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Supplemental Information

The Set7 Lysine Methyltransferase Regulates Plasticity in Oxidative Phosphorylation Necessary for Trained Immunity Induced by β-Glucan

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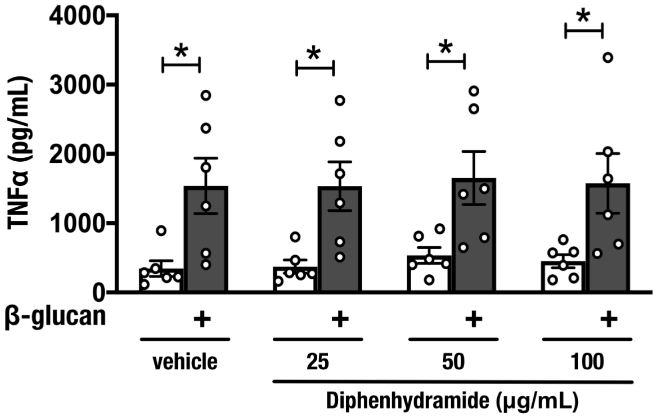

Figure S1. Diphenhydramide does not inhibit trained immunity induced by β-glucan, Related to Figure 2.
Production of TNFα by β-glucan-trained macrophages incubated with diphenhydramide for the first 24 hours of *in vitro* training and restimulated with LPS (n=6 healthy volunteers).

Data are represented as mean ± SEM, *$p < 0.05$; Wilcoxon signed-rank test.

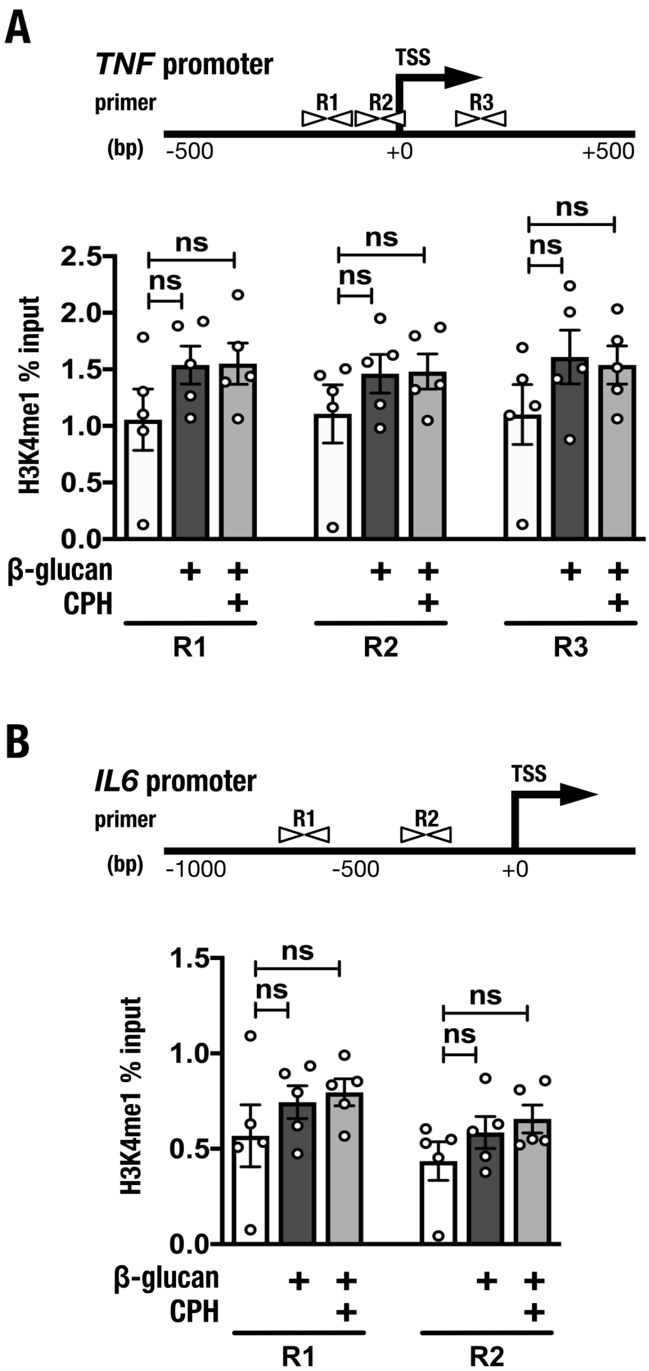

Figure S2. β-glucan and CPH do not influence H3K4me1 enrichment at the promoters of *TNF* and *IL6*, Related to Figure 2 and Table S1.
H3K4me1 enrichment at the gene promoters of (**A**) *TNF* and (**B**) *IL6* (n=5 healthy volunteers). The positions of primers relative to the transcription start site (TSS) are indicated.

Data are represented as mean ± SEM, Wilcoxon signed-rank test.

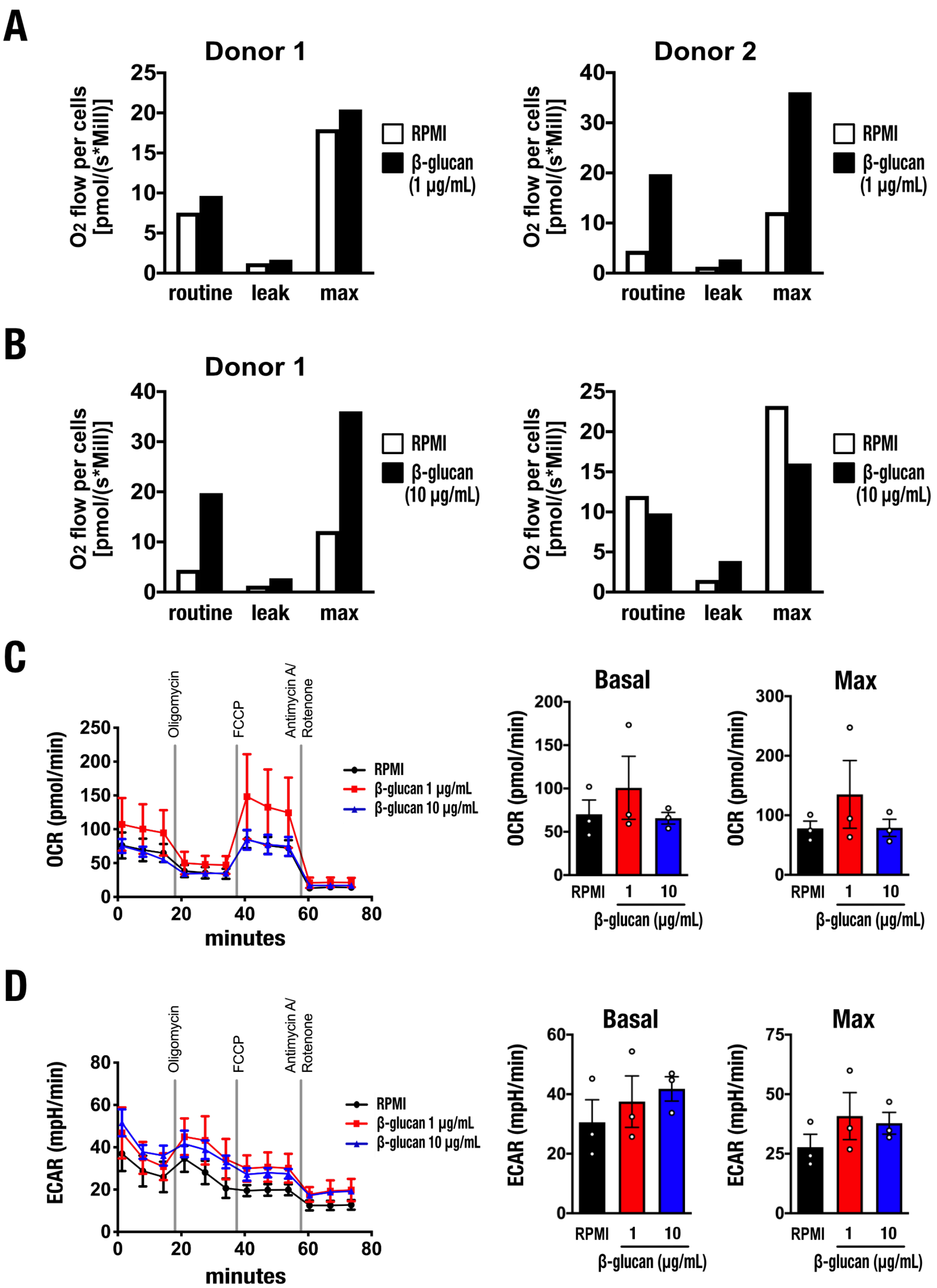

Figure S3. Metabolic analysis of cells trained with different concentrations of β-glucan, Related to Figure 4.

A) Respirometry measurements of macrophages from 2 health volunteers 5 days after incubation with 1 μg/mL of β-glucan using the Oxygraph-2k. (**B**) Respirometry measurements of macrophages from 2 health volunteers 5 days after incubation with 10 μg/mL of β-glucan using the Oxygraph-2k. (**C**) Oxygen consumption analysis (Seahorse system) of macrophages 5 days after incubation with 1 μg/mL of β-glucan or 10 μg/mL of β-glucan. Basal and maximum oxygen consumption rates (OCR) are indicated (n = 3 healthy volunteers). (**D**) Extracellular acidification rate (ECAR) analysis (Seahorse system) of macrophages 5 days after incubation with 1 μg/mL of β-glucan or 10 μg/mL of β-glucan. Basal and maximum ECAR are indicated (n = 3 healthy volunteers).

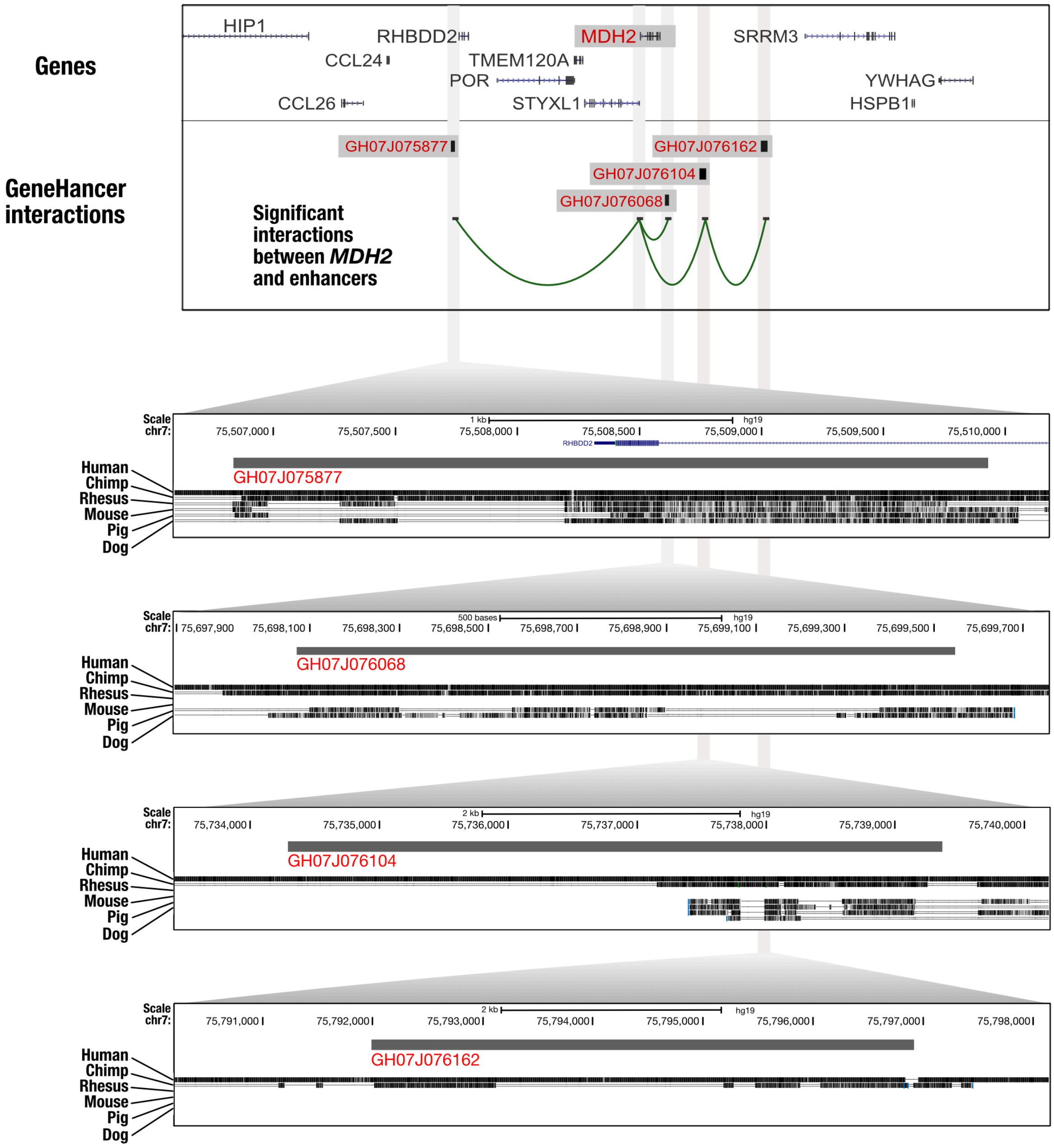

Figure S4. Evolutionary conservation of distal enhancers associated with *MDH2* gene regulation in humans, Related to Figure 6. Alignment of genomic sequences from human, chimp, rhesus, mouse, pig and dog at GH07J075877, GH07J076068, GH07J076104 and GH07J076162

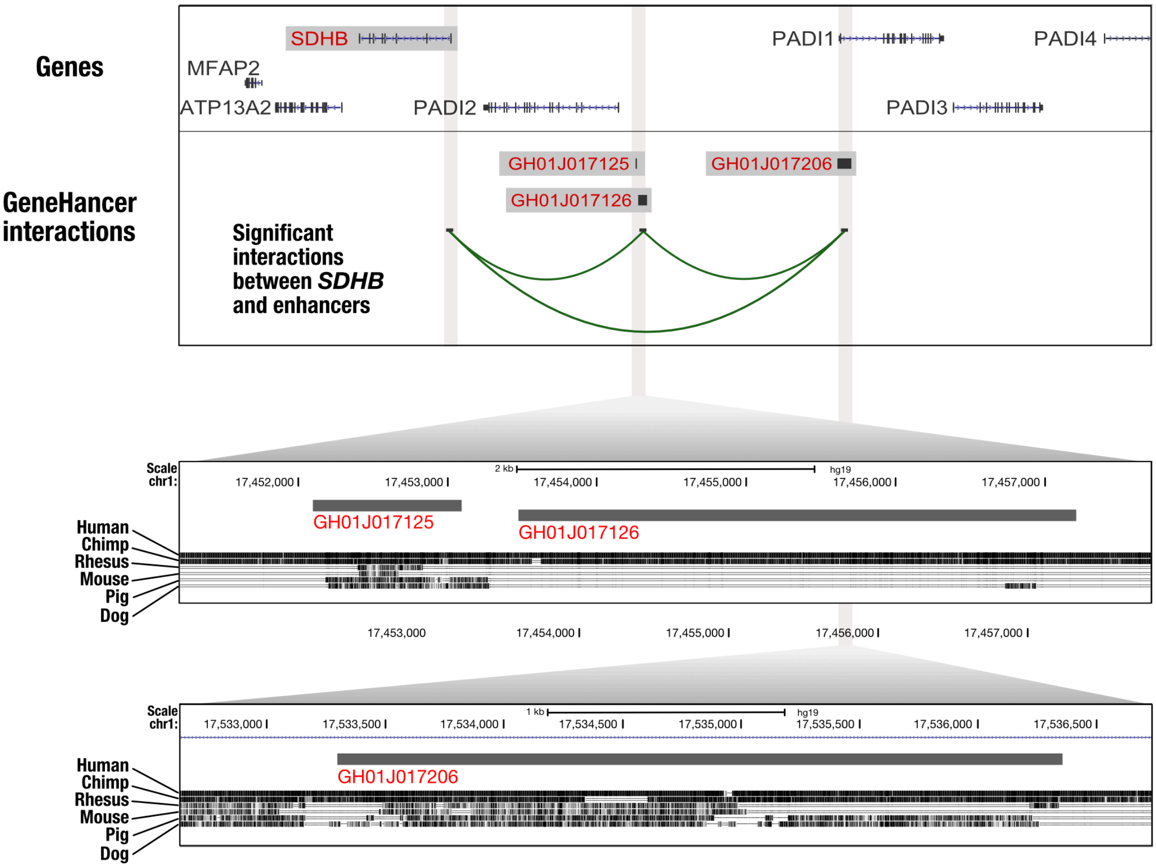

Figure S5. Evolutionary conservation of distal enhancers associated with *SDHB* gene regulation in humans, Related to Figure 6. Alignment of genomic sequences from human, chimp, rhesus, mouse, pig and dog at GH01J017125, GH01J017126 and GH01J017206.

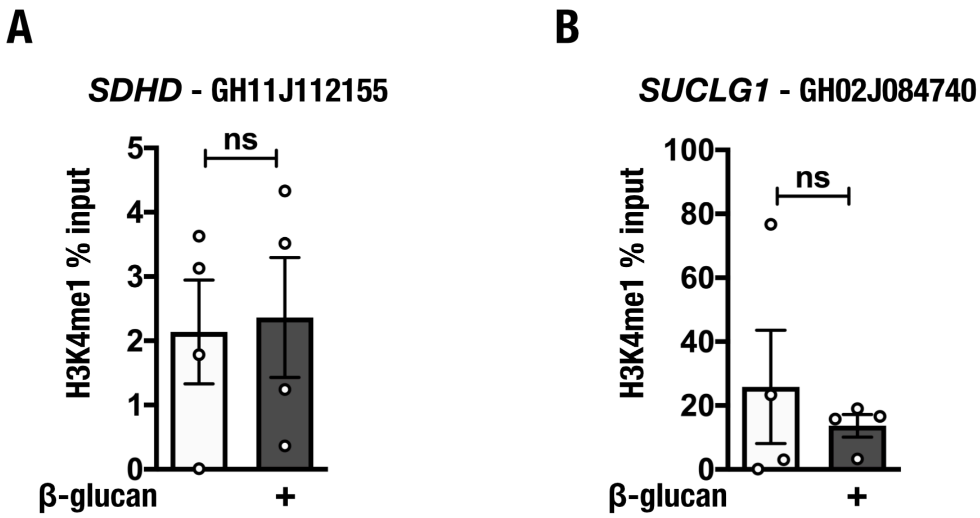

Figure S6. β-glucan did not induce significant changes to H3K4me1 at distal enhancers associated with *SDHD* and *SUCLG1* gene regulation, Related to Figure 6 and Table S1. (**A**) Levels of H3K4me1 at the GH11J112155 enhancer, associated with transcriptional regulation of *SDHD*, measured in primary human macrophages 5 days after incubation with β-glucan (n = 4 healthy volunteers). (**B**) Levels of H3K4me1 at the GH02J084740 enhancer, associated with transcriptional regulation of *SUCLG1*, measured in primary human macrophages 5 days after incubation with β-glucan (n = 4 healthy volunteers).

Data are represented as mean ± SEM, Wilcoxon signed-rank test.

Table S1. Primers used for qRT-PCR analysis of mRNA expression and immunoprecipitated chromatin. Related to STAR Methods, *Quantitative RT-PCR* and *Chromatin immunoprecipitation.*

qRT-PCR primers for gene expression analysis		
Human		
Gene	**Forward (5'→3')**	**Reverse (5'→3')**
SETD7	AGTGTAAACTCCCTGGCCCT	GTTCACGGAGAAAAGAACGG
RPL29	CACACAACCAGTCCCGAAAA	TTGTGCTTCTTGGCAAAGCG
SUCLG1	TATGGCACCAAACTCGTTGGA	GAAGCCGTTGCTCCTGTCT
FH	GGAGGTGTGACAGAACGCAT	CATCTGCTGCCTTCATTATTGC
MDH2	TCGGCCCAGAACAATGCTAAA	GCGGCTTTGGTCTCGATGT
CS	GGTGGCATGAGAGGCATGAA	TAGCCTTGGGTAGCAGTTTCT
SDHA	CAGCATGTGTTACCAAGCT	GGTGTCGTAGAAATGCCAC
SDHB	ACAGCTCCCCGTATCAAGAAA	GCATGATCTTCGGAAGGTCAA
SDHC	AGAAACTGGACGGGCTCTAC	TGTGGCAGCGGTATAGAGAG
SDHD	CATCTCTCCACTGGACTAGCG	TCCATCGCAGAGCAAGGATTC
18s	GATGGGCGGCGGAAAATAG	GCGTGGATTCTGCATAATGGT
Mouse		
Gene	**Forward (5'→3')**	**Reverse (5'→3')**
Setd7	CGCTCAGCCACCAGGAGCAC	GTCCAGGTGCCCTTCCACGG
Csf2	ATGCCTGTCACGTTGAATGA	TGGTGAAATTGCCCCGTAGA
Il1b	ACGGACCCCAAAAGATGAAGGG	ACTGCCTGCCTGAAGCTCTTGT
Cd34	ACATCACCCACCGAGCCATA	AAACTCCTCACAACTAGATGCTTC
Mdh2	TACCTTGGACCGGAGCAGTT	TCATCCCGTGTCATTCCTGG
Sdhb	AGAGAAGGCATCTGTGGCTC	AGACTTTGCTGAGGTCCGTG
Fh1	AAGCCAGAGCTCGAATGACA	TGTAACCCTGGCAACAGGAC
Suclg2	GGTCTTACACAGCCTCTCGG	AGGTACCCTGTTTGCCTGTG
H3f3a	GAGCTCCAGCCGAAGGAGAAG	CAGTACCAGGCCTGTAACGATGAG
qRT-PCR primers for analysis of immunoprecipitated chromatin		
Region	**Forward (5'→3')**	**Reverse (5'→3')**
TNF promoter R1	CAGGCAGGTTCTCTTCCTCT	GCTTTCAGTGCTCATGGTGT
TNF promoter R2	AGAGGACCAGCTAAGAGGGA	AGCTTGTCAGGGGATGTGG
TNF promoter R3	GTGCTTGTTCCTCAGCCTCT	ATCACTCCAAAGTGCAGCAG

IL6 promoter R1	TCGTGCATGACTTCAGCTTT	GCGCTAAGAAGCAGAACCAC
IL6 promoter R2	AGGGAGAGCCAGAACACAGA	GAGTTTCCTCTGACTCCATCG
GH07J075877 R1	AAGATAAAGCTGCCCCTGGC	GAGGGCCCTGGGTAATTCAG
GH07J075877 R2	TCTTGCTCTCCGTGTTCCAC	CTTGGAGAGCGAGCATGGAT
GH07J075877 R3	GGCCTAAGCCCCACTGAAAA	TCCAAAGGCAGAAGACACCC
GH07J075877 R4	ATGAAGCCTCTGGTGATGGC	GAACCCCAGAAAGTGGGAGG
GH07J076068 R1	AGGACCTGGGACTCAAGCTA	GGGTAGCCCCTGGTTTATGG
GH07J076104 R1	CAGGGGTGCGCATTTTTCAG	TCTGTCCAGAACCCCAGTGA
GH07J076104 R2	GCTCACTGGGGTTCTGGACA	AGTGCCTCCAGAAAGGGTTG
GH07J076162 R1	ACCAAGTTGGAACCCCTAGC	GGGATAGGCCCGTCCTGTAT
GH07J076162 R2	CGCCCCTTCTGTAGAACCAA	GCAGTGGTAAAGCTCGTCCT
GH01J017206 R1	AGACGAGGACAGCTCAGACT	GAGGGCCCTGGGTAATTCAG
GH01J017206 R2	GAGGTTGCTCTGGGATCCTG	CCAACACCCAGGTGAAGGTT
GH01J017206 R3	GGGAAAGAGGGGCATGGAAT	GTGTAACCCCTTCCTCCTGC
GH01J017206 R4	CCTGATTCCCTGGATCTGGC	CACAGGACCGCAGATGGATT
GH01J017206 R5	AATCCATCTGCGGTCCTGTG	TGCATTGCTGCTTTTGCAGT
GH01J017126 R1	GGTTCCATTGACAATCTTGGCT	TCAAGGCTGAAGTGTGTCGG
GH01J017126 R2	AGACTCTGACGCTCCTGGTTA	GTGCTTGAGAAAGTTGTGTTTGTT
GH01J017125 R1	CCATCTTGGAAGCAGGGAGG	GCCCCTGAATTCTGACCCAA
GH01J017125 R2	TTGGGTCAGAATTCAGGGGC	CCCTTTGTCCAGCGAGAAGT
GH01J017125 R3	GGGAACTTCTCGCTGGACAA	GAATCAACGACCCAGGCTCA
GH01J017125 R4	ATCCTAGCCCTTCCTGGCTT	GGTGCCATGATTAACCCCCA
GH11J112174 R1	TCCGCATTAAAGCACCCGAT	CCCCGGGTGTGTCAATAAGT
GH02J084740 R1	TGACCCATGCAGACCAGTTC	GACTGGAGTGGGAGGAGAGT