29,856 number CNVs (14,275 deletion and 15,581 duplication types) for 750 case and 750 control samples. We first examined the distribution of both frequency and size of CNVs from multiple real datasets (experimentally identified CNVs) [21–23] to identify the structure underlying the CNV genotype data. According to these two obtained distributions, we generated a random set of genomic coordinates (10,000 genomic regions as CNV genomic coordinates pool) using “random” function of the bedtools package to synthesize a simulated dataset which mimics the real data architecture and structure. We took advantage of a hypergeometric distribution model to identify a set of high confident odds ratios (case to control ratio) for true and false associated CNVRs. We defined 2.3/C20 case-to-control ratio as a cut-off for true associated CNVRs. The cut-off for false associated CNVRs defined as ≥ 0.42 case-to-control ratio. Based on these criteria we randomly selected 34,663 CNVs from CNV genomic coordinate pool. The simulated dataset contained 20 true positive phenotype-associated CNVRs (including 10 case enriched deletion-CNVRs and 10 case enriched duplication-CNVRs) and 20 false phenotype-associated CNVRs (including 10 control enriched deletion-CNVRs and 10 control enriched duplication-CNVRs). Application of PeakCNV on this simulated dataset showed that PeakCNV identifies true associated CNVRs with the 82% accuracy, 86% precision, 89% recall and 86% F-measure, respectively. The simulated dataset is provided in Supplementary Table 1.

3.2. Case study-two: Prostate cancer (PC)

To identify CNVRs associated with susceptibility to PC, the genotype data for 11,564 CNVs (3625 deletions and 7939 duplications) from 194 patients with PC were obtained from the International Cancer Genome Consortium [21]. The CNV genotype data for 2,392 healthy individuals were also obtained from the 1000 Genomes Project [22] containing the genomic coordinates for 32,449 CNVs (22,318 deletions and 10,131 duplications). The list of CNVs used in this study is also provided in Supplementary Table 2. Fig. 4A indicates the statistically significant (p value < 0.05) CNVRs (both deletion and duplication CNVRs) for PC that were identified

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**Algorithm 1. Clustering Process**

```
Input
CNV: The significant CNV list
eps: Distance threshold
Minpts: The minimum number of points required to form a cluster (default value is 5)

Output
Result: Clustered matrix

1: Begin algorithm
2: For each chromosome
3: Compute Uniqueness matrix contains the number of samples after removing the common samples between each two regions.
4: Compute distance matrix between each two regions
5: Combine distance matrix and Uniqueness matrix as the input matrix
6: End for
7: For each input in each chr
8: For each unvisited point p in input
9: Mark p as visited
10: NeighborPts = find the neighboring points of p
11: If (length(NeighborPts) < Minpts)
12: Mark p as Noise
13: Else
14: C = next cluster
15: Add p to cluster C
16: For each point p’ in NeighborPts
17: If p’ is not visited
18: Mark p’ as visited
19: NeighborPts’ = find the neighboring points of p
20: If (length(NeighborPts’) >= Minpts)
21: NeighborPts = NeighborPts’ ∪ NeighborPts
22: End If
23: If p’ is not yet member of any cluster
24: Add p’ to cluster C
25: End If
26: End If
27: End for
28: End if
29: End for
30: Return clustered matrix as the result
31: End for
32: End algorithm
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Fig. 2. The pseudo-code for the clustering step. First, the genomic distance and uniqueness value for each CNVR was calculated in a pairwise comparison with other CNVRs (lines 2–6). Then, values of these two features for each CNVR were merged to be used as an input in the clustering step (lines 7–31).
by PeakCNV and other tools. The risk CNVs identified by PeakCNV and other tools (SNATCNV, PLINK, CoNVaQ, and CNVRuler) for PC are provided in Supplementary Table 3. Fig. 4A also shows that clearly, the risk CNVRs identified by PeakCNV are less noisy (higher rate of true positive than false positive hits) compared to other tested tools. PeakCNV identified 291 risk CNVRs for PC with a total length of 2661.43 Mbp (Fig. 4B). Although PeakCNV identified a fewer number of risk-CNVRs with a shorter length for PC compared to other tools, these risk-CNVRs cover a greater proportion of cases over controls (Fig. 4C). Risk CNVRs identified by PeakCNV for PC had 2.05, 1.14 and 2.04 case over control coverage rate (case-to-control ratio) for duplication, deletion and total (both duplication and deletion together) risk CNVRs which are 1.46, 1.44 and 1.19 times greater than the highest case-control ratio of risk-CNVRs identified by other tools. The list of CNVgenes identified by PeakCNV and other tools for PC is also provided in Supplementary Table 4.

3.3. Case study-three: Neurodevelopmental disorders (NDD)

The CNV genotype data for 47,143 (26,546 deletions and 20,597 duplications) and 24,859 (14,025 deletions and 10,834 duplications) CNVs for 19,644 individuals with different types of NDD and 6,452 healthy individuals was obtained from AutDB database (https://mindspec.org/autdb; download date: Sep 2018) [23] that contains multiple large CNV datasets (with different microarray versions and different 'individual-level' CNV callers). To validate the performance of PeakCNV and other tools tested here in identifying meaningful NDD-associated CNVRs; a) CNV-affected genes (genes that overlap with identified CNVRs - CNVgenes) were determined, then b) a list of nervous system specific expressing genes was used to assess the relative biological importance of identified CNVgenes within the NDD pathogenic contexts [24], and lastly c) the Clinical Genomic Database [25] was used as a source of pathogenic genes for neurological disorders to assess the association of identified CNVgenes with potentially relevant NDD pathogenic molecular processes.

Fig. 5A indicates the statistically significant (p value < 0.05) CNVRs (both deletion and duplication CNVRs) for NDD that were identified by PeakCNV and other tools. The risk CNVs identified by PeakCNV and other tools (SNATCNV, PLINK, CoNVaQ and CNVRuler) for NDD are provided in Supplementary Table 5. Fig. 5A also shows that clearly the risk CNVRs identified by PeakCNV are less noisy (higher rate of true positive than false positive hits) compared to other tested tools. PeakCNV identified 52 CNVRs for NDD with a total length of 58.56 Mbp (Fig. 5B). PeakCNV identified a fewer number of risk-CNVRs with a shorter length for NDD compared to other tools. However, these risk-CNVRs cover a
greater proportion of cases over controls (Fig. 5B). Risk CNVRs identified by PeaKCNV had 4.07 case over control coverage rate (case-to-control ratio) for NDD, which are 1.07 times greater than the highest case-control ratio of risk-CNVRs identified by other tools. Then, we identified CNV-affected genes with the similar strategy to PC. The same analysis for CNV-affected genes in PC was performed.

We then estimated the enrichment of CNV genes identified by PeakCNV and other tools for the 508 NDD-related genes (acquired from the Clinical Genomic Database and provided in Supplementary Table 6,7) using Equation (3).

$$\text{Enrichment for NDD} = \frac{\# \text{CNV affected coding genes overlapping with NDD associated coding genes}}{\# \text{CNV affected coding genes}} 
\times \frac{\# \text{NDD associated coding genes}}{\# \text{coding genes}}$$

(3)

The result shows that from 1,746 NDD risk CNV genes identified by PeakCNV, 321 genes were putatively pathogenic for neurological disorders (representation factor 1.14, p value < 0.001), which is 1.21 times greater than the highest over-representation obtained by other tools (Fig. 5f-h).

We also identified the brain-specific expressing genes (BSG) using our previously published approach, with some modifications. Briefly, the expression data of 59,111 number genes from 1,897 samples related to 347 cells and tissues was obtained from FANTOM5. Then, for any given gene we first excluded samples with an expression level of less than one counts per million reads mapped (CPM), then sorted the remaining samples in descending order by their expression level. We then determined a gene as a BSG if the brain related samples were over-represented with p value threshold <0.001 for the top ranked samples (Supplementary Table 8). To estimate the enrichment of CNV genes identified by different methods for BSGs, we used Equation (4). The list of BSG is provided in Supplementary Table 9.

$$\text{Enrichment for BSG list} = \frac{\# \text{CNV affected genes overlapping with BSG}}{\# \text{CNV affected genes}} 
\times \frac{\# \text{All expressing genes (CPM more than 1CPM)}}{\# \text{All expressing genes (CPM more than 1CPM)}}$$

(4)

PeakCNV identified a greater number of CNV genes that are dominantly expressed in the NDD relevant pathogenic contexts (nervous system) compared to other tools (24 out of 831 CNV genes, representation factor 1.15, p value < 0.001), which is 1.07 times greater than the highest enrichment obtained by other tools (Fig. 5I-K).

4. Conclusion

The current existing tools for performing a CNVR-phenotype association study fall short to generate a false positive free list of CNVRs associated with the phenotype of interest. To address this issue, in the present study we developed PeakCNV, an AI-based tool to filter out false positive hits and keep true positive candidate CNVRs. This can enhance the efficiency of downstream analyses for diagnosis or purposes significantly. The aim of the proposed method is to identify associated CNVRs with disease using two new objectives including genomic distance and uniqueness. The results of benchmarking analysis showed that PeakCNV improves the CNVR based CNV-phenotype association study by correcting the biases arising from the overlapping and co-occurrence of confounding CNVRs, and therefore outperforms other currently existing tools by identifying more biologically meaningful candidate CNVRs.
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Authors’ contributions

HAR and ML conceived the idea and HAR supervised the study. ML designed and implemented the PeakCNV tool. ML analyzed the results with the assistance from AA. ML generated all Supplementary Figures and Tables with the assistance from AA. ML and AA generated Figure 1. All authors contributed to the discussions. AA drafted the manuscript with the assistance from ML and HAR. HAR, NL and AB revised the manuscript. NL helped with proof reading, simulation analysis, and improving the efficiency of the toolset. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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Appendix A. Supplementary data

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