MAPPING OF QTL CONTROLLING RESISTANCE TO TRYPANOSOMOSIS IN N'DAMA X BORAN CATTLE

O. Hanotte[1], A. Korol[2], M. Agaba[3,7], P. Nilsson[4,8], A. Gelhaus[5], R. Horstmann[5], Y. Sugimoto[3], S. Kemp[4], J. Gibson[1], M. Soller[6] and A. Teale[1,7]

[1] International Livestock Research Institute (ILRI), P.O. Box 30709, Nairobi, Kenya
[2] University of Haifa, Institute of Evolution, Haifa 31905, Israel
[3] Shirakawa Institute of Animal Genetics, Fukushima 961-8006, Japan
[4] University of Liverpool, School of Biological Sciences, Liverpool L69 7ZD, UK
[5] Bernhard Nocht Institute for Tropical Medicine, Hamburg 20359, Germany
[6] Hebrew University of Jerusalem, Department of Genetics, Jerusalem 9190, Israel
[7] Present address: University of Stirling, Institute of Aquaculture, Scotland FK9 4L4, UK
[8] Present address: Waagstraat 8-7, 6701 EA Wageningen, The Netherlands

INTRODUCTION

Trypanosomosis is endemic in 7 million km^2 of sub-Saharan Africa and is one of the major constraints to livestock productivity, with 60 million cattle at constant risk of infection (FAO, 1991). The disease in cattle is largely due to infection with the tsetse fly-transmitted parasite *Trypanosoma congolense* and costs are estimated at over US$ 1.3 billion per annum (Kristianson *et al*., 1999). While most breeds of cattle are highly susceptible to trypanosomosis, some exhibit trypanotolerance, which is the ability to control levels of parasitaemia and anaemia, and to maintain productivity under challenge (Kemp and Teale, 1998). An F_2 resource population derived from trypanotolerant *Bos taurus* N'Dama bulls and susceptible *Bos indicus* improved Kenya Boran cows, was developed at the International Laboratory for Research on Animal Diseases (now the International Livestock Research Institute) for mapping the quantitative trait loci (QTL) controlling trypanotolerance (Kemp and Teale, 1991 ; Kennedy, 1994).

MATERIAL AND METHODS

One hundred and eighty two twelve month old F2 cattle were challenged with *T. congolense* via the bites of four infected tsetse flies, and then monitored weekly for 22 weeks for body weight (BW), anaemia (packed cell volume, PCV) and parasitaemia (dark ground buffy coat examination, PAR). A genome wide scan was performed based on genotypes for 477 markers (mostly microsatellites). Single trait maximum likelihood QTL interval mapping analyses were performed using the method of Korol *et al.* (2001). Statistical significance of putative QTL was determined by chromosome-wise permutation testing, with significance thresholds set to probability levels using the approach of pre-set false discovery rate (FDR) (Benjamini and Hochberg, 1995).

RESULTS

Descriptions of the trypanotolerance traits analysed are presented in Table 1. Summaries of significant QTL detected are presented in table 2. The FDR threshold was set at 10 %, which means that of the QTL presented in table 2, 90 % are expected to represent real genetic effects.

Table 1. Trypanotolerance traits included in QTL mapping analyses

- PCV Final	: Final PCV (day_{150} or day before treatment)
- PCV Minimum	: Minimum PCV recorded during the post challenge period (day_0 to day_{150})
- PCV Initial – Final	: Initial PVC (day_0) *minus* PCV Final
- PCV Initial – Minimum	: Initial PVC (day_0) *minus* PCV Minimum PCV
- PCV Variance	: Variance of the mean PCV values post-challenge (day_0 to day_{150})
- PCVD150	: Percentage decrease in PCV after challenge ((mean PCV $days_{0 \text{ to } 11}$) – (mean PCV $days_{13\text{-}150}$)) / (mean PCV $days_{0 \text{ to } 11}$)
- PCVD100	: Percentage decrease in PCV up to day 100 after challenge ((mean PCV $days_{0 \text{ to } 11}$) – (mean PCV $days_{13\text{-}100}$)) / (mean PCV $days_{0 \text{ to } 11}$)
- Body Weight Final/Initial	: Final body weight scaled by initial body weight, W_F/W_0
- BWD150	: Percentage decrease in body after challenge((mean BW $days_{0 \text{ to } 11}$) - (mean BW $days_{13\text{-}150}$)) / (mean BW $days_{0 \text{ to } 11}$)
- PAR Ln mean	: Ln of the mean number of parasites after challenge
- PAR Mean Ln	: Mean of ln (N_i + 1), N_i = number of parasites at day_i after challenge
- DR 60-150	: Detection rate of infection. Number of times an individual is detected infected between days 60 and 150

Where QTL are detected on a chromosome, effects (with the exception of those on *Bta*16) were in the same direction with respect to tolerance versus susceptibility for all traits. This is consistent with a single QTL affecting several correlated traits on these chromosomes. Thus, for each chromosome the weighted average location (Loc, in cM from the beginning of the linkage group) of the QTL is presented. For *Bta* 16 the direction of effects reversed from position 1.8 cM to position 18.0 / 19.6 cM, indicating the possible presence of two QTL. Estimates of QTL effects indicate that the trypanotolerant allele comes from the trypanotolerant N'Dama parent on *Bta* 2, 7, 16 (position 18.0 / 19.3 cM), 26, 27 and from the susceptible Boran parent on *Bta* 4, 13, 17, 20 and also for the largest QTL effect detected on chromosome 16 (position 1.8 cM).

CONCLUSION

Of the putative 10 trypanotolerance QTL detected, the expectation is that one will be a false positive given the FDR criterion of 10 % applied here. The five trypanotolerance QTL coming from the relatively susceptible improved Kenya Boran breed are all based on moderate to high levels of statistical significance, giving confidence that these effects are real. In the present case the results indicate that a synthetic breed from a cross of N'Dama and improved Kenya Boran could be selected to carry trypanotolerance alleles at more loci than either parent, with reasonable probability of achieving higher tolerance levels than currently exists in any existing breed. There are also exciting implications for the possible creation of novel high levels of other forms of disease resistance and adaptation, by appropriate combination of long separated breeds in cattle and other livestock species.

Table 2. Results of single trait interval mapping of trypanotolerance QTL

Traits	Chromosome	LOD	*P*-value	Loc ± sd (cM)	PEV (%)*
PCV Initial - Final	2	3.32	0.0008	42.6 ± 5.7	11.9 ± 5.3
PCV Initial - Minimum	**2**	4.31	0.0000	41.6 ± 4.3	15.3 ± 6.1
PCV Minimum	**2**	2.10	0.0209	53.2 ± 15.7	7.4 ± 3.8
PCV Initial	**2**	2.12	0.0227	46.3 ± 10.1	9.3 ± 4.0
PCVD 150	**2**	2.79	0.0048	46.7 ± 8.2	9.0 ± 4.9
PCVD 100	**2**	1.98	0.0238	45.9 ± 12.7	6.7 ± 4.2
Weighted			**44.4 ± 8.9**		
PAR Mean Ln	**4**	3.98	0.0001	73.7 ± 7.2	6.4 ± 0.6
PCV Final - Minimum	7	2.90	0.0280	43.1 ± 16.8	10.0 ± 5.3
PAR Ln Mean	7	3.73	0.0005	11.7 ± 11.2	11.3 ± 2.8
Body Weight 150	7	1.94	0.0275	64.0 ± 14.8	7.0 ± 3.4
DR 60-150	7	1.94	0.0313	38.5 ± 15.6	8.2 ± 4.2
Weighted			**47.8 ± 29.8**		
PCVD 150	**13**	2.83	0.0035	28.2 ± 7.6	14.1 ± 6.4
PCVD 100	**13**	2.45	0.0054	25.4 ± 8.5	11.3 ± 5.0
DR 60-150	**13**	2.27	0.0085	51.1 ± 13.7	6.7 ± 3.5
Weighted			**30.9 ± 13.4**		
PCV Initial - Minimum	**16**	3.50	0.0013	1.8 ± 8.2	9.0 ± 4.3
PCV Final – Minimum	**16**	1.64	0.0381	19.6 ± 13.2	5.2 ± 3.0
Body Weight 150	**16**	1.91	0.0181	18.0 ± 13.2	6.2 ± 3.4
Weighted			**18.8 ± 13.2**		
PCV Initial - Final	**17**	2.35	0.0043	0.5 ± 2.6	7.9 ± 3.9
PCV Final – Minimum	**17**	2.26	0.0062	1.4 ± 2.9	7.4 ± 3.6
PCV Variance	**17**	3.41	0.0004	0.8 ± 2.0	11.7 ± 4.8
PCV Final	**17**	2.75	0.0015	0.7 ± 2.5	8.2 ± 3.9
PCVD 150	**17**	4.18	0.0000	0.1 ± 0.9	12.8 ± 4.6
PCVD 100	**17**	3.28	0.0002	0.2 ± 1.5	10.5 ± 4.0
Weighted			**0.27± 1.4**		
PCV Initial – Minimum	**20**	2.40	0.0048	33.4 ± 4.9	7.7 ± 3.8
PCV Variance	**20**	2.68	0.0029	32.4 ± 5.8	8.2 ± 4.4
PAR Ln Mean	**20**	1.99	0.0165	7.8 ± 10.1	7.6 ± 3.8
PCVD 150	**20**	1.66	0.0303	31.2 ± 9.5	5.6 ± 2.8
Body Weight 150	**20**	1.89	0.0204	29.7 ± 7.8	6.6 ± 3.0
Weighted			**30.0 ± 9.8**		
PCVD 150	**26**	2.54	0.0026	23.1 ± 8.3	7.6 ± 3.7
PCVD 100	**26**	2.53	0.0029	25.7 ± 7.8	9.9 ± 3.9
Body Weight Final/Initial	**26**	1.97	0.0119	16.6 ± 8.6	6.7 ± 3.9
Body Weight 150	**26**	2.17	0.0088	12.0 ± 8.4	7.6 ± 3.9
Weighted			**17.4 ± 10.5**		
PCV Initial - Minimum	**27**	2.15	0.0138	14.5 ± 3.3	8.1 ± 3.8
PCV Variance	**27**	2.12	0.0116	17.3 ± 5.5	8.1 ± 4.0
PCVD 150	**27**	2.57	0.0041	16.6 ± 4.9	8.7 ± 4.4
PCVD 100	**27**	3.42	0.0005	15.0 ± 2.7	10.7 ± 5.0
Weighted			**15.3 ± 3.8**		

*PEV, proportion of phenotypic variance explained by the QTL

ACKNOWLEDGEMENTS

ILRI research was principally funded by program grants from the United Kingdom, Japan, The European Union, Ireland, Germany (BMZ) and France, and unrestricted funding from other donors to the CGIAR.

REFERENCES

Benjamini Y. and Hochberg, Y., (1995) *J. Royal Stat. Soc. Series B* **57** : 289-300.

FAO (1991) Programme for the Control of African Animal Trypanosomiasis and Related Development : Second meeting of the Inter-secretariat Coordinating Group. Food and Agriculture Organisation of the United Nations, Rome.

Kemp, S.J. and Teale, A.J. (1991) Bovine Genome Mapping and Trypanotolerance. The International Laboratory for Research on Animal Disease (ILRAD), Nairobi, Kenya 29-30.

Kemp, S.J. and Teale, A.J. (1998) *Parasitology Today* **14** : 450-454.

Kennedy, D.J. Leak, S.G.A., Kemp, S.J. and Teale, A.J. (1994) *Theriogenology* **41** : 226.

Korol, A.B., Ronin Y.I., Itskovich, A.M., Peng, J. and Nevo, E. (2001) *Genetics* **157** : 1789-803.

Kristjanson, P.M., Swallow, B.M., Rowlands, G.J., Kruska, R.L. and de Leeuw, P.N. (1999) *Agric. Systems* **59** : 79-98.