

Principles of marker-assisted selection

II. Quantitative traits

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Introduction

Most economically important traits of crop plants follow a continuous distribution caused by the action and interaction of many genes and various environmental factors. Phenotypic selection (PS) for such „quantitative traits“ is the more effective the higher their heritability (h^2), i.e. the proportion of the phenotypic variance explained by genotypic effects, is (Falconer and Mackay, 1996). For complex characters, such as grain yield, h^2 can be improved considerably by increasing the number of test environments and replicates when evaluating the respective progenies (lines, testcrosses, clones etc; Wricke and Weber, 1986). Molecular marker analysis allows to identify genome segments, so-called quantitative trait loci (QTL), contributing to the genetic variance of a trait and thus to select superior genotypes at these loci without uncertainties due to genotype by environment interaction and experimental error. Selecting for favorable QTL effects based on marker data (marker-assisted selection, MAS) therefore has great potential for improving quantitative traits. In evaluating the possible impact of MAS it is important to know that in general a quantitative trait is controlled by quite a large number of genes. Evidence for this is provided by long-term selection experiments (for theory see Falconer and Mackay, 1996). For example, in the famous Illinois High Oil Content experiment the oil content was steadily increased by about 15 additive genetic standard deviations over 75 generations (Slide 1). This means that at least 100 genes must have contributed to the genetic variance.

Reliability of QTL estimates

For MAS to be effective, reliable estimates of QTL positions and effects are required. An adequate power, precision and accuracy of QTL analyses can only be expected from large, well suited mapping populations, using a marker set with good genome coverage, and phenotypic values based on multi-environment field trials (Van Ooijen, 1992; Utz and

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Melchinger, 1994; Beavis, 1998; Slides 2-4). In a recent literature review of Kearsley and Farquhar (1998), updated by Lynch and Walsh (1998), it became evident that in most QTL studies the number of QTL is considerably underestimated and the percent of variation explained by markers is highly erratic (Slide 5). In a verification study with maize, Melchinger *et al.* (1998) found that only about 50% or less of the variance attributable to markers in the calibration experiment could be recovered in an independent sample of progenies of the same initial F₂ population (Slide 6). Such uncertainties of QTL analyses would seriously reduce the efficiency of MAS. Verification of individual QTL, e.g. by re-estimation in advanced generations or by evaluating near-isogenic backcross lines (NILs) contrasting in the genome segments of interest (Romagosa *et al.*, 1998), is therefore imperative. An additional need to verify estimated QTL effects are possible epistatic interactions of the QTL alleles with the genetic background of the material to improved (Phillips, 1999, Kern *et al.*, 1999).

Close linkage between marker loci and QTL is required not only for minimizing the bias of estimated QTL effects but also for maximizing the frequency of the desired QTL genotypes under MAS (Slide 7). The importance of close linkage is even higher, if MAS is continued in recurrent cycles with intercrossing the selected progenies after each cycle (Slide 8).

Theoretical studies on the efficiency of MAS

Marker-assisted selection may be based on marker information only (pure MAS) or on an index of marker plus phenotypic data (combined MAS) (Lande and Thompson, 1990). In both cases, markers can only lead to progress if gametic phase disequilibrium exists between the marker loci and their pertinent QTL. In generations derived from a cross between two homozygous lines, the disequilibrium is caused by linkage. In broader populations or whole gene pools, disequilibria may arise from drift or selection (Bulmer, 1980) but according to theory they can only be utilized by MAS if marker and trait loci are tightly linked.

The relative efficiency (RE) of MAS compared with phenotypic selection (PS) increases as h^2 decreases and the portion of the genetic variance explained by markers (p) increases (Slide 9). In addition, MAS gains in superiority as selection is intensified (Slide 10). Both MAS and PS are less effective if part of the QTL are linked in repulsion rather than coupling. But MAS is more affected than PS and therefore loses much of its merits in this situation (Slide 11). Interestingly, the marker spacing in the mapping population has much less effect on the gain from MAS than the prevailing gametic phase of the QTL (Slide 12).

Considering the large number of genes controlling quantitative traits it is important to note that the RE of MAS decreases as the number of QTL increases. This applies in particular to traits with low h^2 , i.e. to highly complex traits governed by very many genes. However, RE is

less affected if the QTL effects follow a geometric distribution with one or few of them explaining great portions of the genetic variance (Slide 13).

Uncertainties of QTL estimation may seriously inflate the expected gain from MAS. The bias due to erratic QTL positions and overestimated QTL effects leads to an overly optimistic appraisal of RE (Slide 14). Considering additionally the low power of most QTL analyses, further deductions from the theoretical RE values given above should be reckoned with. If unbiased QTL estimates exist, even markers explaining a small portion of the genetic variance can substantially increase the RE of combined MAS. This is reflected in the exponential rise of the heritability of the MAS index as p increases (Slide 15). Including marker information in the index is the more rewarding the smaller the heritability of the phenotypic values is.

In applying MAS to backcrossing (BC) programs the population size needed to end up with at least one genotype carrying all favorable QTL alleles progressively rises as the number of target QTL increases (Slide 16). The effort required for transferring more than six QTL alleles therefore appears prohibitive in most practical situations. Further, the more genes are transferred the larger is the portion of the genome being fixed for unwanted genes (linkage „drag“ by non-target genes linked to the QTL).

Studies on the economics of MAS are scarce so far. Xie and Xu (1998) showed theoretically that MAS is only superior over PS if the costs of the phenotypic data are not lower than those of the marker data and if p is high compared with h^2 (Slide 17). At the present state of marker technology, in most practical situations the first condition is only fulfilled if mapping costs are not taken into account.

Empirical results

Encouraging results were generally obtained by MAS in BC programs aiming at the transfer of quantitative traits from non-adapted resources to elite breeding lines. An example is the successful transfer of drought tolerance and cornborer resistance to tropical maize (Ribaut *et al.*, 1999; Bohn *et al.*, 1997; Slides 18 and 19, respectively). Tanksley and Nelson (1996) suggested to combine QTL analysis and BC line development in introgression programs and to directly apply the results to the improvement of NILs. Interestingly, in tomato this method was even successful if genome segments from wild relatives (*Lycopersicon pimpinellifolia*, *L. pennellii*) were used as donors (Tanksley *et al.*, 1996; Zamir and Fridman 1999). Recent results in rice seem to corroborate these findings (Slide 20). Positive results were also reported about marker-assisted early testing for combining ability in maize (Eathington *et al.*, 1997). QTL for testcross performance were identified in F_2 -derived S_1 lines and used to predict the combining ability of S_5 lines. The agreement between predicted and observed S_5 testcross yields was increased when the phenotypic data were supplemented by marker

information. For grain moisture, predictions based on phenotypic data alone were equivalent to those based on phenotypic plus marker data (Slide 21).

Only two applications of MAS for quantitative traits in other crops are known to the authors. Romagosa *et al.* (1999) compared PS, pure MAS, and tandem selection (first pure MAS, then PS) for the improvement of grain yield in DH lines of barley. The lines originated from the same cross as the mapping population but represented an independent sample. In this sample only two of four mapped QTL proved useful for selection. Pure MAS based on the QTL with the largest effect turned out to be as effective as PS. Inclusion of the second QTL further increased the gain from MAS whereas tandem selection did not enhance the response (Slide 22). Tuinstra *et al.* (1998) developed NILs in sorghum to verify the estimated gene effects for grain yield at three QTL. In their case, the NILs were directly derived from the mapping population. The superiority of the favorable over the unfavorable homozygous genotypes ranged from 8% to 34% among the three QTL tested (Slide 23).

Integration of MAS into breeding programs

At the present state of the art, MAS can significantly accelerate the improvement of quantitative traits in BC programs. It may also be useful for selecting among progenies in advanced generations of a mapping population. In both cases, only verified, important QTL effects should be included in the selection index. Overestimated or environment-specific QTL effects reduce the efficacy of the selection index or may even be counter-productive. Including QTL with minor effects adds little to the gain from selection but increases the overall linkage drag (fixation of non-target genes) and thus reduces the potential progress achievable by PS.

However, application of MAS to recurrent population improvement or to selection among experimental hybrids or synthetics would require universally (i.e. for a whole population) valid QTL/marker associations or periodically repeated QTL analyses for each group of breeding material. At present no economically realistic solution exists to meet these requirements in routine breeding. Future progress in functional genomics is expected to provide new approaches to the problem (see Outlook).

Theoretical studies of Hospital *et al.* (1997) show that under long-term selection combined MAS is superior to PS in the initial phase but becomes inferior once the target QTL are close to fixation. Interestingly, PS reaches higher selection limits than MAS, since unfavorable non-QTL alleles are less likely to be fixed. The authors therefore suggested a periodic alternation of MAS and PS. Further research is needed to evaluate the usefulness of this approach.

No studies are known to us on the optimum allocation of resources to marker-assisted breeding programs. Such studies would have to consider the efforts required for obtaining reliable QTL estimates, the costs of phenotypic and marker data assessment, the genetic and non-genetic-population parameters, and the operational possibilities of the breeder. Stochastic as well as deterministic approaches could be used for this purpose (Geiger and Tomerius, 1998).

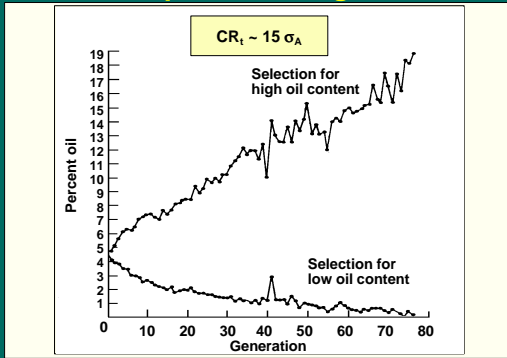
Outlook

Recent reviews on QTL estimation (Kearsey and Farquhar, 1998; Lynch and Walsh, 1998) revealed that different mapping populations generally share only small sets of common QTL. Thus very few QTL/marker associations seem to be valid in a genetically broad breeding population or a whole gene pool. To overcome this obstacle, research is needed to find out whether extremely tight linkages between marker loci and QTL may lead to highly conserved allele associations. If so, observing marker allele frequency changes in long-term selection experiments or determining markers that explain significant portions of the combining ability variance in diallel or factorial crosses might reveal universally applicable markers (Ribaut *et al.*, 1999; Vuylsteke, 1999). Another approach would be to conduct QTL analyses in genetically broad-based panmictic populations by means of highly saturated, integrated genetic marker maps. For a maximal efficiency of MAS, direct QTL-allele specific markers, such as STS (sequence tagged site) markers derived from cloned QTL alleles are needed (Sorrells and Wilson, 1997). Cloning of QTL alleles may be achieved by map-based as well as candidate gene approaches (Lynch and Walsh, 1998). In any case, it's a long way to go in most crops. Positive impacts in this regard can be expected from the rapid progress of functional genomics in *Arabidopsis thaliana* and other model plants.

Conclusions

Marker-assisted selection offers great potential for an accelerated improvement of quantitative traits in crop plants. Theoretical studies showed that (i) combined MAS (based on marker *and* phenotypic data) is more effective than pure MAS, (ii) the relative efficiency of MAS compared to PS increases as i and p increase and h^2 decreases, and (iii) uncertainties of QTL estimation as well as repulsion phase linkage between QTL seriously reduce the superiority of MAS. Experimental studies revealed that (i) MAS is well suited for introgressing exotic germplasm, (ii) MAS is effective in improving materials derived from mapping populations, (iii) pure MAS is equivalent to PS in most practical situations, and (iv) QTL estimates need to be verified before applying them to MAS. Further research is needed (i) to obtain universally valid QTL estimates for elite breeding populations or whole gene pools, (ii) to develop QTL-allele-specific, direct markers based on DNA sequences of the respective genes, and (iii) to optimize the integration of MAS into breeding plans.

Cumulated response to long-term selection



From Hartl 1988

1

Factors determining the power, precision, and accuracy of QTL estimation

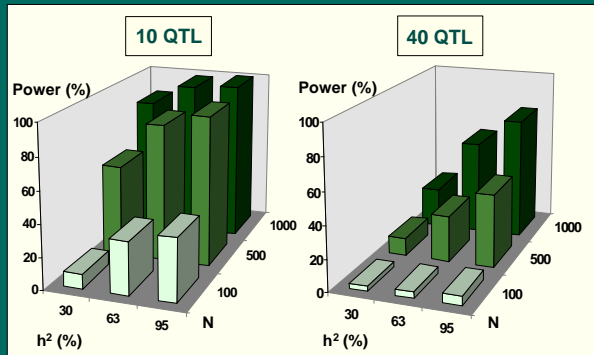
- **Power:** probability of identifying a QTL
- **Precision:** agreement betw. repeated independ. estimates
- **Accuracy:** agreement betw. estimates and true values

Main determining factors:

- Type and size of mapping population
- Number and distribution of (true) QTL
- Heritability
- Type and genome coverage of the markers
- Method of QTL data analysis

2

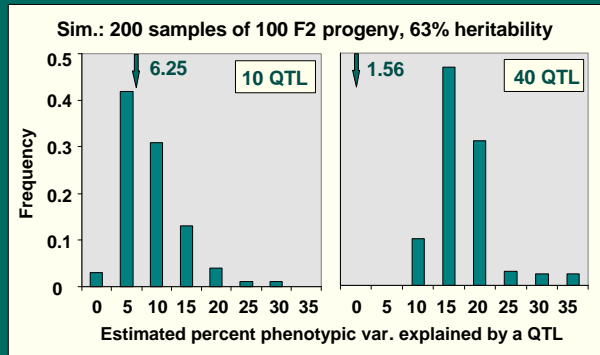
Power of identifying simulated QTL



Data from Beavis 1998

3

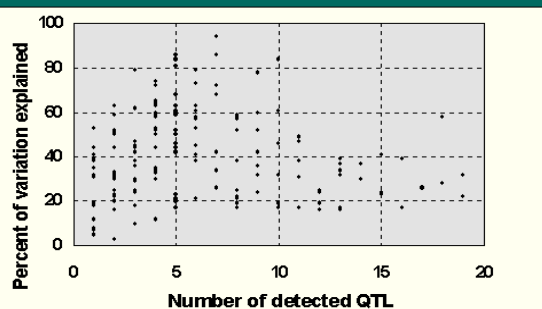
Accuracy of estimated genetic effects



From Beavis 1998

4

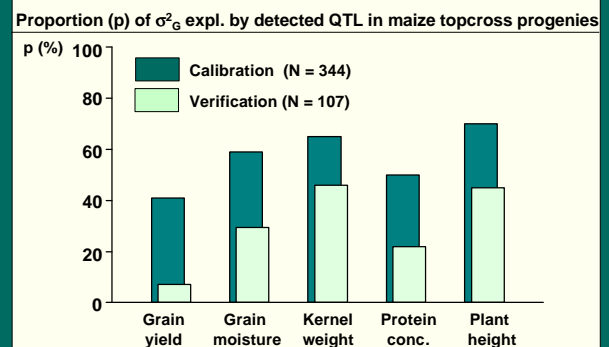
QTL number and total percent of variation explained - a survey of 52 experiments



From Lynch and Walsh 1998

5

Verification of QTL estimates in maize



After Melchinger et al. 1998

6

MAS: Close linkage required for high efficiency in F₂-derived populations

Recomb. frequency (r)	Array of QTL genotypes associated with homozygous favourable marker in F ₂			Allele frequ.
	QQ	Qq	qq	
0	1	0	0	1
0.02	0.960	0.039	0.000	0.98
0.04	0.922	0.077	0.002	0.96
0.08	0.846	0.147	0.006	0.92
0.16	0.706	0.269	0.026	0.84
General	(1-r) ²	2r(1-r)	r ²	1-r

7

MAS: Decay of efficiency by random mating

Recomb. frequ. (r)	Gene-ration (t)	Array of QTL genotypes associated with homozygous marker genotype		
		QQ	Qq	qq
0.04	1 = F ₂	0.922	0.077	0.002
	3	0.854	0.141	0.006
	9	0.692	0.280	0.028
0.10	1	0.810	0.180	0.010
	3	0.679	0.290	0.031
	9	0.452	0.441	0.108
General ¹		4(1/4+d) ²	8(1/4+d)(1/4-d)	4(1/4-d) ²

¹ Linkage disequilibrium: $d_i = 1/4 (1 - 2r)(1 - r)^{t-1}$

8

Relative efficiency (RE) of MAS compared with PS

h^2	Pure MAS		
	h^2	1.00	1.29
0.2	0.5	1.00	1.29
	0.2	0.63	1.05
	0.5	1.00	1.15
	0.8	0.79	1.05

¹ RE = $(p/h^2)^{1/2}$; ² RE = $[p/h^2 + (1-p)^2/(1-ph^2)]^{1/2}$
 Assumption: infinite population size

After Lande and Thompson 1990

9

Number of progenies to be evaluated under combined MAS relative to PS to be 99% certain of selecting at least one progeny with a genotypic value belonging to the $\alpha\%$ best fraction

α	p		
	0.2	0.4	0.6
10 %	1.20	1.42	1.64
5 %	1.25	1.53	1.82
1 %	1.39	1.84	2.36

p = prop. of the additive genetic variance associated with markers.
 Assumption: $h^2 = 0.5$.

After Knapp 1998

10

Influence of the linkage phase on the selection response

Sel. method	Repulsion
Pure MAS	23
PS : $h^2 = 0.1$ $h^2 = 0.3$	20
	33

-derived autogamous RIL population; randomly dispersed QTL; geometric QTL effect distribution; marker interval = 20 cM; selection aim: obtain 'extreme' genotypes accumulating as many advantageous alleles as possible by crossing pairs of sel. RIL.

After van Berloo and Stam 1998

11

Influence of marker spacing and linkage phase on the gain from 'practically' pure MAS

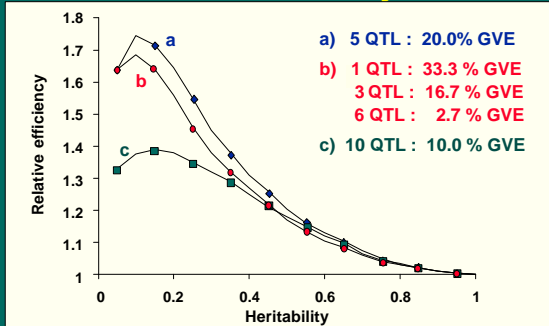
Linkage phase	p		
	20	10	1
Coupling		1.45	1.39
Repulsion	0.74	0.70	0.70

Ass.: 10 chrom. of 100cM length each; 15 QTL in total (1, 2, or 3 p. chrom.); sum of additive QTL effects = 15; MAS based on 7 markers; $\alpha = 0.25$; h^2

After

Lande 1995

Effect of heritability and genetic model on the relative efficiency of MAS



After Moreau et al. 1998

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Relative efficiency (RE) of combined MAS: Influence of QTL estimation bias

m^2	$h^2 = 0.15$		$h^2 = 0.45$	
	Bias correct.	Bias uncorr.	Bias correct.	Bias uncorr.
0.3	1.00	1.24	1.06	1.09
0.5	1.35	1.55	1.16	1.19
0.7	1.71	1.89	1.26	1.30

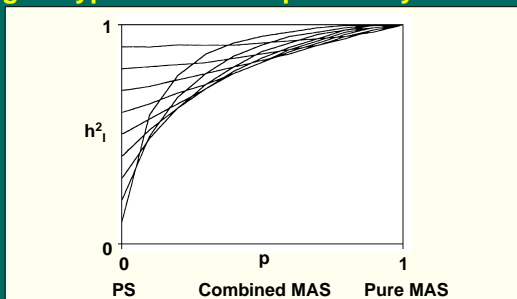
[†] Proportion of genotypic variance truly associated with markers: $m^2 = (1-2r)^2$ with r = recombination value.

Assumptions: N = 300 DH lines, five unlinked QTL of equal effects, 10 chromosomes with 3 markers each, P = 0.05 (type I error risk).

After Moreau et al. 1998

14

Heritability of the optimum MAS index (h^2) as a function of the proportion (p) of the genotypic variance explained by markers



From Knapp 1998

15

Minimum population size per generation for a three-generation marker-assisted BC program

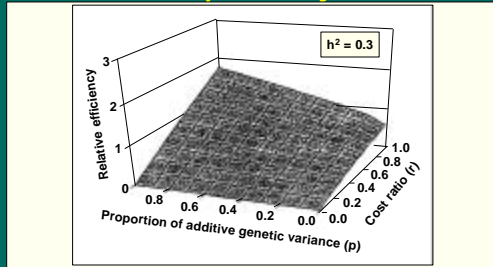
Length of CI (P = 0.01)	Number of QTL to be transferred			
	3	4	5	6
10 cM	54	118	256	551
20 cM	62	143	324	731
40 cM	77	190	461	1115

Foreground selection; 1 QTL per chromosome; 2 flanking markers per QTL; 0.01 risk level for obtaining at least one individual with the desired genotype.

After Hospital and Charcosset 1997

16

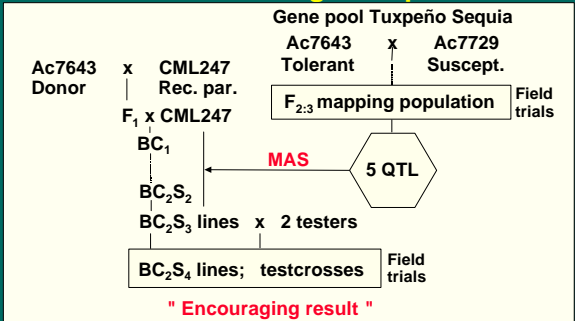
Efficiency of two-stage MAS[†] as a function of the cost ratio and the proportion of genetic variance explained by markers



[†] 1st stage pure MAS, 2nd stage combined MAS; r = cost ratio of assessing the phenot. value relative to the marker index.
From Xie and Xu 1998

17

Transfer of drought tolerance by marker-assisted backcrossing in tropical maize

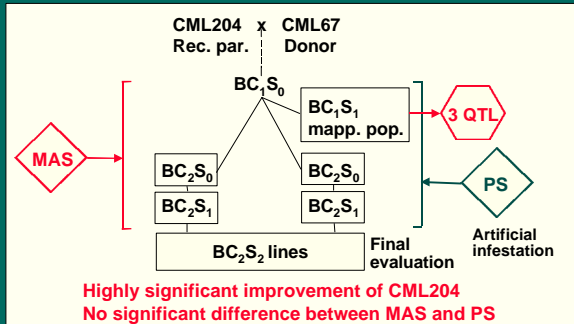


" Encouraging result "

After Ribaut *et al.* 1999

18

Transfer of SWCB resistance by MAS versus PS in maize



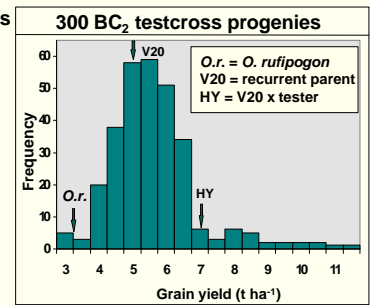
After Bohn *et al.* 1997

19

Introgression of favourable alleles from exotic germplasm - an example from rice

Introgressed segments from *O. rufipogon*

- 7 QTL for grain yield (GY) identified
- 4 QTL alleles from *O.r.* that increase GY by 0.98 to 1.22 t ha⁻¹
- 2 of the 4 QTL with no deleterious effect on plant height or maturity



After Xiao *et al.* 1998

20

Prediction of S₅ lines for testcross performance based on S₁ line data

Trait	Prediction based on		
	phenotype alone	markers alone	combined
	----- Reliability rank -----		
Grain yield	2	3	1
Grain moisture	1	2	1

Mapping pop.: 190 S₁ lines derived from BS11(FR)C7 x FRMo17, 157 RFLP markers;
Target pop.: 190 S₅ lines (derived from the above lines);
Evaluation criterion: Combining ability to a B73 type inbred tester;
Experiments: 8 environments in Illinois and Iowa 1992 and 1993.

After Eathington *et al.* 1997

21

Relative selection gain (%) for grain yield in barley

Strategy	WA 96 [†]	ID 96
PS	0.9	6.5
Pure MAS		
- QTL1	2.0	4.8
- QTL 1+3	5.0	6.6
Tandem selection		
- QTL1 → PS	0.5	7.1
- QTL 1+3 → PS	2.4	7.0

[†] WA 96 = Pullman, WA, USA, 1996; ID 96 = Aberdeen, ID, USA, 1996.
Mapping pop.: 150 DH lines from Steptoe x Morex → 4 QTL;
Verification pop.: 92 DH lines (independ. sample) → QTL 1 > QTL 3, QTL 2 and 4 inconsistent; Selected fraction α = 0.25.

After Romagosa *et al.* 1999

22

Grain yields[†] [g m⁻²] of NILs homozygous for the favourable (A) and unfavourable (B) allele at three QTL in sorghum

Genotype	QTL [§]		
	tM5/75	tH19/50	t329/132
AA	438	375	395
BB	326	305	365
Ratio AA/BB	1.34	1.23	1.08

[†] Averaged across 6 NILs per marker genotype and 7 environments.
[§] Identified in a mapping pop. of 98 RI lines derived from the cross TX7078 x B35.
The NILs trace back to 3 of the above RI lines per marker.

After Tuinstra *et al.* 1998

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MAS: Integration into breeding programs

- Tandem genotypic and phenotypic selection (Han *et al.* 1997, Romagosa *et al.* 1999)
- Alternate selection on markers with and without phenotypic evaluation of the candidates (Hospital *et al.* 1997; Gallais *et al.* 1997)
- Exploitation of gene-pool-specific marker-QTL associations (Georges *et al.* 1995, Vuylsteke 1999)

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