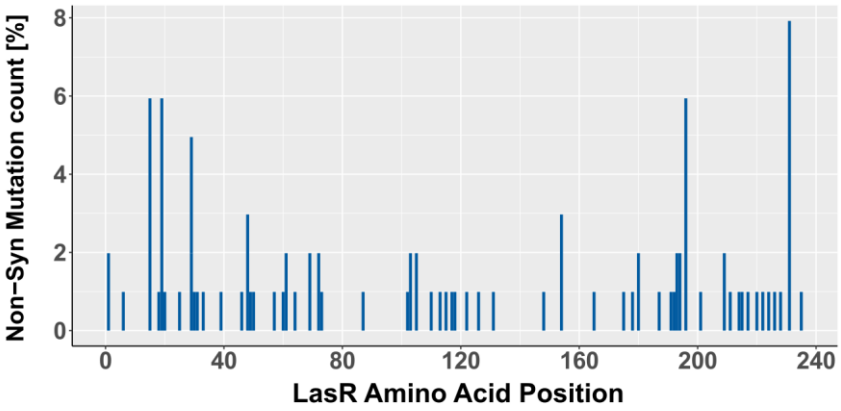
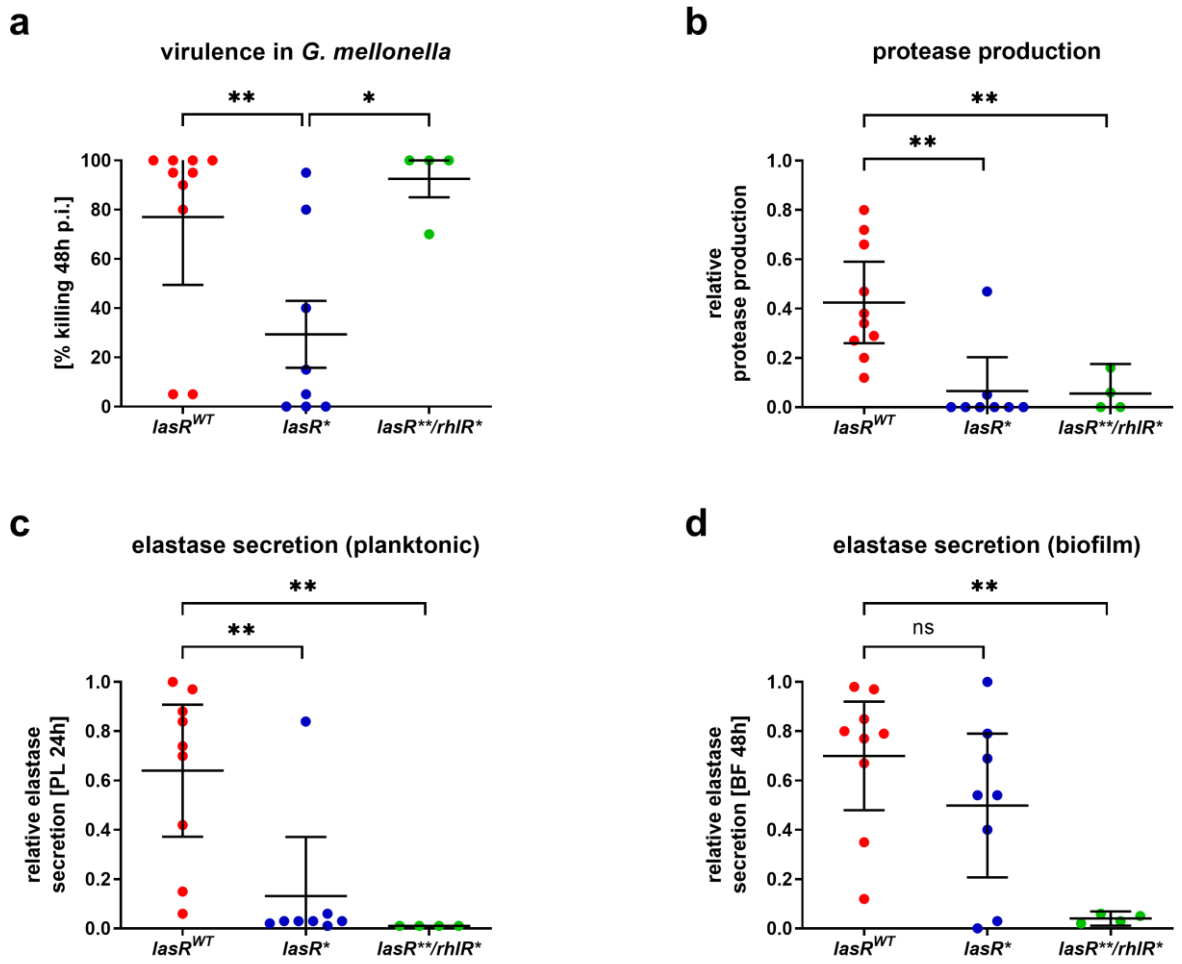
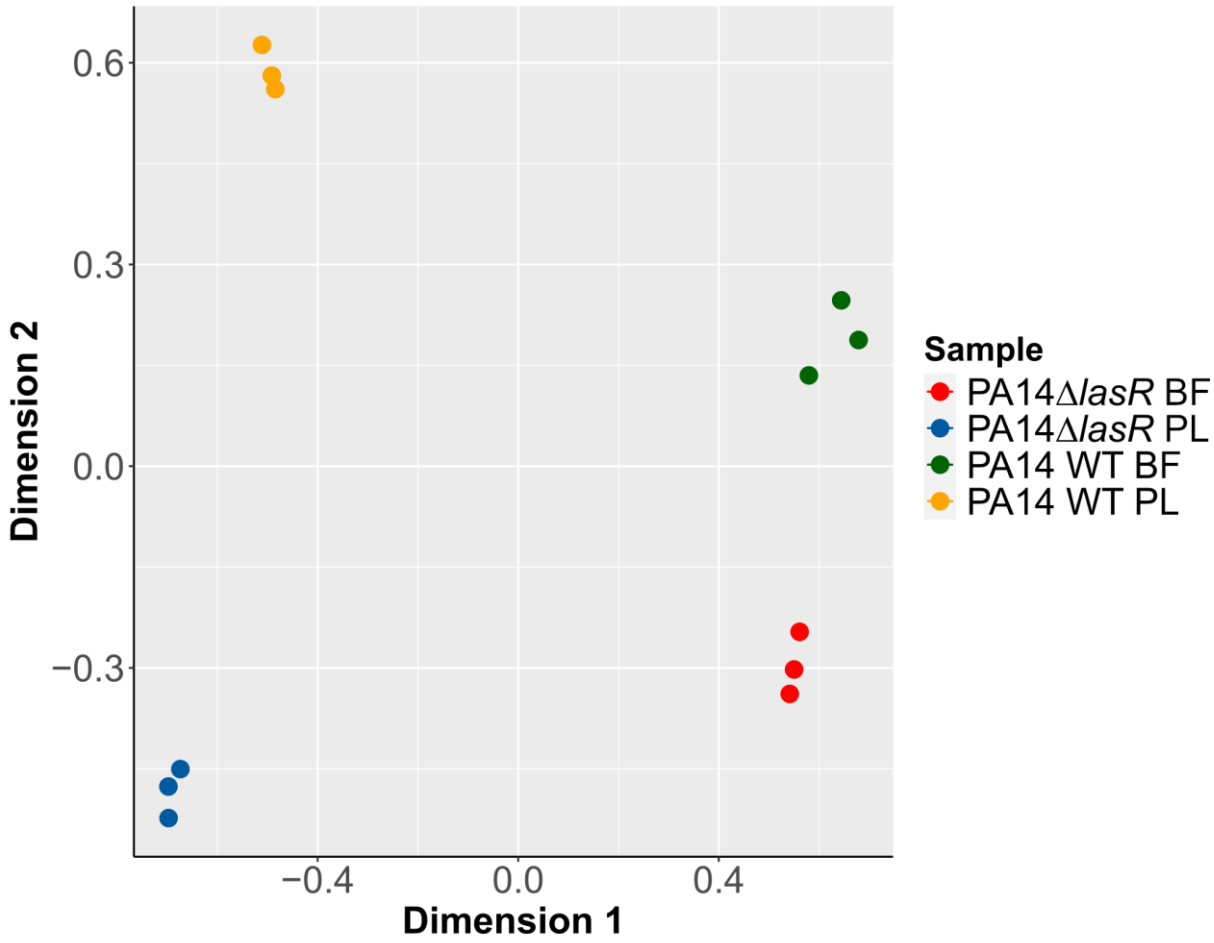
Supplementary Information



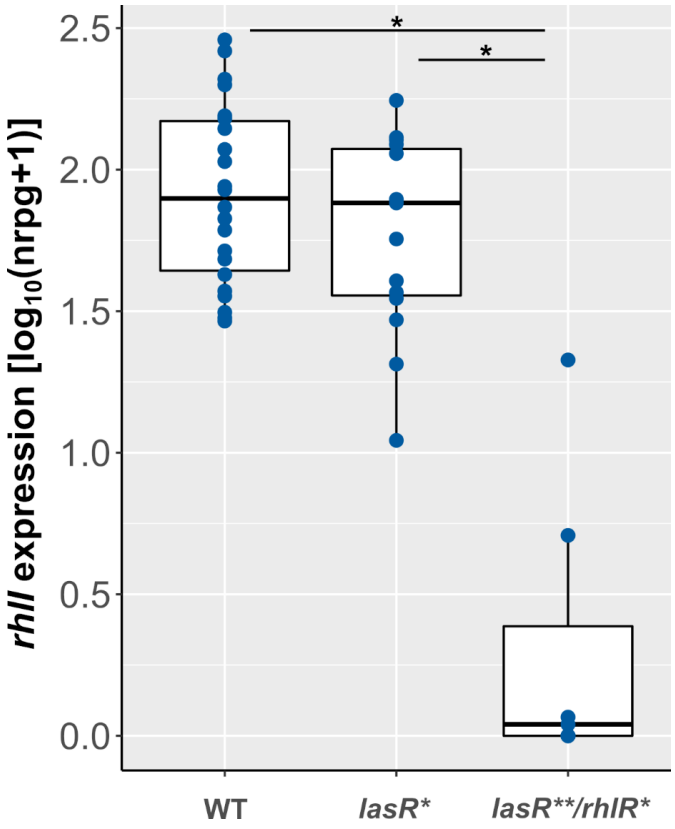
Supplementary Figure 1: Mapping of the non-synonymous amino acid exchanges to the LasR PAO1 and PA14 reference. The *lasR* gene sequences of all 414 clinical isolates that harbored non-synonymous sequence variations within *lasR* were mapped to their amino acid position within the protein. The *lasR* gene sequence of PA14 and PAO1 served as a reference. The relative number of clinical isolates harboring the respective amino acid variation is shown. Insertions/Deletions and premature stop codons were excluded.



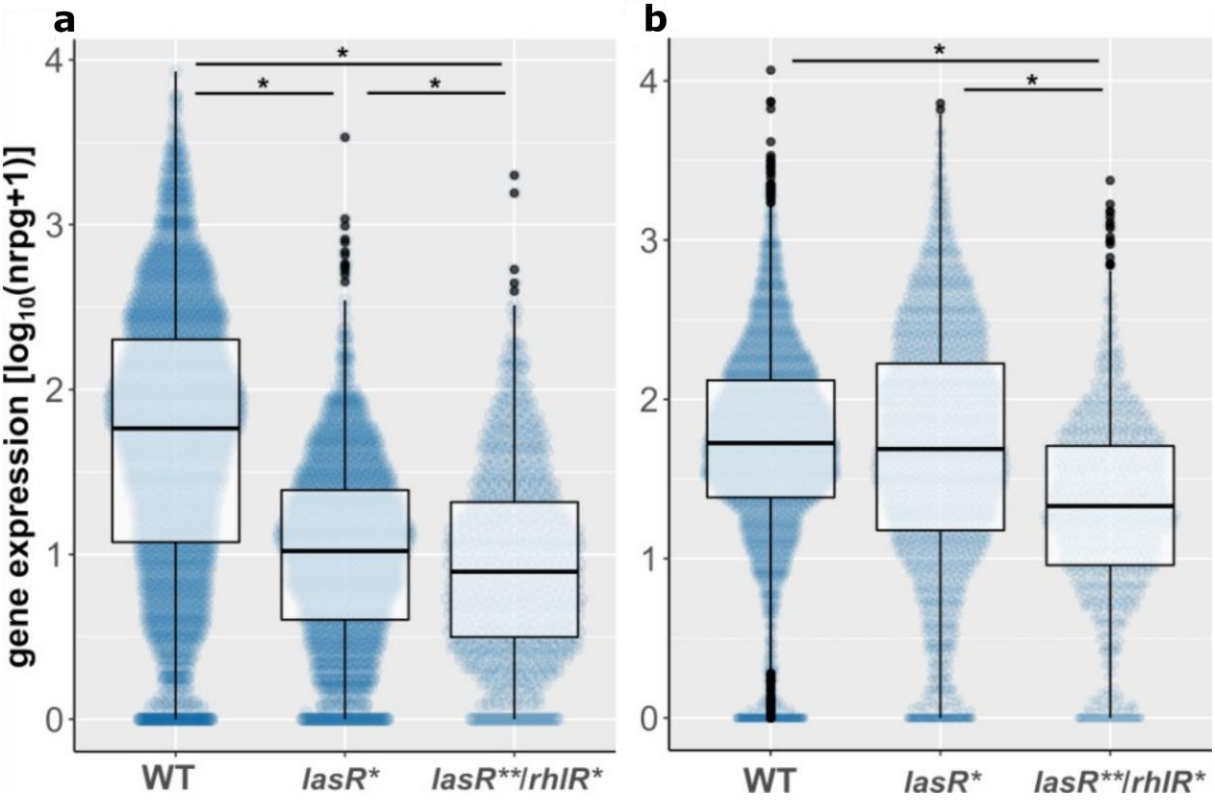
Supplementary Figure 2: Selected clinical isolates exhibit distinct phenotypic characteristics based on their allele status of the *lasR* and *rhlR* genes. Strains with a defective LasR (*lasR**) are significantly less virulent than wild-type isolates (*lasR*^{WT}) or strains lacking functional LasR and RhlR (*lasR***/*rhlR**) in an *in vivo Galleria mellonella* infection model (**a**). Protease production and elastase secretion (planktonic growth) are significantly reduced in *lasR** and *lasR***/*rhlR** isolates compared with *lasR*^{WT} (**b** + **c**). Elastase secretion for *lasR**, but not *lasR***/*rhlR** strains, is restored when cultivated under biofilm growth conditions (**d**). Each dot represents an individual clinical isolate. The solid line represents the mean and the whiskers display the 95 %-confidence intervals. Levels of statistical significance were calculated using Kruskal-Wallis and Mann-Whitney tests and are indicated as ** (*p*-value < 0.01), or * (*p*-value < 0.05).



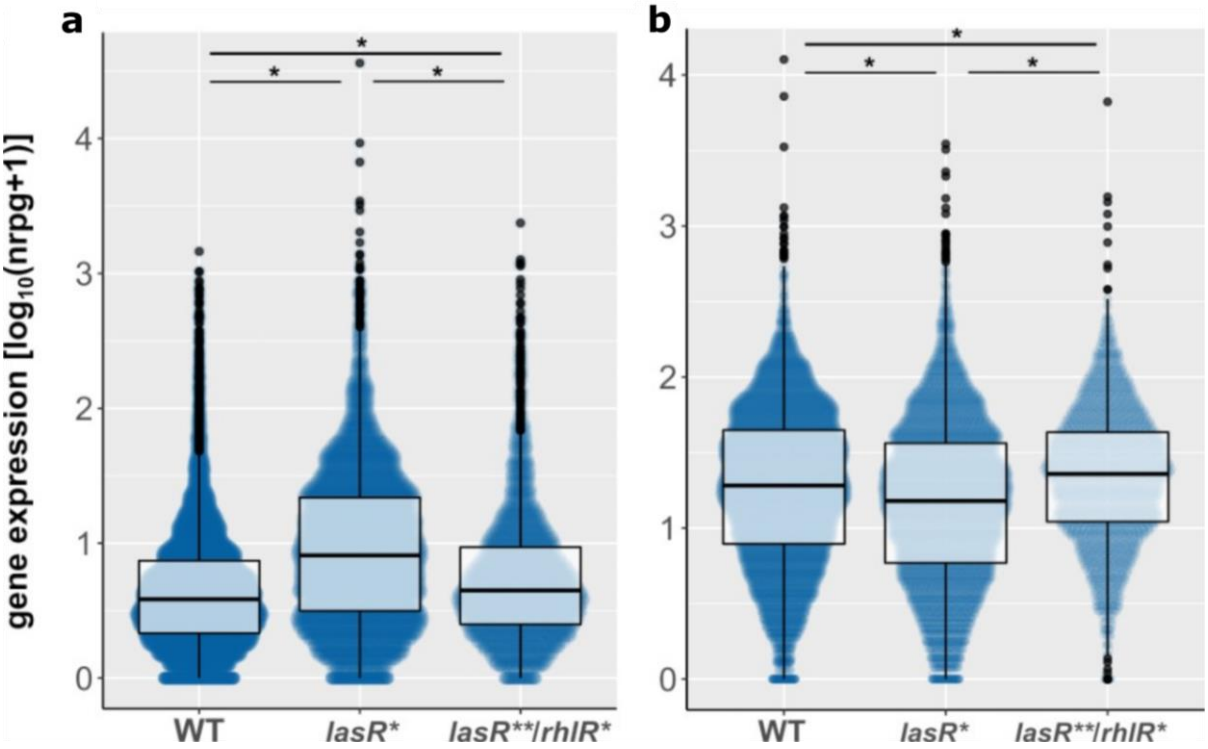
Supplementary Figure 3: Transcriptomes of *P. aeruginosa* PA14 and its Δ*lasR* mutant under biofilm and planktonic growth conditions. MDS plot depicts normalized global gene expression values of PA14 WT and its clean *lasR* deletion mutant (PA14Δ*lasR*) under planktonic growth conditions (in yellow and blue) and 48h biofilm growth (in green and red).



Supplementary Figure 4: *lasR/rhlR** clinical isolates exhibit a reduced *rhlI* expression compared to *lasR** and wild-type isolates.** Expression of *rhlI* encoding the autoinducer synthase RhlI in clinical *P. aeruginosa* isolates is depicted. Clinical isolates with InDel mutations or premature stop codons in either only *lasR* (*lasR**; n = 15), both *lasR* and *rhlR* (*lasR**/rhlR**; n = 7) or in none of the two genes (WT; n = 22) were included in the analysis. The 7 *lasR**/rhlR** isolates also included strains exhibiting non-synonymous amino acid exchanges in the gene sequence of *lasR*. Reads are shown as $\log_{10}$ normalized million reads per gene. A value of 1 was added to all nrpg values prior to $\log_{10}$ transformation in order to prevent the creation of infinite values. Each box includes 50% of the data. *p*-values < 0.05 (Wilcoxon rank sum test) are marked with an asterisk.

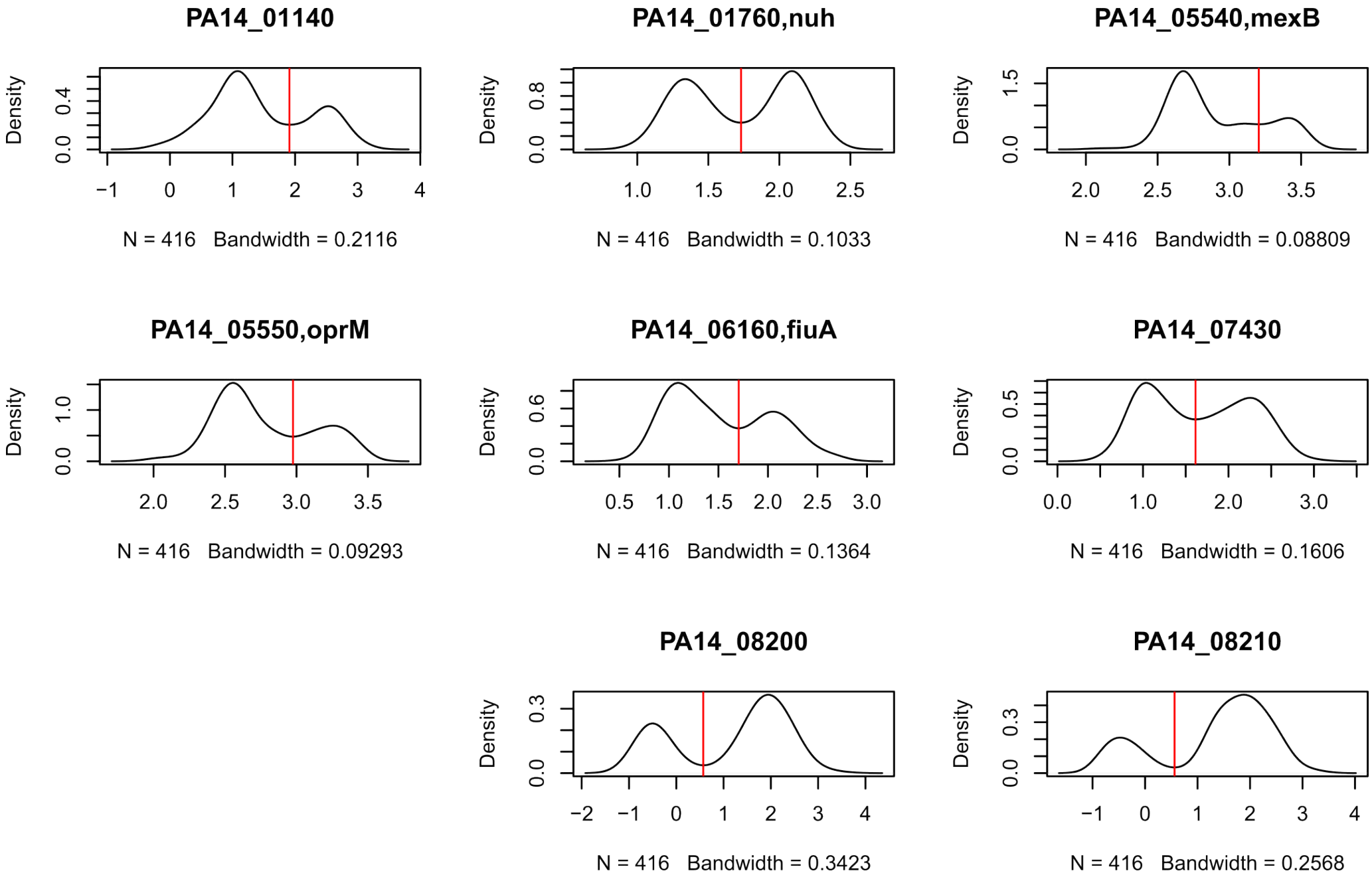


Supplementary Figure 5: Expression of all LasR core regulon genes (n = 138) among the *lasR*^{WT}, *lasR and *lasR**/rhlR** isolates.** Gene expression values (log_{10}(nrpg+1)) of the core *lasR* regulon genes in the *lasR*^{WT} (n = 22), *lasR** (n = 15) and *lasR**/rhlR** (n = 7) clinical isolates under planktonic (**a**) and biofilm (**b**) growth conditions. Asterisk: *p*-value < 0.05 (Wilcoxon rank sum test).



Supplementary Figure 6: Expression of all genes that are negatively affected by the presence of *lasR* among the *lasR*^{WT}, *lasR and *lasR**/*rhlR** isolates.** Gene expression values (log_{10}(nrpg+1)) of the *lasR* repressed genes in the *lasR*^{WT} (n = 22), *lasR** (n = 15) and *lasR**/*rhlR** (n = 7) clinical isolates under planktonic (**a**) and biofilm (**b**) growth conditions. Asterisk: *p*-value < 0.05 (Wilcoxon rank sum test).

Supplementary Figure 7: Bi-modal genes show characteristic expression patterns in a collection of 414 clinical *P. aeruginosa* isolates. Figures display distributions and cut-off visualization. Density plots for each of the identified 136 genes with an at least bi-modal pattern display the expression distribution (based on normalized expression values; y-axis) across the population of strains (x-axis). Multimodality was calculated using the R package *multimode* in default mode, a corrected *p*-value of < 0.1 was used as a threshold. Red lines indicate expression cut-offs between lowly expressing and highly expressing isolates. n = number of analyzed isolates; Bandwidth = value used in the density() function (default mode) of R to smoothen the plot.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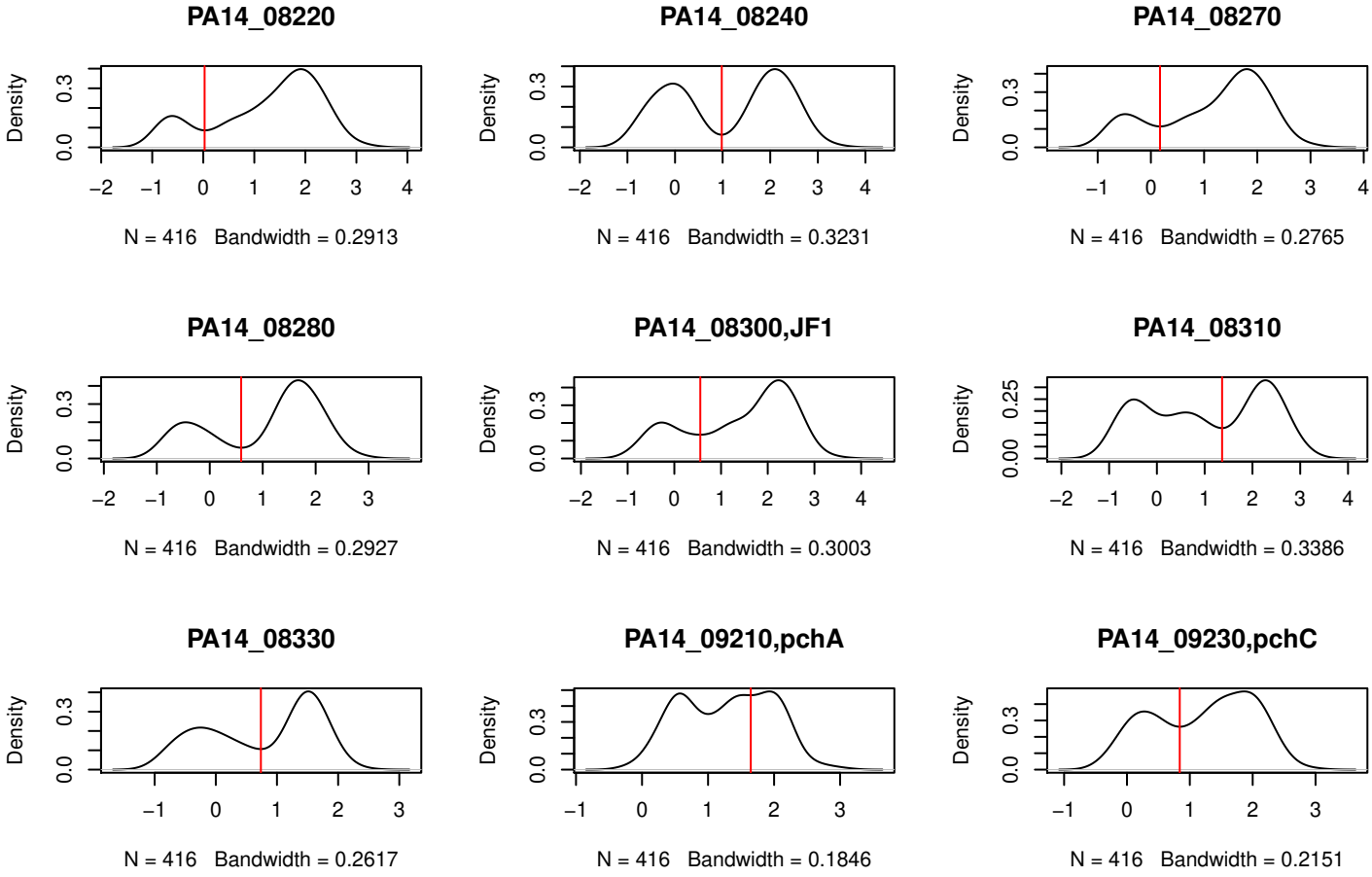
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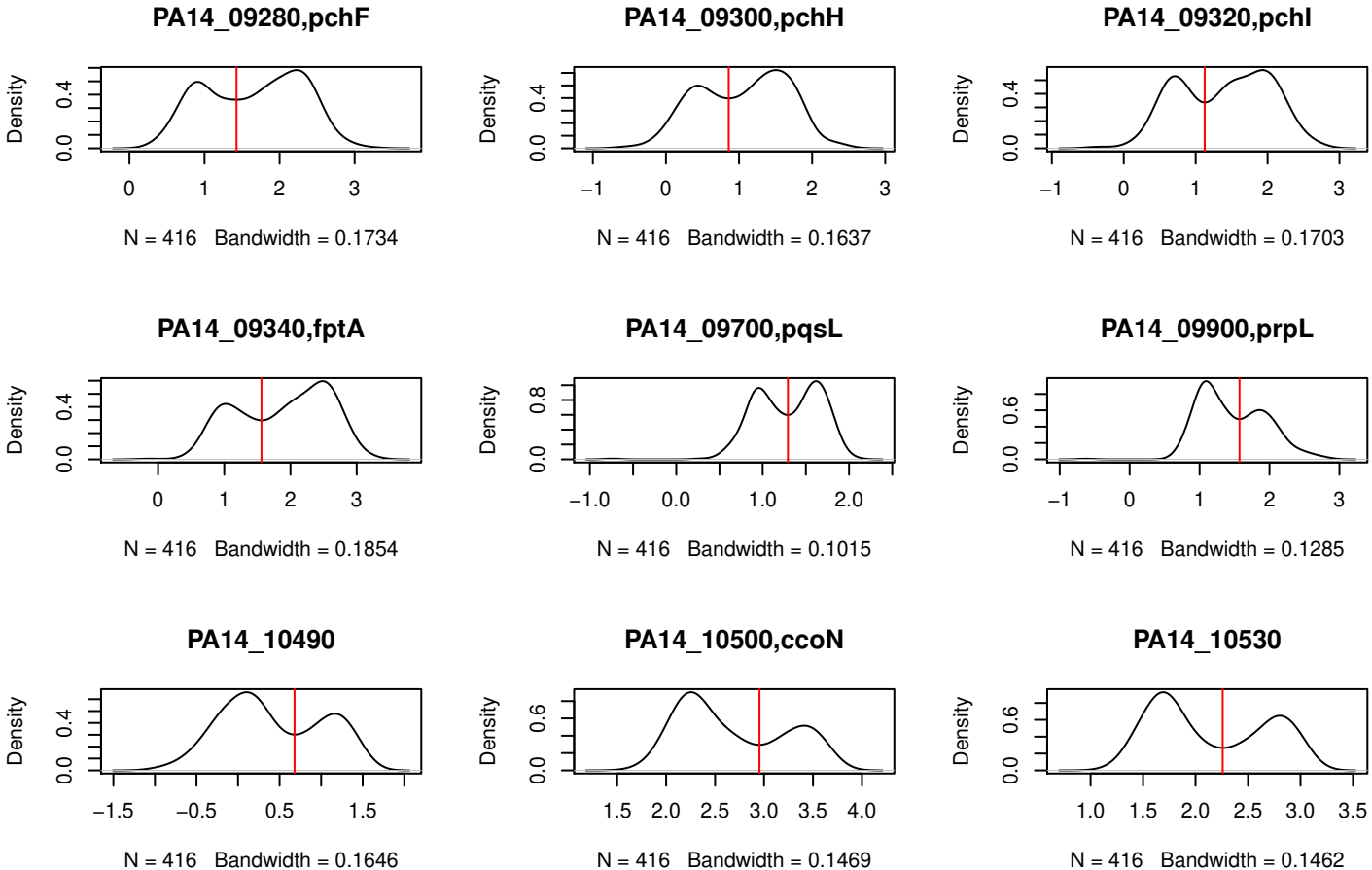
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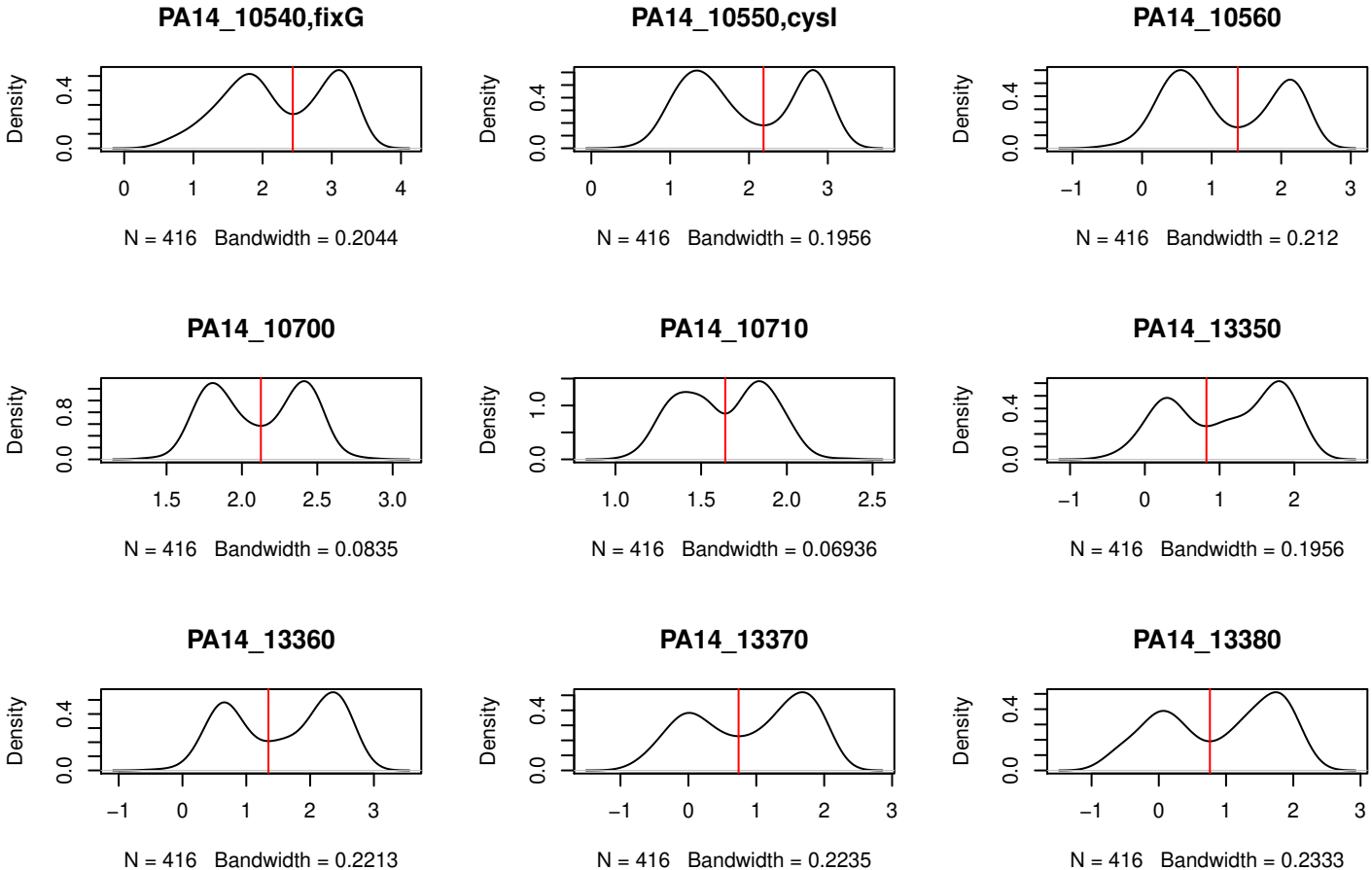
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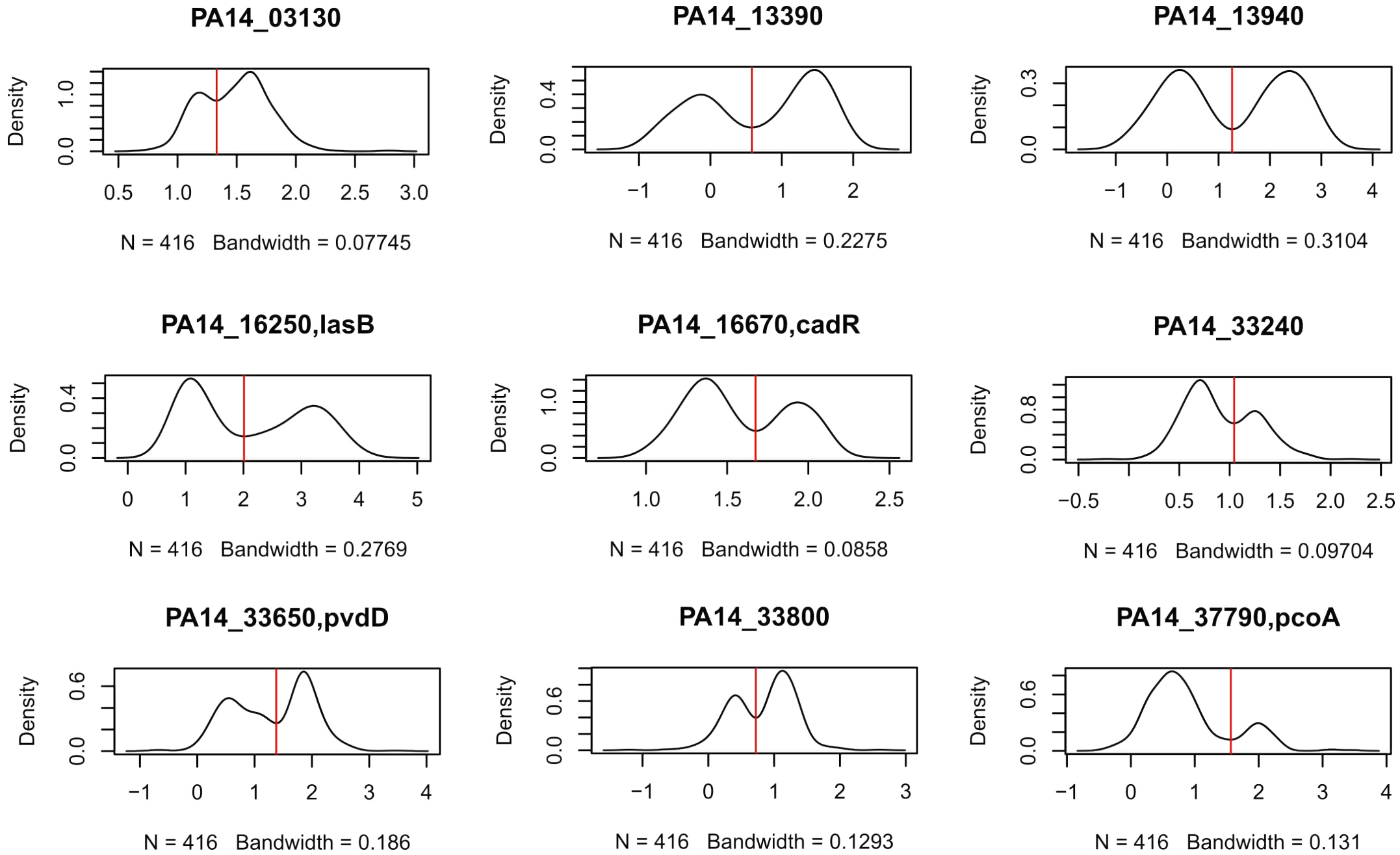
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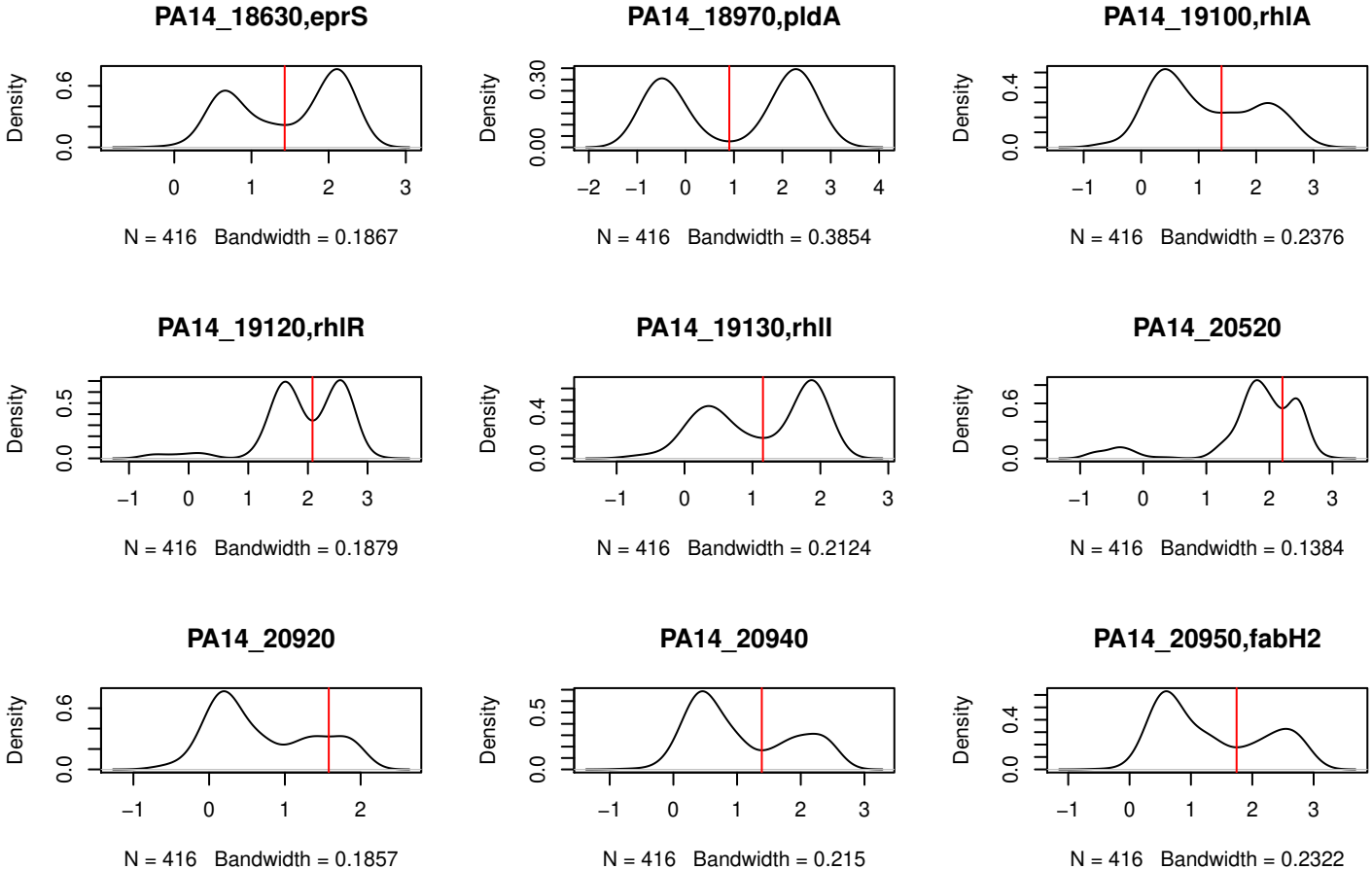
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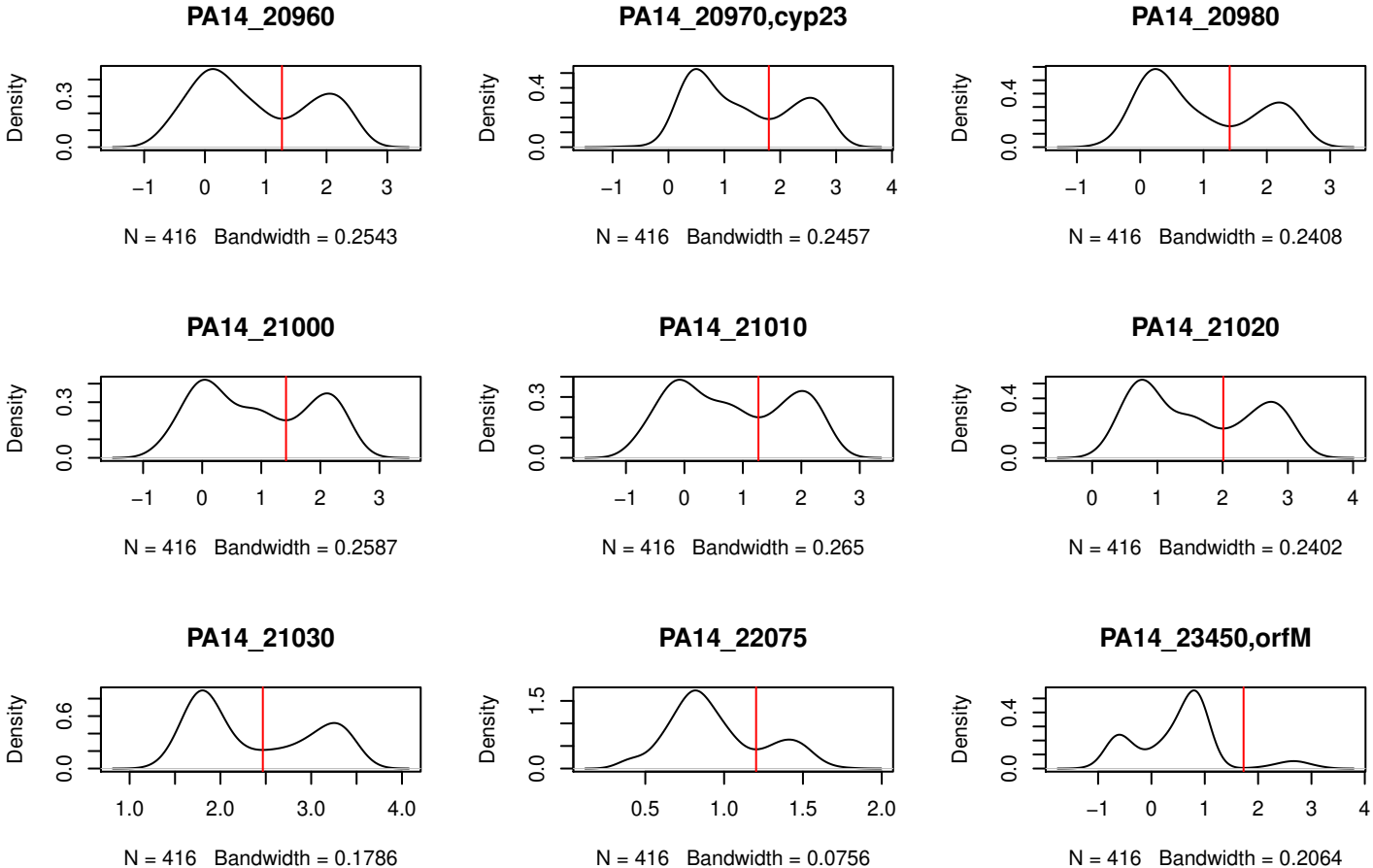
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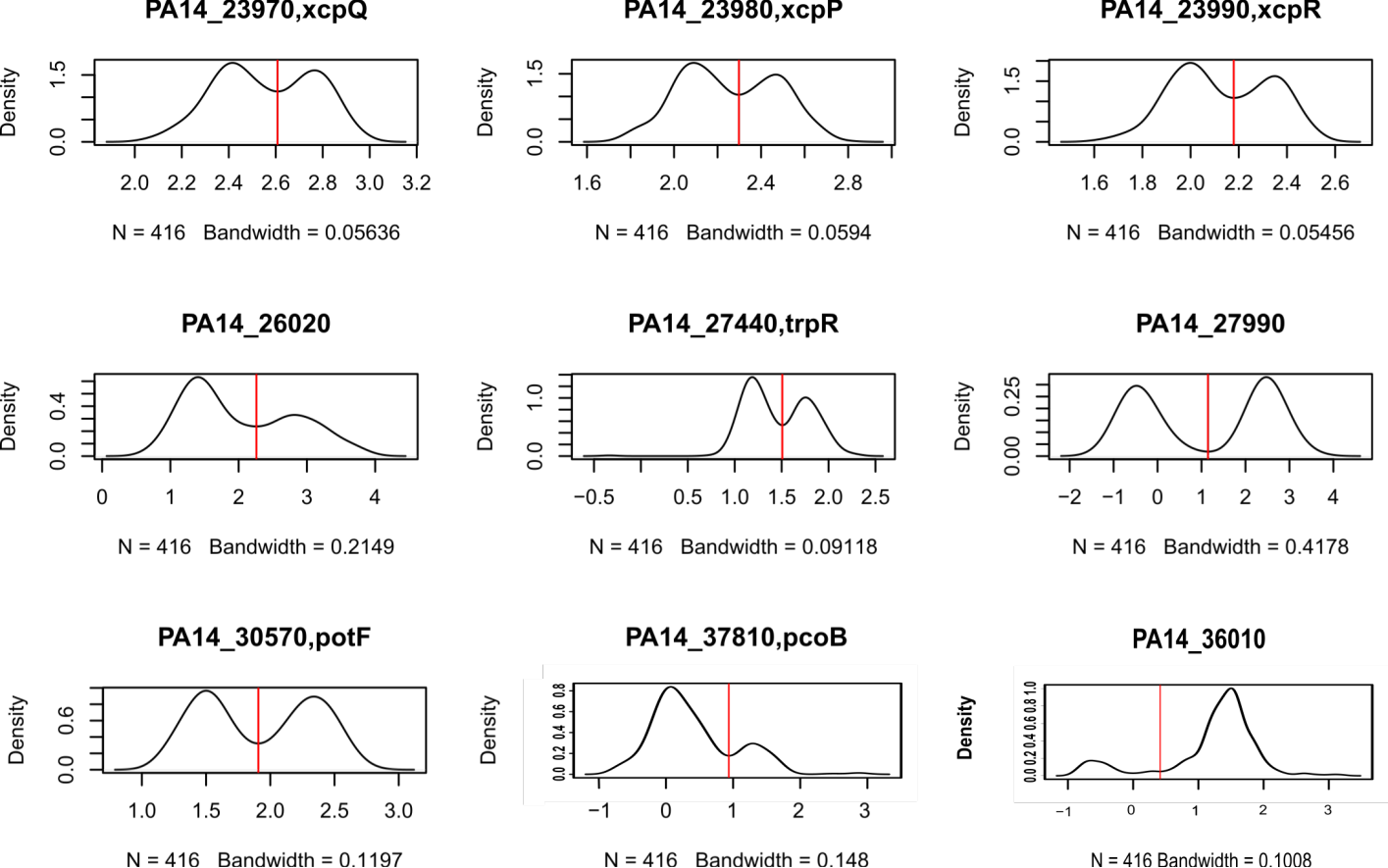
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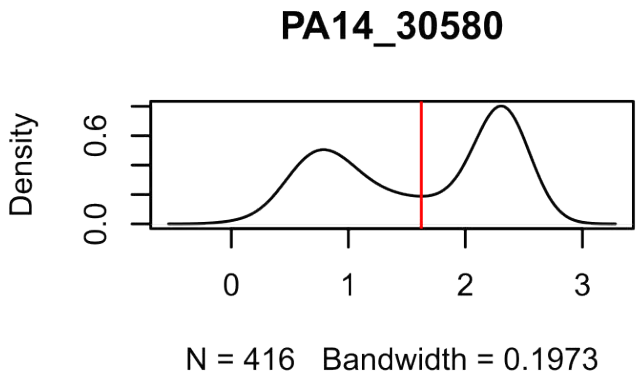
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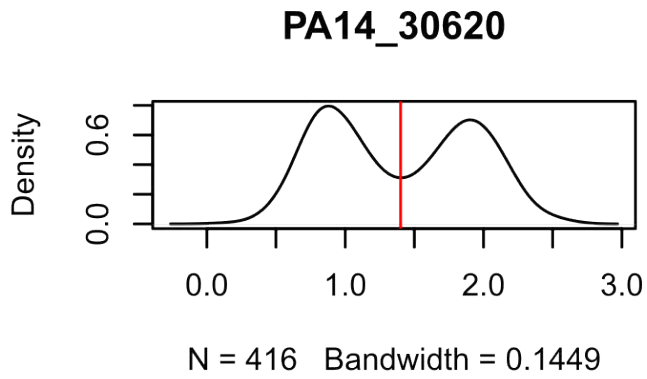
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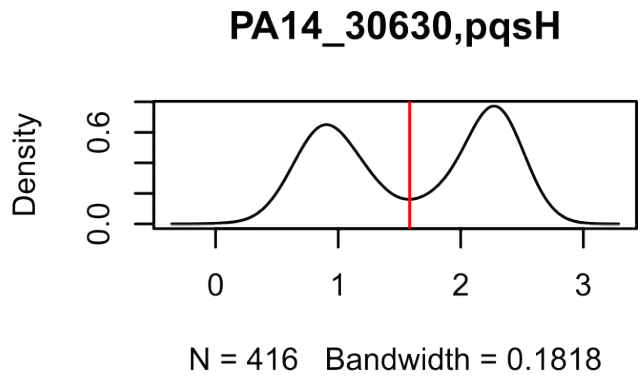
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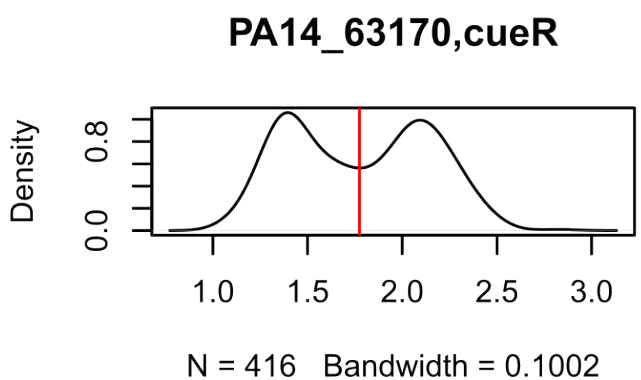
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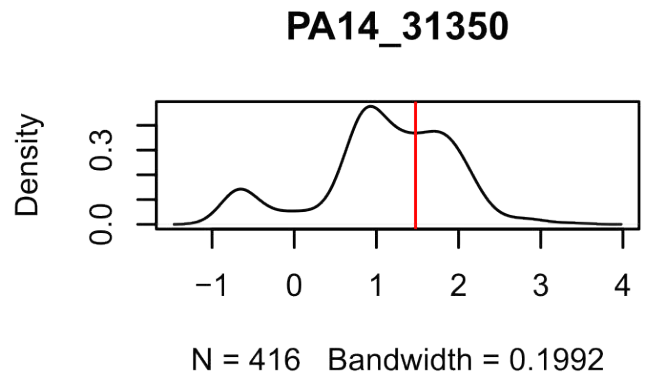
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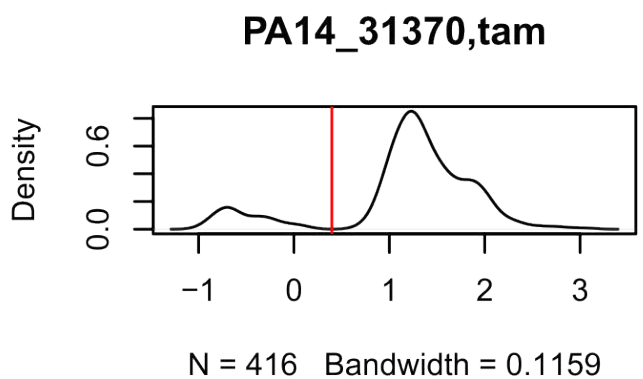
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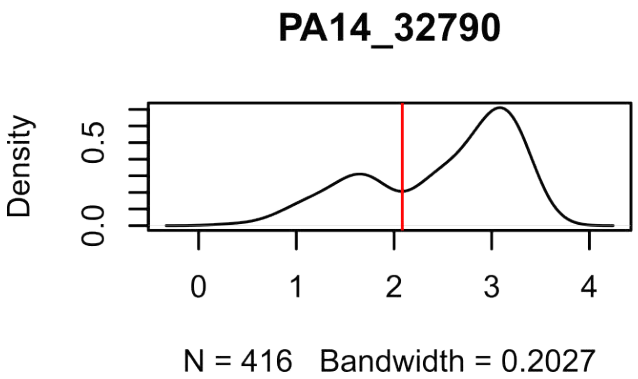
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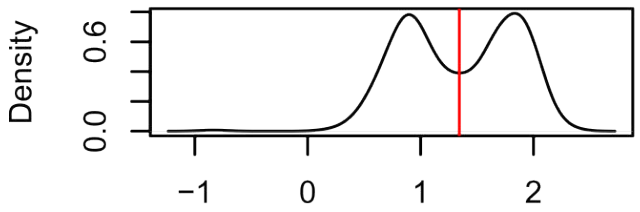

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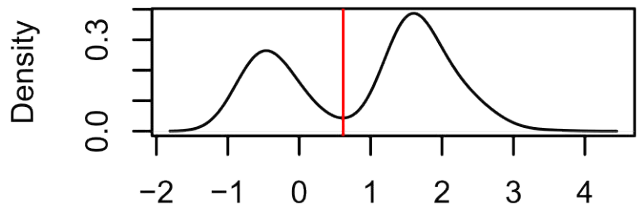

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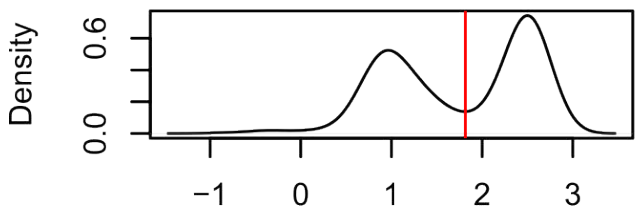

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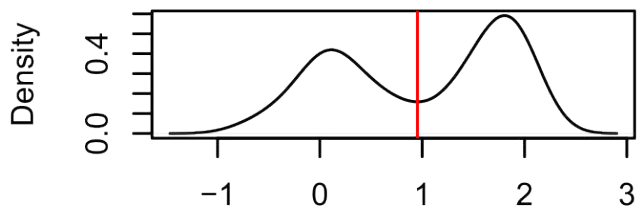

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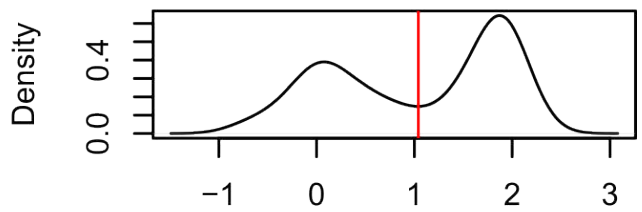

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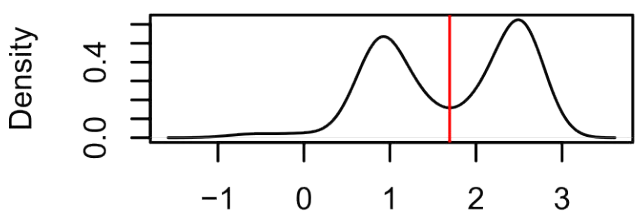

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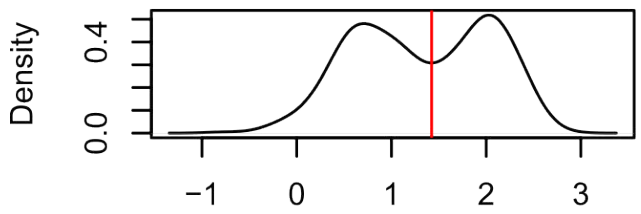

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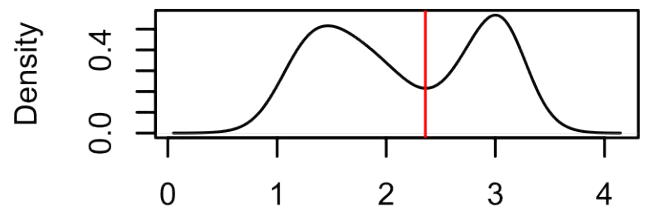

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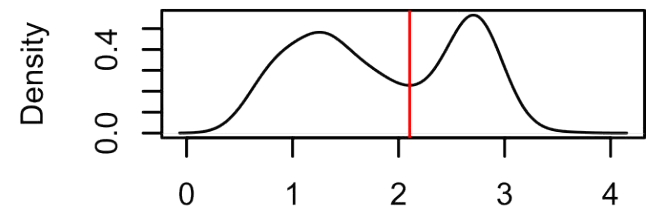

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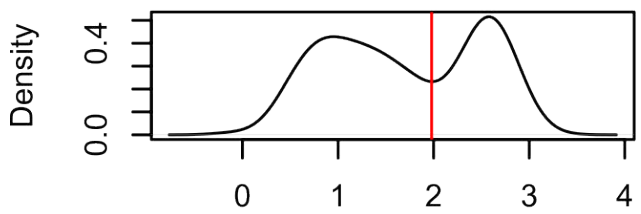

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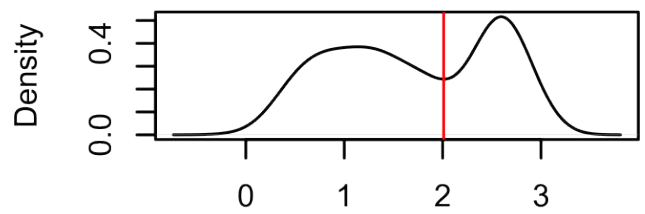
PA14_51410,pqsC



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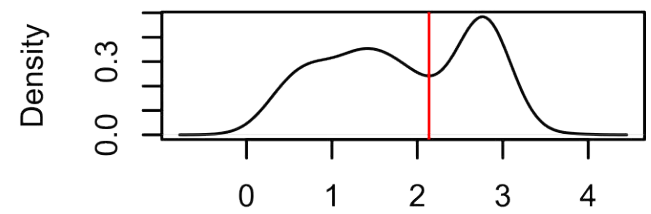

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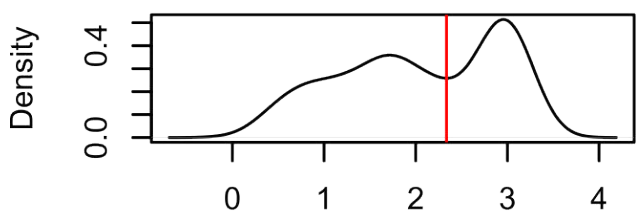

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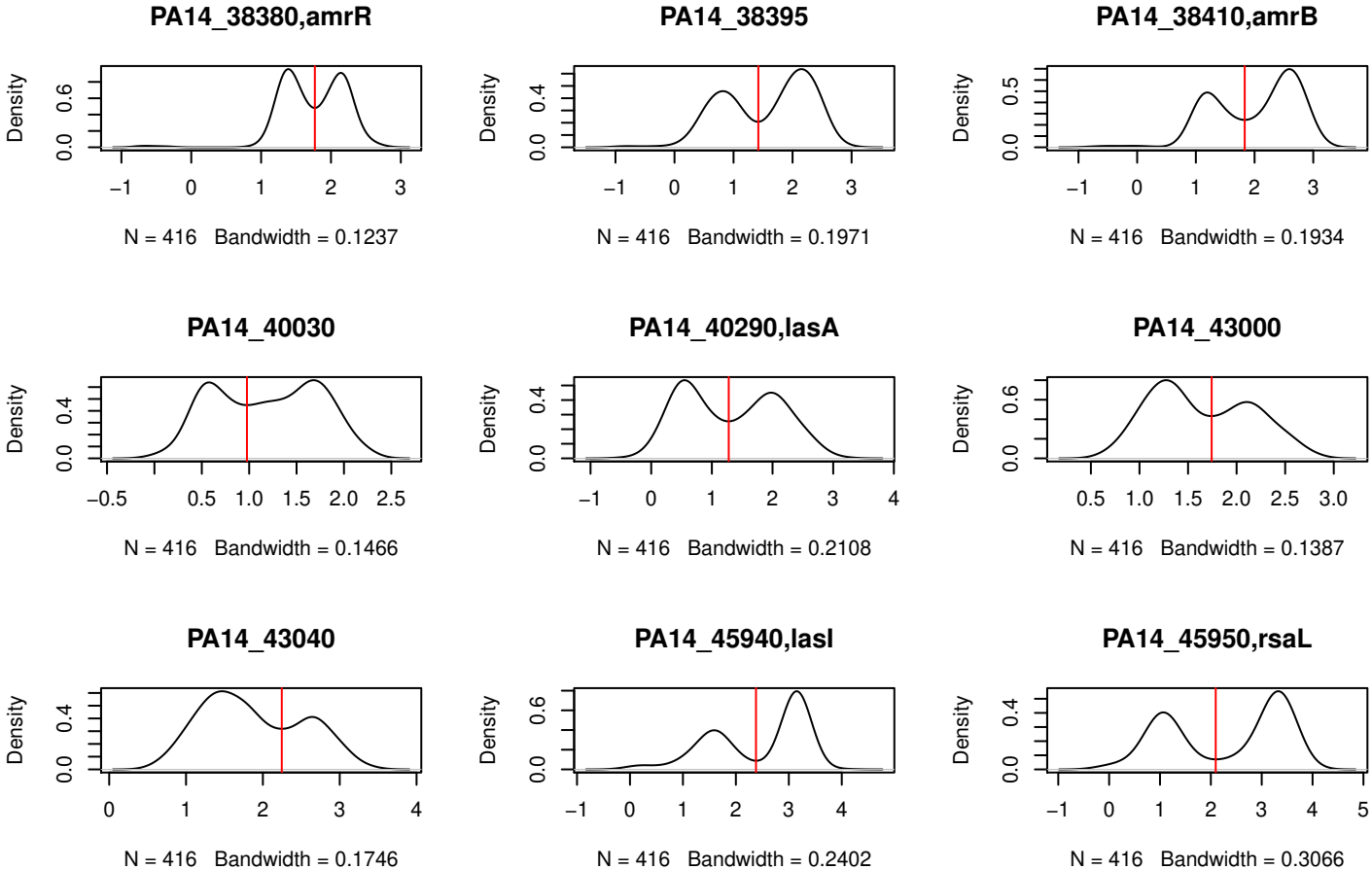
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Density
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PA14_38395
Density
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PA14_38410,amrB
Density
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PA14_40030
Density
N = 416 Bandwidth = 0.1466
PA14_40290,lasA
Density
N = 416 Bandwidth = 0.2108
PA14_43000
Density
N = 416 Bandwidth = 0.1387
PA14_43040
Density
N = 416 Bandwidth = 0.1746
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Density
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PA14_45950,rsaL
Density
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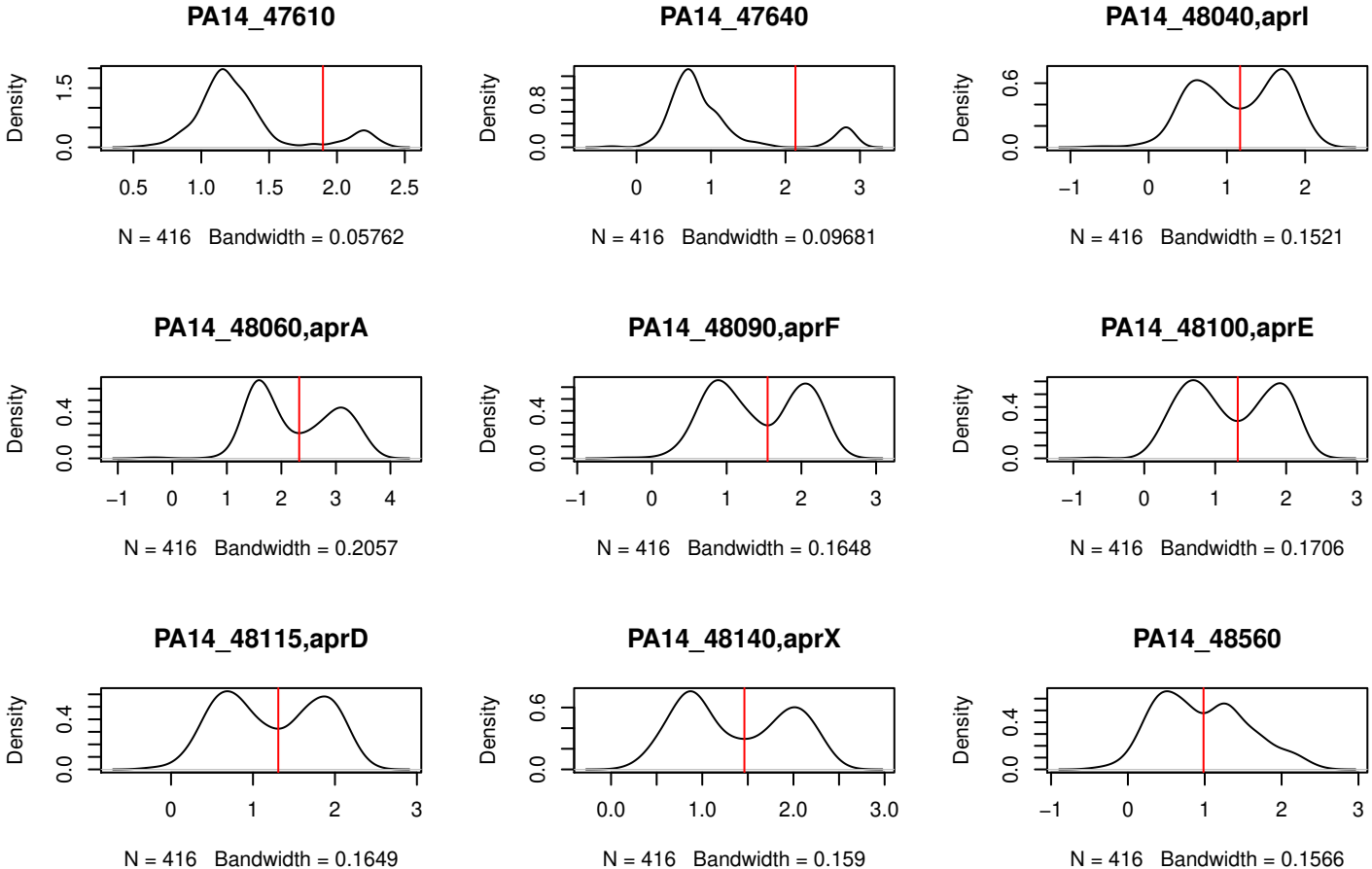
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PA14_47640
Density
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0.8
0
1
2
3
N = 416 Bandwidth = 0.09681
PA14_48040,aprI
Density
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0.6
−1
0
1
2
N = 416 Bandwidth = 0.1521
PA14_48060,aprA
Density
0.0
0.4
−1
0
1
2
3
4
N = 416 Bandwidth = 0.2057
PA14_48090,aprF
Density
0.0
0.4
−1
0
1
2
3
N = 416 Bandwidth = 0.1648
PA14_48100,aprE
Density
0.0
0.4
−1
0
1
2
3
N = 416 Bandwidth = 0.1706
PA14_48115,aprD
Density
0.0
0.4
0
1
2
3
N = 416 Bandwidth = 0.1649
PA14_48140,aprX
Density
0.0
0.6
0.0
1.0
2.0
3.0
N = 416 Bandwidth = 0.159
PA14_48560
Density
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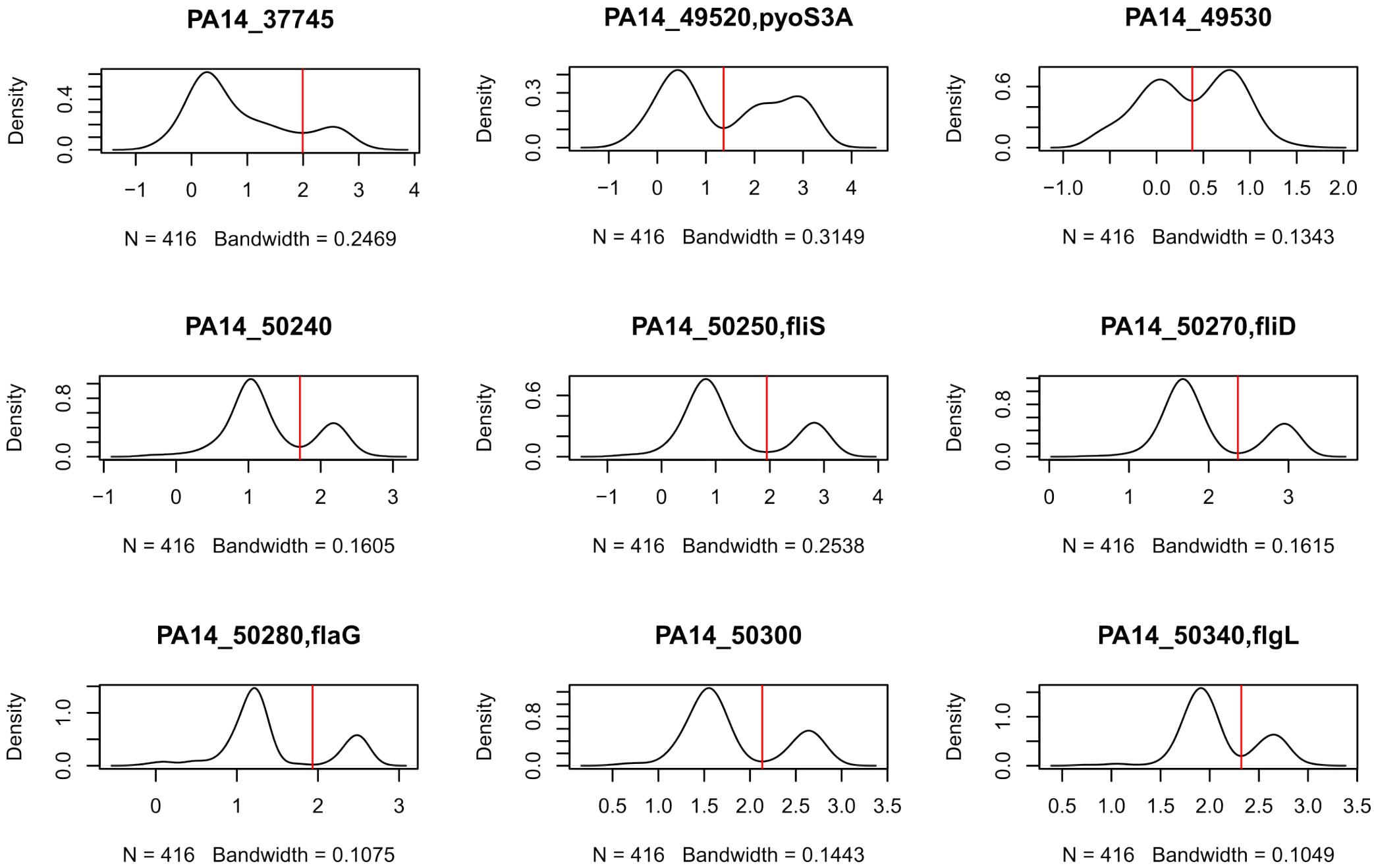
2
3
N = 416 Bandwidth = 0.1566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Density
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PA14_49530
Density
N = 416 Bandwidth = 0.1343
PA14_50240
Density
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PA14_50250,fliS
Density
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PA14_50270,fliD
Density
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PA14_50280,flaG
Density
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PA14_50300
Density
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PA14_50340,flgL
Density
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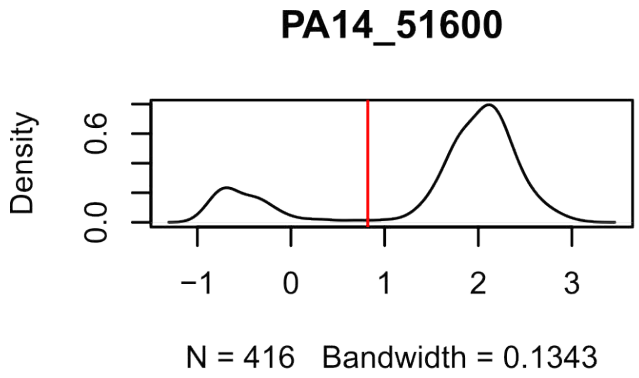
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2
3
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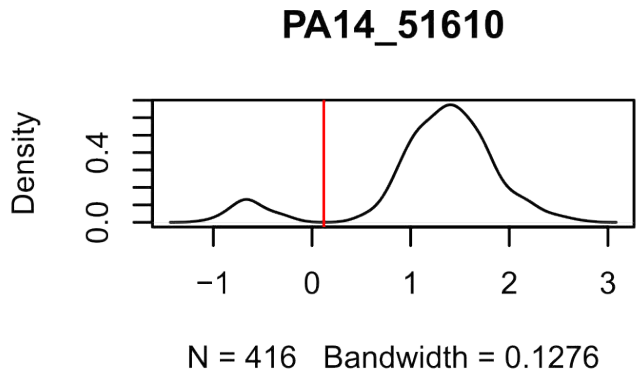
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1
2
3
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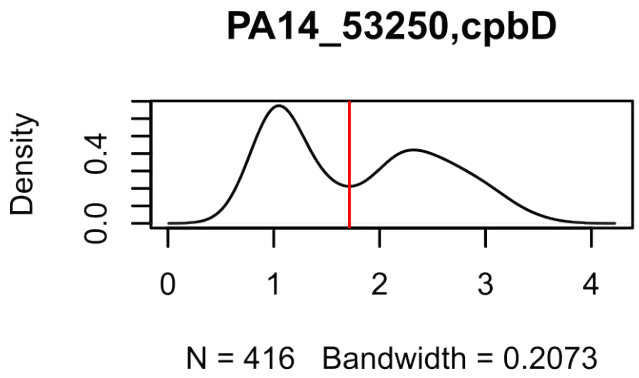
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2
3
4
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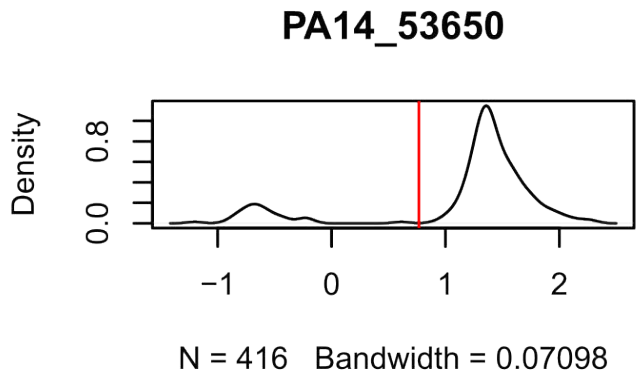
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1
2
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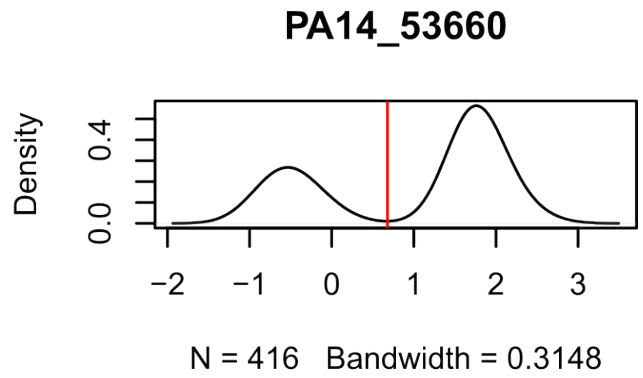
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−1
0
1
2
3
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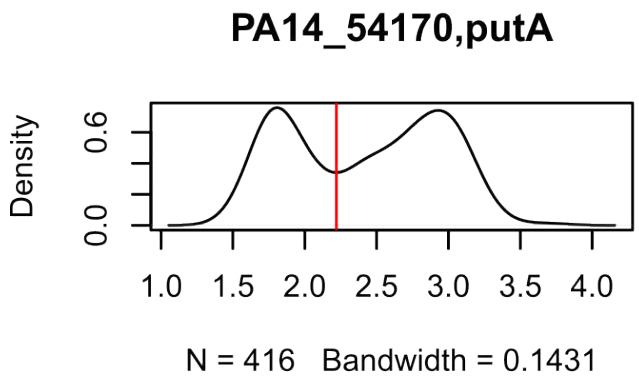
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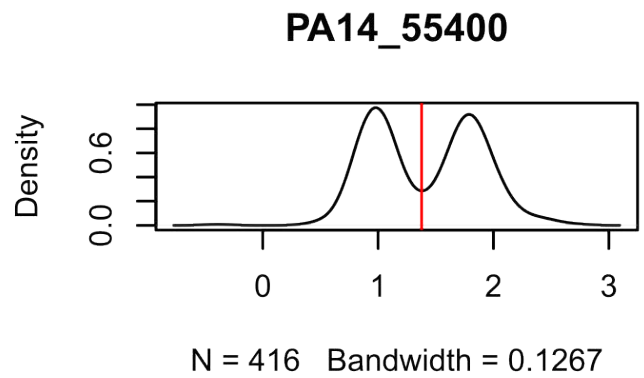
4.0
N = 416 Bandwidth = 0.1431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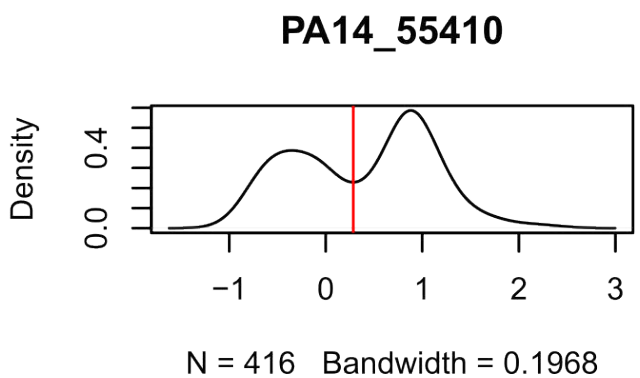
N = 416 Bandwidth = 0.1267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1
2
3
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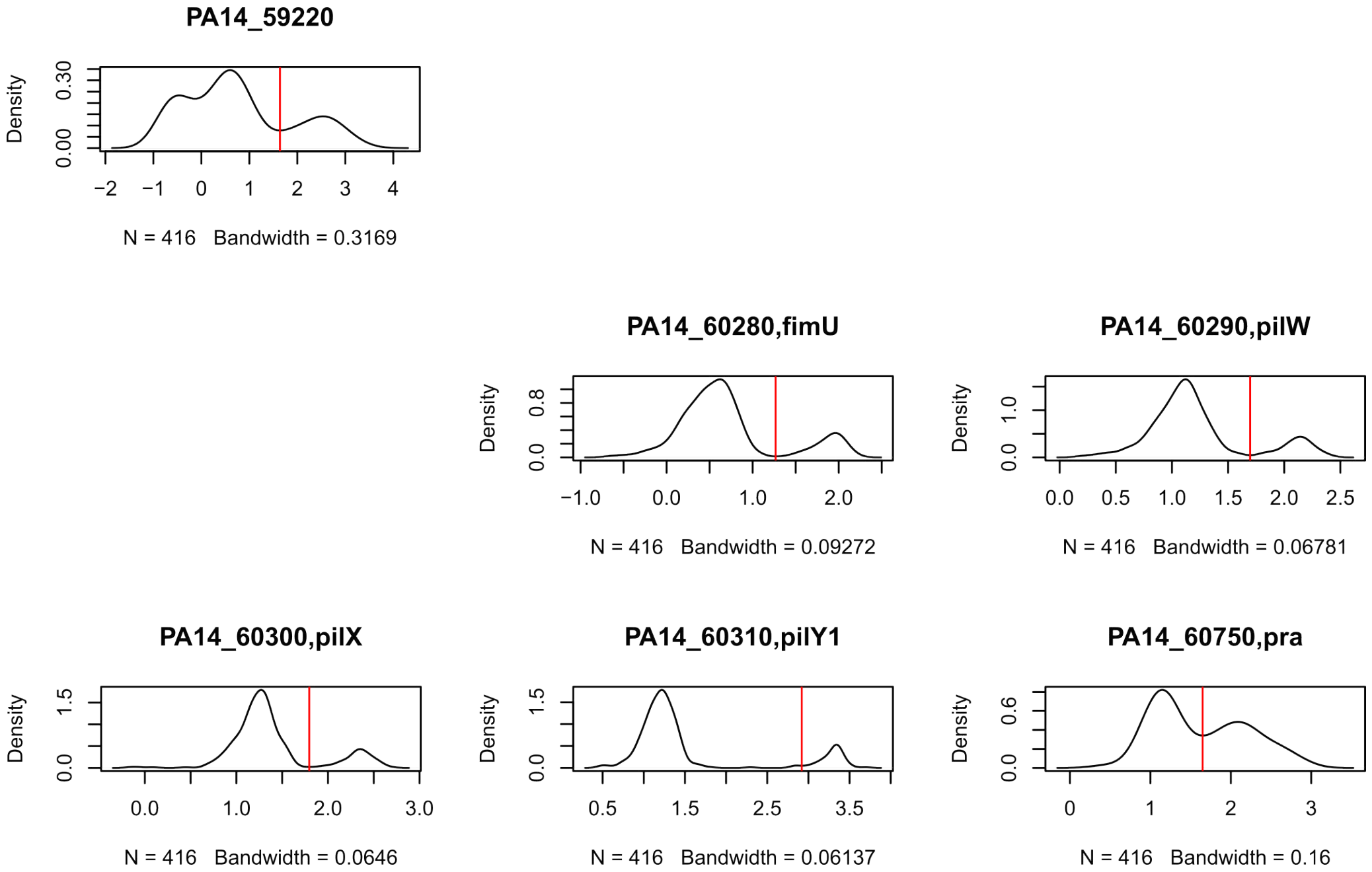
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2
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PA14_60280,fimU
Density
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2.0
N = 416 Bandwidth = 0.09272
PA14_60290,pilW
Density
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1.5
2.0
2.5
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PA14_60300,pilX
Density
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2.0
3.0
N = 416 Bandwidth = 0.0646
PA14_60310,pilY1
Density
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0.5
1.5
2.5
3.5
N = 416 Bandwidth = 0.06137
PA14_60750,pra
Density
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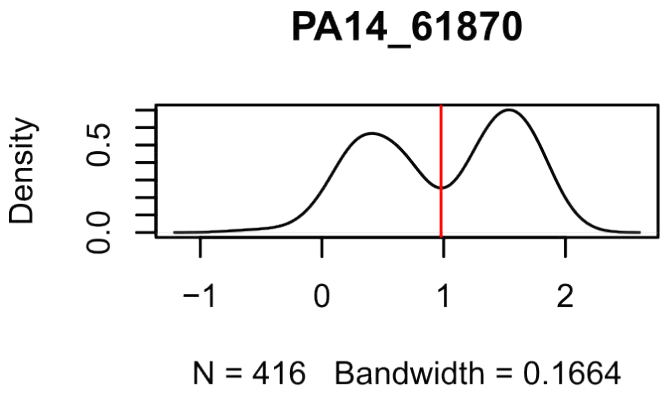
0.6
0
1
2
3
N = 416 Bandwidth = 0.16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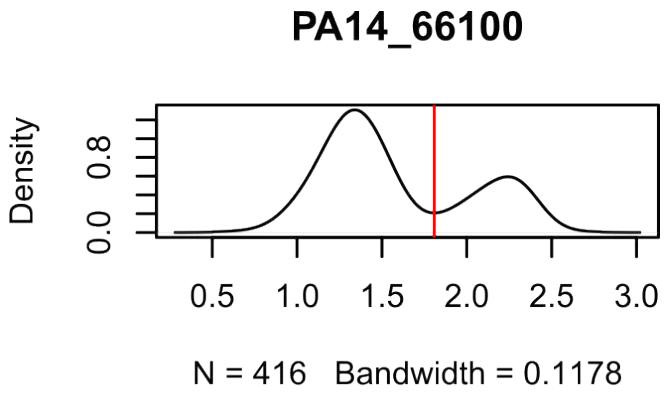
1
2
N = 416 Bandwidth = 0.1664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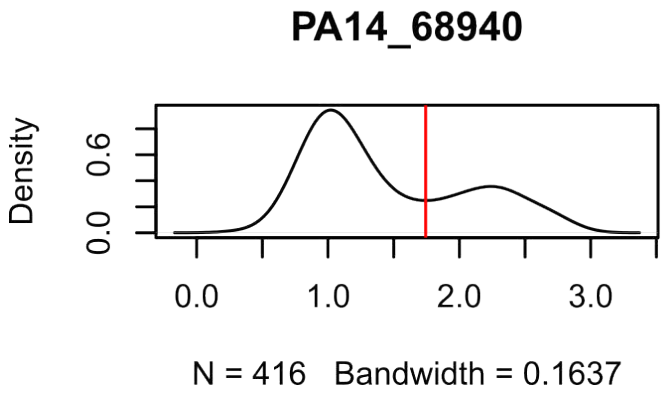
PA14_68940
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1.0
2.0
3.0
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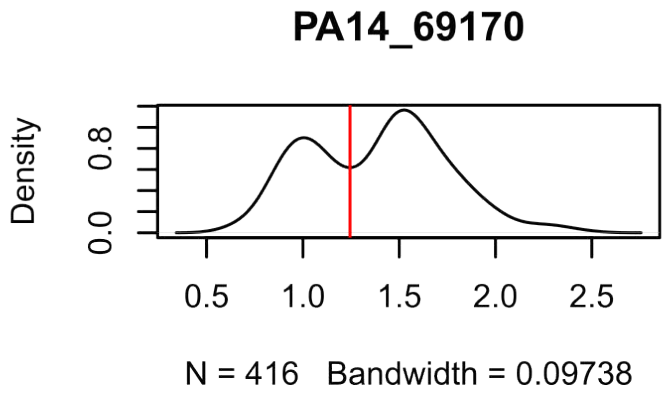
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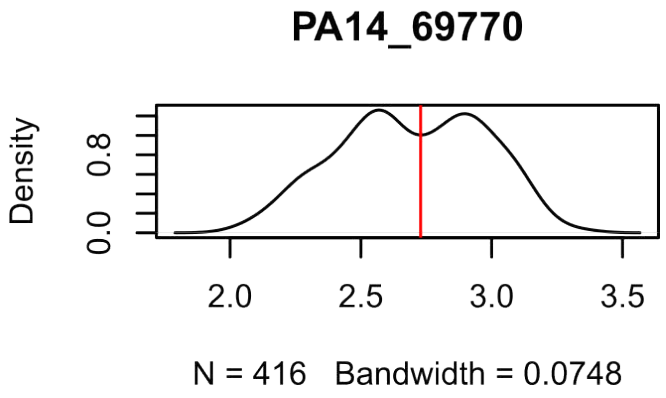
N = 416 Bandwidth = 0.09738


PA14_69770
Density
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2.5
3.0
3.5
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Supplementary Table

Supplementary Table 1: Oligonucleotides used in this study

Name	Sequence (5' - 3')	Goal of the primer	Other characteristics
rhlR_PA14_spc2_F	**gcgcg**GGCTTCGATTACTACGCCTA	Oligonucleotide in the sense orientation for the construction of the *rhlR*-targeting sgRNA	The nt depicted as bold characters were added to reconstruct the Eco31I protruding ends after plasmid hibridization for cloning in pS448·CsR
rhlR_PA14_spc2_R	**aaac**TAGGCGTAGTAATCGAAGCC**c**	Oligonucleotide in the antisense orientation for the construction of the *rhlR*-targeting sgRNA	The nt depicted as bold characters were added to reconstruct the Eco31I protruding ends after plasmid hibridization for cloning in pS448·CsR
phoB_PA14_spc2_F	**gcgcg**ACGGCGATCATCTCGCGAAT	Oligonucleotide in the sense orientation for the construction of the *phoB*-targeting sgRNA	The nt depicted as bold characters were added to reconstruct the Eco31I protruding ends after plasmid hibridization for cloning in pS448·CsR
phoB_PA14_spc2_R	**aaac**ATTCGCGAGATGATCGCCGT**c**	Oligonucleotide in the antisense orientation for the construction of the *phoB*-targeting sgRNA	The nt depicted as bold characters were added to reconstruct the Eco31I protruding ends after plasmid hibridization for cloning in pS448·CsR
rhlR_PA14(+)-Rec	cgggccaattctgctgtgatgcattttatcgatcaggg cttactgca**ATGTGA**agcgtagggcgcgccg gccggcgcgccctaccagatctggcaggttg	Recombineering oligonucleotide used for the deletion of *rhlR* in PA14	The start (ATG) and stop codons of *rhlR* are depicted as bold characters
phoB_PA14(+)-Rec	tttcgttatctaatgcggcgcaagacagatcgaccc gaggcaagacc**ATGTGA**ccccgcgcccggc cgcccggcggccggagtcgtttcccctggacggt	Recombineering oligonucleotide used for the deletion of *phoB* in PA14	The start (ATG) and stop codons of *phoB* are depicted as bold characters
rhlR_PA14-Seq-F	CTGTCGGCGTTTCATGGAATTG	Forward primer used for PCR and sequencing of the *rhlR* deletion	Tm = 58ºC
rhlR_PA14-Seq-R	AAGACTTGATGCCGGTAGCGTC	Reverse primer used for PCR and sequencing of the *rhlR* deletion	Tm = 60ºC
phoB_PA14-Seq-F	CGCCAGGTGGATTCTGTTCATCG	Forward primer used for PCR and sequencing of the *phoB* deletion	Tm = 61ºC
phoB_PA14-Seq-R	GCGTTGCAGGTGGTAGATATTG	Reverse primer used for PCR and sequencing of the *phoB* deletion	Tm = 57ºC

aaSSR-1F	TGAGCCAAGTAGCCAGGGTCG	Forward primer used to check the prescence of *ssr* gene by PCR	Tm = 60ºC
aaSSR-1R	GATTTGTAGACGTTGGCAGCGCAG	Reverse primer used to check the prescence of *ssr* gene by PCR	Tm = 60ºC
aaCas9-1F	AAGCACAAGTGTCTGGACAAGG	Forward primer used to check the prescence of *S. pyogenes cas9* gene by PCR	Tm = 58ºC
aaCas9-1R	TCACTCAAACCTCCACGTTCAGC	Reverse primer used to check the prescence of *S. pyogenes cas9* gene by PCR	Tm = 58ºC

Supplementary Data

Supplementary Data 1: Bimodally expressed genes and their affiliation to clusters containing genes with similar expression patterns across clinical isolates. KEGG pathways were assigned using the R package KEGGREST (version 1.26.1).

Supplementary Data 2: Genes that are significantly (FDR ≤ 0.05) and relevantly ($log_2FC \geq 1$; $log_2FC \leq -1$) differentially expressed in clinical *lasR** compared to *lasR*^{WT} isolates under planktonic growth conditions ($OD_{600} = 2$).

Supplementary Data 3: Genes that are significantly (FDR ≤ 0.05) and relevantly ($log_2FC \geq 1$; $log_2FC \leq -1$) differentially regulated between PA14Δ*lasR* compared to PA14 WT under planktonic growth conditions ($OD_{600} = 2$).

Supplementary Data 4: Genes that are significantly (FDR ≤ 0.05) and relevantly ($log_2FC \geq 1$; $log_2FC \leq -1$) differentially regulated between clinical *lasR** compared to *lasR*^{WT} isolates under biofilm growth conditions (48h growth in LB at 37°C).

Supplementary Data 5: Genes that are significantly (FDR ≤ 0.05) and relevantly ($log_2FC \geq 1$; $log_2FC \leq -1$) differentially regulated between PA14Δ*lasR* compared to PA14 WT under biofilm growth conditions (48h growth in LB at 37°C).

Supplementary Data 6: **Strain-specific as well as common transcriptional signatures associated with *lasR* deficiency.** Genes (PA14 Locus Tags) that are expressed below $log_2FC = -1$ in the respective number of *lasR** isolates compared to all *lasR*^{WT} isolates (sheet “lasRmut vs all lasRWT down”). Genes (PA14 Locus Tags) that are expressed above $log_2FC = 1$ in the respective number of *lasR** isolates compared to all *lasR*^{WT} isolates (sheet “lasRmut vs all lasRWT up”).

Supplementary Data 7: Differential gene expression between biofilm and planktonic growth in clinical isolates harboring a *lasR* wildtype allele or a lasR deficiency. Genes that are significantly (FDR ≤ 0.05) and relevantly ($log_2FC \geq 1$; $log_2FC \leq -1$) differentially expressed in clinical *lasR*^{WT} under planktonic growth conditions ($OD_{600} = 2$) compared to *lasR*^{WT} isolates under biofilm growth conditions (48h growth in LB at 37°C) (sheet “lasR WT PL vs BF”). Genes that are significantly (FDR ≤ 0.05) and relevantly ($log_2FC \geq 1$; $log_2FC \leq -1$) differentially expressed in clinical *lasR** isolates under planktonic growth conditions ($OD_{600} = 2$) compared to *lasR** isolates under biofilm growth conditions (48h growth in LB at 37°C) (sheet “lasR Mutants PL vs BF”).