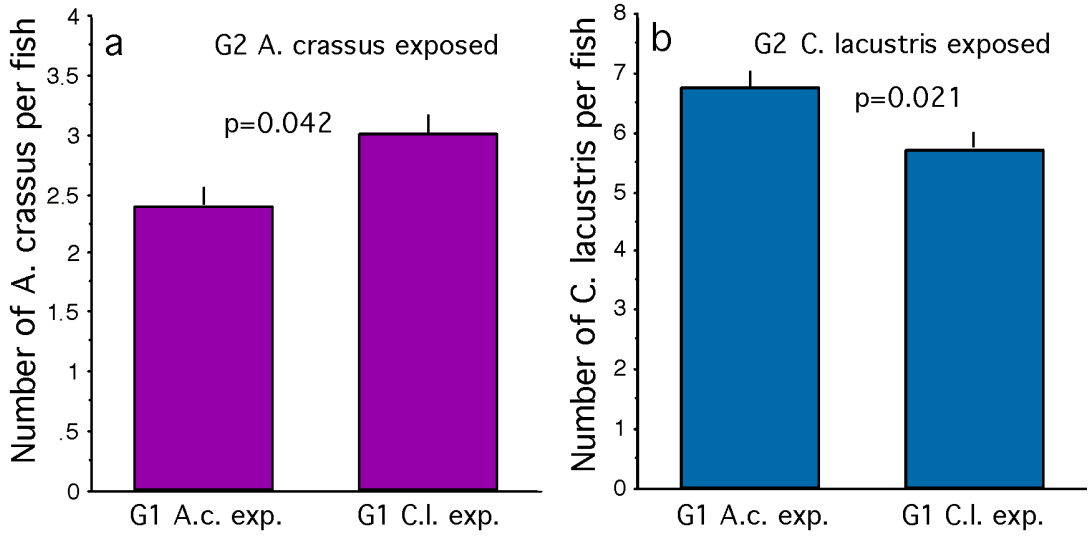
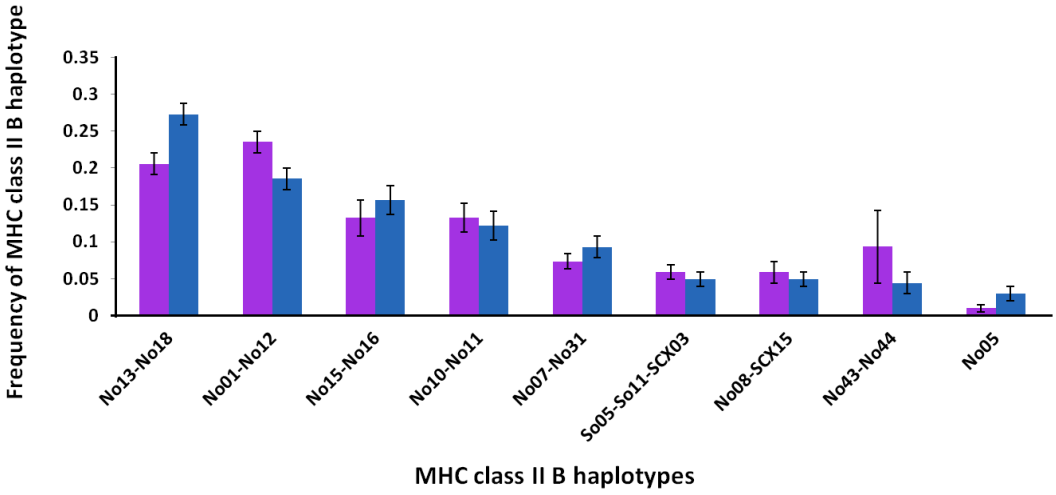
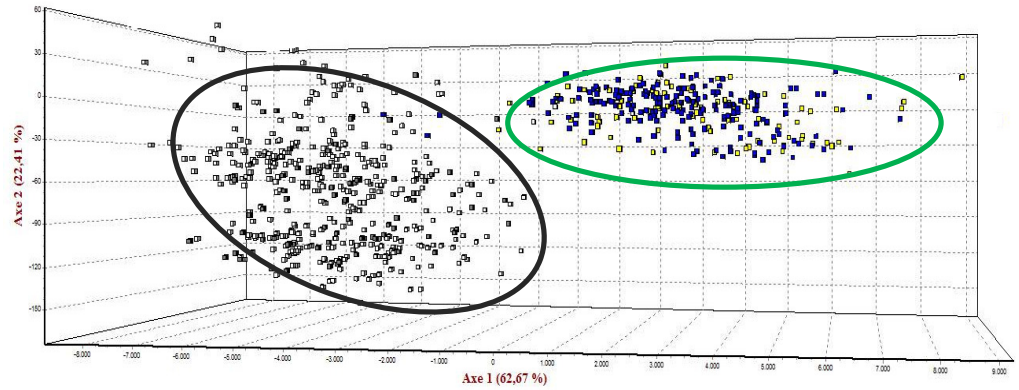
Supplementary Information



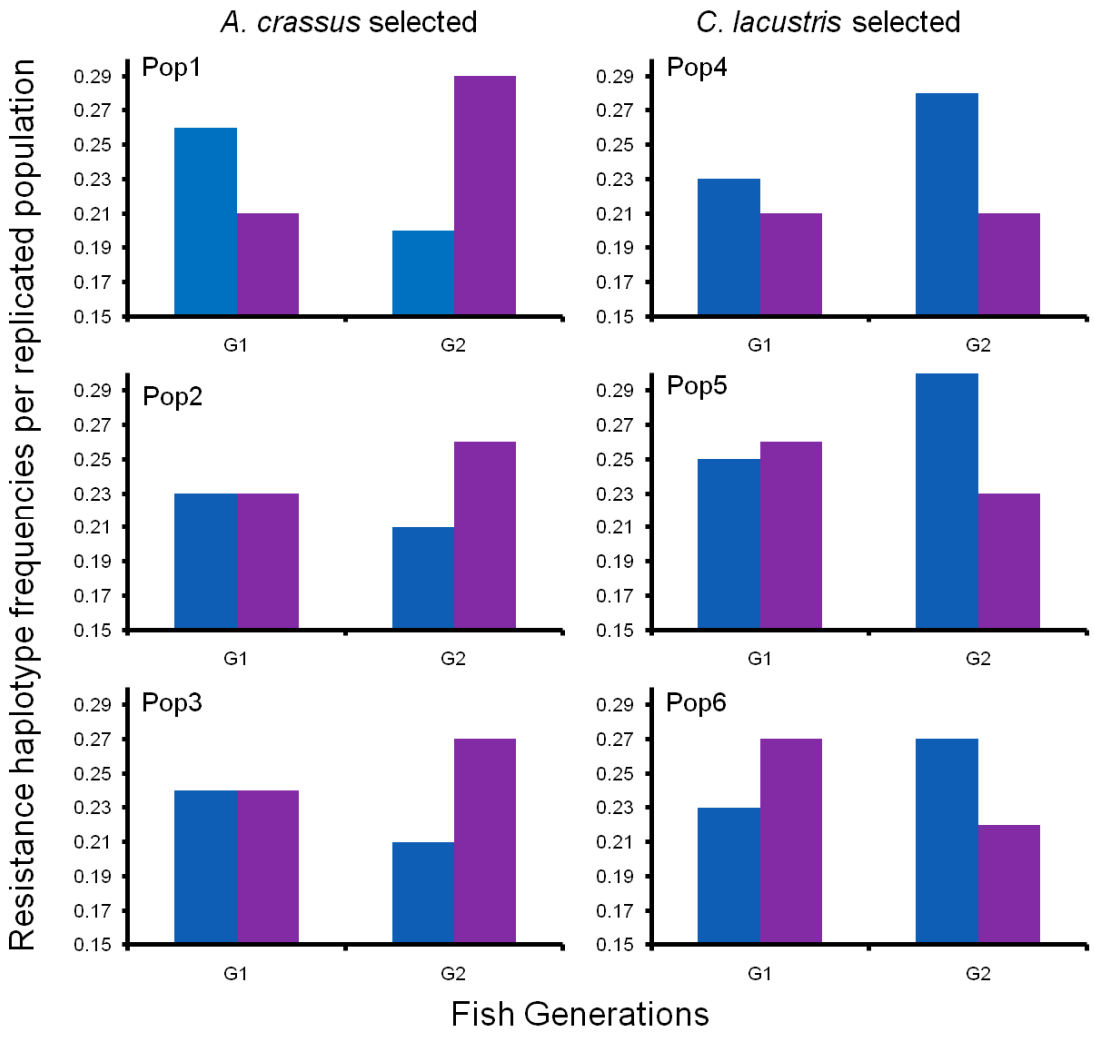
Supplementary Figure S1. Parasite mediated selection. Parasite load (number of parasites per fish) in G2, depending upon G1 parasite treatment (*A. crassus* or *C. lacustris* exposed, in purple and blue respectively. N= 450 *A. crassus* and N=450 for *C. lacustris*. Error bars are 1 standard error). G2 fish exposed to the same parasite as their parents show lower infection intensity compared to fish which arose from the other selection line respectively.



Supplementary Figure S2. Frequencies of MHC haplotypes. Differences in MHC haplotype frequencies in the second fish generation (G2). Frequencies are averaged (+/- SD) over the three replicates per treatment. Alleles segregate in linked haplotypes (NCBI accession numbers are given in parentheses) No13.No18 (AF395711/AY687846), No01.No12 (DQ016399/DQ016399), No15.No16 (DQ016410/DQ016417), No10.No11 (AF395722/AY687843), No31.No07 (GQ277654/AF395718), SCX15.No08 (EU541449/AY687842), So05.SCX03.So11 (DQ016402/AJ230191/DQ016404), No43.No44 (FJ360532/ FJ360533) and No05 (AY687829), which segregates as a single allele. Pools of haplotypes are significantly different between treatments ($N_{A.\ crassus}$= 450, $N_{C.\ lacustris}$= 450, ANOSIM, R=0.033, p=0.001). The haplotypes No13.No18 and No01.No12 contribute most to the difference by explaining respectively 20.3% and 19.6% of the total difference. Purple correspond to fish exposed to *A. crassus*, while blue correspond to sticklebacks exposed to C. *lacustris*.



Supplementary Figure S3. Trans-generational neutral variation. Factorial Analysis on microsatellite loci provided by Genetix[38]. G1 fish (blue and yellow dots) are surrounded by green circle, whereas G2 fish (grey and white dots) are surrounded by the black circle. Yellow dots represent G1 genotypes under *A. crassus* treatment, blue dots represent G1 genotypes under *C. lacustris* treatment, white dots represent G2 genotypes under *A. crassus* treatment and grey dots represent G2 genotypes under *C. lacustris* treatment. Differentiation was neither significant between G1 treatments nor between G2 treatments (Supplementary Table 2). Fish of the parental generation (G1) were randomly assigned to the experimental populations from 6 different families (i.e. 12 parents x up to 2 alleles =up to 24 microsatellite alleles per locus). The difference between the first and the second fish generation therefore arises from the recombination of all those potential genotypes.



Supplementary Figure S4. MHC frequency shifts. Variation of the resistance haplotype across the six replicated populations: 3 were selected by the nematode *A. crassus*, while the three others were under *C. lacustris* selection. Purple bars depict the frequencies of the haplotype No01.No12, while blue bars depict the frequencies of the haplotype No13.No18 in each population.

Supplementary Table S1. MHC polymorphism.

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            25   30   35   40   45   50   55   60   65   70   75   80   85   90

       ....|..*.*.*..|.**.|....|.*..|....|*...**...*...**...*|..*.|**..**.**|...
No13   ~~~~EYIRSSYFNKKEDTRFSSSVGKFVGFTEQGVKNAEYWNNDPSKLSAMKAQKEVYCLHNIQIKYDNALTKS
No18   ~~~~.F...Y.Y..L.F..............Y..R........A.L..GE..............W.N.M....
No01   ~~~~...D.YF...L.L..............Y..R.......N..Y.............NHVPVY.S......
No12   ~~~~.F.............................I.AN..K.A.F.............NHVPVY.TA.....
No15   ~~~~...D.Y.Y..L.Y.........Y.....R..RI.AA....A.F..GE.....A.......NW.N.M....
No16   ~~~~.....Y.Y..L.Y.........Y.....Y.....AA...N..I..RA.....A........D.N.M....
No11   ~~~~.F...V.Y..L.F..............Y..............V........G........D.TA.....
No10   ~~~~...D.Y.Y..L.Y..............R..............V........G....S...D.TA.....
No31   ~~~~.F.Q............................Y.AN..K.A.Y....R.W......NHV.SD.N.I....
No07   ~~~~...D.Y.Y..L.L..............Y..R.........................N.V...H.......
No08   ~~~~.....Y.Y..L.F..............Y.............I.........G...N....D.N.V....
SCX15  ~~~~...D.Y....L.Y..............Y..R........A.I..GE.....G.......NW.N.M....
So05   ~~~~.F........L.Y..............Y..R........A.L.............NH...E.N.M....
SCX03  ~~~~.F...Y..........................R..AA...N..I..N..........NHV..D.N.I....
So11   ~~~~.................................F.AA...N..I..RA.........NHVPVY.N.I....
No43   ~~~~...E.Y.Y..L.F..............Y..R......S........R....A...NHVPVY.S......
No44   ~~~~...D.Y......F.........Y........RI.AA....A.F..GE.....A.......NW.N.M....
No05   ~~~~.F.D.Y....L.Y..............Y..R........A.F....R........NHVPVY.N.V....
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Amino acid sequences of the 18 MHC class II*β* alleles found in the experimental fish. Dots represent identical amino acid as the reference (here No13). * denotes suspected peptide binding sites based on the crystallization of the MHC molecule by [39].

Supplementary Table S2. Neutral divergence.

Fst\p-val	G1. *A. crassus*	G1. *C. lacustris*	G2. *A. crassus*	G2. *C. lacustris*
G1. *A. crassus*	***	0.3773	0.0000	0.0000
G1. *C. lacustris*	0.0013	***	0.0000	0.0000
G2. *A. crassus*	0.1222	0.1305	***	0.2385
G2. *C. lacustris*	0.1283	0.1346	0.0038	***

Testing for population differentiation between parasite treatments at microsatellite loci. Wright fixation indices (Fst) were calculated using Arlequin 3.5[37]. Critical significance levels were corrected for multiple tests following the Bonferroni procedure. Below diagonal (***) are given Fst, above the diagonal are given p-values. G1_Ang = first generation of fish exposed to *A. crassus*, G1_Cam= first generation of fish exposed to *C. lacustris*, G2_Ang= second generation of fish exposed to *A. crassus* and G2_Cam= second generation of fish exposed to *C. lacustris*. The table shows no differentiation between G1 treatments. Contrary to MHC genes, differentiation is not observed at microsatellites in G2.

Supplementary Table S3. Linear mixed effect model on infection intensity in the second generation.

A	**Estimate**	**Coefficient**	**D.F**	**T value**	**P value**
(Intercept)	0.010	0.029	392	0.337	0.736
Treatment.G1	0.046	0.021	392	2.184	**0.030**
Presence of No01.No12	0.0256	0.030	392	0.850	0.396
Zygosity	-0.004	0.048	392	-0.077	0.938
Treatment.G1* No01.No12	-0.027	0.018	392	-1.524	0.128
Treatment.G1*Zygosity	0.083	0.036	392	2.293	**0.022**
No01.No12*Zygosity	-0.050	0.021	392	-2.353	**0.021**
Treatment.G1* No01.No12*Zygosity	0.039	0.025	392	1.592	0.112
B	**Estimate**	**Coefficient**	**D.F**	**T value**	**P value**
(Intercept)	0.039	0.0248	385	1.482	0.139
Treatment.G1	-0.016	0.020	385	-0.816	0.415
Presence of No13.No18	0.018	0.025	385	0.727	0.467
Zygosity	-0.002	0.032	385	-0.072	0.942
Treatment.G1 * No13.No18	0.004	0.017	385	0.232	0.816
Treatment.G1*Zygosity	0.058	0.030	385	1.895	0.059
No13.No18*Zygosity	-0.051	0.020	385	-2.605	**0.009**
Treatment.G1* No13.No18*Zygosity	-0.000	0.023	385	-0.004	0.996

A: Results from the linear mixed effect model on infection intensity of *A. crassus* in the second generation (G2). **B**: results of the linear mixed effect model on the infection intensity of *C. lacustris* in G2. Parasite intensity was log+1 transformed to meet normal distribution. Family was used as random factor. Treatment.G1 refers to whether G1 fish had been exposed to *A. crassus* or *C. lacustris*. Zygosity refers to whether individual G2 fish were homozygous (i.e twice the same haplotype) or heterozygous (two different haplotypes) for the MHC II*β*.

Supplementary Table S4. Linear mixed effect model on infection intensity in the first generation.

A	Estimate	Coefficient	D.F	T value	P value
(Intercept)	-0.070	0.059	196	-1.195	0.234
No01.No12	-0.211	0.063	196	-3.344	0.001
Zygosity	0.195	0.053	196	3.721	0.0003
No01.No12 * Zygosity	-0.508	0.069	196	-7.399	0.0001
B	**Estimate**	**Coefficient**	**D.F**	**T value**	**P value**
(Intercept)	0.020	0.058	196	0.341	0.733
No13.No18	-0.336	0.063	196	-5.297	0.000
Zygosity	-0.013	0.030	196	-0.428	0.670
No13.No18 * Zygosity	-0.281	0.072	196	-3.875	0.0001

A: results from the linear mixed effect model on infection intensity of *A. crassus* in the first generation (G1). **B:** results of the linear mixed effect model on the infection intensity of *C. lacustris* in G1. Parasite intensity was log+1 transformed to meet normality assumptions. Artificial pond ID was used as random factor. Zygosity refers to whether individual G2 fish were homozygous (i.e twice the same haplotype) or heterozygous (two different haplotypes) for the MHC IIβ.

Supplementary References

37. Excoffier L, Laval G, & Schneider S (2005) Arlequin ver. 3.0: An integrated software package for population genetics data analysis. . *Evolutionary Bioinformatics Online* 1:47

38. Belkhir, K., P. Borsa, et al. (1996-2004). GENETIX 4.05, University of Montpellier II, Montpellier (France).

39. Brown, J. H. *et al.* 3-Dimensional structure of the human clss-II histocompatibility antigen HLA-DR1. *Nature* **364**, 33-39, doi:10.1038/364033a0 (1993).