

Position of the *Phi* and *Po2* loci in the *Hal* linkage group in pigs

P. Vögeli 

Institute of Animal Sciences, Breeding Section, Federal Institute of Technology (ETH), CH-8092
Zürich, Switzerland

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Summary — Families of Swiss Landrace (165 litters with 1348 offspring) were tested for halothane sensitivity, *A-O(S)*, *H*, *Phi*, *Pgd* and *Po2* phenotypes. Informative matings for the determination of the gene sequence of these linked loci were selected. Recombinations were observed between *Phi-Hal*, *Phi-H* and *H-Po2*. On the basis of these results the most likely order of loci is *Hal-Phi-H*. Confirmation for a locus for genes for *Po2* separate from the locus for *H* is presented. The location of *Po2* is between *H* and *Pgd*. A gene order *S-Hal-Phi-H-Po2-Pgd* is proposed.

pig – linkage group – S-Hal-Phi-H-Po2-Pgd – halothane sensitivity – gene order

Résumé — La position des loci *Phi* et *Po2* dans le groupe de liaison *S*, *Hal*, *Phi*, *H*, *Po2*, *Pgd* des porcs. Des familles de Porc amélioré suisse (165 portées avec 1348 descendants) ont été testées pour la sensibilité à l'halothane, ainsi que pour les phénotypes *A-O (S)*, *H*, *PHI*, *PGD*, et *Po2*. Des accouplements informatifs pour déterminer l'ordre de ces loci liés ont été sélectionnés. Des recombinaisons ont été trouvées entre *Phi-Hal*, *Phi-H* et *H-Po2*. Ces résultats ont permis de préciser la position du locus *Phi* dans le groupe de liaison. L'ordre le plus probable des loci est *Hal-Phi-H*. Ces données confirment que les gènes *Po2* et *H* se situent à deux loci distincts. *Po2* se situe entre *H* et *Pgd*. En conclusion est proposé l'ordre génique *S-Hal-Phi-H-Po2-Pgd*.

porcs – groupe de liaison – S-Hal-Phi-H-Po2-Pgd – sensibilité à l'halothane – ordre de loci

Introduction

The linkage between the *H* blood group locus and the loci for the variants of 6-phosphogluconate dehydrogenase (*Pgd*) and phosphohexose isomerase (*Phi*) was first described by Andresen (1971). Rasmusen & Christian (1976) reported an association between *H* genotypes and susceptibility to halothane-induced stress. Jørgensen *et al.* (1976) postulated that the association between *H* and porcine stress and the linkage of *Phi* and *H* was the causal link for the association between *Phi* genotypes and stress susceptibility. The inheritance of halothane-induced stress has been shown to be controlled by a recessive gene at a single locus (*Hal*) with incomplete penetrance (Ollivieret *et al.*, 1975; Smith &

Bampton, 1977). N symbolizes Hal^N and n , Hal^n . Pigs that are N/N or N/n should therefore be HAL^- non reactors and n/n signifies a HAL^+ reactor.

Linkage studies between Hal and Phi have not made it possible to place the Hal locus accurately within the linkage group. Using a method for calculation of relative linkage disequilibrium coefficients, Andresen (1979) proposed that Hal was located between Phi and H . The gene order $Phi-Hal-H-Pgd$ was also supported by Rasmusen *et al.* (1980). Their data, however, did not permit them to distinguish between the order $Phi-Hal-H-Pgd$ as opposed to $Hal-Phi-H-Pgd$. Guérin *et al.* (1983) described two recombinants which supported the order as $Hal-Phi-Pgd$. The recombinants were both HAL^- offspring of matings between $Hal^{N/n}$ and $Hal^{n/n}$ animals. The failure of these animals to react to halothane could, however, have resulted from the incomplete penetrance of the Hal^n gene.

The S locus controls the expression of the A and O antigens of the $A-O$ blood group system in pigs by an epistatic interaction (Rasmusen, 1964 and Hojný & Hála, 1965). Two alleles are known, S being dominant over s .

The relationship between $A-O$ blood group phenotypes determined by genes at the S locus and HAL^+ animals (Rasmusen & Christian, 1976) was in agreement with the associations found between $A-O$ and H blood group systems (Rasmusen, 1972). Hojný (1974) suggested that this association resulted, indirectly, from the genetic linkage between the H system and the S locus. Rasmusen (1981) proposed the order $Phi-Hal-S-H-Pgd$ on the basis of recombinants between S and H as well as between S and $Phi-Hal$. Later, two other reports provided evidence that the S locus is not within the $Phi-Pgd$ region, but adjacent to Phi (Hojný *et al.*, 1985; Van Zeveren *et al.*, 1985).

Recently it has been found that the serum postalbumin-2 ($Po2$ locus) also belongs to the S - ($Phi-Hal-H$)- Pgd linkage group and is probably located between the H and Pgd loci (Juneja *et al.*, 1983; Gahne & Juneja, 1985; Čepica *et al.*, 1986).

The aim of this paper is to reconsider the gene order in the linkage group, especially of the Phi and $Po2$ loci and to establish the haplotypes (including Hal genotypes) in a population of Swiss Landrace pigs. Estimation of recombination frequencies is given elsewhere (Vögeli *et al.*, 1988).

Materials and Methods

Description of the data

Data for this study came from Swiss Landrace pigs kept at the experimental station of the Institute of Animal Sciences during the period 1983-1988. The total number of offspring was 1348. The animals came from 165 litters produced by 29 boars and 64 sows over 3 successive generations.

Halothane test

At an age of 8 to 12 weeks the animals were tested for halothane sensitivity by the method of Eikelenboom & Minkema (1974). The anesthetic was a mixture of oxygen and 4% halothane (1.5 liters/min). Negatively reacting animals were exposed for 5 min. In HAL^+ pigs the anesthesia was withdrawn as soon as the symptoms of hyperthermia (muscular rigidity, increased heart rate and elevated body temperature) became apparent.

Serological tests

The A and O reagents were prepared from normal serum of 2 goats and were used in the hemolytic test. The alloimmune anti-Aw was applied in the dextran agglutination test.

The blood group factors *Ha* and *Hc* were tested using two reagents each. One of each exhibited dosage effects, *i.e.*, they hemolysed red blood cells of homozygous (H^A/H^A , H^C/H^C) pigs sooner than those derived from heterozygous (H^A/H^- , H^C/H^-) pigs. The validity of the reaction pattern of these reagents was verified in International Pig Comparison Tests (1984 and 1987, the latter being organized by our laboratory).

Electrophoresis

The *Phi* and *Pgd* phenotypes were determined by horizontal one-dimensional agarose or starch-gel electrophoresis of hemolysates of erythrocytes (Saison & Giblett, 1969; Gahne & Juneja, 1985). The *Po2* variants were detected by two-dimensional electrophoresis by the method of Juneja *et al.* (1983).

Parentage control

Tests for other blood marker systems (*B*, *G*, *ADA*, *PGM*, *PI1*, *PO1A*, *PI2*) were conducted on all animals for the exclusion of incorrect pedigrees.

Haplotyping

The method used in the present study to determine the haplotypes was based on deducing linkage phases involving *Hal* and marker loci of both the parents and their offspring. A detailed description of the procedure is given by Vögeli *et al.* (1988). Several instances of crossing over were observed in progeny from multiheterozygous parents mated to multihomozygous parents. These were used to determine the order of the loci.

Results

Table I provides a summary of recombinations involving the *Hal* and *Phi* loci recovered in progeny from matings in which one parent was at least triply heterozygous and the other doubly or multiply homozygous. All the recombinations are informative with respect to the location of the *Phi* locus. The structure of parental haplotypes was inferred from various informative matings.

Assuming that the gene order is *Phi-Hal-H* as suggested by Rasmusen (1981) and not *Hal-Phi-H*, the first 5 recombinants of the first 3 matings given in Table I would have required the occurrence of a double crossover, *i.e.*, a crossover between *Phi* and *Hal* as well as a crossover between *Hal* and *H* which is statistically extremely unlikely.

Mating of boar 8888 with female 8849 produced a recombinant (offspring 9925) resulting in an unexpected halothane negative reaction of this offspring. This recombinant could be explained as being a result of double crossover. However, incomplete penetrance of Hal^n / Hal^n seems more likely. Unfortunately, the recombinant offspring 9925 was not saved for breeding to determine his actual genotype. In the offspring of animals with Hal^n / Hal^n genotype mated to Hal^N / Hal^n , about 10% are classified as HAL^- (Gahne & Juneja, 1985.). The failure of one offspring from a total of six to react to halothane could well be the result of incomplete penetrance of the Hal^n gene. From these considerations the gene order of *Hal-Phi-H* is suggested.

Table I. The occurrence of crossover of *Hal* and *Phi* loci with respect to other loci in the *S*-(*Hal*-*Phi*-*H*-*Po2*)-*Pgd* linkage group.

Parents and offspring	Phenotypes and genotypes						Haplotypes of parents and probable haplotypes of offspring (order <i>S</i> - <i>Hal</i> - <i>Phi</i> - <i>H</i> - <i>Po2</i> - <i>Pgd</i>)			
	S	<i>Halo</i> thane type ^a	Phi	H	Po2	Pgd	from sire		from dam	
	Sire 9116	s/s	+	B/B	a/a	S/S	A/B	snBaSA	/	snBaSB
Dam 6825	S/S	-	A/B	c/-	F/F	A/A	SnB-FA	/	SNAcFA	
Offspring, (5:2) ^a										
272	S/s	-	B/B	a/-	F/S	A/B	snBaSB	/	SN↑B-FA	
275	S/s	+	A/B	a/c	F/S	A/B	snBaSB	/	Sn↑AcFA	
Sire 782	S/S	+	A/B	c/-	F/F	B/B	SnAcFB	/	SnB-FB	
Dam 7514	S/s	-	A/B	a/-	F/S	A/B	SNA-FA	/	snBaSB	
Offspring, (4:1)										
675	S ^b	-	A/B	a/c	F/S	B/B	SnAcFB	/	SN↑BaSA	
Sire 782	S/S	+	A/B	c/-	F/F	B/B	SnAcFB	/	SnB-FB	
Dam 5602	S/s	-	A/B	a/-	F/S	A/B	SNA-FB	/	snBaSA	
Offspring, (10:2)										
687	S/	-	B/B	a/-	F/S	A/B	SnB-FB	/	SN↑BaSA	
695	S/	+	A/A	c/-	F/F	B/B	SnAcFB	/	sn↑A-FB	
Sire 8888	S/s	-	A/B	a/a	S/S	A/A	snBaSA	/	SNAaSA	
Dam 8849	s/s	+	B/B	a/a	S/S	A/A	snBaSA	/	snBaSA	
Offspring, (9:1)										
9925	s/s	- ^c	B/B	a/a	S/S	A/A	s↑N↑BaSA	/	snBaSA	

^aFirst number: total number of offspring; second number: number of offspring with recombinant types.

^bThe genotype is either *S*/*S* or *S*/*s*.

^cIncomplete penetrance for *HAL*+ ?.

↑ Recombinant.

**HAL*+ reactors, genotype *Hal* *n/n*; *HAL*- non reactors, genotype *Hal* *N/n* or *N/N*.

Table II shows most informative recombinants between *S*, *Hal*, *Phi* and *H* on one side and *Po2* and *Pgd* on the other. All five recombinants are informative in determining the position of the *Po2* locus. From these data the gene order is *H-Po2-Pgd* as proposed by Juneja *et al.* (1983). If the gene order were *Po2-H-Pgd*, all 5 recombinants could only have resulted from double crossovers (*Phi* ↑-*Po2* ↑-*H-Pgd*), which is highly improbable.

Table III shows the parents and offspring of 2 litters which include recombinants involving a crossover between loci for *Phi* and *H* types. These marker loci are also consistent with a gene order of *Phi-H-Po2* as opposed to *H-Phi-Po2*.

Discussion

The expected *Hal* genotype of offspring receiving (a) recombinant haplotype (s) can be determined if the sequence between *Hal* and marker loci has been established. The most likely order of the marker loci including *Hal* was indicated as *S*-(*Phi*-*Hal*)-(H-*Po2*)-*Pgd* by Hojný *et al.* (1985) and van Zeveren *et al.* (1985). As these authors did not detect crossing over between *Phi* and *Hal*, they could neither prove nor disprove the reverse

Table II. The occurrence of crossingover of *H* and *Po2* loci with respect to other loci in the *S*-(*Hal*-*Phi*-*H*-*Po2*)-*Pgd* linkage group.

Parents and offspring	Phenotypes and genotypes						Haplotypes of parents and probable haplotypes of offspring (order <i>S</i> - <i>Hal</i> - <i>Phi</i> - <i>H</i> - <i>Po2</i> - <i>Pgd</i>)		
	<i>S</i>	<i>Halothane</i> type*	<i>Phi</i>	<i>H</i>	<i>Po2</i>	<i>Pgd</i>	from sire		from dam
Sire 8264	<i>S</i> / <i>s</i>	-	<i>B</i> / <i>B</i>	<i>a</i> -	<i>F</i> / <i>S</i>	<i>A</i> / <i>B</i>	<i>SNB</i> - <i>FA</i>	/	<i>sNBa</i> <i>SB</i>
Dam 8411	<i>S</i> / <i>s</i>	-	<i>B</i> / <i>B</i>	<i>a</i> / <i>c</i>	<i>F</i> / <i>S</i>	<i>A</i> / <i>B</i>	<i>s</i> ? <i>Ba</i> <i>SA</i>	/	<i>S</i> ? <i>Bc</i> <i>FB</i>
Offspring, (8:1) ^a 75	<i>s</i> / <i>s</i>	-	<i>B</i> / <i>B</i>	<i>a</i> / <i>a</i>	<i>F</i> / <i>S</i>	<i>A</i> / <i>A</i>	<i>snBa</i> ↑ <i>FA</i>	/	<i>s</i> ? <i>Ba</i> <i>SA</i>
Sire 8289	<i>s</i> / <i>s</i>	+	<i>B</i> / <i>B</i>	<i>a</i> / <i>a</i>	<i>S</i> / <i>S</i>	<i>A</i> / <i>A</i>	<i>snBa</i> <i>SA</i>	/	<i>snBa</i> <i>SA</i>
Dam 8292	<i>s</i> / <i>s</i>	+	<i>B</i> / <i>B</i>	<i>a</i> / <i>c</i>	<i>F</i> / <i>S</i>	<i>A</i> / <i>B</i>	<i>snBa</i> <i>SA</i>	/	<i>snBc</i> <i>FB</i>
Offspring, (6:1) 9133	<i>s</i> / <i>s</i>	+	<i>B</i> / <i>B</i>	<i>a</i> / <i>c</i>	<i>S</i> / <i>S</i>	<i>A</i> / <i>A</i>	<i>snBa</i> <i>SA</i>	/	<i>snBc</i> ↑ <i>SA</i>
Sire 8511	<i>S</i> / <i>s</i>	-	<i>B</i> / <i>B</i>	<i>a</i> / <i>c</i>	<i>F</i> / <i>S</i>	<i>A</i> / <i>A</i>	<i>snBa</i> <i>SA</i>	/	<i>SNBc</i> <i>FA</i>
Dam 8649	<i>S</i> / <i>s</i>	-	<i>B</i> / <i>B</i>	<i>a</i> / <i>c</i>	<i>F</i> / <i>S</i>	<i>A</i> / <i>B</i>	<i>snBa</i> <i>SA</i>	/	<i>SNBc</i> <i>FB</i>
Offspring, (10:1) 9251	<i>S</i> / <i>b</i>	-	<i>B</i> / <i>B</i>	<i>a</i> / <i>c</i>	<i>S</i> / <i>S</i>	<i>A</i> / <i>A</i>	<i>snBa</i> <i>SA</i>	/	<i>SNBc</i> ↑ <i>SA</i>
							<i>SNBc</i> ↑ <i>SA</i>	/	<i>snBa</i> <i>SA</i>
Sire 8402	<i>S</i> / <i>s</i>	-	<i>B</i> / <i>B</i>	<i>a</i> -	<i>F</i> / <i>S</i>	<i>A</i> / <i>A</i>	<i>sNB</i> - <i>FA</i>	/	<i>SNBa</i> <i>SA</i>
Dam 8310	<i>S</i> / <i>s</i>	-	<i>B</i> / <i>B</i>	<i>a</i> / <i>c</i>	<i>F</i> / <i>S</i>	<i>A</i> / <i>B</i>	<i>snBa</i> <i>SA</i>	/	<i>SNBc</i> <i>FB</i>
Offspring, (10:1) 9826	<i>S</i> /	-	<i>B</i> / <i>B</i>	<i>a</i> / <i>a</i>	<i>F</i> / <i>S</i>	<i>A</i> / <i>B</i>	<i>SNBa</i> <i>SA</i>	/	<i>snBa</i> ↑ <i>FB</i>
Sire 9752	<i>S</i> / <i>s</i>	-	<i>B</i> / <i>B</i>	<i>a</i> / <i>c</i>	<i>F</i> / <i>S</i>	<i>A</i> / <i>B</i>	<i>snBa</i> <i>SA</i>	/	<i>SNBc</i> <i>FB</i>
Dam 9657	<i>s</i> / <i>s</i>	+	<i>B</i> / <i>B</i>	<i>a</i> / <i>a</i>	<i>S</i> / <i>S</i>	<i>A</i> / <i>B</i>	<i>snBa</i> <i>SB</i>	/	<i>snBa</i> <i>SA</i>
Offspring, (7:1) 456	<i>S</i> / <i>s</i>	-	<i>B</i> / <i>B</i>	<i>a</i> / <i>c</i>	<i>S</i> / <i>S</i>	<i>A</i> / <i>A</i>	<i>SNBc</i> ↑ <i>SA</i>	/	<i>snBa</i> <i>SA</i>

^aFirst number: total number of offspring; second number: number of offspring with recombinant types.

^bThe genotype is either *S*/*S* or *S*/*s*.

^cTwo haplotype combinations are possible.

↑ Recombinant.

* See footnote Table I.

sequence for the *Phi* and *Hal* loci proposed by Guérin *et al.* (1983). However, they confirmed that the two loci are located very close to each other.

The most important contribution of this paper is the evidence that the *Phi* locus is located, most probably, between *Hal* and *H* as proposed by Guérin *et al.* (1983) and van Zeveren *et al.* (1988) and not between *S* and *Hal* as previously reported by Andresen (1981) and Rasmussen (1981). This location is more firmly established by complex *S*-*Hal*-*Phi*-*H*-*Po2*-*Pgd* haplotypes of the majority of parents and offspring, including recombinants. Probably because of incomplete penetrance of the *Halⁿ* gene one animal with presumed genotype *Halⁿ / Haⁿ* failed to react to halothane. Two recombinants (Table I,

Table III. The occurrence of crossingover of *Phi* and *H* loci with respect to other loci in the *S*-(*Hal*-*Phi*-*H*-*Po2*)-*Pgd* linkage group.

Parents and offspring	Phenotypes and genotypes						Haplotypes of parents and probable haplotypes of offspring (order <i>S</i> - <i>Hal</i> - <i>Phi</i> - <i>H</i> - <i>Po2</i> - <i>Pgd</i>)		
	<i>S</i>	<i>Halothane type</i> ^a	<i>Phi</i>	<i>H</i>	<i>Po2</i>	<i>Pgd</i>	from sire		from dam
Sire 8591	<i>S/S</i>	—	<i>B/B</i>	<i>a/c</i>	<i>F/S</i>	<i>A/B</i>	<i>SnBaSA</i>	/	<i>SNBcFB</i>
Dam 8718	<i>S/a</i>	—	<i>A/B</i>	<i>a/c</i>	<i>F/S</i>	<i>B/B</i>	? <i>NBaSB</i>	/	?? <i>AcFB</i>
Offspring, (8:1) ^b 9332	<i>S/</i>	—	<i>B/B</i>	<i>c/c</i>	<i>F/F</i>	<i>B/B</i>	<i>SNBcFB</i>	/	? <i>NB</i> ↑ <i>cFB</i>
Sire 9682	<i>S/S</i>	—	<i>B/B</i>	<i>c/—</i>	<i>F/F</i>	<i>B/B</i>	<i>SNBcFB</i>	/	<i>SNB-FB</i>
Dam 9948	<i>S/S</i>	—	<i>A/B</i>	<i>a/c</i>	<i>F/S</i>	<i>A/A</i>	<i>S?BaSA</i>	/	<i>SNAcFA</i>
Offspring, (8:1) 450	<i>S/S</i>	—	<i>A/B</i>	<i>a/—</i>	<i>F/S</i>	<i>A/B</i>	<i>SNB-FB</i>	/	<i>SNA</i> ↑ <i>aSA</i>

^a The genotype is either *S/S* or *S/s*.

^b First number: total number of offspring; second number: number of offspring with recombinant types.

↑ Recombinant.

* See footnote Table I.

offspring 275 and 695) being informative with respect to the location of the *Phi* locus were classified as *HAL*⁺. These two reactors certainly are *Hal*ⁿ/*Hal*ⁿ homozygotes because the probability of a *Hal*^N/*Hal*^N or *Hal*^N/*Hal*ⁿ pig being falsely tested as *HAL*⁺ is very low (Vögeli *et al.*, 1988).

The data in Tables II and III are consistent with a gene order of *Phi*-*H*-*Po2*-*Pgd*. The data assembled in Tables I, II and III and those contained in earlier publications indicate a gene order *S*-*Hal*-*Phi*-*H*-*Po2*-*Pgd*. The knowledge of the halothane locus and its linkage relationships is already being used in practical animal breeding to reduce the frequency of the *Hal*ⁿ gene (Gahne & Juneja, 1985; Vögeli *et al.*, 1988). Looking to the future, molecular analysis of the halothane linkage group may provide a means for identifying more reliable markers for the stress genes as well as the identity of the halothane gene itself. One step in this development is the assignment of the *Hal* linkage group to chromosome 6 by *in situ* hybridization (Davies *et al.*, 1988).

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