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Assessing the genetic contribution to behaviour: What we can learn from man's best friend

Juliane Friedrich
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Domestication of the dog: a “long-term selection experiment”

- Belyaev’s “Farm fox experiment”: selection for tameness in Silver foxes resulted in significant behavioural and morphological changes

(Trut, 1999)

- Domestication of dogs 14,000 years ago → start point for intense selection on different traits, e.g. behaviour
- Dog = interesting resource on the genetic architecture of behaviour variation

The dog as powerful animal model for genetic analyses

- Structure of canid genome: higher LD compared to humans
- Intense artificial selection generated diverse phenotypes (including behaviour)
- Informative pedigrees
- Resemblance of many diseases between dogs and humans
- Shared coexistence with humans (e.g. environment, diet, stressors)

Aims

Identify genetic variation associated with behavioural characteristics

Identify signatures of selection for behaviour by artificial selection (recent)

Can dogs provide general insights into behaviour?

What is the role of selection for behaviour diversification?

Association study: DATA & METHODS

- Phenotype data:
  - C-BARQ (Canine Behavioral Assessment & Research Questionnaire)
  - 13 behaviour characteristics, e.g. on aggression, fearfulness, trainability, playfulness

- German Shepherd dogs (GSDs):

  - Pet, show & working dogs
  - Random sample of the UK GSD population

  - Pet, show & working dogs
  - Selected for behaviour (test of the Swedish Armed Forces)

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Association study: DATA & METHODS

- Genotype data:
  - 741 GSDs genotyped with Illumina Canine HD Beadchip (173,662 SNPs) → 78,088 SNPs after QC
- Statistical analyses:
  - Heritability (h^2) estimates (pedigree & genomic information)
  - Genome-wide association study (GWAS) & Regional-heritability mapping (RHM)

Association study: RESULTS

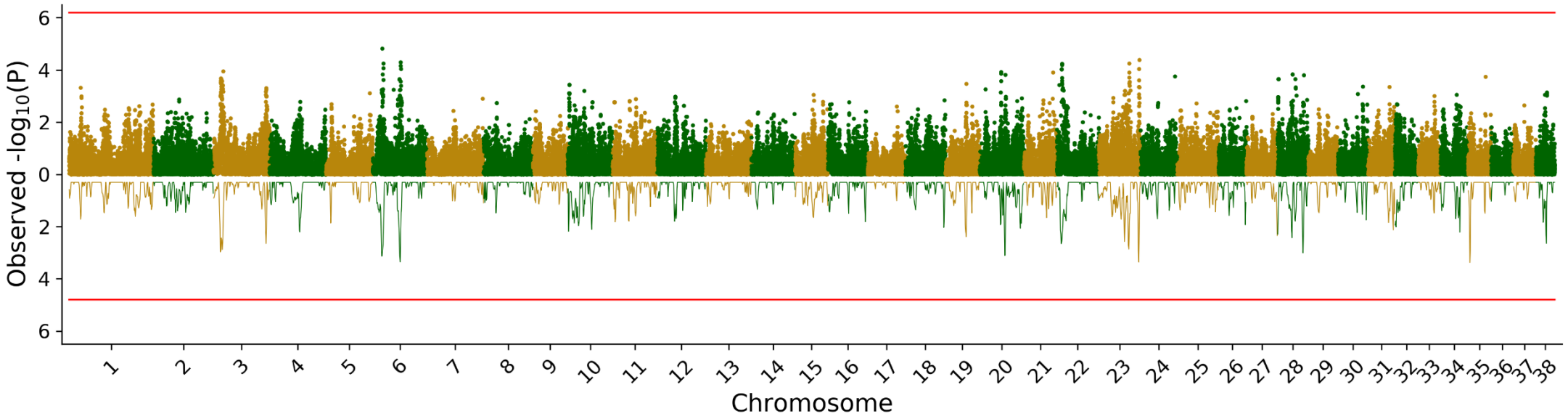
Behaviour trait	h^2	
	Pedigree-based	Genome-based
Stranger-directed aggression		
Dog-directed aggression		
Stranger-directed fear	0.04 ± 0.05	0.04 ± 0.05
Human-directed playfulness	**0.23 ± 0.08**	**0.17 ± 0.07**
Excitability	0.05 ± 0.05	0.06 ± 0.05
Separation anxiety		
Lack of obedience		
Stranger-directed interest	0.10 ± 0.06	0.01 ± 0.05
Attachment/ Attention seeking		0.02 ± 0.05
Chasing	0.09 ± 0.06	0.13 ± 0.06
Non-social fear	0.12 ± 0.06	0.16 ± 0.06
Dog-directed fear	0.01 ± 0.04	
Touch sensitivity	0.02 ± 0.04	

Association study: RESULTS

Human-directed playfulness

GWAS

RHM



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Association study: RESULTS

- GO analysis of the top 0.5% significance SNPs for Human-directed playfulness (n= 394; 202 genes)

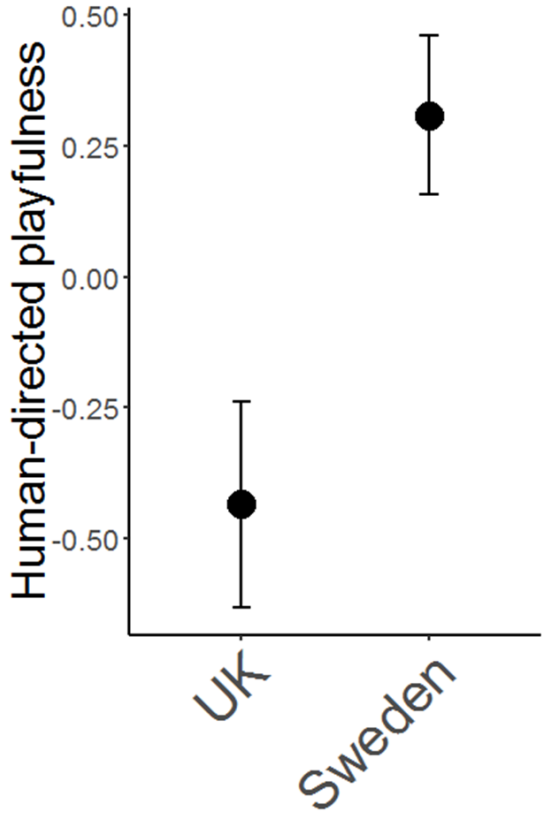
Enrichr

Panther pathway	P-value
Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway	0.01
Metabotropic glutamate receptor group III pathway	0.02
Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway	0.02
PDGF signaling pathway	0.03
Axon guidance mediated by Slit/Robo	0.01

Progressing from genetic associations to signatures of selection for behaviour

- Human-directed playfulness as promising trait:
  - moderate h^2
  - significant SNPs

- Human-directed playfulness differs between populations:



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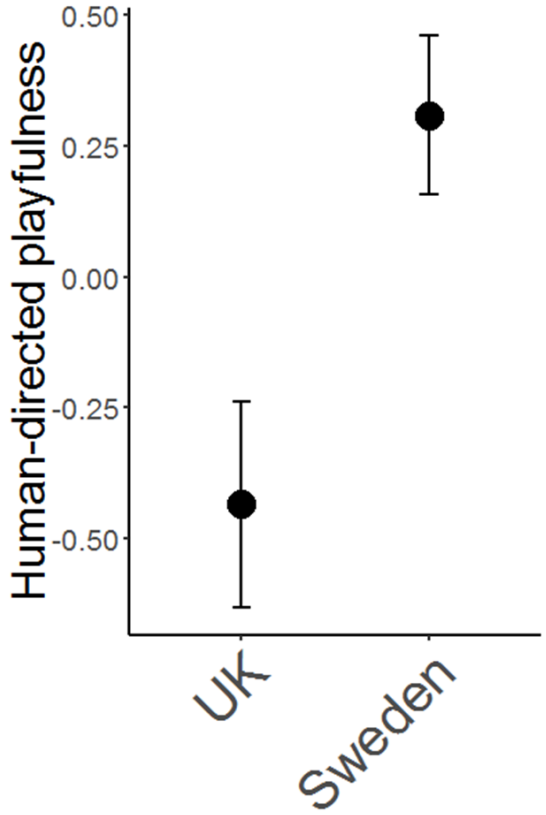

Dissecting genetic architecture of behaviour using selection signals

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Selection signatures: DATA & METHODS

– Random sample of the UK GSD population

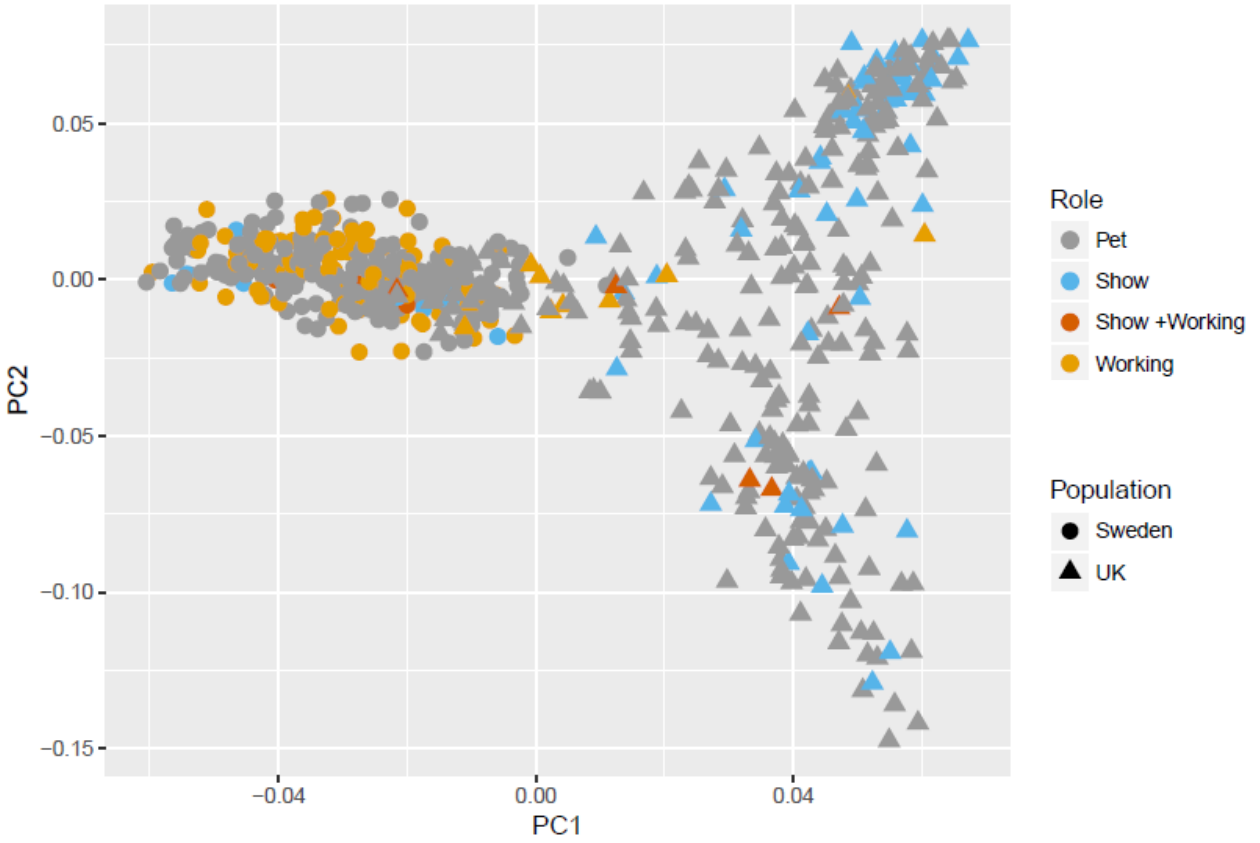
vs.

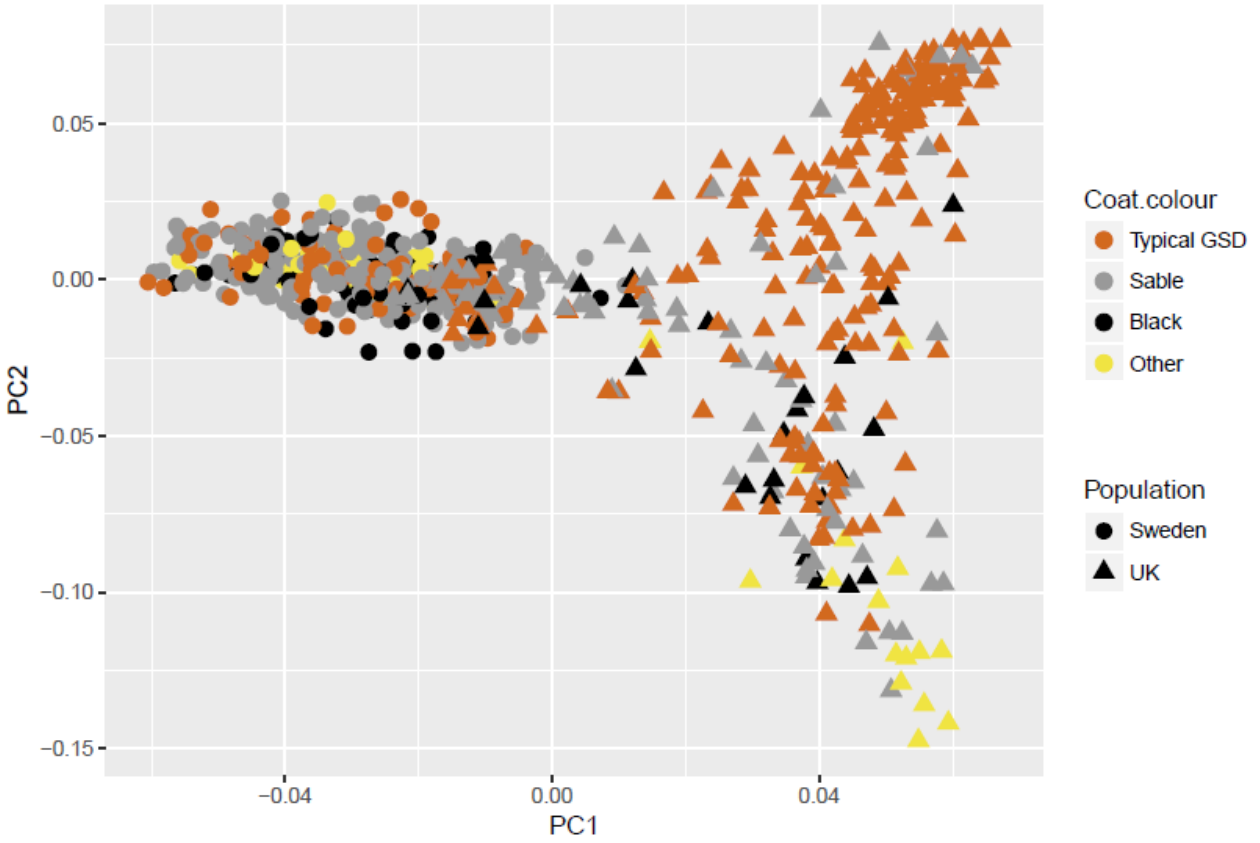
– Selected for behaviour (test of the Swedish Armed Forces)

- Analyses:
  - Genomic population structure (PCA, ADMIXTURE)
  - Within populations: integrated Haplotype score (iHS)
  - Between populations: Difference between ROH (|H-score|), F_{ST}, XP-EHH

Selection signatures: RESULTS

Genomic population structure





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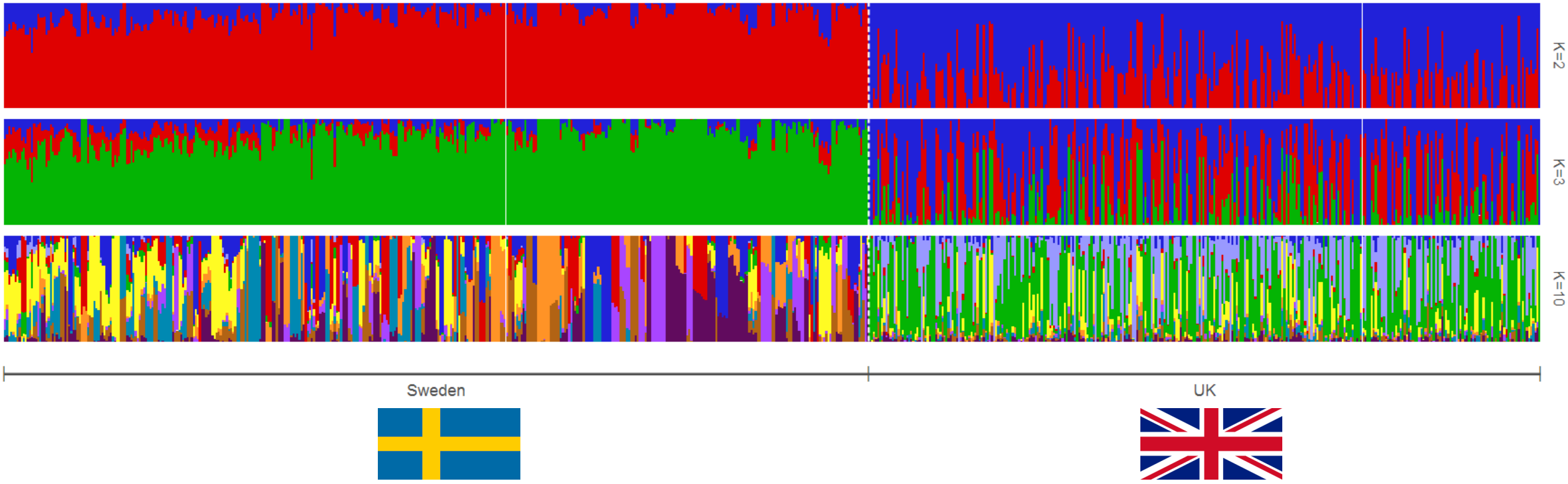
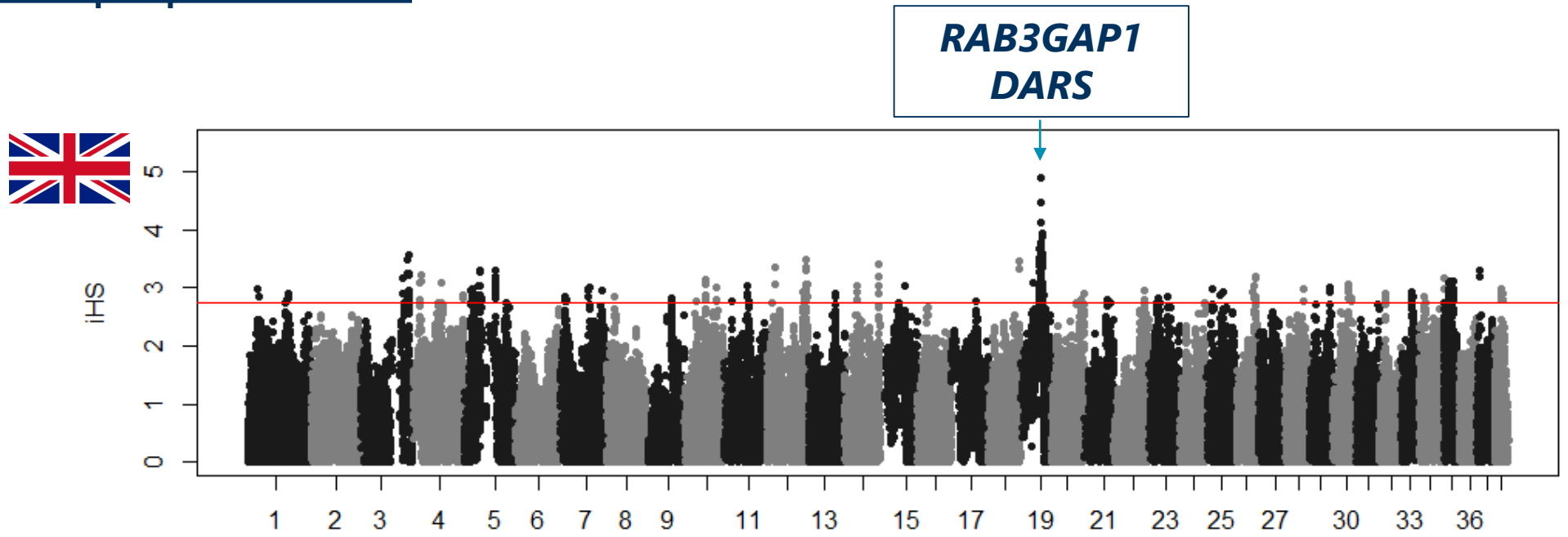
Selection signatures: RESULTS

Genomic population structure



Selection signatures: RESULTS

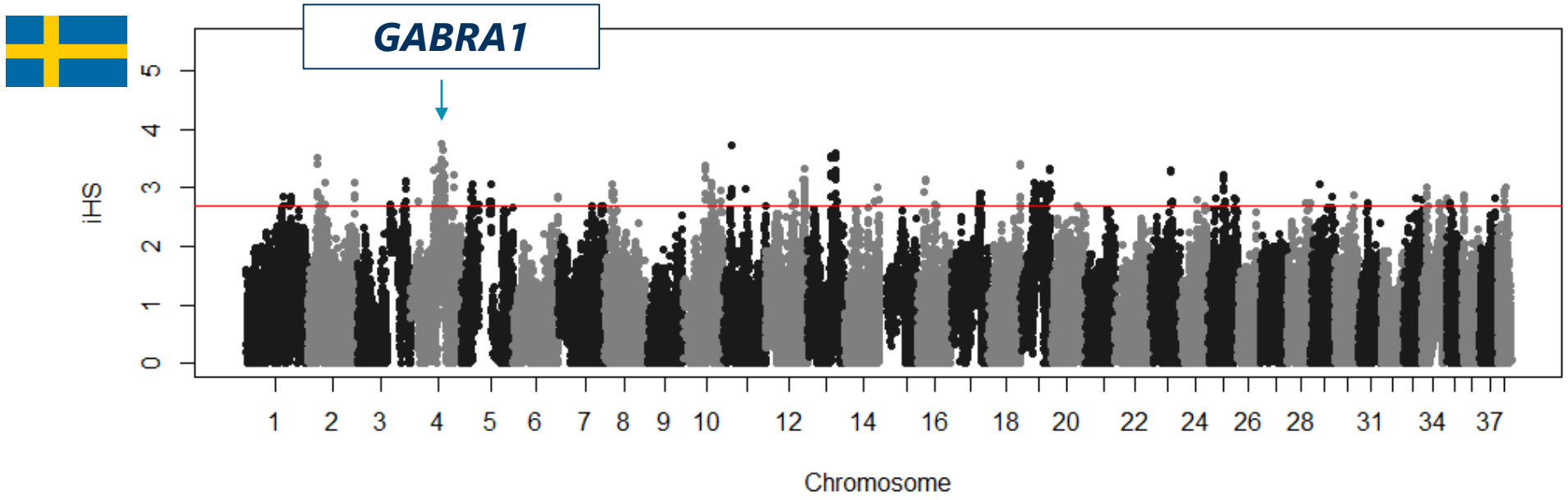
Within populations



- Mutations in *RAB3GAP1* are associated with neurologic diseases in different dog breeds (Mhlanga-Mutangadura et al. 2016)
- Impaired attentional processing in *DARS*+/− mice (Froehlich et al. 2017)

Selection signatures: RESULTS

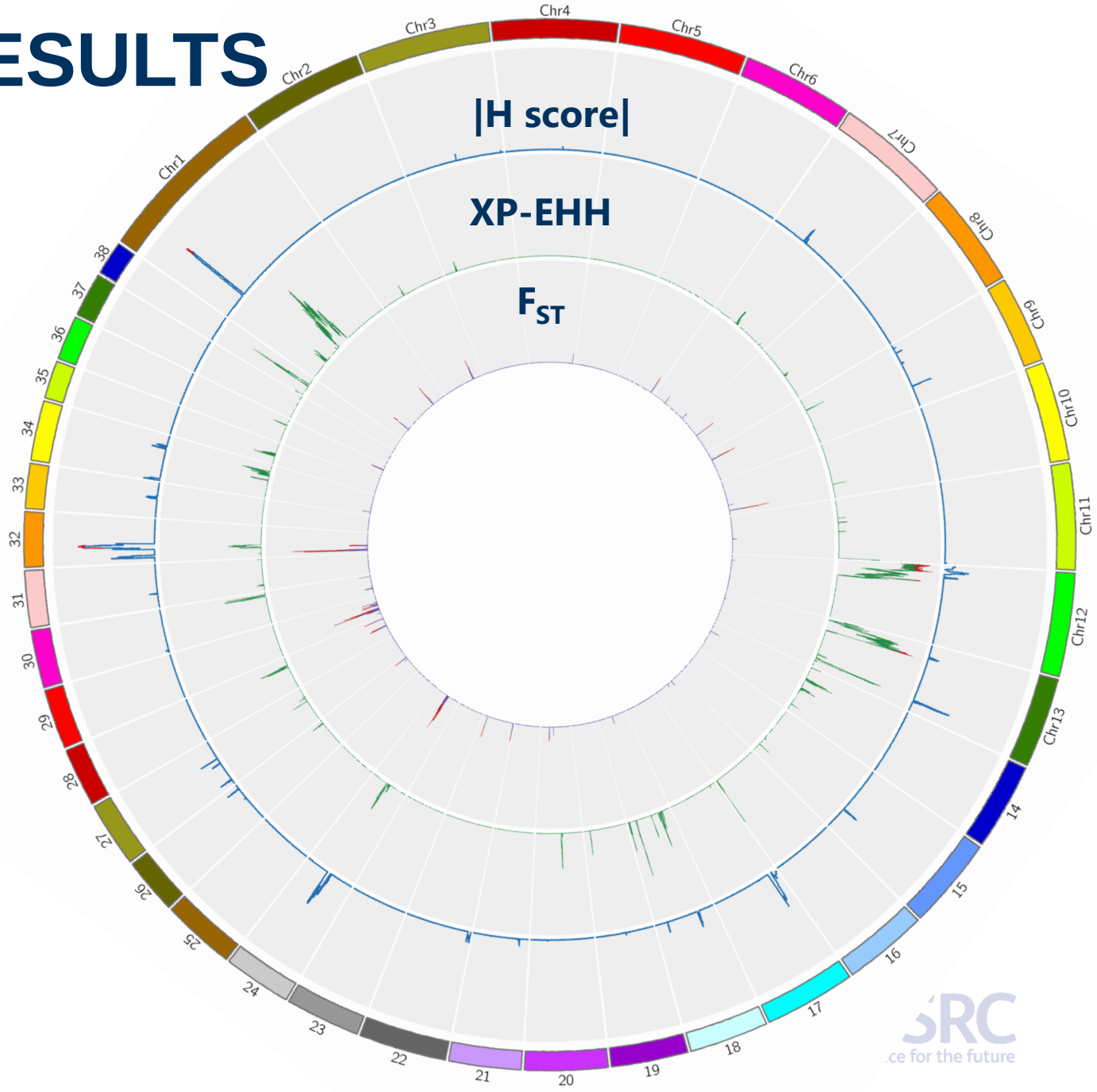
Within populations



- *GABRA1* is strong candidate gene for personality and anxiety across species
- Candidate gene for epilepsy in dogs (Ekenstedt et al. 2011)
- Differential expression in dogs after exposure to chronic stress (Luo et al. 2015)

Selection signatures: RESULTS

Between populations



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Selection signatures: RESULTS

Between populations

ANIMAL GENETICS
Immunogenetics, Molecular Genetics and Functional Genomics

Full Access

The long and the short of it: evidence that *FGF5* is a major determinant of canine 'hair'-itability

D. J. E. Housley, P. J. Venta

OPEN ACCESS Freely available online PLoS

Variation of *BMP3* Contributes to Dog Breed Skull Diversity

Jeffrey J. Schoenebeck[1], Sarah A. Hutchinson[2], Alexandra Byers[1], Holly C. Beale[1], Blake Carrin
Daniel L. Faden[1], Maud Rimbault[1], Brennan Decker[1], Jeffrey M. Kidd[4], Raman Sood[3], Adam R.
John W. Fondon III[6], Robert K. Wayne[7], Carlos D. Bustamante[4], Brian Ciruna[2,8], Elaine A. Ostrander

Original article

EDITOR'S CHOICE

Microdeletion at chromosome 4q21 defines a new emerging syndrome with marked growth restriction, mental retardation and absent or severely delayed speech

C Bonnet,[1] J Andrieux,[2] M Béri-Dexheimer,[1] B Leheup B,[1,3] O Boute,[4] S Manouvrier,[4] B Delobel,[5] H Copin,[6] A Receveur,[6] M Mathieu,[7] G Thiriez,[8] C Le Caignec,[9] A David,[9] MC de Blois,[10] V Malan,[10,11] A Philippe,[11,12] V Cormier-Daire,[11,12] L Colleaux,[12] E Flori,[13] H Dollfus,[14] V Pelletier,[14] C Thauvin-Robinet,[15] A Masurel-Paulet,[15] L Faivre,[15] M Tardieu,[16] N Bahi-Buisson,[17] P Callier,[18] F Mugneret,[18] P Edery,[19] P Jonveaux,[1] D Sanlaville[19]

RESEARCH ARTICLE Open Access

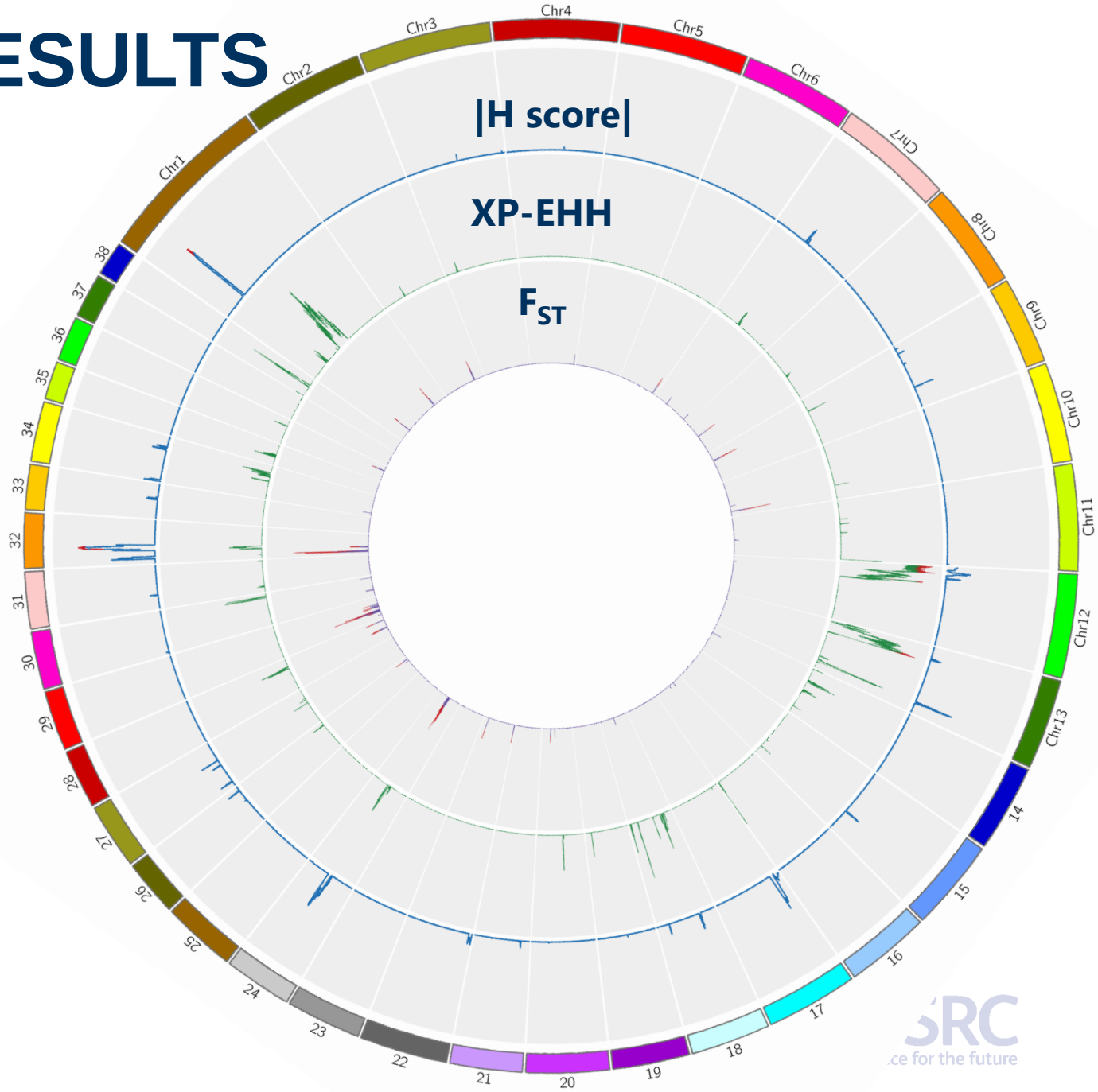
CrossMark

Genetic mapping of canine fear and aggression

Isain Zapata[1], James A. Serpell[2] and Carlos E. Alvarez[1,3,4*]

RGH

FGF5
BMP3
PRKG2
RASGEF1B



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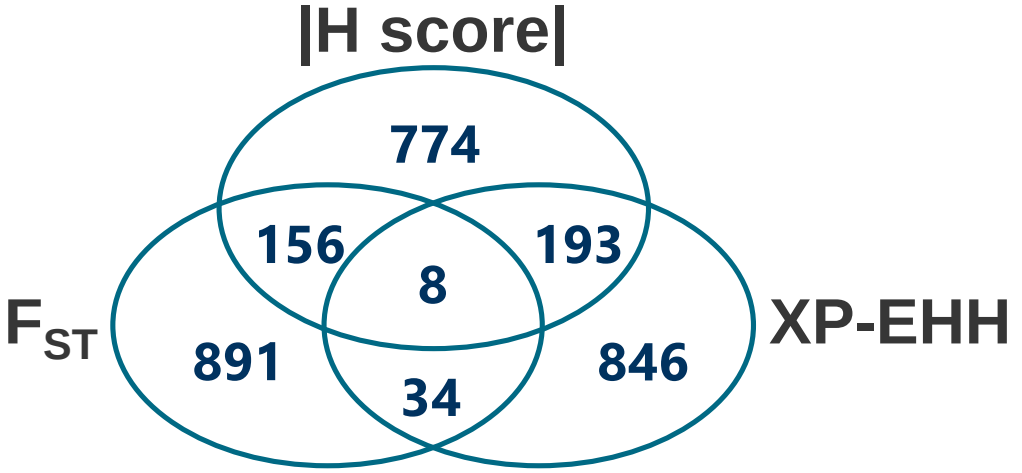
Selection signatures: RESULTS

Between populations

►GO analysis of the top 1% consensus SNPs (n= 391; 141 genes)

Enrichr

Panther pathway	P-value
p53 pathway feedback loops 2	1.07E-02
TGF-beta signalling pathway	6.64E-02
B cell activation	9.63E-02
Oxidative stress response	1.01E-01
Parkinson disease	1.01E-01



Summary & conclusions

- Evidence for genetic variation of behavioural characteristics within dogs
- *Human-directed playfulness* shows potential for selection and might reflect the domestication history of the dog
- Identified candidate genes previously linked to psychological disorders or behaviours in other species highlight the dog as model animal
- Dog as promising resource to analyse behavioural selection

Thanks to…

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Erling Strandberg
Per Arvelius
Susanne Gustafsson
Gabriela Bottani Claros

Owners of German Shepherd dogs participating in this study

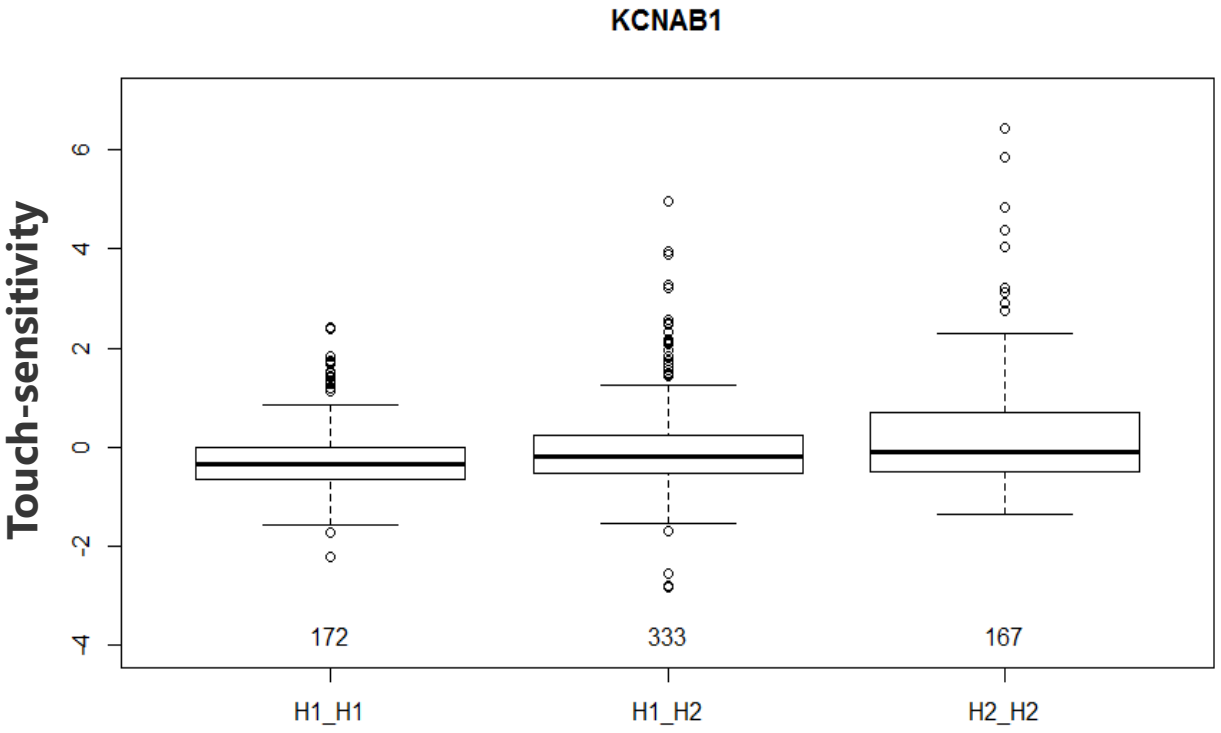
UK Kennel Club

British Association for German Shepherd Dogs

German Shepherd Dog Breed Council of Great Britain

Haplotype analysis for multiple significant SNPs located in genes

- Candidate genes were previously linked to neurodevelopmental disorders (*TLK2*) and autism in humans (*LRRN3, DIAPH3)* and to aggressive behaviour in mice (*NRXN1*)



KCNQ knock-out mice showed an increased sensitivity of mechanoreceptors in the skin (Schütze et al., 2016)

variation in *KCNAB1* (also encoding a potassium channel) could have a similar effect in dogs

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