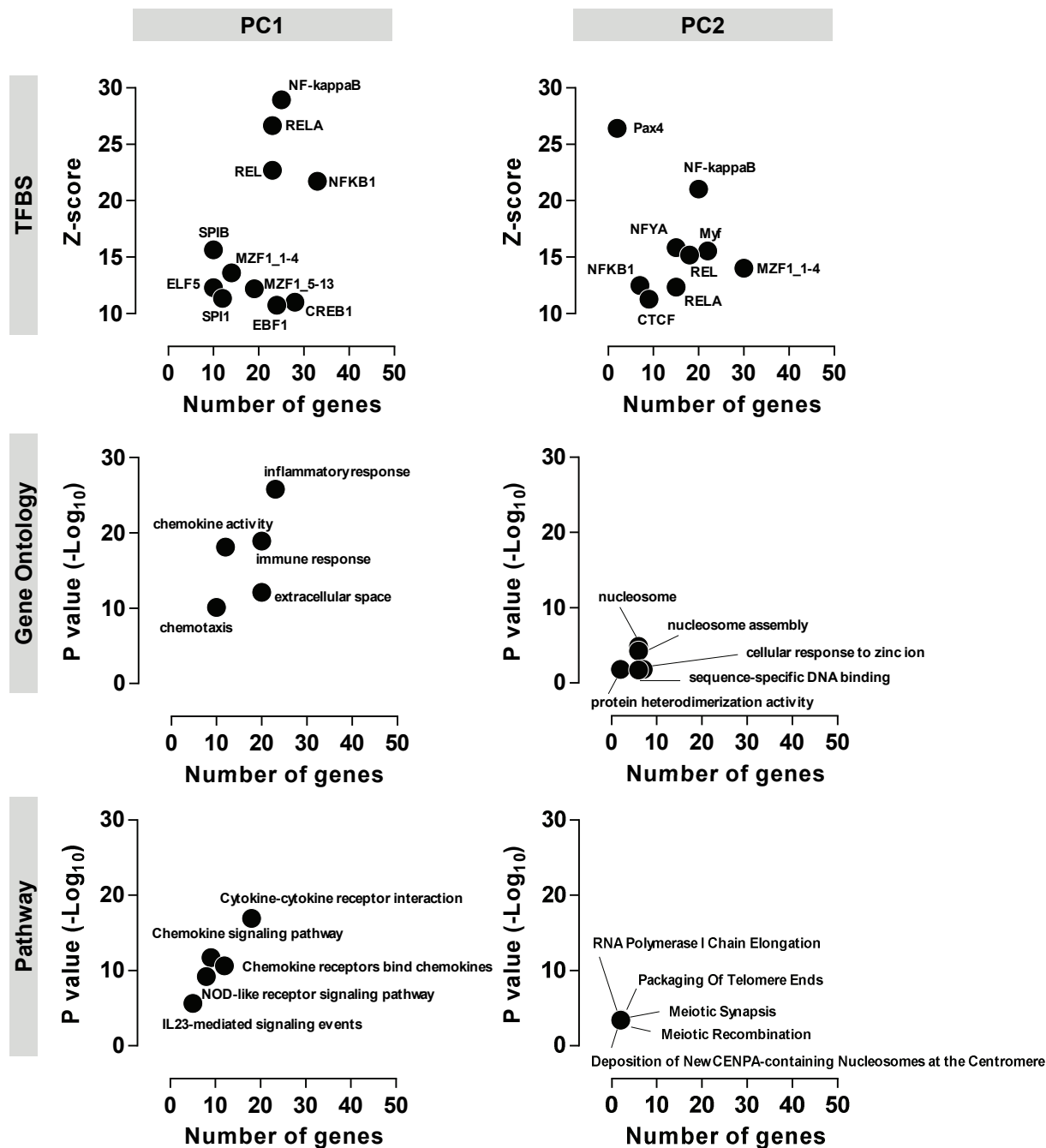


Supplementary Table 1.

Single nucleotide polymorphisms identified in the genome sequences of the TIGR4 and D39 *Algt* strains compared to their parental strains.

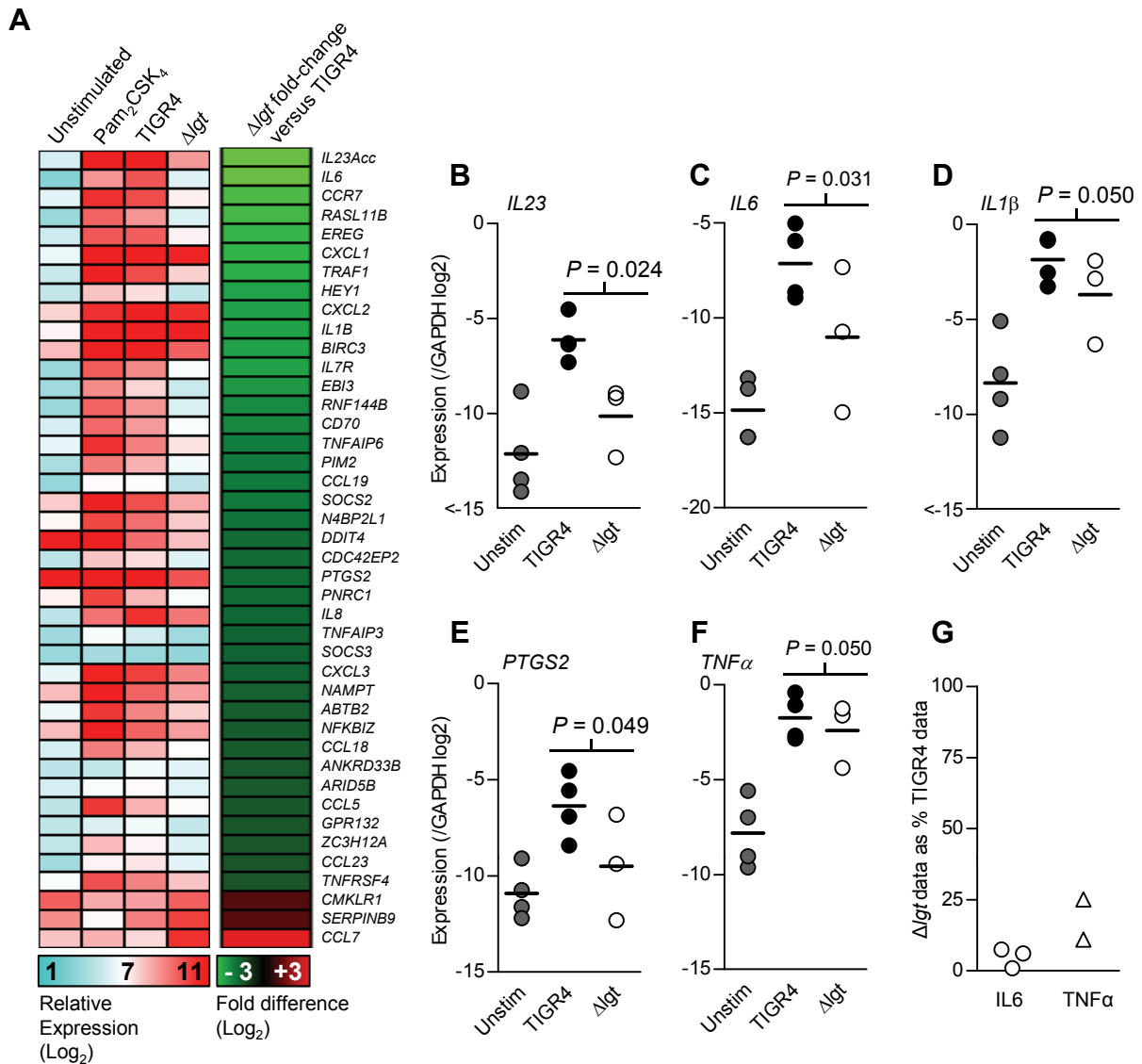
Genome position	Gene affected	Reference bp / codon	Mutant bp / codon	Notes
D39<i>Algt</i>				
1272512	SPD_1244 <i>hprK</i>	ATC	ATA	Synonymous mutation
1272548	SPD_1244 <i>hprK</i>	GCG	GCT	Synonymous mutation
TIGR4<i>Algt</i>				
730678	Intergenic region	C	T	n/a
1332449	SP_1413 <i>hprK</i>	GCG	GCT	Synonymous mutation
1332584	SP_1413 <i>hprK</i>	AAT	AAC	Synonymous mutation
2092182	SP_2175 <i>dltB</i>	CAT	CGT	Non-synonymous mutation: changes a histidine for an arginine at position 336 of 413

Supplementary Fig. 1



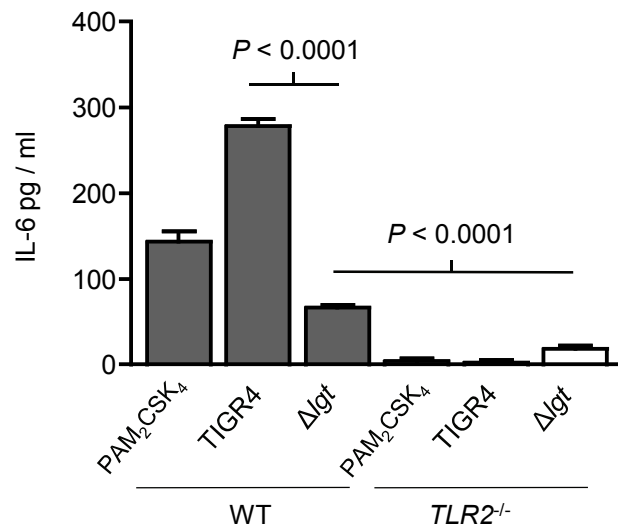
The top 50 transcriptional responses associated with principal component (PC)1 and PC2 in Figure 6D-E were subjected to transcription factor binding site (TFBS) enrichment analysis using oPossum (<http://opossum.cisreg.ca/oPOSSUM3/>), and to Gene Ontology and Pathway enrichment analyses using innateDB (<http://www.innatedb.com/>). In each case the test statistic (Z-score or corrected P value) and the number of genes associated with each annotation is presented as an individual data point. A Z-score >10 and $-\text{Log}_{10} P > 1.3$ are considered statistically significant.

Supplementary Fig. 2



(A) Gene expression heat map for mean relative gene expression levels and fold differences for the 42 genes showing significant differences in expression ($P < 0.05$) between human monocyte derived macrophages (MDM) from at least three different donors stimulated for four hours with TIGR4 or Δ lgt *S. pneumoniae*. (B-F) Validation using qPCR (normalised to GAPDH expression) of selected pro-inflammatory genes showing reduced expression in the transcriptional array analysis after incubation with Δ lgt strain compared to TIGR4. (G) Relative supernatant levels of IL-6 and TNF α (measured using a luminex system) in cell culture supernatants of MDMs incubated with the Δ lgt strain expressed as a percentage of the result for the same donor when incubated with the TIGR4 strain. For panels (B) to (G) each symbol represents results from a single donor, and the bars medians. P values are for comparisons of results for MDM stimulated with the TIGR4 or Δ lgt strains (paired t tests).

Supplementary Fig. 3



IL6 concentrations in cell culture supernatants from BMDMs obtained from C57BL/6 and *TLR2*^{-/-} mice incubated for 4 hours with the TLR2 agonist Pam₂CSK₄, or TIGR4 or TIGR4Δlgt *S. pneumoniae* strains. n = 3 to 4, error bars represent SEMs, and the stated P values were obtained using unpaired t tests.