

**Molekulární genetik a zvířat 4**  
**Antonín Stratil**

**Česká zemědělská univerzita v Praze**

# Osnova

## Strategie detekce lokusů pro užitkové znaky

- kandidátní geny
- mapování QTL

## Mapování QTL – předpoklady

- vazbové mapy
- vhodné populace (experimentální křížení; outbrední linie)

## Mapování QTL – metodologie

- asociační testy
- intervalové mapování
- metoda vnuček

## Mapování QTL – statistické přístupy

- regrese
- metoda maximální pravděpodobnosti
- metoda nejmenších čtverců
  - \* prahy významnosti

## Detailní mapování QTL

- metoda IBD (identical-by-descent)
- analýza založená na gametické nerovnováze
- “selective sweep“
- kombinované intervalové mapování; mnohonásobné intervalové mapování
- následné linie kříženců

## Mapování QTL – výsledky a problémy

### Mapování QTL u prasat

### Mapování QTL u skotu

### Mapování QTL u jiných druhů hospodářských zvířat

### Studium exprese genů podmiňujících QTL

### Identifikace genů z QTL intervalů

## Základní vlastnosti lokusu

Frekvence alel (např.  $q^A = \frac{2AA + AB}{2n}$  )

Frekvence genotypů (např.  $q^{AA} = \frac{AA}{n}$  ;  $q^{AB} = \frac{AB}{n}$  ;....)

## Hardy-Weinbergova rovnováha

Vztah mezi frekvencemi alel a frekvencemi genotypů:

$$p^2 + 2 pq + q^2 = 1$$

$$(q^A)^2 + 2 q^A \cdot q^B + (q^B)^2 = 1$$

$q^A$ ;  $q^B$  - frekvence alely A; frekvence alely B

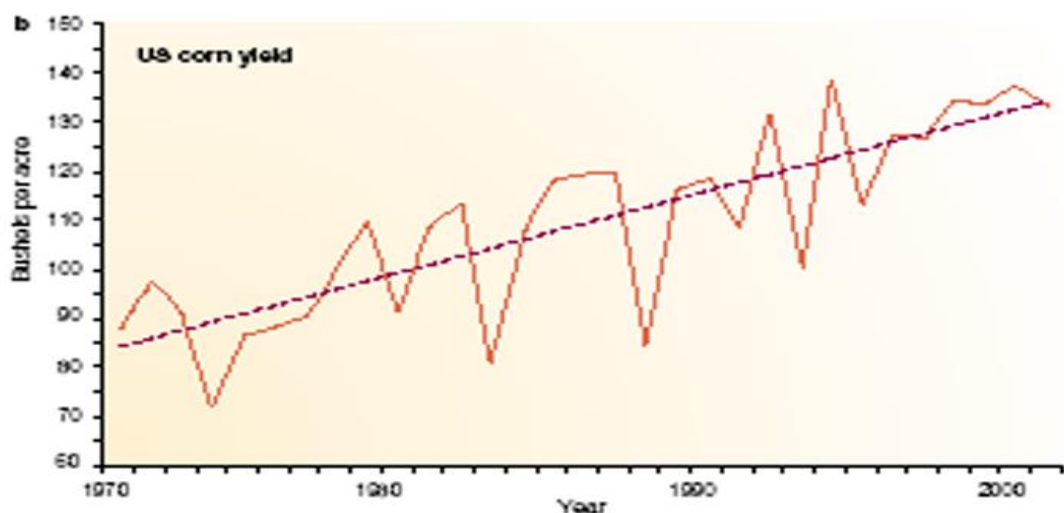
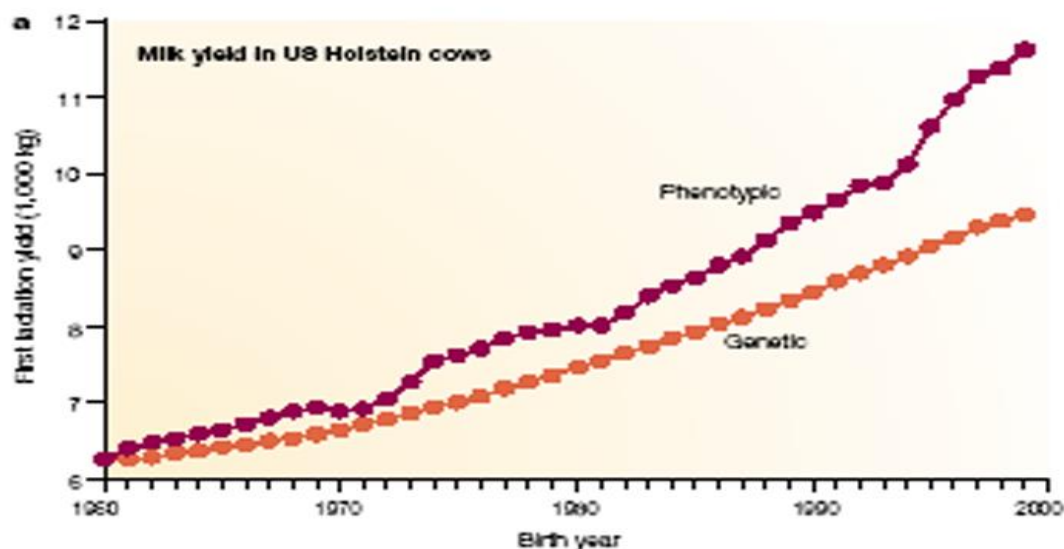


Figure 1 | Examples of genetic improvements in livestock and crops. a | Average milk production per lactation of US Holstein cows has nearly doubled during the past 40 years, as shown by the top line (phenotypic yield) (Animal Improvement Programs Laboratory; <http://aipl.arsusda.gov/pub/trend/tnd1114/>). More than half of this has been due to improved genetics, as shown by the bottom line, which plots the progression of the population average genetic value for milk yield. b | For corn, yields have increased fourfold during the past 60 years (<http://www.usda.gov/nass/aggraphs/corn/yld.htm>). Although yields have fluctuated from year to year, primarily due to weather, there has been a consistently increasing trend, as shown by the regression line (dashed). Again, more than half of this increased yield has been a result of genetic improvement<sup>22</sup>.

# Strategie detekce genů pro užitkový znak

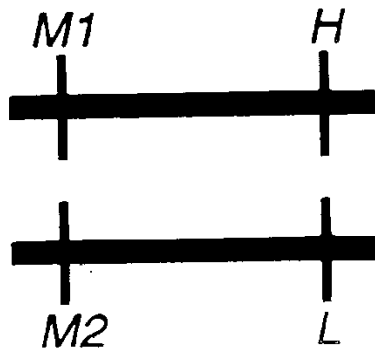
- **studium kandidátních genů** (zaměřuje se na omezený počet známých genů jejichž fyziologická funkce naznačuje, že genetická variabilita v genu může způsobit fenotypovou variabilitu studované užitkové vlastnosti)
- **celogenomová analýza** (analýza celého genomu zaměřená na identifikaci oblastí, které jsou asociovány s variabilitou ve studované vlastnosti, bez ohledu na to, jestli jsou v těchto oblastech přítomny kandidátní geny)

# Vztah mezi markerem a ETL (QTL)

marker nemusí být příčinný, ale může být pouze ve vazbě s příčinným lokusem

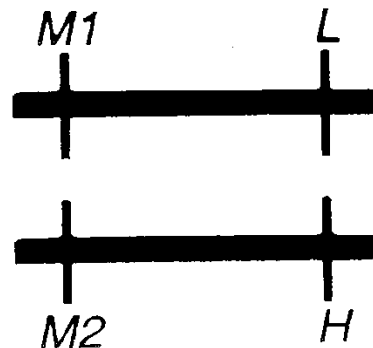
(studium asociace)

**Kanec 1**



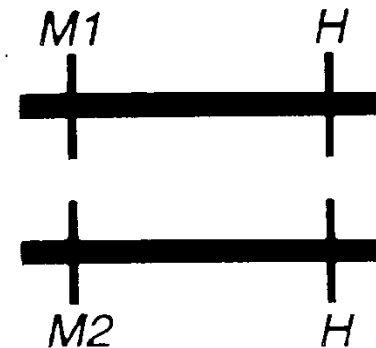
**M1 alela je asociována s vysokou užitkovostí u potomstva**

**Kanec 2**



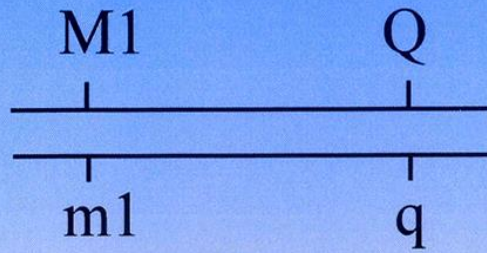
**M1 alela je asociována s nízkou užitkovostí u potomstva**

**Kanec 3**

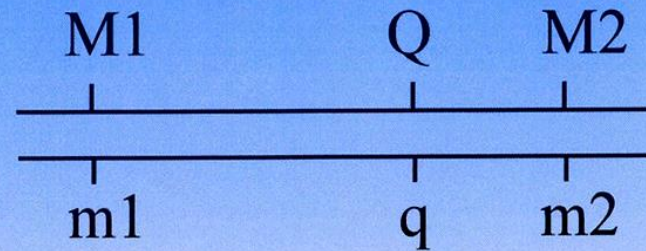


**Potomstvo s alelami M1 a M2 má stejnou užitkovost**

# Single vs multiple markers



Single markers: not possible  
to distinguish between  
**QTL effect** and **QTL position**



Two (or more) markers: a lot  
less confounding between  
**QTL effect** and **QTL position**

*Proper mapping of a QTL requires the use of  
multiple marker genotypes*

# Mapování QTL - předpoklady

- středně husté vazbové mapy
- vhodné populace:
  - experimentální křížení (prasata, drůbež, ovce, masný skot)
  - outbrední rodokmeny (skot)

**Experimentální křížení** u druhů s větším počtem potomků a krátkým generačním intervalem. Používají se třígenerační rodiny vzniklé křížením kontrastních plemen (např. u prasat divoké prase x pietrain, nebo meishan x pietrain). Toto uspořádání zajišťuje segregaci v markerech i QTL.

**Outbrední rodokmeny** – u skotu

Metoda vnuček (granddaughter design). Testování markerů a vazbová analýza se provádí u synů a průměry užitkovosti jejich dcer jsou používány jako hodnoty užitkových vlastností.



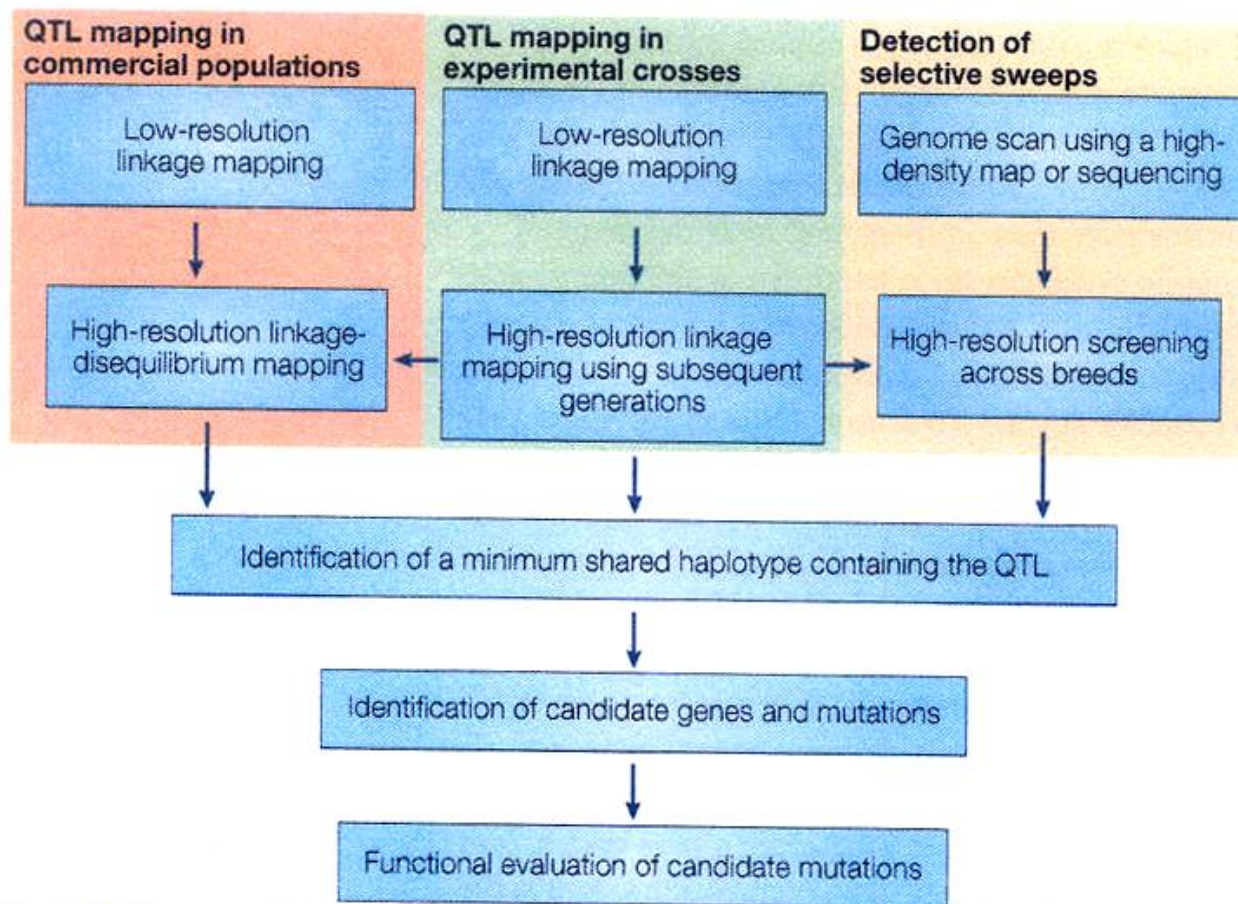


Figure 3 | **Approaches to mapping and positional cloning of QTLs in domestic animals.** The segregation of quantitative trait loci (QTLs) can be detected in family material from commercial populations or from experimental crosses. QTL mapping in intercrosses between divergent populations has an excellent power for QTL detection, owing to the high heterozygosity at QTLs in the  $F_1$  generation. However, the resolution is rather poor as it is based on those recombination events that occur in the experimental pedigree. So, an initial low-resolution mapping in an intercross can be followed up by high-resolution linkage-disequilibrium mapping within a commercial population, if the QTL is segregating within such populations, or by the detection of the minimum shared haplotype representing a selective sweep. The identification of the causative mutation for the insulin-like growth factor 2 (*IGF2*) QTL in pigs is an excellent illustration of how this combined approach has been used (BOX 3).

# Mapování QTL - metodologie

## - asociační testy (association tests)

Zjišťuje se asociace genotypů určitého genu (**kandidátního genu**) nebo markeru s užitkovým znakem. Může být velmi efektivní, jedná-li se o **příčinný gen** (i pro geny s malým účinkem). Studium zjištěných účinků genů (markerů), které jsou ve vazbě s QTL je závislé na síle vazby a velikosti QTL efektu.

## - intervalové mapování (interval mapping)

Metoda pro testování efektů poloh v intervalech mezi markery (neznáme genotypy QTL v polohách mezi markery, ale při použití vazbových vzdáleností markerů můžeme zjistit pravděpodobnosti genotypů v těchto polohách).

## - metoda vnuček (grand-daughter design)(u skotu)

Každá rodina zahrnuje jednoho býka, jehož synové (20 a více) byli vybráni jako plemeníci. Každý syn má 100 a více dcer s fenotypovými údaji, a ty jsou použity pro odhad přesné plemenné hodnoty býků. Genotypy markerů jsou zjišťovány pro děda (grand-sire) a jeho syny, a QTL mapování je realizováno analýzou segregace markerů od děda k synům ve vztahu k rozdílům v plemenné hodnotě. Jestliže děd je heterozygotní v QTL s velkým účinkem, u synů, kteří zdělili příznivou alelu, bude možno očekávat vyšší plemennou hodnotu než u synů, kteří zdělili nepříznivou alelu.

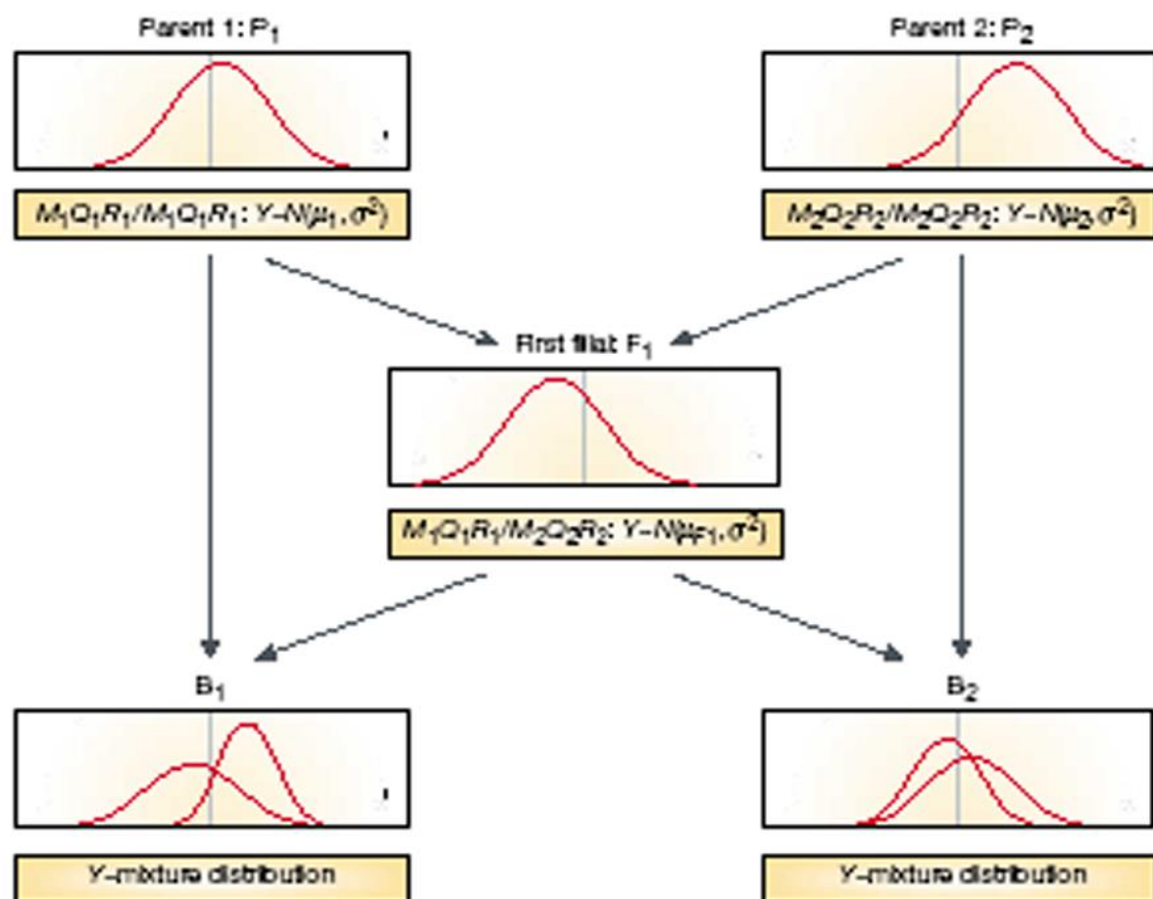
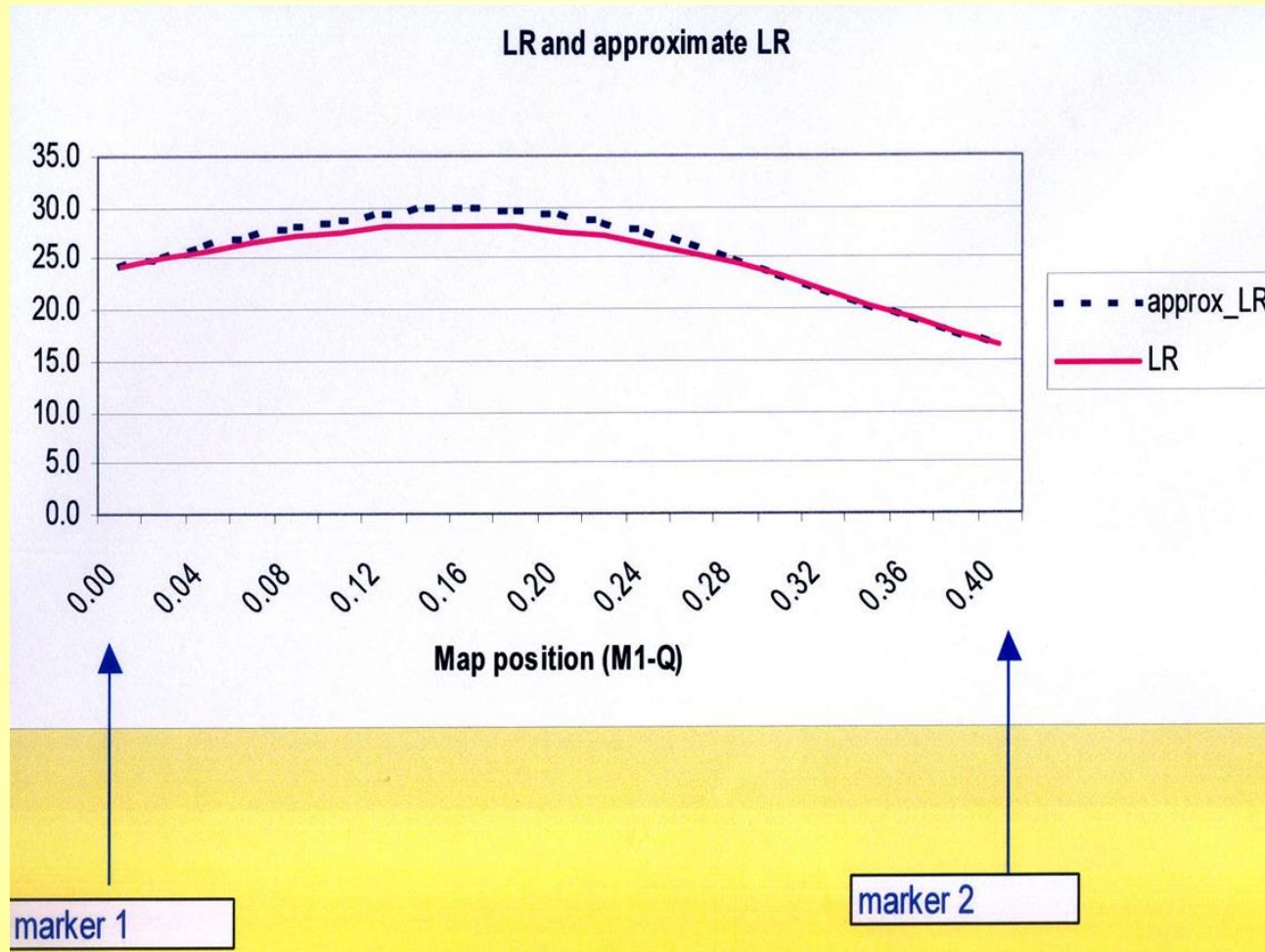


Figure 1 | Experimental design for quantitative trait loci mapping. Standard backcross mating design for markers  $M$  (with alleles  $M_1$  and  $M_2$ ) and  $R$  (with alleles  $R_1$  and  $R_2$ ). The hypothetical quantitative trait locus (QTL)  $Q$ , with alleles  $Q_1$  and  $Q_2$ , is also illustrated. The haplotypes are separated by a solidus. The trait value ( $Y$ ) is assumed to have a normal distribution ( $N$ ) with mean  $\mu$  and variance  $\sigma^2$  in the parental populations  $P_1$  and  $P_2$ .  $B_1$  and  $B_2$  represent the reciprocal backcross progeny. The trait value in the backcross progeny has a distribution that represents the mixture of the  $F_1$  trait distribution and the respective (recurrent) backcrossed parental line. Statistical tools are applied to test whether there is an association between the genotypic and quantitative trait information collected from either backcross population.

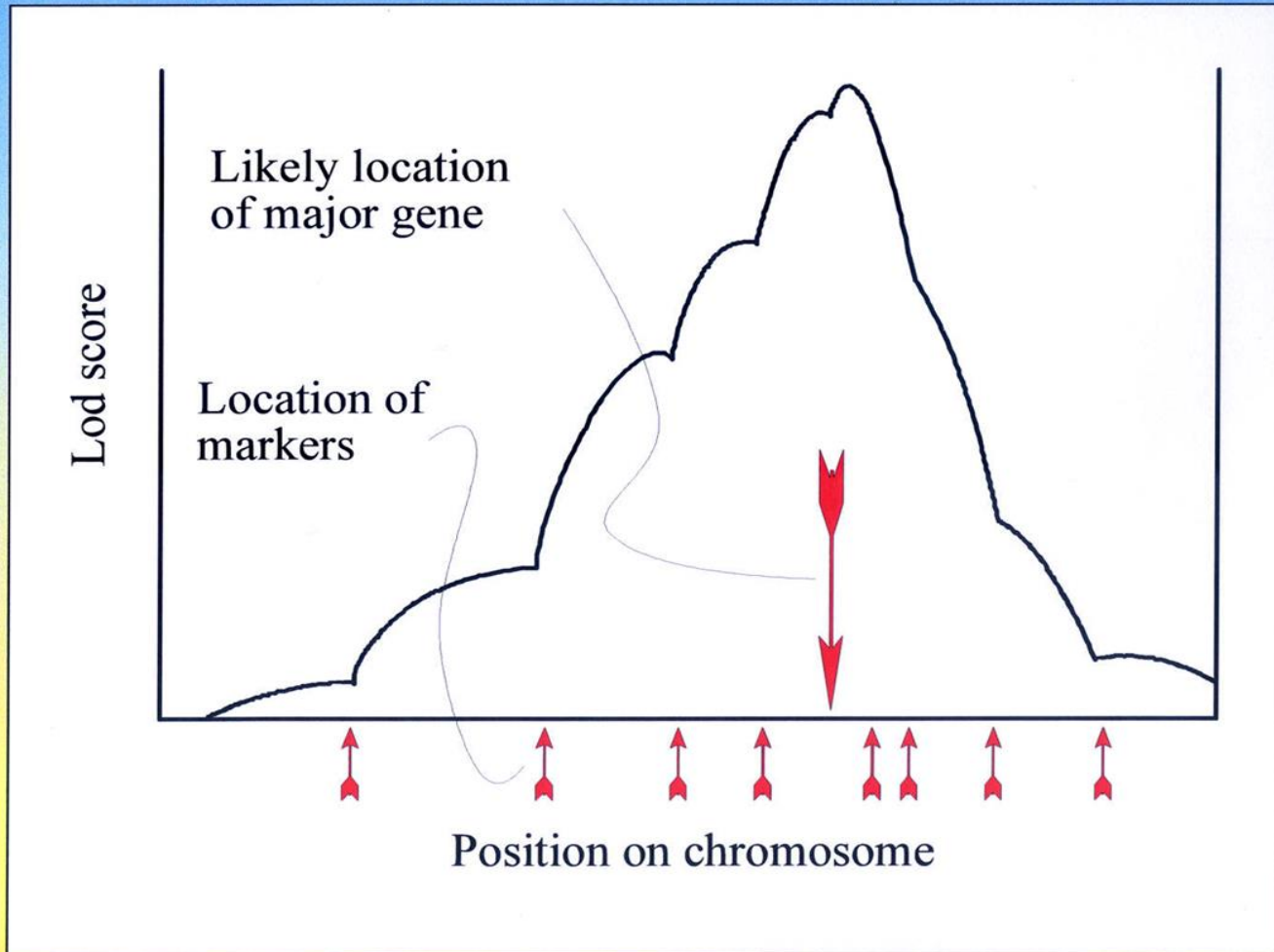
# Intervalové mapování

- **Intervalové mapování je metoda pro zjišťování pozice QTL v intervalech mezi markery.**
  - **neznáme genotypy v pozicích mezi markery, ale když máme vazbové mapy ukazující vzdálenosti markerů a jejich genotypy, můžeme zjistit pravděpodobnosti genotypů QTL v určitých pozicích.**
  - **výpočet je založen na metodě maximální pravděpodobnosti (maximum likelihood) (Lander a Botstein, 1989) a analýzy LOD skóre, a provádí se pro každý 1 – 2 cM.**
- Dalšími používanými metodami je analýza regrese a metoda nejmenších čtverců.**
- Pro celogenomovou analýzu je nutné stanovit prahy významnosti (significance thresholds).**

# Intervalové mapování QTL



# QTL detection with markers



## Mapování QTL u skotu – metoda vnuček (grand-daughter design)

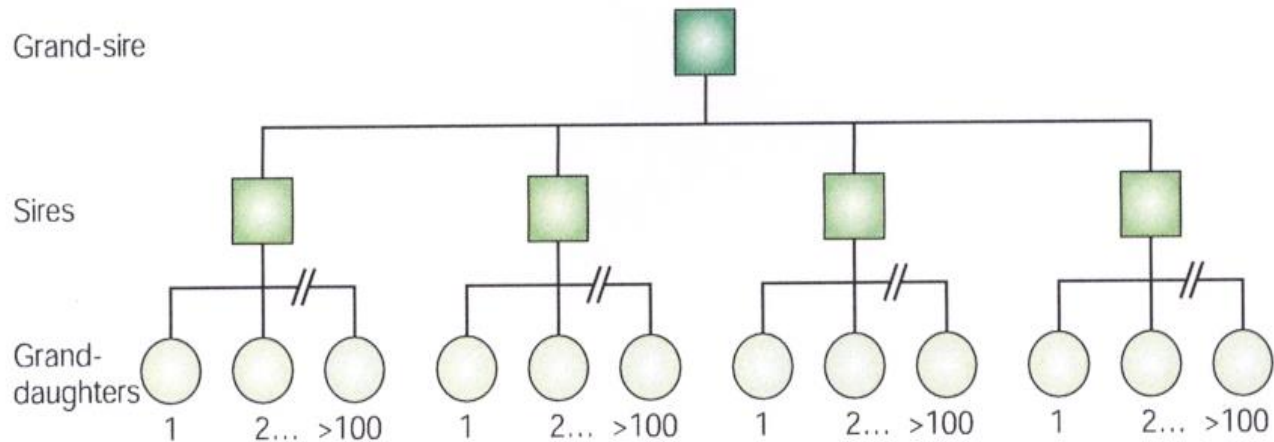


Figure 3 | **Half-sib families and breeding value.** The pedigree illustrates the grand-daughter design for mapping quantitative trait loci (QTL) using half-sib families<sup>70</sup>. Each family comprises one grand-sire whose sons (20 or more) have been selected as sires. Each son has 100 or more daughters with phenotypic data, and these are used to estimate accurate breeding values for the sires, even for traits with a considerable environmental influence. Marker genotypes are only collected for the grand-sire and his sons, and QTL mapping is carried out by analysing the segregation of markers from the grand-sire to the sires in relation to differences in breeding values. If the grand-sire is heterozygous for a QTL with a major effect, the sons that have received the favourable allele will tend to have higher breeding values than those that received the unfavourable allele.

# Detailní mapování QTL

(high-resolution mapping)

- nezbytná větší hustota markerů ve studovaném intervalu
- potomstvo s rekombinantními chromozómy v dané oblasti  
(vyžaduje velké množství potomků  $F_2$  generace nebo generace zpětného páření)

- **kombinované intervalové mapování** (composite interval mapping), a
- **mnohonásobné intervalové mapování** (multiple interval mapping)

Metody, které zvyšují citlivost QTL mapování ve studovaném chromozómovém intervalu eliminací genetického pozadí způsobeného segregací v ostatních QTL zahrnutím jiných markerů (které nejsou ve vazbě s testovanou pozicí) jako kofaktorů ve statistickém modelu.

- **metoda IBD** (identical-by-descent)(u mléčného skotu)

Kombinuje **gametickou nerovnováhu** a určování QTL genotypů pomocí segreganční analýzy existující rodiny s využitím markerů. V první fázi se identifikuje býk metodou vnuček nebo dcer, který by měl mít QTL genotyp Qq. V druhé fázi se provádí analýza určitého počtu jedinců pomocí vazbové mapy s vysokou hustotou markerů v oblasti předpokládané lokalizace QTL za účelem identifikace sdílených chromozómových segmentů, ve kterých se nacházejí alely QTL s velkým účinkem. Jinými slovy, nejdříve se použije vazbová analýza ke stanovení QTL genotypu a pak se pomocí vysokého počtu genetických markerů zjistí **minimální haplotyp**, který je sdílen (identical-by-descent) zvířaty nesoucími Q alelu.

- **analýza založená na gametické nerovnováze** (linkage disequilibrium analysis)

studuje se v outbredních populacích. Využívá nenáhodných asociací alel v různých lokusech, které existují v populaci, a tím se zvyšuje citlivost mapování.

- **následné linie kříženců** (advanced intercross lines)(u slepic a modelových organismů)

Následující generace ( $F_3$ ,  $F_4$  a další) kříženců, které jsou vytvářeny za účelem detailního mapování QTL.



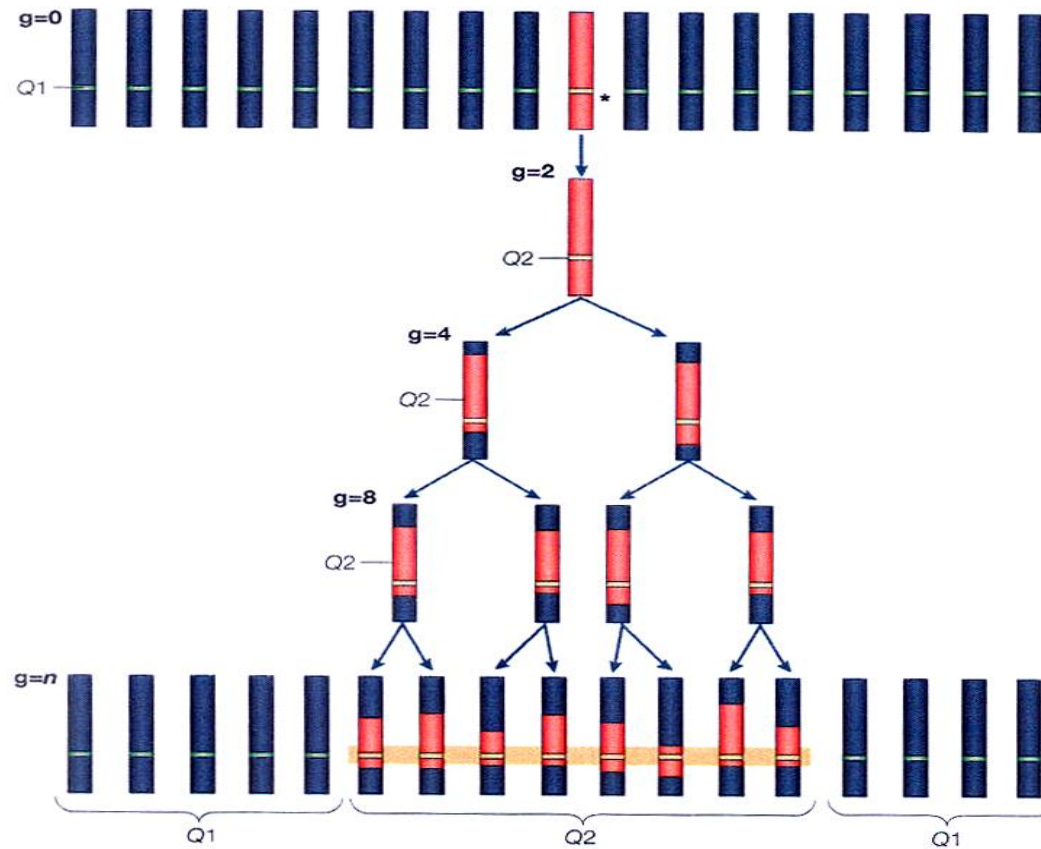
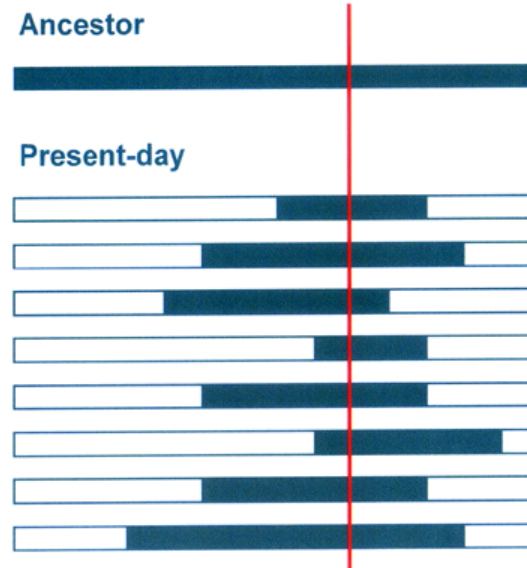


Figure 1 | **Identical-by-descent mapping.** Assume that the quantitative trait locus (QTL) allele  $Q2$  originates by mutation from allele  $Q1$  at generation 0. There will be a complete linkage disequilibrium between  $Q2$  and alleles at all other loci in the first gamete carrying  $Q2$ . This linkage disequilibrium will then gradually decay through each generation owing to recombination, but linkage disequilibrium will persist for closely linked loci. At generation  $n$  a sample of chromosomes are collected and classified ( $Q1$  or  $Q2$ ) by segregation analysis. Genetic markers and sequence analysis are then used to define the minimum haplotype that is shared identical by descent among animals carrying  $Q2$  (indicated by the yellow bar).

# Linkage Disequilibrium

- Chromosomes are mosaics
- Extent and conservation of mosaic pieces depends on
  - Recombination rate
  - Mutation rate
  - Population size
  - Natural selection
- Combinations of alleles at very close markers reflect ancestral haplotypes



# Gametická nerovnováha (vazbová nerovnováha)

(gametic disequilibrium; linkage disequilibrium)

Nenáhodná asociace alel různých lokusů.

Ve dvoulokusovém systému se dvěma alelami v každém lokusu jsou možné čtyři gamety:

Gamety	$A_1 B_1$	$A_1 B_2$	$A_2 B_1$	$A_2 B_2$
Frekvence	$x_{11}$	$x_{12}$	$x_{21}$	$x_{22}$

Počítáme hodnotu  $D$ , která je mírou nerovnováhy:

$$D = x_{11} \cdot x_{22} - x_{12} \cdot x_{21}$$

Když  $D \neq 0$ , populace je v gametické (vazbové) nerovnováze. Když  $D = 0$ , populace je v gametické (vazbové) rovnováze.

# Gametická nerovnováha

**$D \neq 0$ , když se uplatňuje:**

- genetická vazba
- selekce
- migrace nebo křížení
- nedávná mutace

**Poznámka:**

**Gametická nerovnováha se může uplatňovat i mezi geny (lokusy), které nejsou ve vazbě. Nerovnováha je statistický fenomén.**

# Selective sweep

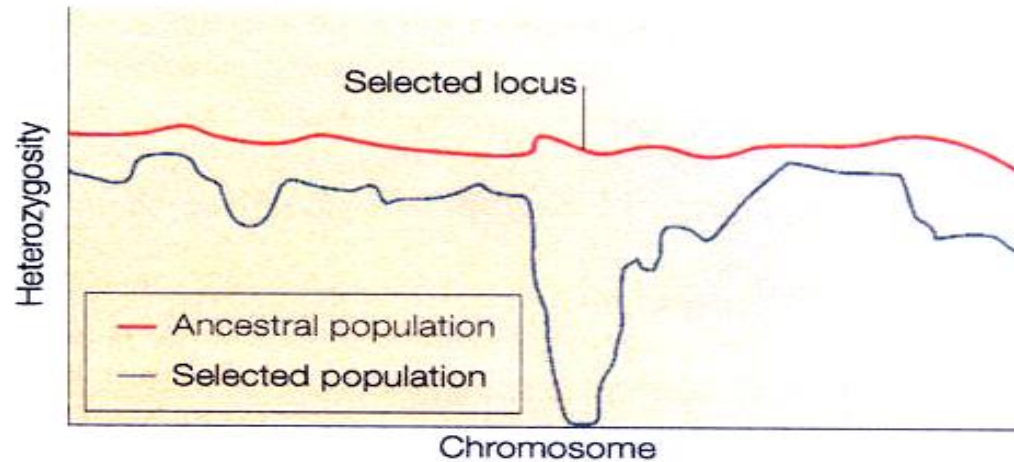
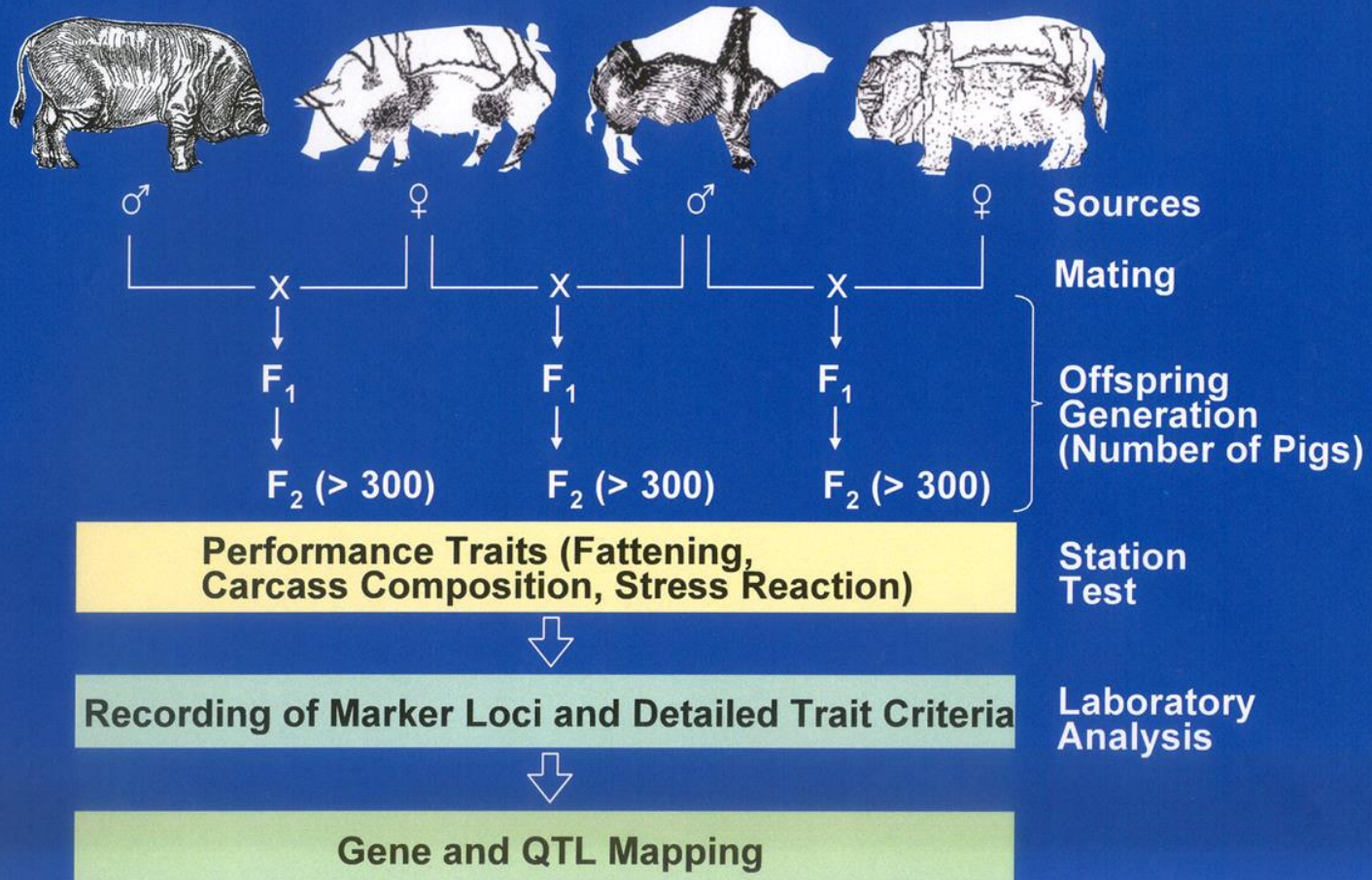


Figure 2 | **Loss of heterozygosity owing to a selective sweep of a favourable mutation.** In an outbred population the heterozygosity varies along a chromosome according to the local mutation rate, previous selection history and genetic drift. Strong directional selection in domestic animals (and in other species) is expected to cause selective sweeps in which a favourable allele replaces other alleles. This leads to homozygosity at the selected locus and also at flanking loci owing to 'hitch-hiking'<sup>34</sup>. This characteristic pattern means that dense genome scans can show regions of the genome that have gone through selective sweeps.

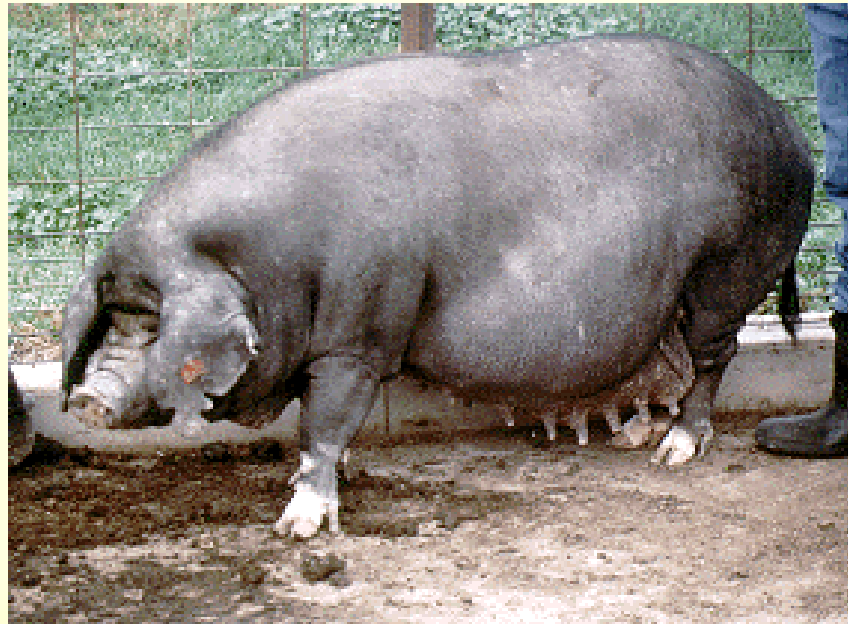
## Mapování QTL – výsledky a problémy

- je obtížné zjistit přesnou polohu QTL. Intervaly jsou obvykle v rozmezí 10 – 20 cM.
- vlastnosti s nízkou dědivostí vyžadují velké populace a více opakování, aby se získaly přesné polohy a efekty QTL.
- použití lepších statistických metod pomáhá, ale neřeší problém.
- při mapování v malých populacích často nejsou zjištěny QTL s malým účinkem.
- u těch QTL, které jsou nalezeny, je často zjištěn větší efekt než skutečně existuje (protože „absorbují“ část informace z nedetekovaných QTL).
- efekty QTL ze vzorku jedné populace často neodpovídají efektům z jiného vzorku stejné populace.
- typické studie mapování QTL jsou pravděpodobně spolehlivé pouze pro QTL s efekty 10% a více.
- poloha QTL pro stejný znak se může výrazně lišit u různých mapovacích populací!

## Informative F<sub>2</sub> Families for QTL Mapping in Pig at Hohenheim University



# Meishan

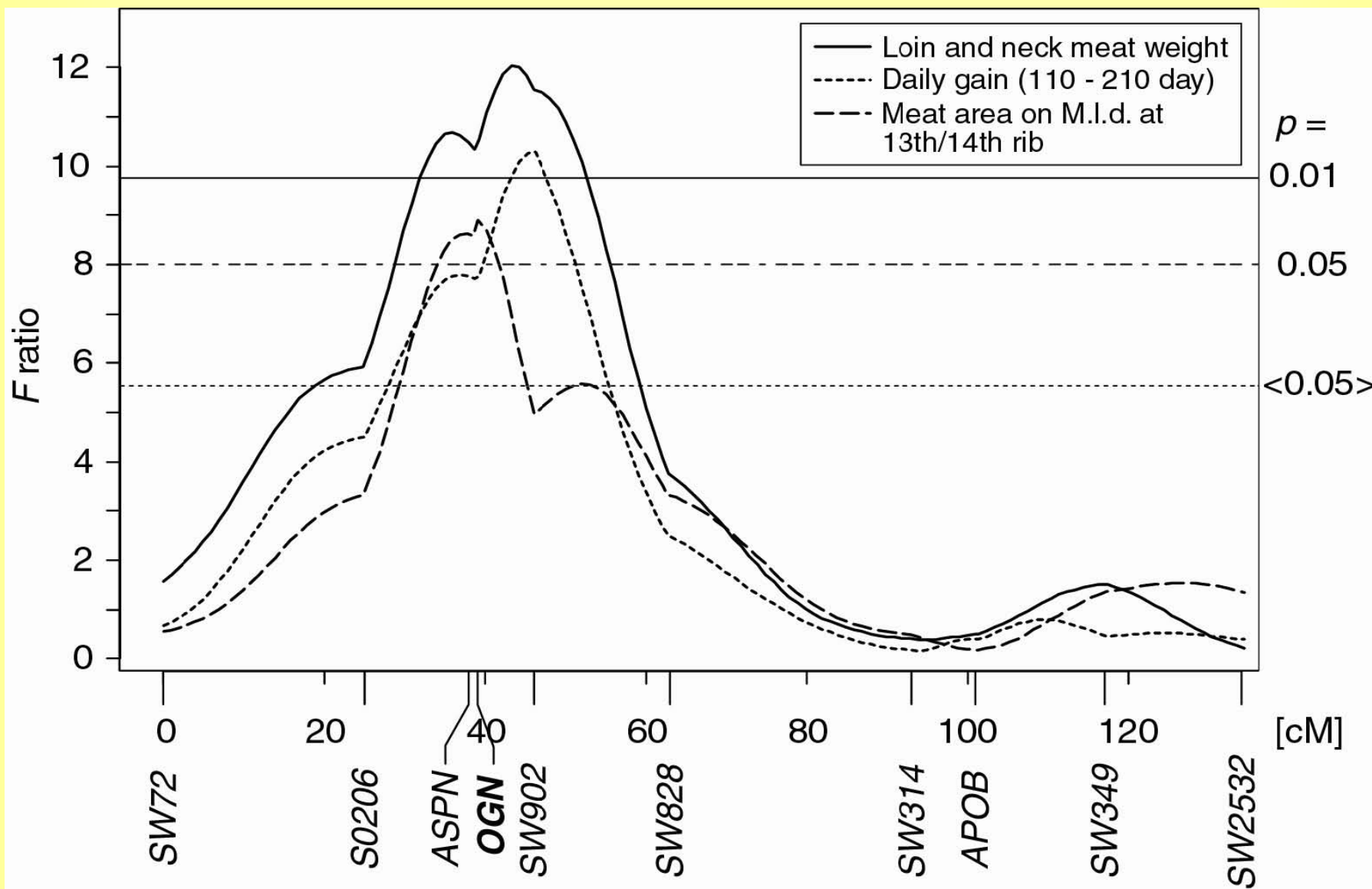




## F<sub>2</sub> Meishan x Large White



# Mapování QTL na chromozómu 3 prasat (MxP)



## Significant QTL effects on SSC3.

Trait	cM	<i>F</i> ratio	VF <sub>2(%)</sub>	a ± SE	d ± SE
Loin and neck meat weight (kg)	43.2	12.0****	6.7	-0.286 ± 0.090	0.528 ± 0.134
Shoulder meat weight without external fat (kg)	43.2	10.4****	5.8	-0.072 ± 0.049	0.324 ± 0.073
Daily gain (110-210 days)(g/day)	46.1	10.3****	5.7	-28.872 ± 10.112	52.804 ± 14.358
Carcass length (cm)	44.2	9.2**	5.1	-0.675 ± 0.472	2.868 ± 0.695
Meat area on M.l.d. at 13th/14th rib (cm <sup>2</sup> )	39.2	8.8**	4.9	-0.787 ± 0.401	2.221 ± 0.581
Ham meat weight without external fat (kg)	42.2	8.5**	4.7	-0.143 ± 0.099	0.581 ± 0.147
Half carcass weight (kg)	46.1	7.2*	3.9	-0.785 ± 0.522	2.638 ± 0.742
Ham weight including bones and external fat (kg)	44.2	6.2*	3.3	-0.152 ± 0.142	0.716 ± 0.209
Weight of head (kg)	46.1	6.1*	3.2	-0.081 ± 0.063	0.300 ± 0.090
Food conversion ratio (kg/kg)	32.9	6.0*	3.2	0.232 ± 0.075	-0.191 ± 0.116
Fat to meat ratio (area at 13th/14th rib)(cm <sup>2</sup> /cm <sup>2</sup> )	35.9	5.9*	3.1	0.017 ± 0.016	-0.082 ± 0.025
Weight of bacon meat relative to lean cuts weight (%)	46.1	5.6*	2.9	0.401 ± 0.124	-0.172 ± 0.176

Significant at \**P* < 0.05 chromosome-wide threshold; \*\**P* < 0.05 genome-wide threshold; \*\*\*\**P* < 0.01 genome-wide threshold.

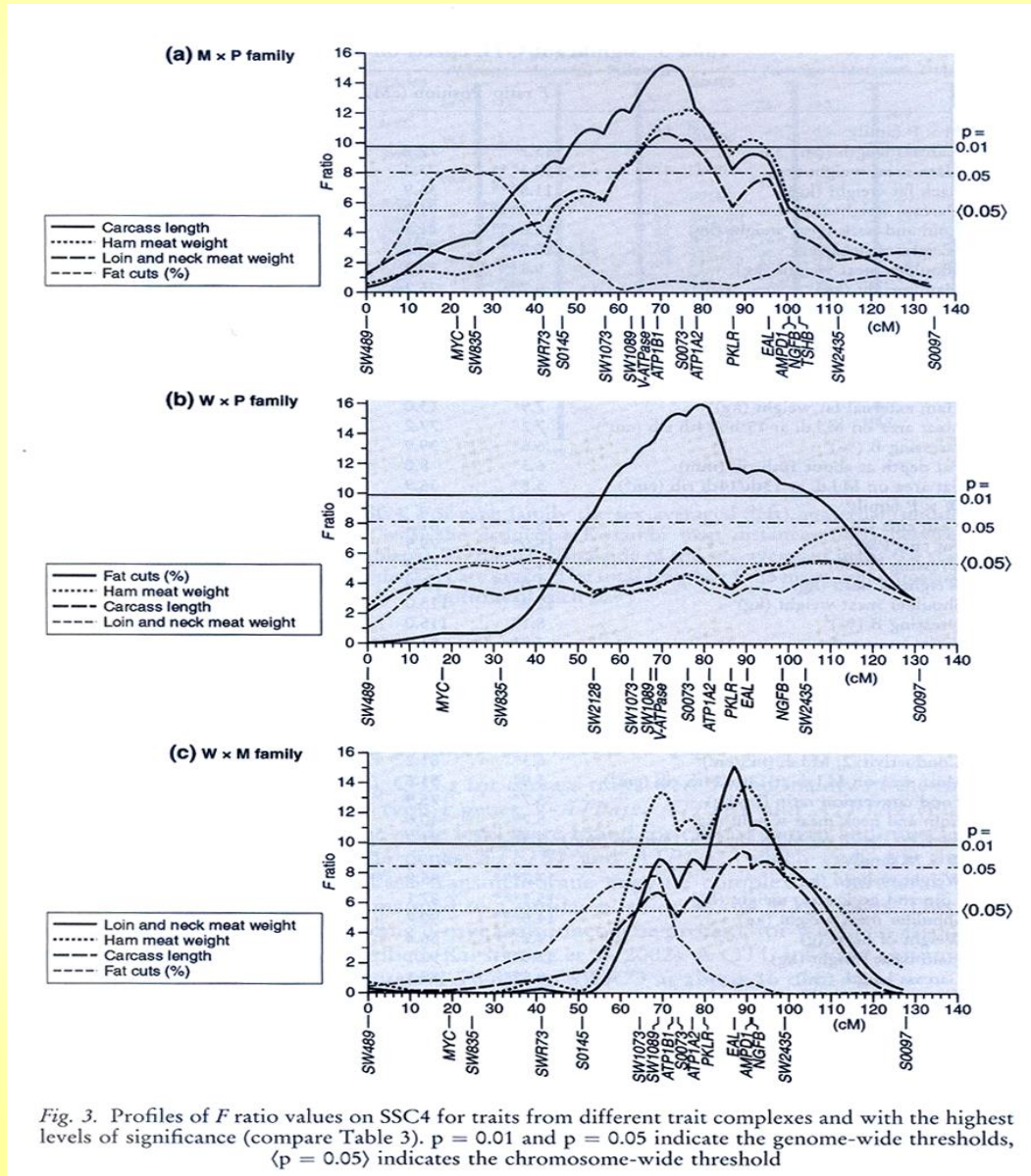
QTL, quantitative trait locus; SSC3, *Sus scrofa* chromosome 3.

a, additive effect (positive/negative signs indicate the superior/inferior trait values inherited from the paternal resource group);

d, dominance effect (positive for higher values of heterozygous individuals than the mean of homozygotes; negative for lower values);

VF2(%), percentage of F2 phenotypic variance explained by the QTL; M.l.d., *Musculus longissimus dorsi*.

# Mapování QTL na chromozómu 4 prasat



# Mapování QTL na chromozómu 6 prasat

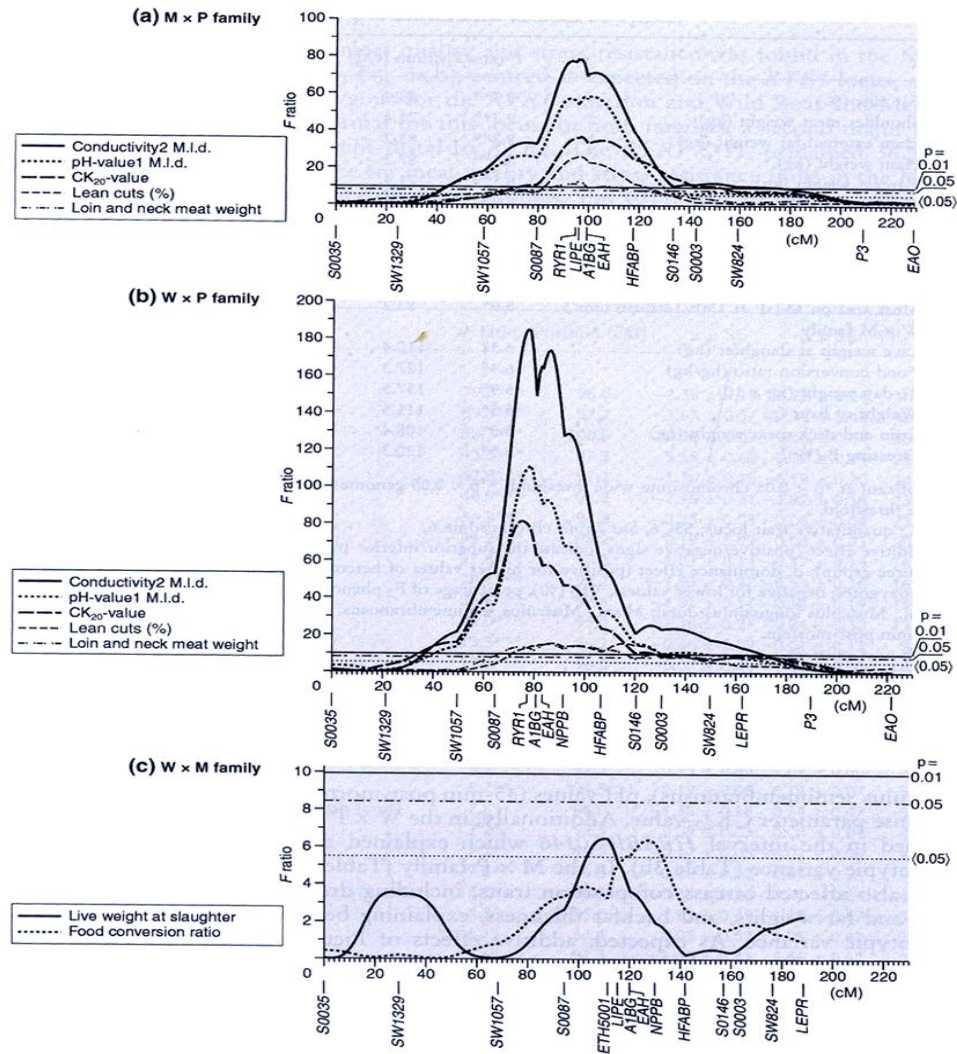
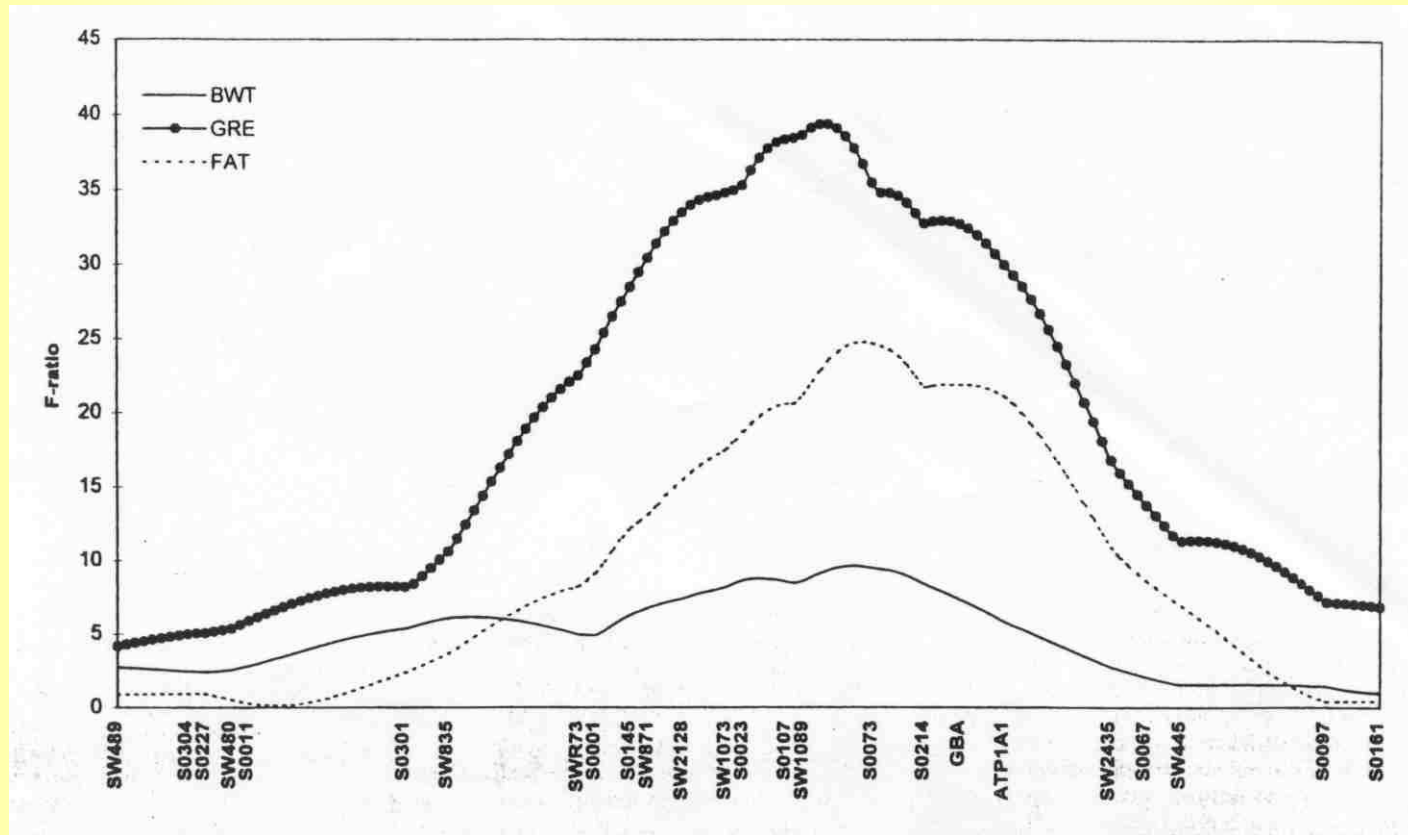


Fig. 3. Profiles of  $F$  ratio values on SSC6 for traits from different trait complexes and with the highest levels of significance (compare Table 3).  $p = 0.01$  and  $p = 0.05$  indicate the genome-wide thresholds, ( $p = 0.05$ ) indicates the chromosome-wide threshold

# Rozložení efektů QTL na SSC 4



Walling *et al.*, *Genetics* 2000

Genome-wide linkage and QTL mapping in porcine F<sub>2</sub> families

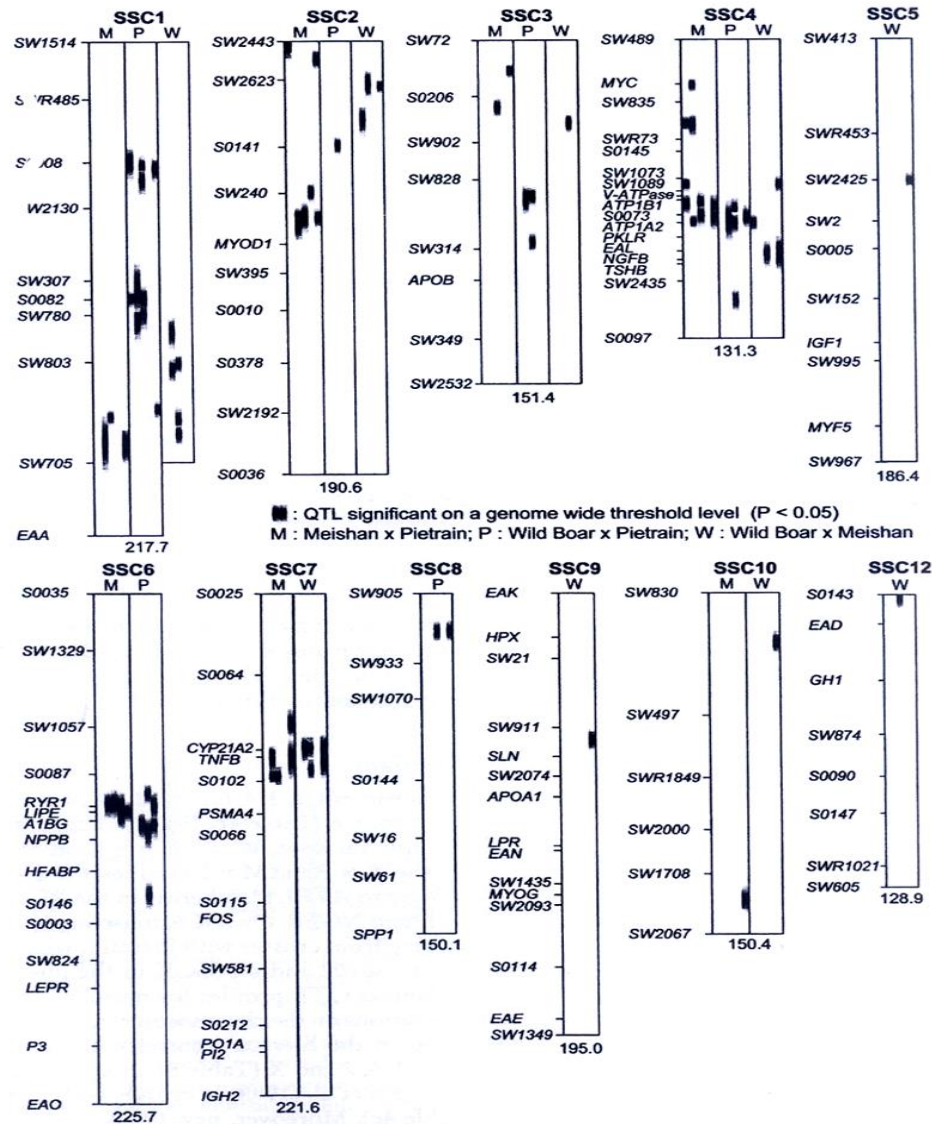


Fig. 2. Location of QTLs. Chromosomes are shown for which genome-wide significant QTLs were detected in the Hohenheim families. Within each chromosome the QTLs for growth/fattening, fat deposition, muscling, meat quality/stress resistance and other traits are ordered from the left to the right hand side. The detailed QTL maps are shown at web site <http://uni-hohenheim.de/tzbiotech/PigQTL/>

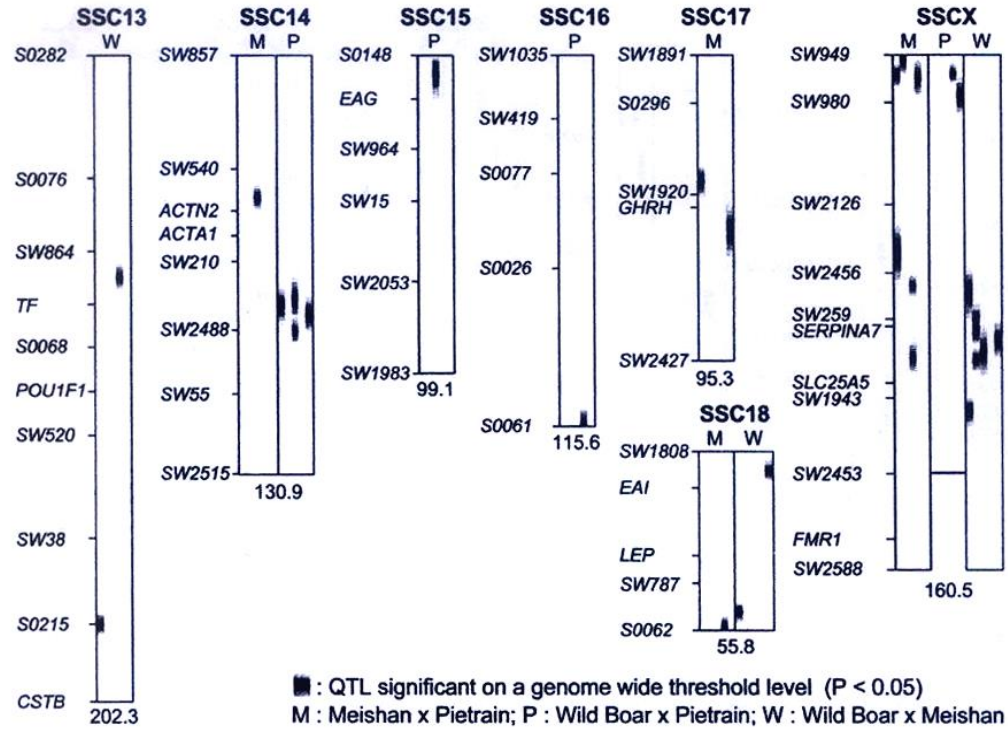


Fig. 2. (Continued).



## Database summary

To date, there are **1287** pig QTLs in the database from **94** publications representing **246** different pig traits ( *These summary data may differ from that appear on the front page as the summary included newly entered QTL which may have not yet become part of the official release* )

1. [Number of QTL by Traits](#)
2. [Number of QTL by Trait Types](#)
3. [Number of QTL by Trait Classes](#)
4. [Number of QTL by Chromosomes](#)
5. [Number of QTL by Years Reported](#)
6. [Number of QTL by Journals Published](#)
7. Number of QTL that are private

### Number of QTL by Pig Trait Types

Trait Types	Number of QTL
Anatomy	423
Behavioral	22
Chemical	11
Coat_color	2
Conductivity	25
Conformation	8
Digestive Organ	9
Disease Resistance	7
Endocrine	4
Enzyme Activity	1
Fat Composition	40
Fatness	318
Feed Conversion	6
Feed Intake	14
Flavor	12
Growth	187
Immune Capacity	8
Litter Size	20
Meat_color	42
Odor	5
PH	42
Reproductive Organ	30
Reproductive Traits	9
Stiffening	3
Texture	42

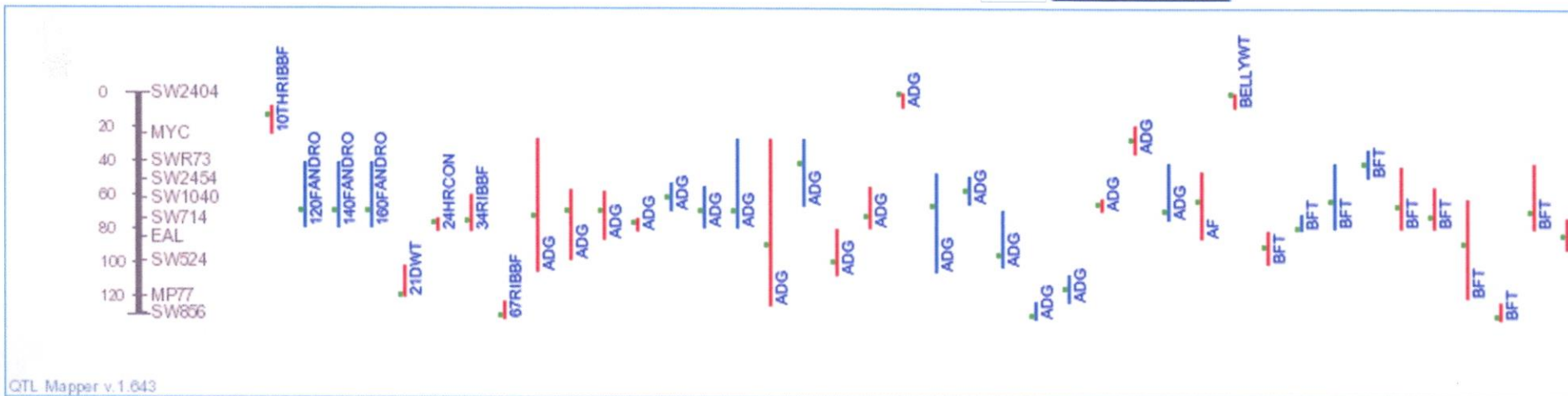


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Display QTL:  Chromosome:  Order by:  Map size:  Marker density:

Link Out: Upper cM:    
 Lower cM:

## QTL on Pig Chromosome 4



**Legend:** Red QTL lines represent for significant and light blue QTL lines for suggestive statistical evidence. Green dots shows the position of QTL peaks. **Acknowledgement:** The mainly based on USDA-MARC Pig Linkage Map





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[F A Q](#)

Display QTL: \_\_\_\_\_ Chromosome:  Order by:  Map size:  Marker density:

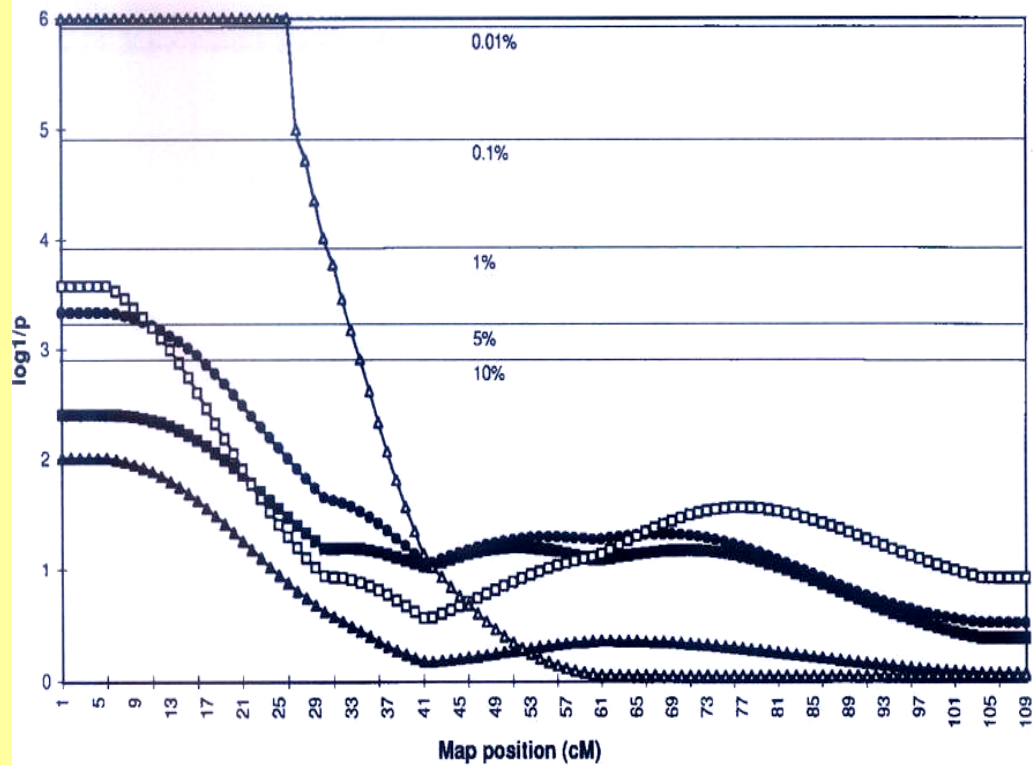
Link Out: Upper cM:    
 Lower cM:

## QTL on Pig Chromosome 7



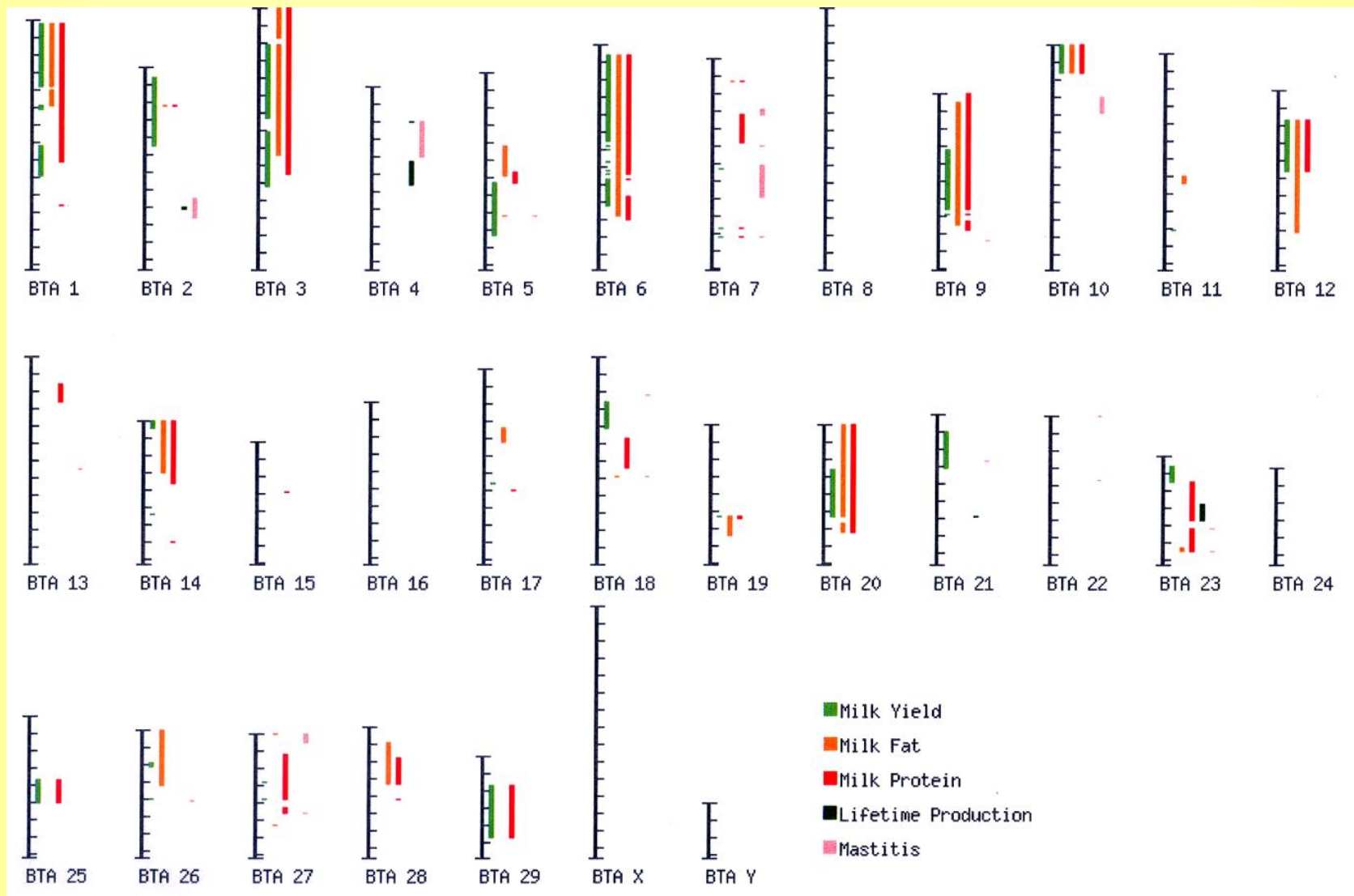
**Legend:** Red QTL lines represent for significant and light blue QTL lines for suggestive statistical evidence. Green dots shows the position of QTL peaks. **Acknowledgement:** The map is mainly based on [USDA-MARC Pig Linkage Map](#)



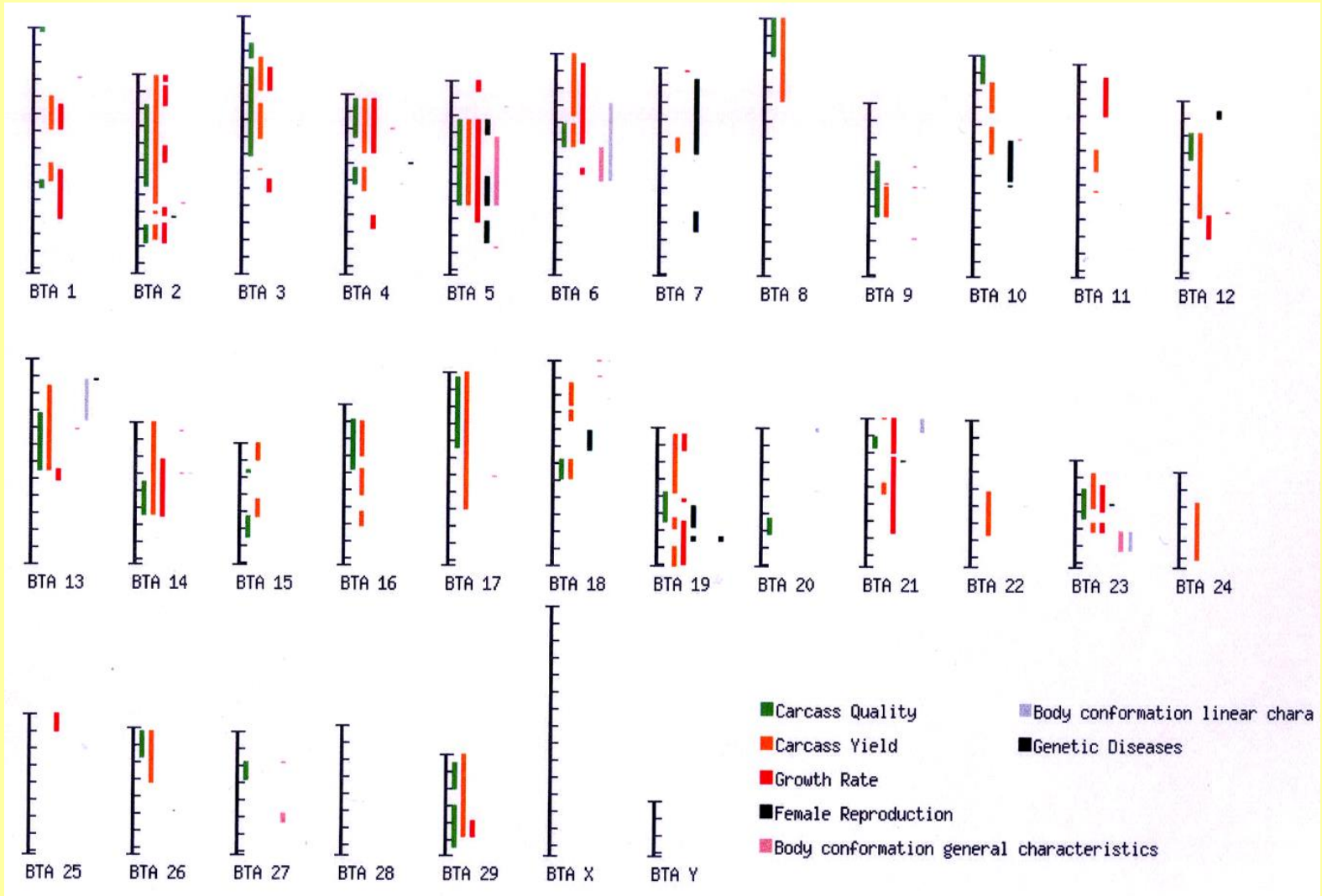


**Fig. 2.** Location scores obtained along the Chr 14 microsatellite map with the sum-of-rank QTL mapping method (Coppieters et al. 1998b). Evidence in favor of the presence of a QTL at a given map position is measured as  $\log(1/p)$  with  $p$  corresponding to the  $p$ -value of the actual data as measured from chromosome-wise analyses of  $10^6$  phenotype permutations. Experiment-wise thresholds obtained by Bonferroni correction of the chromosome-wise thresholds to account for the analysis of three multiple traits and 29 chromosomes are indicated by horizontal bars. ●: milk yield; ■: protein yield; □: protein percentage; ▲: fat yield; △: fat percentage. For fat percentage (△) the location profiles are flat between positions 0 and 26cM because the  $\chi^2$  values obtained from the real data within this segment exceeded all values obtained from the  $10^6$  permutations.

# QTL pro mléčnou užitkovost krav



# QTL pro masnou užítkovost a reprodukci skotu

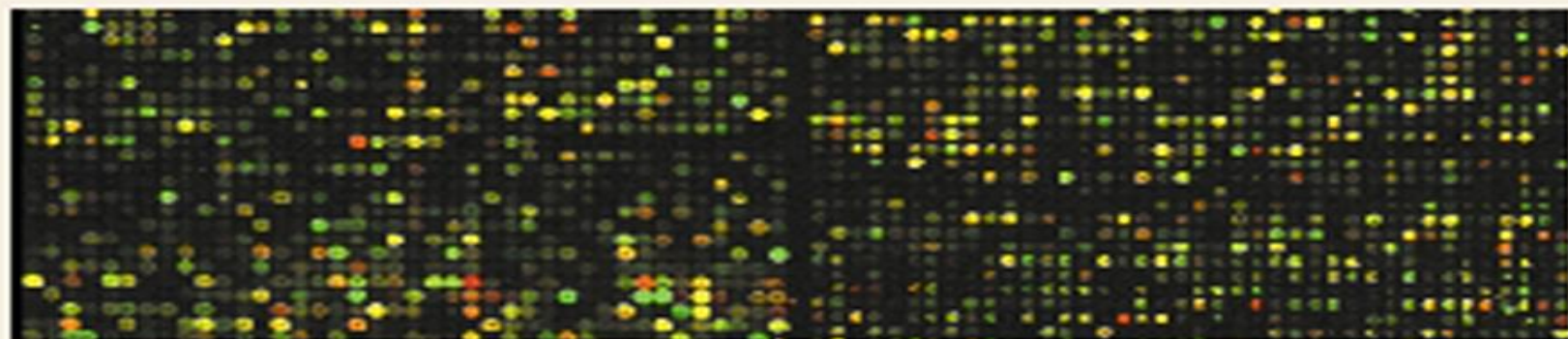


### Box 3 | **Transcriptional profiling with microarrays**

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A microarray comprises a set of hundreds or thousands of nucleic-acid spots, or features, on a solid support — often a glass slide. Each spot represents an expressed sequence, and consists of an oligonucleotide or cDNA probe. When a labelled cDNA is hybridized to the array, the amount of hybridization to each feature is quantified as an intensity reading that represents individual gene activity. This provides a global picture of gene transcript levels, and has become a widely used technique that is being used to study gene expression during development, in particular disease states and so on.

Various statistical methods<sup>30,32–36</sup> can be used to identify statistically significant changes and groupings of gene expression. At present, these statistical methods are viewed as either linear-model-based approaches<sup>33,34</sup> that account for both biological variation and technological variation, or multivariate approaches, such as clustering<sup>35,36</sup>, that allow the relationships among gene profiles (across time or treatments) to group the genes according to similar behaviour. Model-based inference is formulated around a scientific hypothesis that can be tested through a statistical calculation (or statistical test), and from which statistically significant conclusions can be drawn. Conversely, multivariate analyses are clustering techniques that are viewed as summary/exploratory in that they are typically not hypothesis based, and the resulting DENDROGRAMS are not testable. However, the testability of gene-expression dendrograms has recently been addressed<sup>37,38</sup> to assess statistical significance.



**Genomická selekce - Whole Genome Selection (WGS)** is a term often used in conjunction with SNP chips. It is the industry application of the SNP chip technology.

Most traits that breeders are interested in are caused by lots of small effects that are spread throughout the whole genome (DNA) of an individual. The new SNP technology will offer more bang for your buck by examining a large portion of the genome - not just a small part.

Instead of current genetic markers that occur on one point in the genome (e.g. muscling with the MyoMAX <sup>PM</sup> gene) WGS offers the power derived from a 50 thousand marker screen throughout the genome of an animal.

Through using SNP chips which contain 50,000 DNA markers, the "Whole Genome" can be investigated to search for multiple genetic markers associated with a variety of traits at one time.

The R&D process is to collect DNA samples and performance data from an extensive and representative set of animals (thousands spread across the industry and the country). DNA samples from these animals are run across the SNP chip and the data analysed to select SNPs that are most predictive for a particular trait, with weightings determined for each SNP. The resulting "SNP Key" consists of 30 to 300 SNPs per trait which account for most of the trait variation and industry animals can then be tested using the SNP Key. Results from the SNP Key can be summed to obtain an estimate of the genetic merit of an individual.

This is similar to a breeding value, but instead of an estimated breeding value predicted from animal measurements and pedigree you will get a **Molecular Breeding Value (MBV)**. If you have both a traditional and a molecular breeding value, these can be combined to give you an even more powerful estimate of breeding merit - a so called **genomic breeding value (GBV)**. This information can be used to make predictions about an animals genetic merit as a parent, even if it has not been measured directly for all of the traits.

Whole Genome Selection marks a point where genomics will move from the laboratory into the paddock and consequently the marketplace.

The benefits of using this technology as a selection tool is that it can result in faster gains through a reduction in the interval from testing to selection and it reduces the need to measure difficult to measure traits such as meat quality or disease resistance.



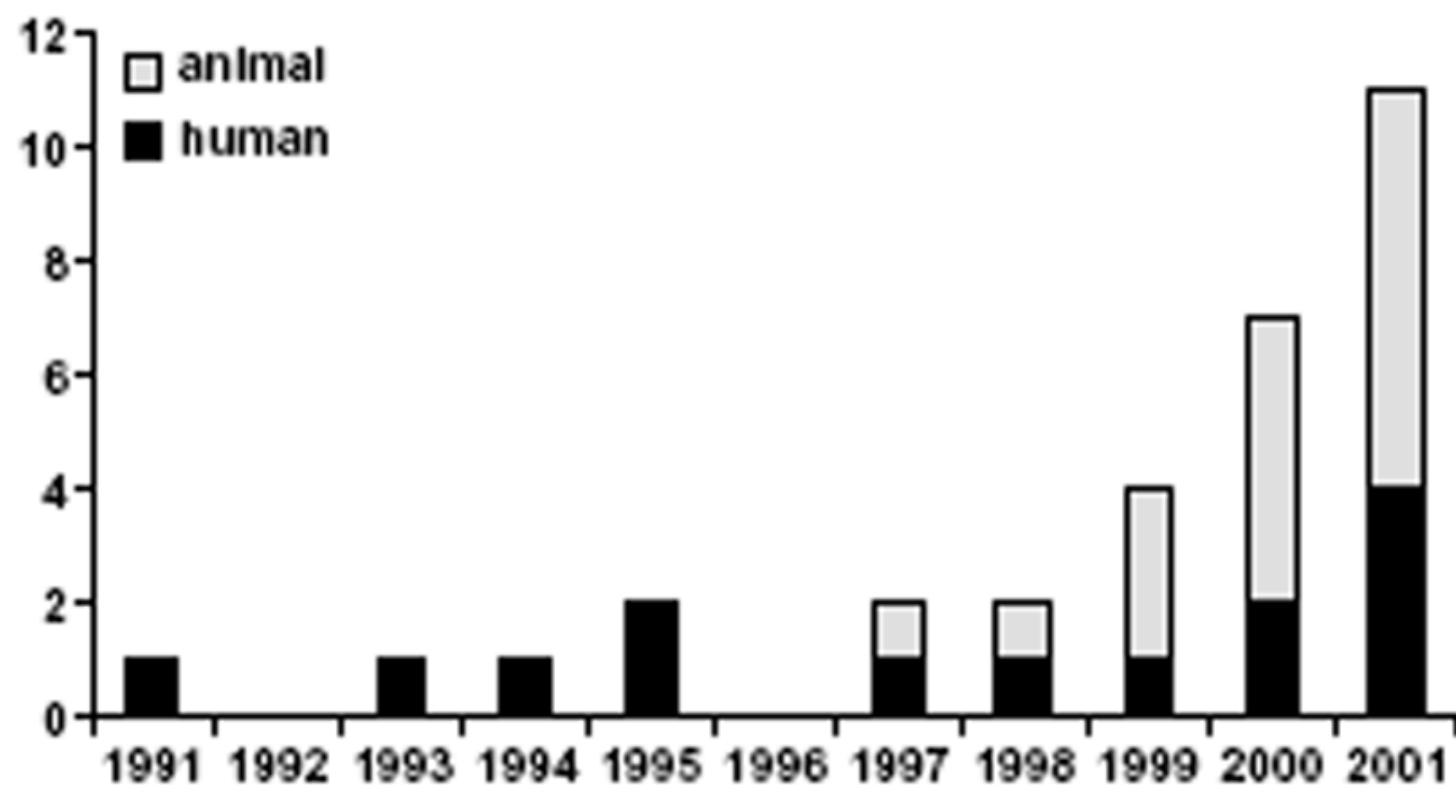


Fig. 1 Number of genes identified from QTL by year. Genes for human QTL are shown in black and genes for experimental models (mouse, rat, and pig) in white. The first QTL gene was identified in 1991. There are 14 from humans and 17 from animal models (5 from rats, 11 from mice, 1 from pigs). These add up to more than 20 because some were identified in both humans and rodent models.

Table 1 • Genes identified from QTL studies

Polygenic trait	Year	Ref.	Gene	Species	pos	tg	ko	fu
Alzheimer disease	1991	9	<i>APP</i>	human				X
Alzheimer disease	1993	10	<i>APOE</i>	human				
Ovarian and breast cancer	1994	11	<i>BRCA1</i>	human	X			X
Breast cancer	1995	12	<i>BRCA2</i>	human	X			X
Insulin resistance	1995	13	<i>FABP2</i>	human				
HDL-cholesterol levels	1997	14	<i>LIPC</i>	human				
Intestinal cancer	1997	15	<i>Pta2g2a</i>	mouse	X	X		
Blood pressure	1998	16	<i>Atp1a1 / ATP1A1</i>	rathuman		X		X
Leptin levels	1999	17,18	<i>POMC</i>	human			X <sup>a</sup>	X
Asthma	1999	19	<i>Il4</i>	mouse	X	X		
Asthma	1999	19	<i>Il13</i>	mouse	X	X		
Insulin-mediated glucose uptake	1999	2	<i>Cd36</i>	rat		X		
Obesity	2000	20	<i>Ptpn1/PTPN1</i>	mouse/human			X <sup>b</sup>	X
Alzheimer disease	2000	21	<i>PSEN1</i>	human	X			
Diabetes	2000	22	<i>Il2</i>	mouse	X		X <sup>b</sup>	X
Gallstones	2000	23	<i>Abcc2</i>	mouse	X			X
Asthma	2000	3	<i>Hc</i>	mouse				
Muscle glycogen content	2000	24	<i>Prkg3</i>	pig	X		X <sup>c</sup>	X
Crohn disease	2001	25,26	<i>NOD2</i>	human	X		X <sup>a</sup>	X
Blood pressure	2001	27	<i>SCNN1A1</i>	human			X <sup>a</sup>	
Blood pressure	2001	28	<i>SCNN1G</i>	human			X <sup>a</sup>	
Blood pressure	2001	29	<i>Slc12a1</i>	rat				
Blood pressure	2001	30	<i>Cyp11b1</i>	rat				X
Bone density	2001	5	<i>COL1A</i>	human				
Left ventricular mass	2001	31	<i>Nppa</i>	rat			X <sup>b</sup>	X
Modifier of tubby hearing	2001	32	<i>Mtap1a</i>	mouse	X	X		X
Taste, saccharin response	2001	33	<i>Tas1r3</i>	mouse	X	X		X
Tumor susceptibility	2001	34	<i>Cdkn2a</i>	mouse	X		X <sup>b</sup>	X
Diabetes	2001	35	<i>B2m</i>	mouse		X	X	

pos, found by positional cloning; tg, transgenic insertion of normal gene changes phenotype to normal (for example, transgenic rescue); ko, knockout provides additional evidence (<sup>a</sup>human monogenic syndrome, <sup>b</sup>deletion of gene by homologous recombination produces a mouse with the phenotype typical of the disease, <sup>c</sup>knockout in yeast); fu, functional difference in candidate gene. *APP*, amyloid precursor protein; *APOE*, apolipoprotein E; *BRCA*, breast cancer gene; *FABP2*, fatty acid binding protein 2; *LIPC*, hepatic lipase; *ATP1A1*,  $\alpha$ -Na,K-ATPase; *POMC*, pre-pro-opiomelanocortin; *il*, interleukin; *Cd36*, fatty acid translocase; *PTPN1B*, protein tyrosine phosphatase-1B; *PSEN1*, presenilin 1; *Abcc2*, ATP-binding cassette, subfamily C2; *Hc*, hemolytic complement (C5); *Prkg3*, protein kinase, AMP-activated,  $\gamma$ ; *NOD2*, caspase recruitment domain-containing protein 15 (*CARD15*); *SCNN*, sodium channel, non-voltage gated; *Slc12a1*, Na,K,2Cl-cotransporter; *Cyp11b1*, 11 $\beta$ -hydroxylase; *COL1A*, collagen-1A; *Nppa*, natriuretic peptide precursor A; *Mtap1a*, microtubule-associated protein 1a; *Tas1r3*, taste receptor-3; *Cdkn2a*, cyclin-dependent kinase inhibitor 2a; *B2m*,  $\beta$ 2-microglobulin.

Table 1 | **Monogenic trait loci for which the causative mutation has been identified**

Species	Trait	Gene	Reference
Cattle	Muscle hypertrophy	<i>MST</i>	72–75
	Coat colour	<i>MC1R</i>	76
	White coat colour	<i>KITLG</i>	23
	Fish odour in milk	<i>FMO3</i>	77
Chicken	Albinism	<i>TYR</i>	78
	Plumage colour	<i>MC1R</i>	79
	Dominant white plumage colour	<i>PMEL17</i>	80
Dog	Narcolepsy	<i>HCRTR2</i>	81
	Coat colour	<i>MC1R</i>	82
Goat	Lack of horns, intersexuality	Non-coding region*	83
Horse	Coat colour	<i>MC1R</i>	84
		<i>ASIP</i>	85
		<i>MATP</i>	86
	White colour, megacolon	<i>EDNRB</i>	87–89
Pig	Malignant hyperthermia	<i>RYR1</i>	21
	Dominant white colour, haematopoiesis	<i>KIT</i>	22,90,91
	Hypercholesterolaemia	<i>LDLR</i>	92
	Coat colour	<i>MC1R</i>	93,94
	Intestinal <i>Escherichia coli</i> adherence	<i>FUT1</i>	95
	Glycogen content in skeletal muscle	<i>PRKAG3</i>	24
Sheep	Fertility, ovulation rate	<i>BMP15</i>	96
		<i>BMPR1B</i>	97
	Muscle hypertrophy	Regulatory mutation*	98,99

\*This is apparently a regulatory mutation that affects the expression of one or more genes in the chromosomal region to which it maps.