

LDBlockShow

Manual

Visualizing linkage disequilibrium and haplotype blocks based on variant call format files

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1. Introduction

LDBlockShow is a fast and effective tool to generate linkage disequilibrium (LD) heatmap from VCF files. It is more time and memory saving than other current tools. LDBlockShow can generate the plots of LD heatmap and interested statistics or annotation results simultaneously. In addition, it also supports subgroup analysis.

2. Download and Install

2.1 Download website

<https://github.com/BGI-shenzhen/LDBlockShow/>

2.2 Pre-install

LDBlockshow is for Linux/Unix/macOS only. Before installing, please make sure the following pre-requirements are ready to use.

- 1) g++ : g++ with --std=c++11 > 4.8+ (<https://gcc.gnu.org/>) is recommended
- 2) zlib : zlib > 1.2.3 (<https://zlib.net/>) is recommended
- 3) Perl: The SVG.pm (<https://metacpan.org/release/SVG>) in Perl should be installed. LDBlockShow uses this module to plot figures. We have provided a built-in SVG module in the package.

2.3 Install

Users can install it with the 3 following options:

1) Option 1:

```
git clone https://github.com/BGI-shenzhen/LDBlockShow.git
chmod 755 configure; ./configure;
make;
mv LDBlockShow bin/; # [rm *.o]
```

2) Option 2:

```
tar -zxvf LDBlockShowXXX.tar.gz
cd LDBlockShowXXX;
cd src;
sh make.sh # or in Linux: make ; make clean
../bin/LDBlockShow
```

3) Option 3:

We also have the static compilation version for Linux/Unix, which can be used directly after

un-compression. You can contact me (hewm2008@gmail.com or hewm2008@qq.com) to get it.

Note: If link failed, please try to reinstall the zip library (<https://zlib.net/>).

Note: For mac OS, if plink does no work, please re-download plink for mac OS (<https://www.cog-genomics.org/plink2/>) and put it in the "LDBlockShowXXX/bin" directory.

3. Parameter description

3.1 LDBlockShow

3.1.1 Main parameters

```
[heweiming@cngb-ologin-25 bin]$ ./bin/LDBlockShow
```

```
Usage: LDBlockShow -InVCF <in.vcf.gz> -OutPut <outPrefix> -Region chr1:10000-20000
      -InVCF      <str>      Input SNP VCF Format
      -OutPut     <str>      OutPut File of LD Blocks
      -Region     <str>      In One Region to show LD info svg Figure

      -SeleVar    <int>      Select statistic for deal. 1: D' 2: R^2 3/4:Both [1]
      -SubPop     <str>      SubGroup Sample File List [ALLsample]
      -BlockType  <int>      method to detect Block [beta] [1]
                           1. Block by PLINK (Gabriel method withed D')
                           2. Solid Spine of LD RR/D' 3. Blockcut with self-defined RR/D'
                           4. FixBlock by input blocks files 5. No Block

      -InGWAS     <str>      InPut GWAS Pvalue File (chr site Pvalue)
      -InGFF      <str>      InPut GFF3 file to show Gene CDS and name

      -BlockCut   <float>    'Strong LD' cutoff and ratio for BlockType3 [0.85:0.90]
      -FixBlock   <str>      Input fixed block region
      -MerMinSNPNum <int>    merger color grids when SNPnumber over N[50]

      -help                          Show more Parameters and help [hewm2008 v1.30]
```

-InVCF	The input file in VCF format
-OutPut	The output file directory and output file name prefix (e.g., /path/pop1)
-Region	The defined region to show the LD heatmap (format: chr:start:end)
-SeleVar	The LD measurement (1: D' 2: R^2; 3 or 4: Both measurements will output),

	<p>the default is 1. When combined with GWAS plot and users want to show the LD between the top SNP (assigned by the <code>-TopSite</code> option in the ShowLDSVG program) and other SNPs in the GWAS plot:</p> <p>1 refers that both the heatmap and GWAS plot use D';</p> <p>2 refers that both the heatmap and GWAS plot use R^2;</p> <p>3 refers that the heatmap uses D', the GWAS plot uses R^2;</p> <p>4 refers that the heatmap uses R^2, the GWAS plot uses D'.</p>
<code>-SubPop</code>	A sample list for subgroup analysis
<code>-BlockType</code>	<p>The definition of blocks. The default 1 is called by PLINK¹ to generate the block defined by Gabriel <i>et al.</i>². Solid spine of LD³ is also supported [2]. Users can also define their own cutoff of r^2 and D' for blocks [3] combined with the option of "<code>-BlockCut</code>" or supply their own block region definition [4] combined with the option of "<code>-FixBlock</code>". 5 can be used as input if users prefer to not show the block region.</p>
<code>-InGWAS</code>	The statistics file (e.g., association statistics, but other values such as Tajima's D can also be accepted) for generate plot together with the LD plot. File formatted as: [chr position Pvalue]
<code>-InGFF</code>	Input GFF3 format file for genomic region annotation
<code>-BlockCut</code>	For block type 3, the defined cutoff for strong LD, and the ratio of strong LD SNP in one block. Default is 0.85:0.9. That's, if the user chose D' in the <code>-SeleVar</code> option, then in one block, the ratio of SNP pairs with D' over 0.85 is 0.9.
<code>-FixBlock</code>	For block type 4, users can use this option to supply a self-defined block region. The file contains three columns, including chromosome, block region start position, and block region end position.
<code>-MerMinSNPNum</code>	The minimum SNP number to merge color grids with the same color. Default is 50. Details please see Fig 1 in this manual.
<code>-help</code>	Show more parameters

3.1.2 Other parameters

```
[heweiming@cngb-ologin-25 bin]$ ./bin/LDBlockShow -h
```

More Help document please see the Manual.pdf file

Para [-i] is show for [-InVCF], Para [-o] is show for [-OutPut], Para [-r] is show for [-Region]

-InGenotype	<str>	InPut SNP Genotype Format
-InPlink	<str>	InPut Plink [bed+bim+fam] or [ped+map] file prefix
-MAF	<float>	Min minor allele frequency filter [0.05]
-Het	<float>	Max ratio of het allele filter [0.90]
-Miss	<float>	Max ratio of miss allele filter [0.25]
-TagSNPCut	<float>	'Strong LD' cutoff for TagSNP [0.80]
-OutPng		convert svg 2 png file
-OutPdf		convert svg 2 pdf file

-InGenotype Input file in genotype format. The format of genotype file is as follows:

##CHROM	POS	REF	BJ1	BJ12	BJ13	BJ14	BJ15	BJ3	BJ4	BJ7	BJ8	BJ9	BJ2	BJ10	BJ11	GZ1	GZ10	GZ11													
JXUM01S000021	441956	T	T	-	Y	C	-	-	C	C	-	-	-	C	C	Y	-	-	C	C	-	-	-	-	Y	C	T				
JXUM01S000021	441958	T	T	-	T	T	-	-	T	T	-	-	T	T	T	-	-	T	T	-	-	T	-	T	T	T					
JXUM01S000021	441959	G	G	-	G	G	-	-	G	G	-	G	G	G	G	-	-	G	G	G	-	G	G	-	G	-	G	G	G		
JXUM01S000021	441963	C	C	-	C	C	-	-	C	C	-	C	C	C	C	-	-	C	C	C	-	C	C	-	C	-	C	C	C		
JXUM01S000021	441965	A	A	-	A	A	-	-	A	A	-	A	A	A	A	-	-	A	A	A	-	A	A	-	A	-	A	A	A		
JXUM01S000021	441971	G	G	-	G	G	-	-	G	G	-	G	G	G	G	-	-	G	G	G	-	G	G	-	G	-	G	-	G	G	G
JXUM01S000021	441974	G	G	-	G	G	-	-	G	G	-	G	G	G	G	-	-	G	G	G	-	G	G	-	G	-	G	-	G	G	G

-InPlink	The prefix of input file in PLINK format.
-MAF	Filter SNPs with low minor allele frequency (default ≤ 0.05)
-Het	Filter SNPs with high heterozygosis ratio (default ≥ 0.9)
-Miss	Filter SNPs with high missing rate (default ≥ 0.25)

-TagSNPCut	The LD cutoff for selecting tag SNPs. Default is 0.8.
-OutPng	Convert the SVG file to PNG file
-OutPdf	Convert SVG file to Pdf file.

Note: If users failed to open small SVG files, please use the “-Outpdf” option to use the PDF file. For large SVG files, “-OutPng” can be used to get a relatively small figure file.

3.2 ShowLDSVG

This program is designed for users to optimize the figure (e.g., change colors) generated by LDBlockShow.

3.2.1 Brief parameters

```
./bin/ShowLDSVG
Options
-InPreFix    <s> : InPut Region LD Result Frefix
-OutPut      <s> : OutPut svg file result
-help        : Show more help with more parameter
```

- InPreFix The prefix of input file (i.e., the output file of LDBlockShow)
- OutPut The out file (svg, png and pdf format plot files)
- help More parameters in detail

3.2.2 Detail parameters

- InGWAS The statistics file (e.g., association statistics, but other values such as Tajima's D can also be accepted) for generate plot together with the LD plot. File formatted as: [chr position Pvalue]
- NoLogP By default, the P value from the -InGWAS file will be $-\log_{10}$ transformed, with this option, the P value will not be transformed.
- Cutline The significance cutline of the -InGWAS file.
- TopSite Default is the most significant SNP, can be changed with chr:pos. Using this option, this SNP will be shown in diamond, and the LD between other sites and it will be shown in different colors. Please see Figure 9.
- PointSize Users can use this option (any number over 0) to set the point size.
- SpeSNPName With this option, users can input a file to indicate the names for interested SNPs, these names will be shown in the heatmap.
- ShowGWASSpeSNP Users can use this option together with the file assigned by "-SpeSNPName" to show the names of interested SNPs in GWAS plot.
- InGFF The GFF file for genomic region annotation. By default, the gene name will be shown in the plot;
- NoGeneName Gene name will not be shown in the plot with this option.
- crGene Define the colors of different genomic regions. By default, CDS, intron, UTR and intergenic regions will be shown in #e7298a, light blue, #7570b3, and #a6cee3, respectively.

Parameters to optimize the color of the heatmap:

- crBegin Color for no LD ($R^2/D'=0$) default: white
- crMiddle Color for $R^2/D'=0.5$, default: yellow
- crEnd Color for complete LD ($R^2/D'=1$), default: red

- NumGradien The number of gradients from crBegin to crEnd
- crTagSNP Color for the tag SNP.

./bin/ShowLDSVG -h

- InGWAS <s> : InPut GWAS Pvalue File(chr site Pvalue)
- NoLogP : Do not get the log Pvalue
- Cutline <s> : show the cut off line of Pvalue
- TopSite <n> : InPut the Special Site as the top site (chr:pos)
- PointSize <n> : set the GWAS point size number
- SpeSNPName <s> : In File for Special SNP Name (chr site Name)
- ShowGWASSpeSNP : show Special SNP Name in GWAS plot with [-SpeSNPName]

- InGFF <s> : InPut GFF3 file to show Gene CDS and name
- NoGeneName : No show Gene name,only show stuct
- crGene <s> : InColor for Gene Stuct [CDS:Intron:UTR:Intergenic]
 default: [#e7298a:lightblue:#7570b3:#a6cee3]

- crBegin <s> : In Start Color RGB [255,255,255]
- crMiddle <s> : In Middle Color RGB [240,235,75]
- crEnd <s> : In End Color RGB [255,0,0]
- NumGradien <s> : In Number of gradien of color
- crTagSNP <s> : Color for TagSNP [31,120,180]

- CrGrid <s> : the color of grid edge [white]
- WidthGrid <s> : the edge-width of gird [1]
- NoGrid : No Show the gird edge

- ShowNum : Show the R^2/D' in the heatmap
- NoShowLDist <n> : NoShow long physical distance pairwise[1000000]
- MerMinSNPNum <s> : merge color grids when SNPnumber over N[50]

- OutPng : convert svg 2 png file
- OutPdf : convert svg 2 pdf file
- ResizeH : resize image height; Width be resize in ratio[4096]

Parameters to optimize the grids in the heatmap:

- CrGrid Border color of the grids, default: white
- WidthGrid The width of the border, default = 1
- NoGrid No border

- ShowNum Show the LD measurement value in the grids (not recommended when SNP number is over 50).
- NoShowLDist When the distance between SNPs over this number, their pairwise LD will not be showed in the figure. Default is 10,000,000.
- MerMinSNPNum When number of SNPs over the default 50, ShowLDSVG will merge adjacent same color grids. User can change this number to any integer numbers.
- OutPng Convert the SVG file to PNG file
- OutPdf Convert SVG file to Pdf file.
- ResizeH Set the height of the image (default 4096), which can be used to adjust the resolution for PNG file. The width will be adjusted automatically.

When SNP number is large (e.g., over 100), the output SVG file might be very large. ShowLDSVG will merge adjacent same color grids. Below is an example to compress a SVG file from 26k to 8k. With smaller number of gradients (set by `-NumGradien`), the figure will be compressed to be smaller. `-MerMinSNPNum` is used to set the minimum number of SNPs, that's, if there is more SNPs than this number (default 50), the output SVG will be compressed.

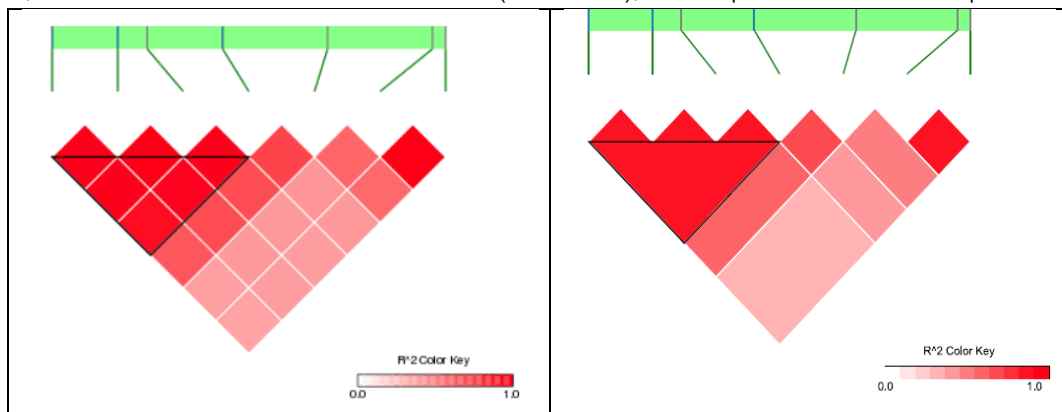


Figure 1. An example to compress LD heatmap with large number of SNPs.

3.3 Output files

Output files	Description
out.site.gz	Remained SNPs after filtering [chr site]
out.blocks.gz	Block file [chr start end block_length SNP_number SNPs]
out.TriangleV.gz	Region Pairwise R^2/D'
out.svg	Output plot in SVG format
out.png	Output plot in png format
out.pdf	Output plot in pdf format

4. Examples

All examples are using R^2 as the LD measurement, but the default measurement is D' .

4.1 Example1: Heatmap + default block generated by PLINK

In the example/Example1 directory, we have provided an example to generate the LD heatmap with the default block generated by PLINK. Example command line is shown in the run.sh file:

```
../bin/LDBlockShow -InVCF Test.vcf.gz -OutPut out -Region chr11:24100000:24200000 -OutPng -SeleVar 2
```

```
sh run.sh
Start Time :
Mon Jun 1 16:30:19 CST 2020
#Detected VCF File is phased file with '|', Read VCF in Phase mode
##Start Region Cal... :Ghir_D11 24100000 24200000; In This Region TotalSNP Number is 7
find blocks...
Start draw... SVG info: SNPNumber :7 , SVG (width,height) = (402.5,297.5)
convert SVG ---> PNG ...
End Time :
Mon Jun 1 16:30:19 CST 2020
```

```
ls
out.blocks.gz out.pdf out.png out.site.gz out.svg out.TriangleV.gz
```

The final plot is shown in Figure 2.

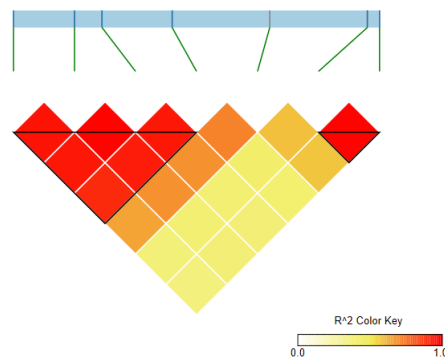


Figure 2. Plot generated in Example 1 using R^2 as the LD measurement. If using D' as the LD measurement, the final plot is shown in Figure 3.

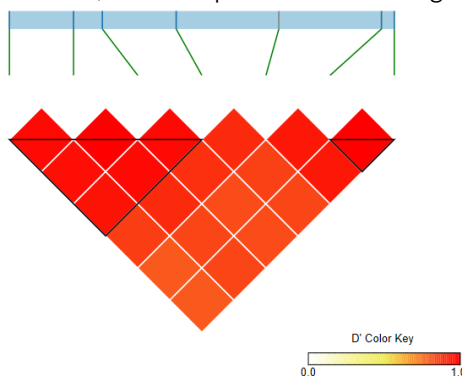


Figure 3. Plot generated in Example 1 using D' as the LD measurement.

4.2 Example 2: Heatmap + block + GWAS

In the example/Example2 directory, we have provided an example to generate the plot with the heatmap, the default block, and GWAS statistics. Example command line is shown in the run.sh file:

```
../bin/LDBlockShow -InVCF ../Example1/Test.vcf.gz -OutPut out -Region chr11:24100000:24200000 -InGWAS gwas.pvalue -SeleVar 2
```

The generated plot is shown in Figure 4. By default, points with $-\log_{10}(P \text{ value})$ larger than 7.3 ($P < 5 \times 10^{-8}$) are shown in red.

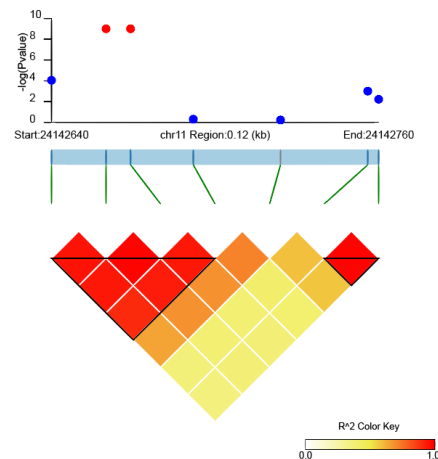


Figure 4. Heatmap + block + GWAS plot in Example 2

Users can further use ShowLDSVG to optimize the plot. Example command line is shown in the run.sh file:

```
../bin/ShowLDSVG -InPrefix out -OutPut out -InGWAS gwas.pvalue -Cutline 7 - ShowNum -PointSize 3
```

The optimized figure is shown in Figure 5.

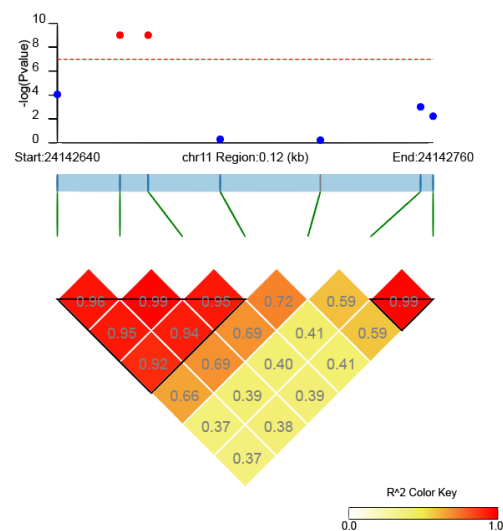


Figure 5. Optimized figure using ShowLDSVG in Example 2.

4.3 Example 3: Heatmap + block + GWAS + Annotation

In the example/Example3 directory, we have provided an example to generate the plot with the heatmap, the default block, GWAS statistics, and genomic annotation. Example command line is shown in the run.sh file:

```
../bin/LDBlockShow -InVCF ../Example1/Test.vcf.gz -OutPut out -InGWAS gwas.pvalue -InGFF In.gff
-Region chr11:24100000:24200000 -OutPng -SeleVar 2
```

The generated plot is shown in Figure 6.

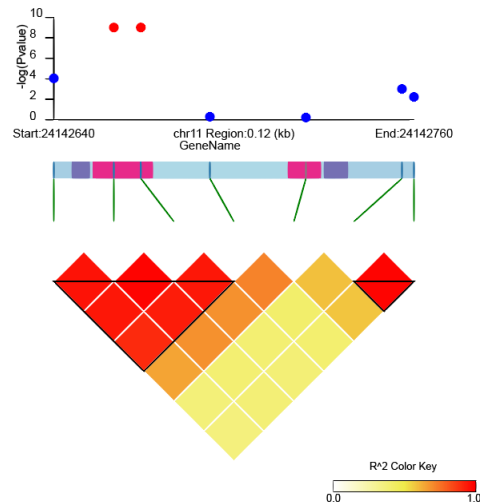


Figure 6. Heatmap + block + GWAS + Annotation plot in Example 3

Users can further use ShowLDSVG to optimize the plot. Example command line is shown in the run.sh file:

```
../bin/ShowLDSVG -InPreFix out -OutPut out -InGWAS gwas.pvalue -Cutline 7 -InGFF In.gff -crGene
yellow:lightblue:pink:orange -showNum
```

The optimized figure is shown in Figure 7.

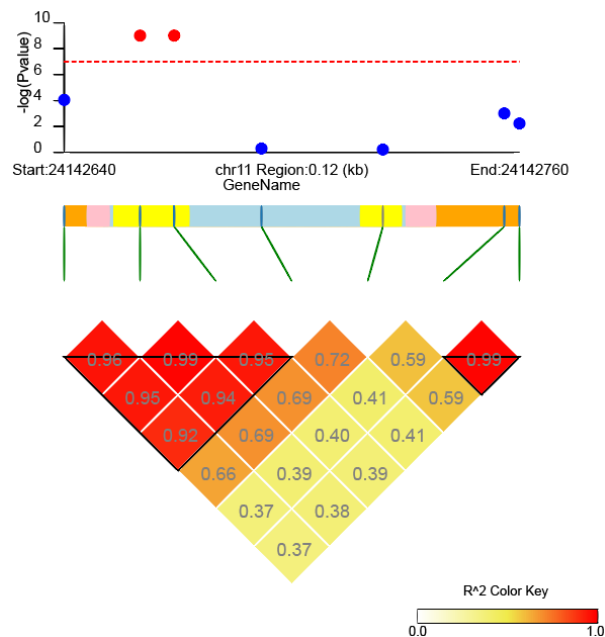


Figure 7. Optimized figure using ShowLDSVG in Example 3.

Users can also show the name of interested SNPs with the following command:

```
../bin/ShowLDSVG -InPreFix out -OutPut out.svg -InGWAS gwas.pvalue -Cutline 7 -InGFF In.gff -crGene
yellow:lightblue:pink:orange -showNum -OutPng -SpeSNPName Spe.snp -ShowGWASSpeSNP
```

The optimized figure is shown in Figure 8.

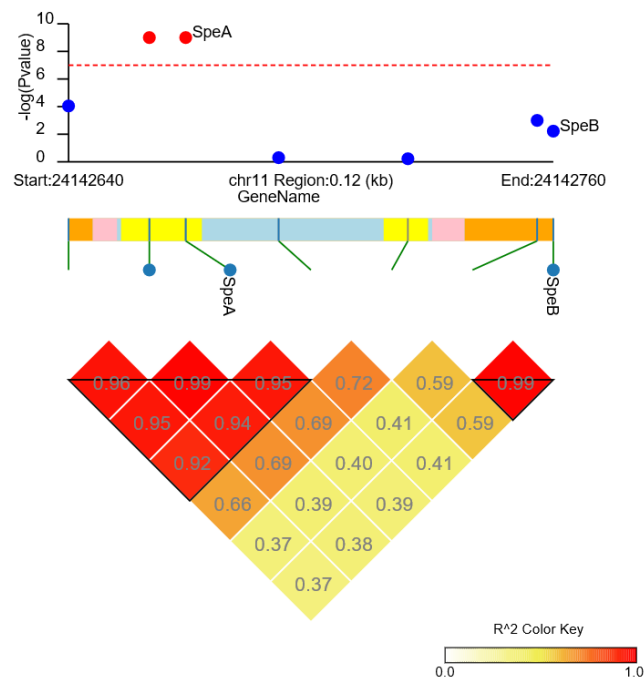


Figure 8. Optimized figure showing names for interested SNPs

4.4 Example 4: Heatmap + Annotation + GWAS plot similar to Locuszoom

Users can also show the LD between the top SNP (assigned by `-TopSite`) and other SNPs in the GWAS plot. The LD measurement can be selected using `-SeleVar`.

```
../bin/LDBlockShow -InVCF ../Example1/Test.vcf.gz -OutPut out -InGWAS ../Example3/gwas.pvalue -
InGFF ../Example3/In.gff -Region chr11:24100000:24200000 -OutPng -SeleVar 3 -TopSite
```

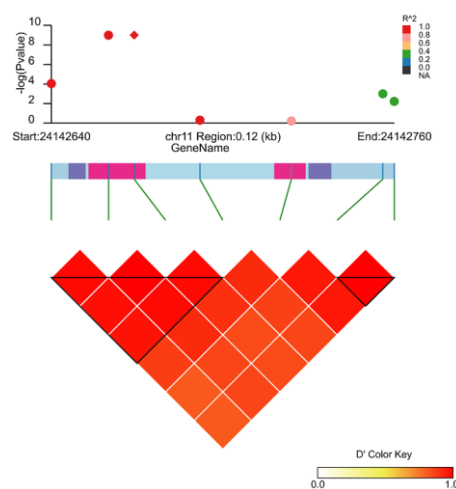


Figure 9. Optimized figure showing the LD between the top SNP and other SNPs in the GWAS plot (Using `-SeleVar 3`, R^2 will be used in the GWAS plot, D' will be used in the heatmap)

5. Advantages

To evaluate the performance of LDBlockShow, we used test VCF files to generate the LD heatmap by using LDBlockShow, Haploview³, LDheatmap⁴ and gpart⁵. The calculated r^2 and D' values of LDBlockShow is the same with other tools. As shown in Figure 10, LDBlockShow is more time and memory saving than other tools.

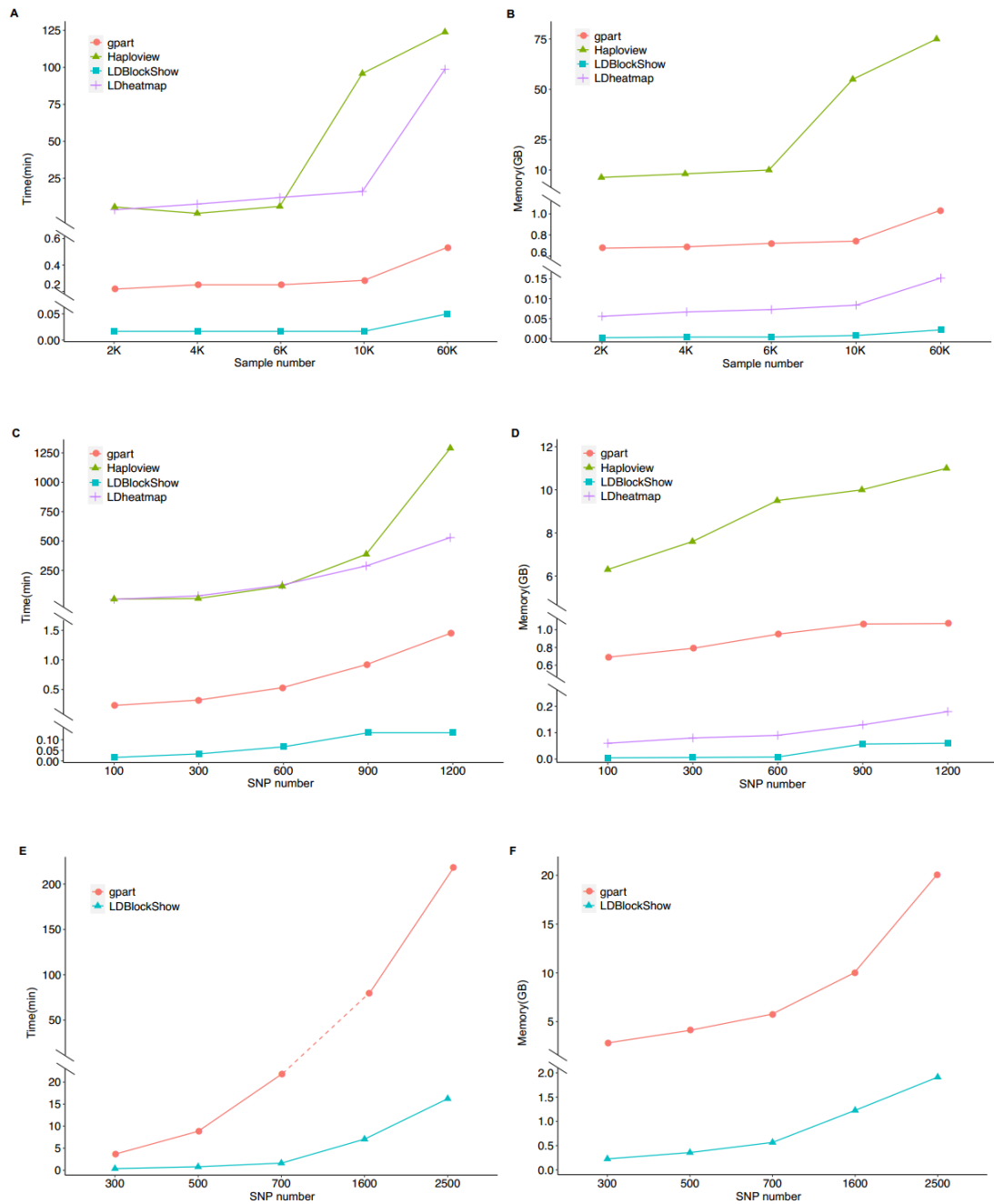


Figure 10. Comparison of computing cost for LDBlockShow, Ldheatmap, Haploview and gpart. CPU time (A) and memory cost (B) for different methods are shown with a fixed SNP number of 100 and sample size ranging from 2,000 to 60,000. CPU time (C) and memory cost (D) for different methods are shown with a fixed sample size of 2,000 and SNP number ranged from 100 to 1,200. When testing datasets in A-D, both

LDBlockShow and gpart finished the analyses within reasonable time and memory. We further tested their performance when handling large dataset. CPU time (E) and memory cost (F) for these two methods are shown with a fixed sample size of 100,000 and SNP number ranged from 300 to 2,500. Computation is performed with one thread of an Intel Xeon CPU E5-2630 v4.

As shown in Table 1, LDBlockShow can generate the plots of LD heatmap and interested statistics or annotation results simultaneously. In addition, LDBlockShow also supports subgroup analysis.

Table 1. Comparison of LDBlockShow with other tools

Performance	LDBlockShow	Haploview	LDheatmap	gpart
Input				
Compressed VCF file	√	×	×	×
Uncompressed VCF file	√	×	×	√
Support subgroup analysis	√	×	×	×
Output				
Visualize additional statistics	√	×	×	×
Visualize genomic annotation	√	×	×	√
Compressed SVG	√	×	×	×
PNG file	√	√	×	√
Block region	√	√	×	√
LD measurement	D'/r^2	D'/r^2	r^2	D'/r^2

6. Frequently ask questions

6.1 How to calculate LD measurement in LDBlockShow

Similar to our previously published tool for LD decay analysis⁶, pairwise LD measurements r^2 and D' were calculated according to previously reported formulas^{7,8}. The calculated r^2 and D' values of LDBlockShow is the same with other tools. For example, as shown in Figure 11, the heat map we generated is the same with LDheatmap.

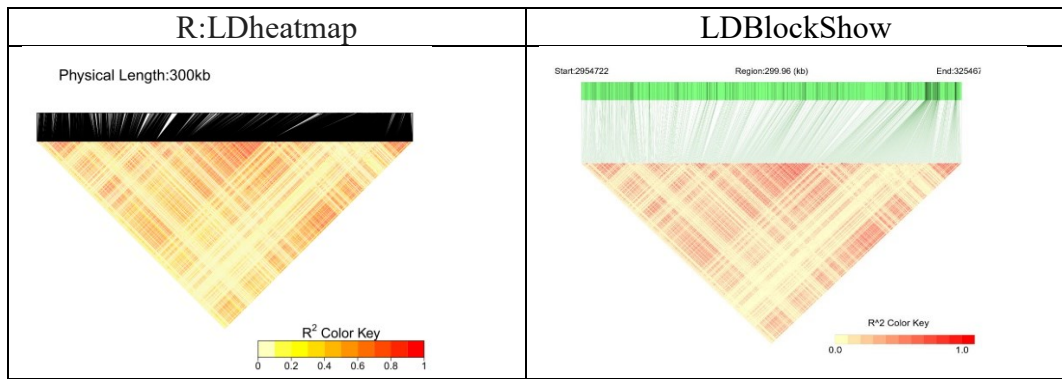


Figure 11. Comparison of the results between LDheatmap and LDBlockShow

6.2 Can another statistics rather than the GWAS results be supported?

Yes, of course. In the file supported by the option `-lnGWAS`, the third column can be defined as any values. With the option `-NoLogP`, the values will not be log transformed.

6.3 Generate not completely triangle?

For large regions ($> 1\text{M}$), LDBlockshow only output heatmaps within 1M. User can use `-NoShowLDist` (default 1000000) to change this. For example, “`-NoShowLDist 2000000`” will output heatmaps within 2M. An example figure is shown in Figure 12.

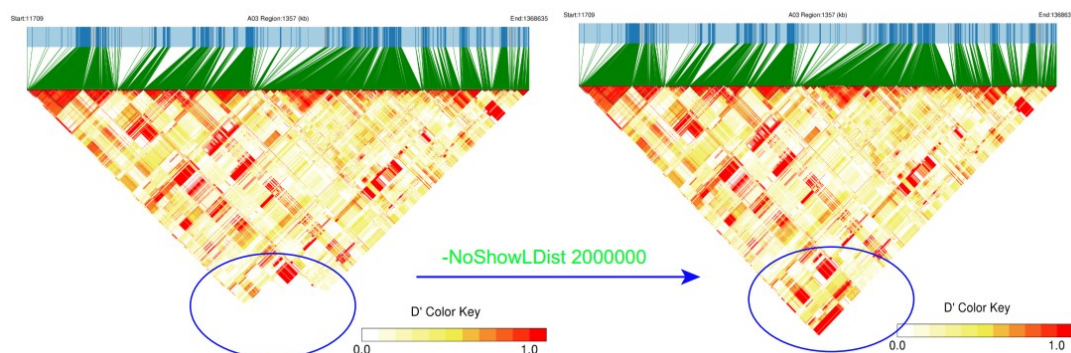


Figure 12. An example to show the full triangle using the “`-NoShowLDist`” option

6.4 Convert SVG to PNG error?

By default, LDBlockShow will use the convert in user's OS to convert SVG to PNG.

However, the "convert" in user's OS might not support converting process well.

Users can use the following command to convert SVG to PNG file:

```
perl LDBlockShow-XXX/bin/svg_kit/svg2xxx.pl xxx.svg -t png --height 50
```

6.5 How to show the names of interested SNPs?

Users can use the option "-ShowGWASSpeSNP" together with the file assigned

by "-SpeSNPName" in ShowLDSVG to show the names of interested SNPs in

GWAS plot. Please see Figure 8 in Example 3 for details.

6.6 How to change the color of the heatmap?

Users can use the "-crMiddle" and "-crEnd" in ShowLDSVG to change the color of the heatmap. For example, if you would to generate a black/white heatmap, just use "-crMiddle 192,192,192 -crEnd 64,64,64".

6.7 The heatmap looks different from the map generated by R:LDheatmap?

The default measurement of LD in LDBlockShow is D' while LDheatmap only use r^2 . Users can use "-SeleVar 2" to change the measurement to r^2 .

6.8 Want to adjust the position of the heatmap?

When showing the name of specific GWAS SNPs, the position of the heatmap will be automatically adjusted according to the length of the SNP name.

However, we have also provided a parameter "-adjHeatmap" in ShowLDSVG for users who want to adjust the position of the heatmap. This parameter accepts

number from -0.25 to 0.25. -0.25-0 refers to move up while 0-0.25 refers to move down. For example, “-adjHeatmap -0.1” corresponds to move the heatmap up 10% of the original canvas.

Feel free to contact me for other requirements!

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