



Translation and the history of modern genomics

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THE UNIVERSITY *of* EDINBURGH



European Research Council

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Plan

About the project

Translation

History of pig genomics

Implications

- Thick/thin sequencing

- Consequences for understanding translation

Ongoing work



TRANS GENE

‘Traditional’ archival research and oral history interviews

Quantitative and social network analysis (SNA) methods from the social sciences

Human

Pig

Yeast (*S. cerevisiae*)

Quantitative/SNA

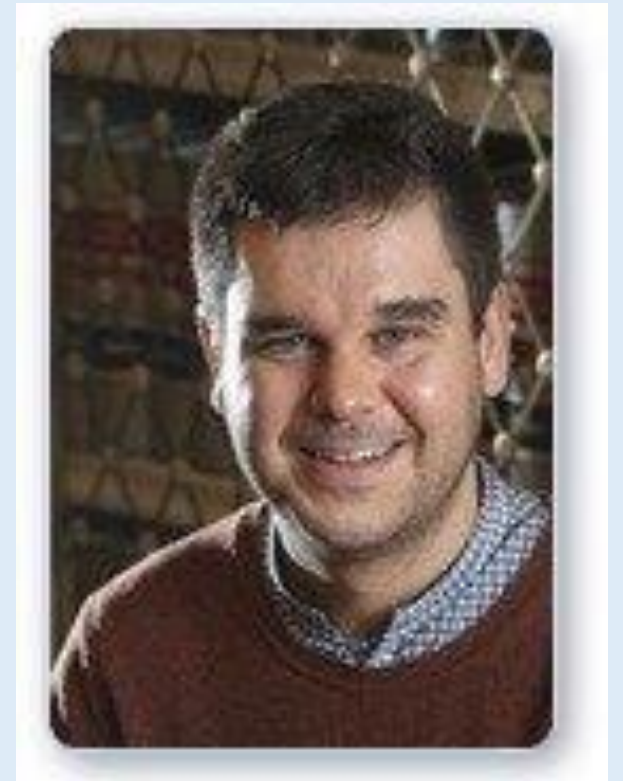


Human

Research on UK Human Genome Mapping Project

Thesis: bottom-up → top-down approach in genomics

Change in composition of community of sequencers and organisation of sequencing

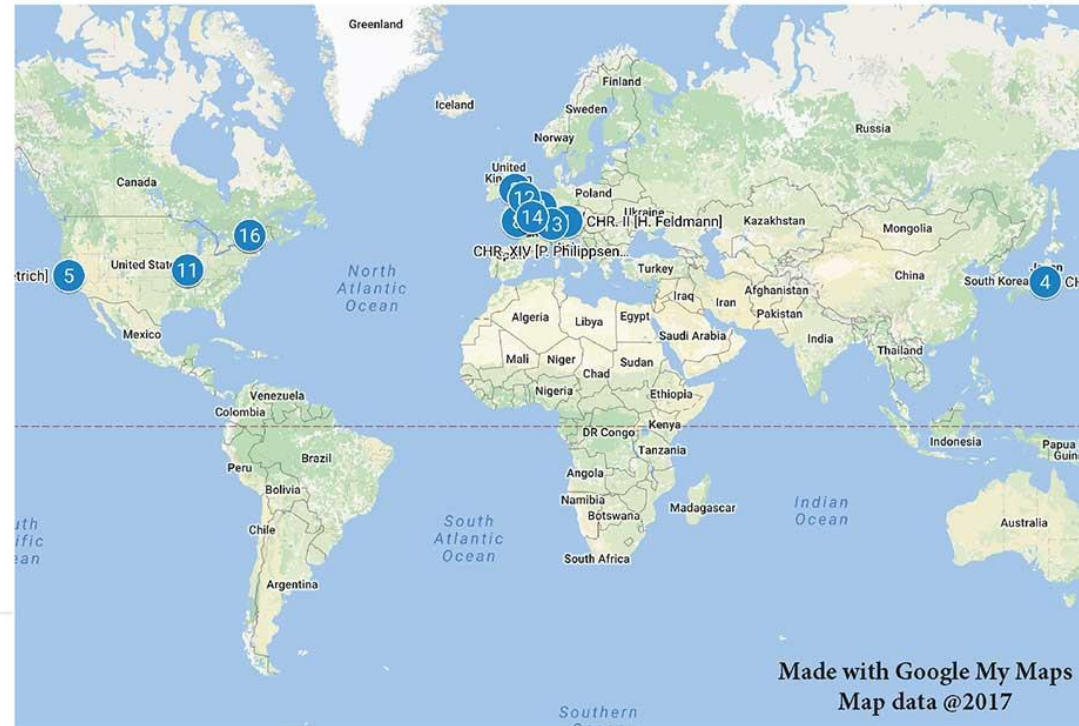


Yeast

Yeast Genome Sequencing Project (1989-1996)

First author in the published sequence

- 1 CHR. II [H. Feldmann]
- 2 CHR. III [S. G. Oliver]
- 3 CHR. IV [C. Jacq]
- 4 CHR. VI [Y. Murakami]
- 5 CHR. V [F.S. Dietrich]
- 6 CHR. VIII [M. Johnston]
- 7 CHR. IX [C. Churcher]
- 8 CHR. X [F. Galibert]
- 9 CHR. VII [H. Tettelin]
- 10 CHR. XI [B. Dujon]
- 11 CHR. XII [M. Johnston]
- 12 CHR. XIII [S. Bowman]
- 13 CHR. XIV [P. Philippsen]
- 14 CHR. XV [B. Dujon]
- 15 CHR. XVI [H. Bussey]
- 16 CHR. I [H. Bussey]

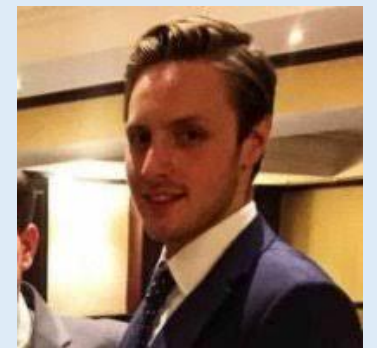


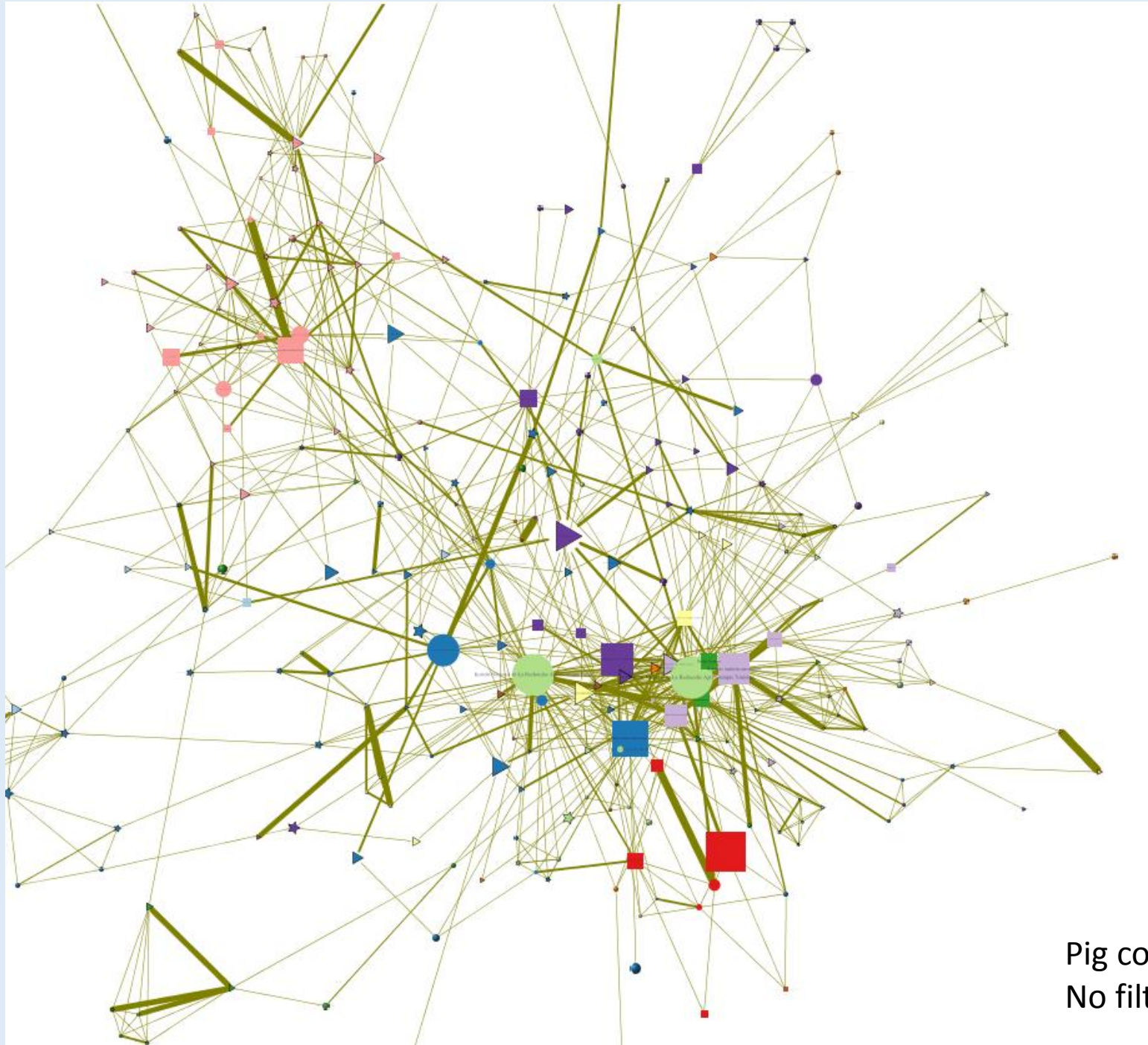
Quantitative/SNA

Develop processes to extract data from European Nucleotide Archive (housed at European Bioinformatics Institute) and Scopus.

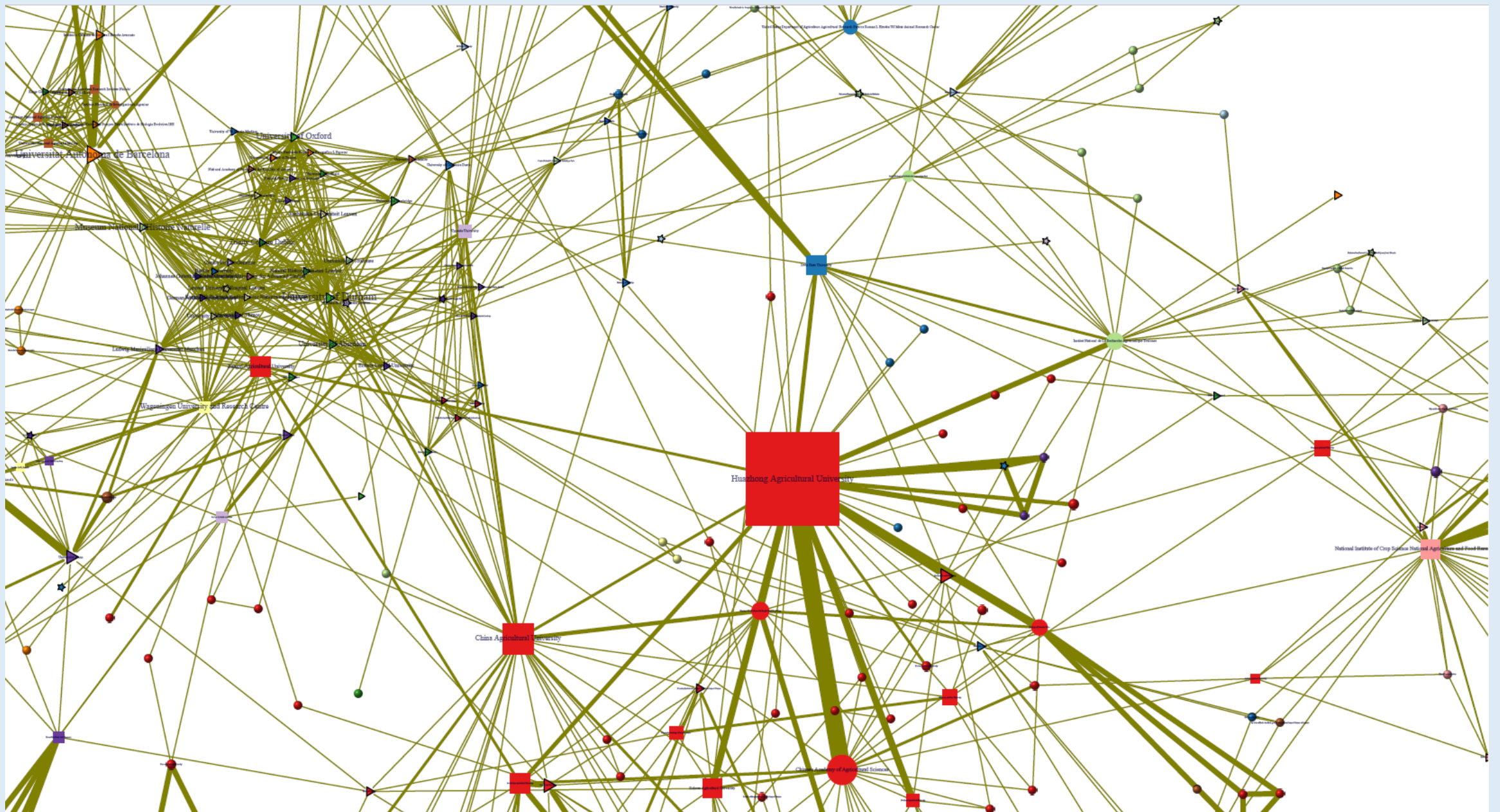
Production of comprehensive datasets of sequence submissions and associated publications.

Production of network visualisations.





Pig co-authorship 1990-2005
No filters



Pig co-authorship 2006-2015
No filters

The problem of translation

‘Gaps’;

‘Obstacles’;

Between research outputs and
therapeutic interventions.

Typical case – sequence data associated
with Human Genome Project

NIH politics and funding, cancer research



Image credit: B. Mellor, *Nature*

Translation: pig genetics and breeding

Close working relationship between publicly-funded animal science research and livestock breeding industry.

USDA/INRA/old AFRC institutes, land-grant universities in US, agricultural universities in Netherlands, Denmark, Sweden.

‘Strategic’ and precompetitive research.

“What then is the relation of science to this art of breeding? ...to place at the disposal of the breeder the instruments of precision which will enable him to carry out his work efficiently.”

A. D. Darbishire, 1917, p. 126



Image credit: Alan L. Archibald

Landmarks

Late 1980s – Start of more systematic mapping of the pig genome.

1991-1994 – PiGMaP 1

Early 1990s – USDA initiatives launched

1994-1996 – PiGMaP 2

Late 1990s, early 2000s – QTL mapping efforts; production of BAC libraries

2006-2009 – Sequencing at Sanger Institute; 2009 draft sequence

2012 – Publication in *Nature*

2016 – New sequence published



Image credit: Alan L. Archibald

History of pig genomics

Mapping and sequencing efforts.

Primary initial focus: PiGMaP collaborations (1991-1996) and Swine Genome Sequencing Consortium (from 2006).

US initiatives (including USDA)

Asian involvement and projects.



European collaboration

PiGMaP

European Laboratory Without
Walls (ELWW)

Funded by European Commission,
national ministries/research
councils. Some private sector
support.



PiGMaP

Distributed, bottom-up project.
Movement of DNA, genotyping
data, linkage analyses, materials

Combination of molecular and
quantitative genetics approaches

Reference families across
Europe, crosses for linkage
analysis



Image credit: Alan L. Archibald



PiGMap objectives

- Produce physical map with >1 distal and >1 proximal landmark focus mapped on each chromosome arm;
- Produce genetic map with sufficiently dense and spaced out markers;
- Link the two maps using landmark loci;
- Develop and characterise a flow karyotype;
- Develop techniques for rapid genotyping for polymorphic markers;
- Evaluate conservation of synteny;
- Plan experiments and develop and evaluate statistical methods to map and analyse QTL;
- [Develop an informatics capacity for pig genetics and genomics].

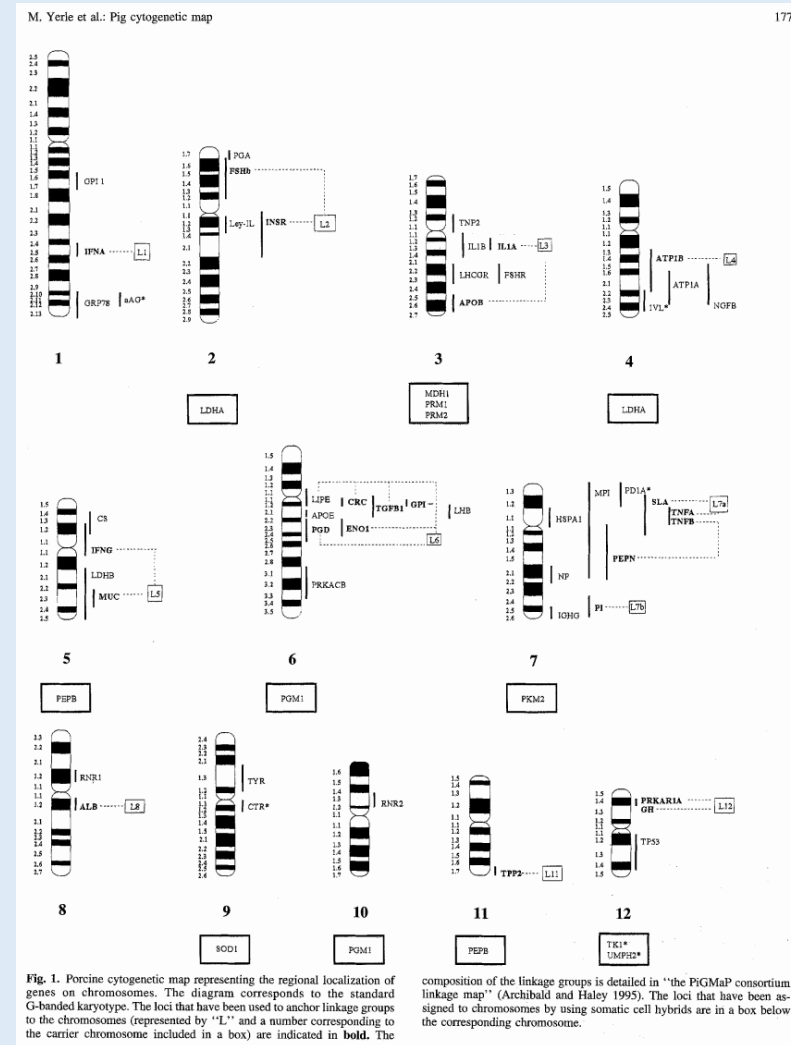




Genetic and cytogenetic mapping

Databases – two databases in PiGMaP, Roslin and INRA. Not integrated, though subsets of the data were collated together in order to produce the linkage maps.

Roslin on genetic mapping,
INRA on cytogenetic mapping.



Yerle et al. (1995) The PiGMaP consortium cytogenetic map of the domestic pig (*Sus scrofa domestica*). *Mammalian Genome*, 6: 176-186.

Physical mapping project, 2003-2005

4 BAC libraries used:

Fingerprint and BAC end sequence summary

Library	Fingerprinted clones	Genome complexity	BES passed reads	Paired ends	Average GC %	Average Phred Q20 length (bp)
CHORI-242	101,434	6.7	340,484	93%	41	705
PigEBAC	73,863	4.2	144,870	93%	42	700
RPCI-44	61,225	3.8	71,847	87%	40	521
INRA	28,465	1.5	62,888	94%	42	613
All	264,987	16.2*	620,089	92%	41	635

*Based on a genome size of 2.6 to 2.7 Gb [30].

Production of physical map based on BAC-end sequencing at Sanger Institute and Genoscope.

Minimum tile path generated.

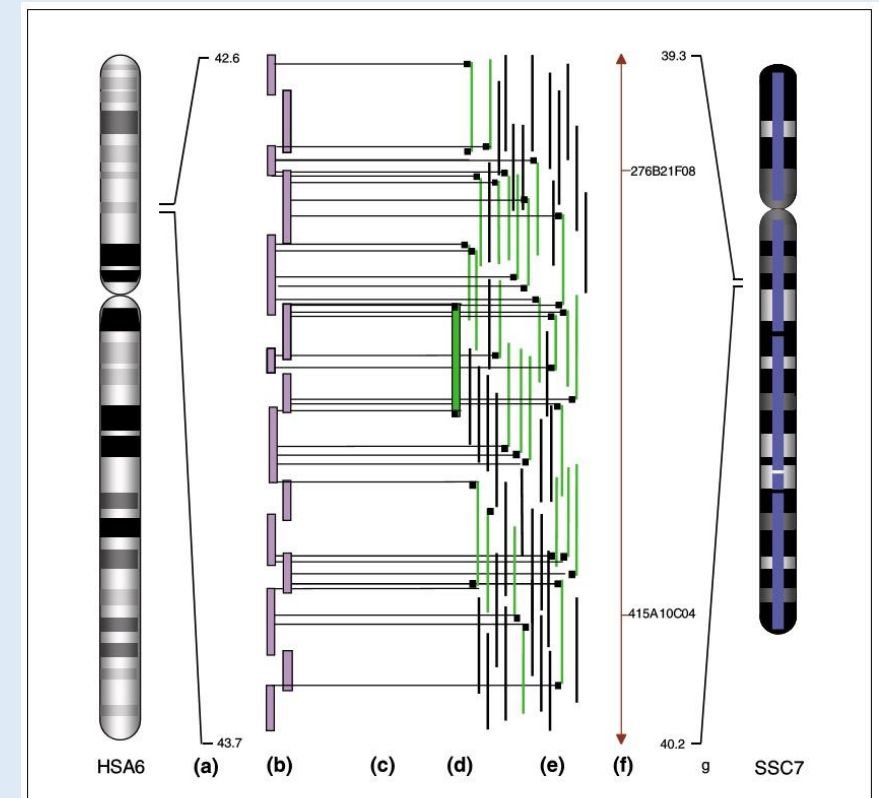


Figure 1
Alignment between human chromosome 6 tilepath and pig chromosome 7 physical map via porcine BES matches. (a) Mb scale; (b) human sequence tilepath; (c) BES matches to human; (d) sequenced clone EMBL:CR956379 (CH242-196P11); (e) pig clone map - green indicate clones with BAC end sequence match to human; (f) UIUC RH map; (g) estimated Mb.

Humphray et al. (2007) A high utility integrated map of the pig genome. *Genome Biology*, 8: R139.

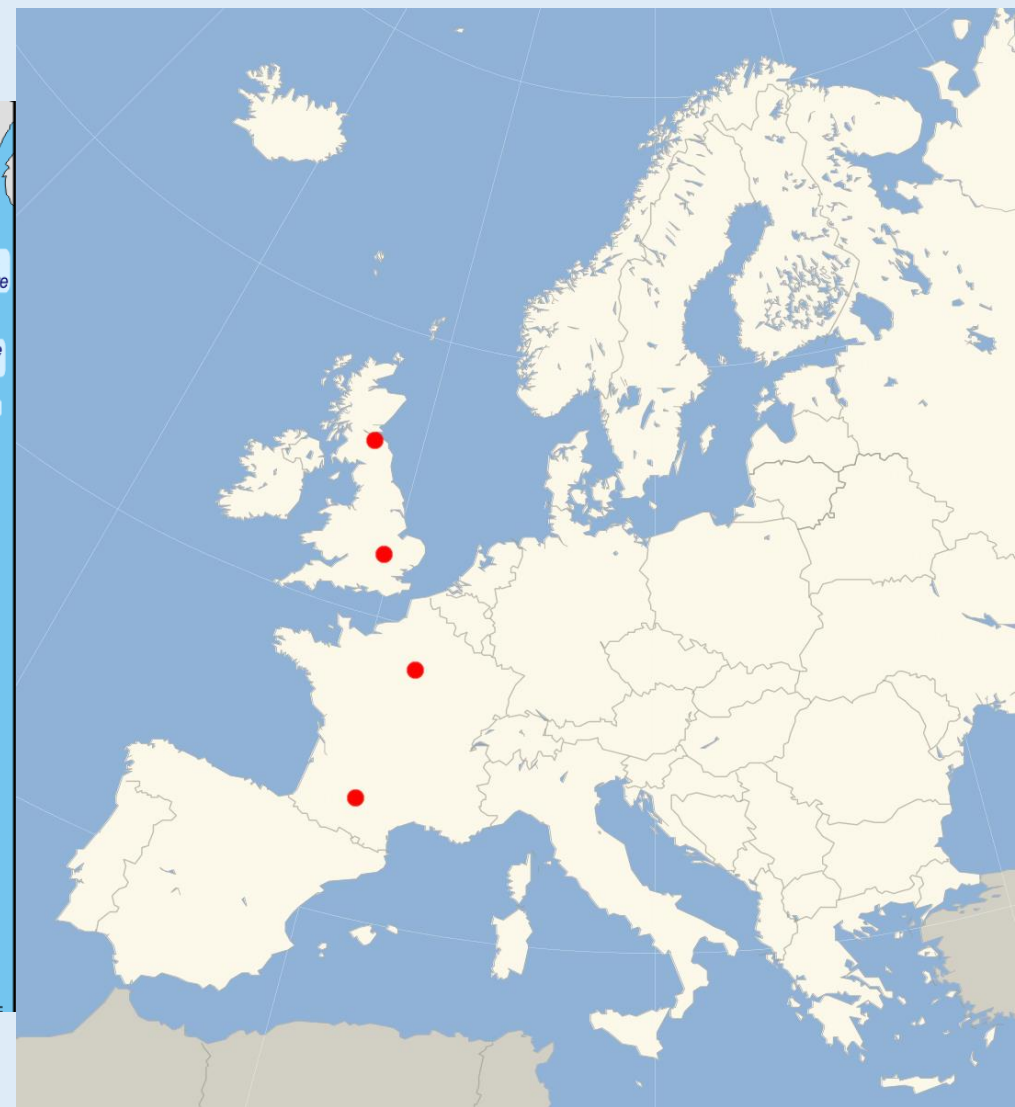
Sequencing

International consortium. Sequencing conducted mainly at Sanger Institute.

Funding from USDA, EU, DEFRA, BBSRC, National Pork Board, Iowa Pork Board, North Carolina Pork Council, Iowa State University, North Carolina State University.



Photo credit:
www.thepigsite.com/focus/contents/breedsofswine/du_sow.jpg



Sequencing project

Involvement of pig genetics community in planning, management, assembly and annotation

Outcomes include the development of SNP chips for genotyping, genomic selection in livestock industry

Sscrofa10.2 assembly; other assemblies and resources produced



Organism	Name	Submitter	Date	Genome representation	Assembly level	Version status	RefSeq category
Sus scrofa (pig)	Sscrofa11.1	The Roslin Institute, University of Edinburgh	02/07/2017	full	Chromosome	latest	representative genome
Sus scrofa (pig)	Sscrofa10.2 Synonyms: susScr3	The Swine Genome Sequencing Consortium (SGSC)	09/07/2011	full	Chromosome	replaced	representative genome
Sus scrofa (pig)	Sscrofa11	The Swine Genome Sequencing Consortium (SGSC)	12/06/2016	full	Chromosome	replaced	na
Sus scrofa (pig)	Sscrofa10	The Swine Genome Sequencing Consortium (SGSC)	05/19/2011	full	Chromosome	replaced	na
Sus scrofa (pig)	Sscrofa9.2	The Swine Genome Sequencing Consortium (SGSC)	02/23/2010	full	Chromosome	replaced	na
Sus scrofa (pig)	Sscrofa9	The Swine Genome Sequencing Consortium (SGSC)	11/02/2009	full	Chromosome	replaced	na
Sus scrofa (pig)	ss10.2_mar2013	F. Hoffmann - La Roche AG	09/16/2015	full	Scaffold	latest	na
Sus scrofa (pig)	minipig_v1.0	BGI-shenzhen	03/18/2015	full	Scaffold	latest	na
Sus scrofa (pig)	minipig_v1.0	BGI-shenzhen	11/30/2012	full	Scaffold	replaced	na
Sus scrofa (pig)	Tibetan_Pig_v1.0	Novogene	02/06/2015	full	Scaffold	replaced	na
Sus scrofa (pig)	SscrofaMinipig	GlaxoSmithKline	01/10/2013	full	Contig	latest	na
Sus scrofa (pig)	Tibetan_Pig_v2	Novogene	08/08/2016	full	Scaffold	latest	na
Sus scrofa (pig)	Large_White_v1	Novogene	08/05/2016	full	Scaffold	latest	na
Sus scrofa (pig)	Rongchang_pig_v1	Novogene	08/05/2016	full	Scaffold	latest	na
Sus scrofa (pig)	Hampshire_pig_v1	Novogene	08/05/2016	full	Scaffold	latest	na
Sus scrofa (pig)	Meishan_pig_v1	Novogene	08/05/2016	full	Scaffold	latest	na
Sus scrofa (pig)	Landrace_pig_v1	Novogene	08/05/2016	full	Scaffold	latest	na
Sus scrofa (pig)	Bamei_pig_v1	Novogene	08/05/2016	full	Scaffold	latest	na
Sus scrofa (pig)	Pietrain_pig_v1	Novogene	08/05/2016	full	Scaffold	latest	na
Sus scrofa (pig)	Jinhua_pig_v1	Novogene	08/05/2016	full	Scaffold	latest	na
Sus scrofa (pig)	Berkshire_pig_v1	Novogene	08/05/2016	full	Scaffold	latest	na
Sus scrofa (pig)	Sscrofa5	The Swine Genome Sequencing Consortium (SGSC)	07/11/2008	partial	Chromosome	replaced	na
Sus scrofa (pig)	WTSL_X_Y_pig_V2	SC	02/08/2017	partial	Chromosome	latest	na
Sus scrofa (pig)	WTSL_X_Y	SC	11/27/2016	partial	Chromosome	replaced	na

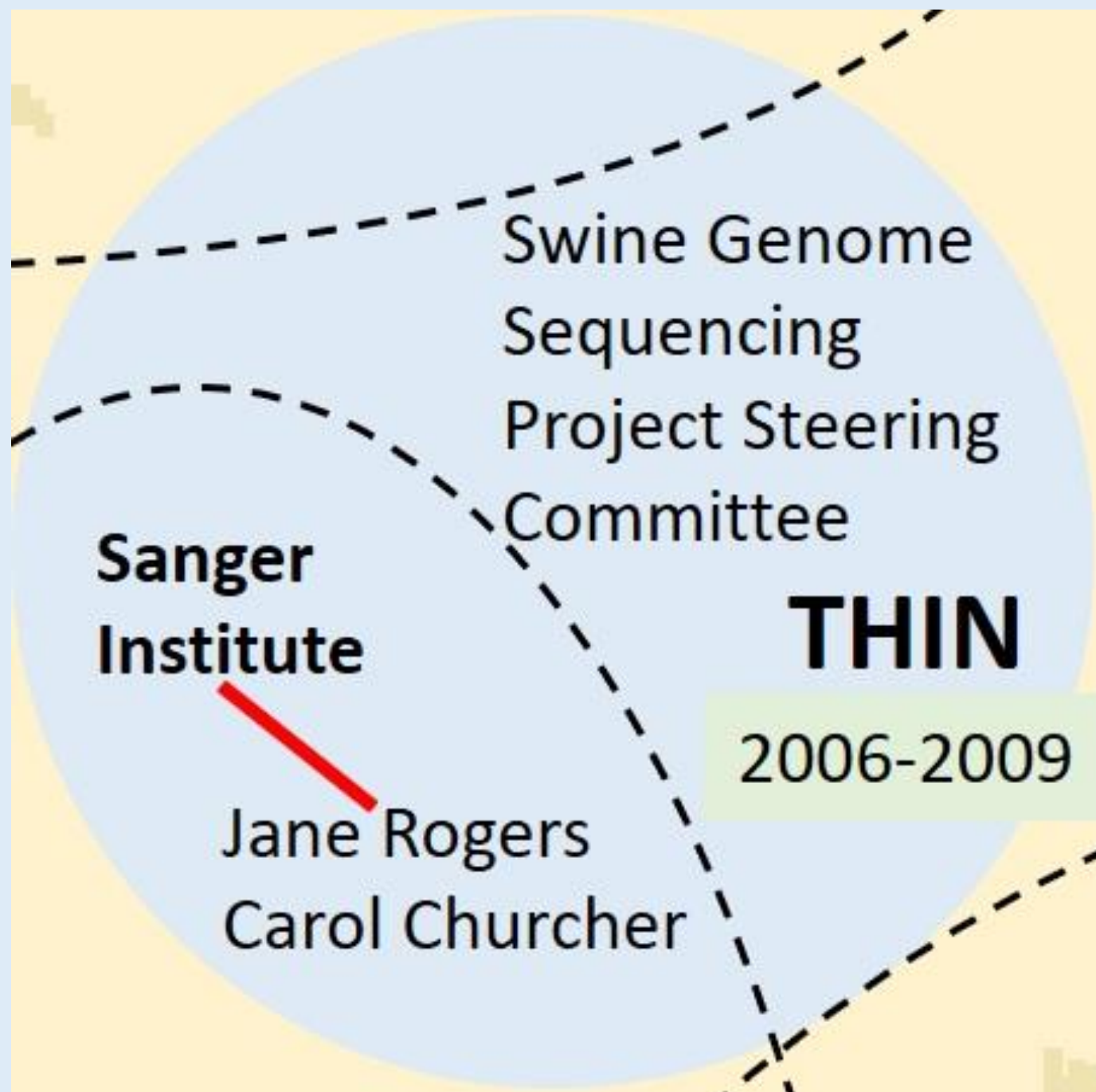
Category	Online resource/database	Description	URL
Genome	US pig genome mapping site	Comprehensive	http://www.animalgenome.org/pigs/
Genome	Pig genome resource at NCBI	Comprehensive	http://www.ncbi.nlm.nih.gov/genome/guide/pig/
Genome	Swine Genome Sequencing Consortium (SGSC)	Comprehensive	http://www.piggenome.org/
Sequencing	Porcine genome sequencing project at Sanger Institute	Physical mapping and genome sequencing	http://www.sanger.ac.uk/Projects/S_scrofa/
Sequencing	Sino-Danish pig genome sequencing project	genome sequences and EST sequences	http://piggenome.dk/
Sequencing	Ensembl (<i>Sus scrofa</i>)	Assemblies for chromosomes 1–18 and X	http://www.ensembl.org/Sus_scrofa/Info/Index
Sequencing	VEGA (<i>Sus scrofa</i>)	Preliminary annotation of the sequenced region on SSC6, 7 and 17	http://vega.sanger.ac.uk/Sus_scrofa/index.html
SNP	dbSNP (<i>Sus scrofa</i>)	Database of SNPs and other genetic variation	http://www.ncbi.nlm.nih.gov/SNP/snp_batchSearch.cgi?org=9823&type=SNP
Linkage map	ArkDB	linkage mapping, RH mapping, physical mapping	http://www.thearkdb.org/arkdb/do/getChromosomeDetails?accession=ARKSPC00000001
Linkage map	USDA/MARC Linkage Map	Genetic linkage map	http://www.marc.usda.gov/genome/swine/swine.html
Physical map	Cytogenetic Map	pig-human comparative map	https://www-lgc.toulouse.inra.fr/pig/cyto/cyto.htm
Physical map	IMpRH maps	IMpRH mapping	https://www-lgc.toulouse.inra.fr/pig/RH/Menuchr.htm
Expression	DFCI Pig Gene Index	ESTs annotation and cluster	http://compbio.dfci.harvard.edu/tgi/cgi-bin/tgi/gimain.pl?gudb=pig
Expression	Ageneae Project	Pig ESTs	http://public-contigbrowser.sigenae.org:9090/Sus_scrofa/index.html
Expression	Pig array	Porcine microarray	http://www.pigoligoarray.org/
Expression	UniGene (<i>Sus scrofa</i>)	transcribed sequences and gene-based clusters	http://www.ncbi.nlm.nih.gov/UniGene/UGOrg.cgi?TAXID=9823
Disease	Online Mendelian Inheritance in Animals	Porcine genetic disorders	http://omia.angis.org.au/adv_search_results.shtml?field1=sci_name&query1=Sus+scrofa
Disease	International PRRS Genomics Consortium	PRRS genomics	http://www.prrs.org/
Disease	MHC database	Swine SLA sequences	http://www.ebi.ac.uk/ipd/mhc/sla/index.html
Disease	IMGT®	Immunogenetics	http://imgt.cines.fr/textes/IMGTveterinary/#Pig
QTL	PigQTLdb	QTL repository and integration of linkage and physical maps	http://www.animalgenome.org/QTLdb/pig.html
QTL	GridQTL	QTL mapping	http://www.gridqtl.org.uk/
Non-coding RNA	miRBase	published miRNA sequences and annotation	http://microrna.sanger.ac.uk/cgi-bin/targets/v5/genome.pl
Non-coding RNA	Rfam database	Non-coding RNAs annotation	http://rfam.sanger.ac.uk/
Bioinformatics	NAGRP Bioinformatics Coordination Program	Bioinformatics tools	http://www.animalgenome.org/bioinfo/
Bioinformatics	Geocities	Bioinformatics tool list	http://www.geocities.com/bioinformaticsweb/tools.html
Bioinformatics	BLAST (<i>Sus scrofa</i>)	BLAST Pig Sequences	http://animalgenome.org/blast/blast.php?bdb=pig10

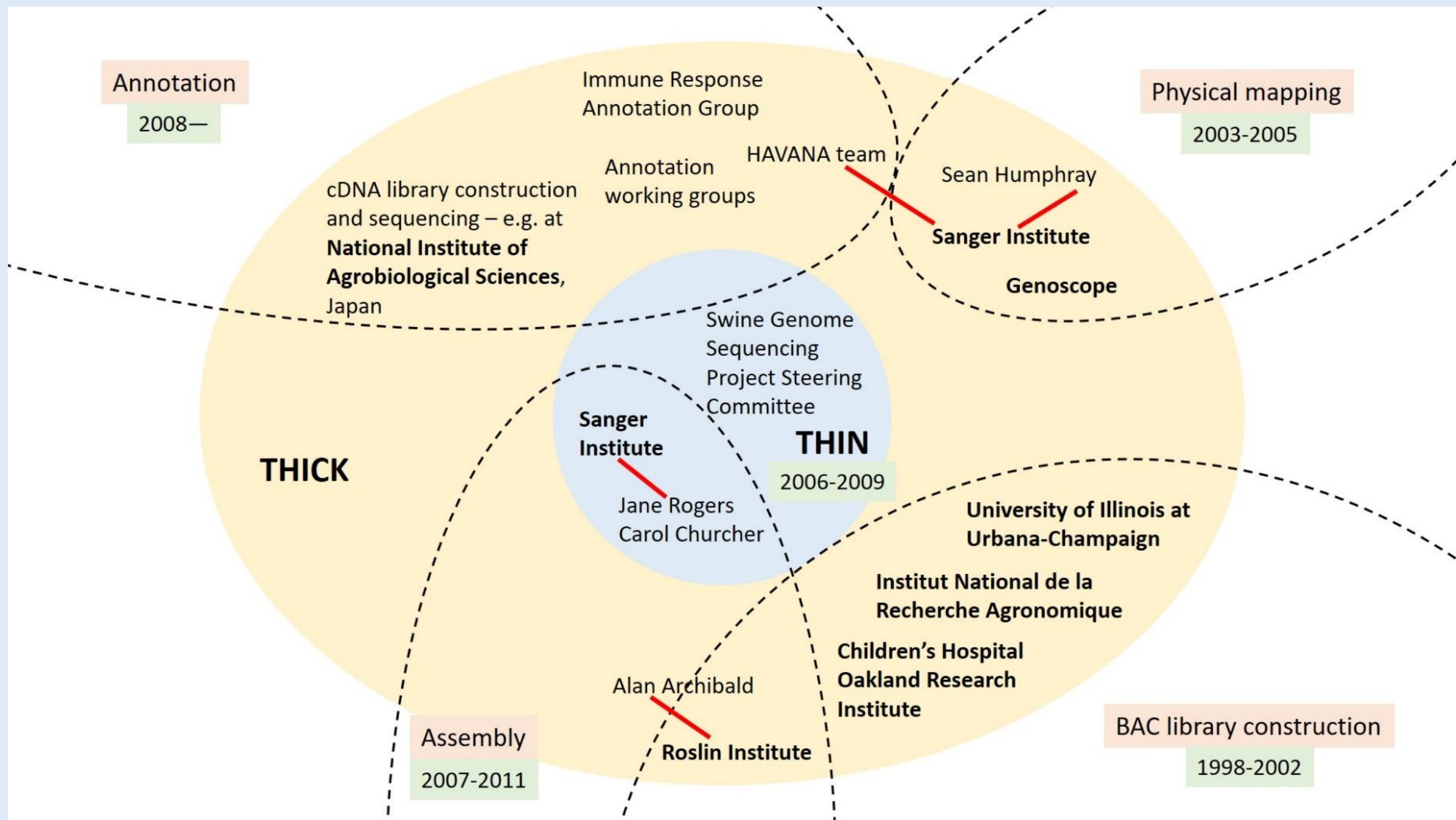
Thin and thick sequencing

Distinction developed to distinguish the determination of the order of bases (thin) from the processes required to produce a sequence that can be used by different potential end-users.

Thick sequencing therefore encompasses:

Prior mapping, library production, construction of minimum tile path, various stages of assembly, quality control and evaluation, and annotation.





Consequences for understanding translation

Sequencing as open-ended process

Importance of considering re-sequencing, non-whole genome sequencing and production of other resources

Importance of understanding thick sequencing concretely to appreciate nature of translational research processes

Nature of production affects the nature of the product and its potential use; problem of translation is the problem of alienation of producer(s) and user(s) of sequence data

OPEN LETTER

Open Access

Coordinated international action to accelerate genome-to-phenome with FAANG, the Functional Annotation of Animal Genomes project

The FAANG Consortium, Leif Andersson^{1,2}, Alan L Archibald³, Cynthia D Bottema⁴, Rudiger Brauning⁵, Shane C Burgess⁶, Dave W Burt³, Eduardo Casas⁷, Hans H Cheng⁸, Laura Clarke⁹, Christine Couldrey¹⁰, Brian P Dalrymple¹¹, Christine G Elsik¹², Sylvain Foissac¹³, Elisabetta Giuffra^{14*}, Martien A Groenen¹⁵, Ben J Hayes^{16,17,18}, LuSheng S Huang¹⁹, Hassan Khatib²⁰, James W Kijas¹¹, Heebal Kim²¹, Joan K Lunney²², Fiona M McCarthy²³, John C McEwan²⁴, Stephen Moore²⁵, Bindu Nanduri²⁶, Cedric Notredame²⁷, Yniv Palti²⁸, Graham S Plastow²⁹, James M Reecy³⁰, Gary A Rohrer³¹, Elena Sarropoulou³², Carl J Schmidt³³, Jeffrey Silverstein³⁴, Ross L Tellam³⁵, Michele Tixier-Boichard¹⁴, Gwenola Tosser-Klopp¹³, Christopher K Tuggle^{30*}, Johanna Vilkki³⁶, Stephen N White^{37,38}, Shuhong Zhao³⁹ and Hualjun Zhou⁴⁰

Abstract

We describe the organization of a nascent international effort, the Functional Annotation of Animal Genomes (FAANG) project, whose aim is to produce comprehensive maps of functional elements in the genomes of domesticated animal species.

Predictive biology: from sequence to consequence

Most phenotypes are complex and quantitative in nature, and a major goal of biological research lies in using genome information to predict such complex outcomes, whether it is the efficacy of a drug, susceptibility to cancer, or the performance of the daughters of an elite dairy bull. Many of the recent advances in biology have been driven by genome sequence information. The capability to sequence and decipher the instructions encoded in complex animal genomes quickly and at modest cost is now well established. The next challenge is to be able to read the subtlety and complexity of these instructions and to predict the resulting phenotypes, that is, to predict the consequences encoded in sequences. While significant progress in functional genome annotation has been made using various human cell types [1], we argue that filling the genotype-to-phenotype gap requires

functional genome annotation of species with substantial phenotype information.

The unique value of domesticated animal species for accelerating our understanding of genomes and phenomes

Research on domesticated animals has important scientific and socioeconomic impacts, including contributing to medical research, improving the health and welfare of companion animals, and underpinning improvements in the animal sector of agriculture. A key to these impacts is the wealth of genetic and phenotypic diversity among domesticated animals, coupled with research to elucidate the genetic architecture underlying quantitative traits.

From association to causation: pioneering success in domesticated species

Deep pedigrees with extensive phenotypic records, genetic and phenotypic diversity shaped by natural and artificial selection, and the latest molecular genomics and statistical tools provide an opportunity to understand the relationship between genotype and phenotype in outbred domesticated and farmed animal species [2]. We cite four examples of past successes. First, the identification of a single base-pair change as the causal genetic variant for the complex callipyge muscle hypertrophy phenotype in sheep [3]. Second, the finding that a single nucleotide change in the 3'-untranslated region of the sheep myostatin gene creates a new microRNA binding site that decreases myostatin protein expression [4]. Third,

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PERSPECTIVE

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Charting a course for genomic medicine from base pairs to bedside

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There has been much progress in genomics in the ten years since a draft sequence of the human genome was published. Opportunities for understanding health and disease are now unprecedented, as advances in genomics are harnessed to obtain robust foundational knowledge about the structure and function of the human genome and about the genetic contributions to human health and disease. Here we articulate a 2011 vision for the future of genomics research and describe the path towards an era of genomic medicine.

Since the end of the Human Genome Project (HGP) in 2003 and the publication of a reference human genome sequence^{1,2}, genomics has become a mainstay of biomedical research. The scientific community's foresight in launching this ambitious project³ is evident in the broad range of scientific advances that the HGP has enabled, as shown in Fig. 1 (see rollfold). Optimism about the potential contributions of genomics for improving human health has been fuelled by new insights about cancer⁴⁻⁷, the molecular basis of inherited diseases (<http://www.ncbi.nlm.nih.gov/omim> and <http://www.genome.gov/GWASStudies>) and the role of structural variation in disease⁸, some of which have already led to new therapies⁹⁻¹³. Other advances have already changed medical practice (for example, microarrays are now used for clinical detection of genomic imbalances¹⁴ and pharmacogenomic testing is routinely performed before administration of certain medications¹⁵). Together, these achievements (see accompanying paper¹⁶) document that genomics is contributing to a better understanding of human biology and to improving human health.

As it did eight years ago¹⁷, the National Human Genome Research Institute (NHGRI) has engaged the scientific community (<http://www.genome.gov/Planning>) to reflect on the key attributes of genomics (Box 1) and explore future directions and challenges for the field. These discussions have led to an updated vision that focuses on understanding human biology and the diagnosis, prevention and treatment of human disease, including consideration of the implications of those advances for society (but these discussions, intentionally, did not address the role of genomics in agriculture, energy and other areas). Like the HGP, achieving this vision is broader than what any single organization or country can achieve—realizing the full benefits of genomics will be a global effort.

This 2011 vision for genomics is organized around five domains extending from basic research to health applications (Fig. 2). It reflects the view that, over time, the most effective way to improve human health is to understand normal biology (in this case, genome biology) as a basis for understanding disease biology, which then becomes the basis for improving health. At the same time, there are other connections among these domains. Genomics offers opportunities for improving health without a thorough understanding of disease (for example, cancer therapies can be selected based on genomic profiles that identify tumour subtypes^{18,19}), and clinical discoveries can lead back to understanding disease or even basic biology.

The past decade has seen genomics contribute fundamental knowledge about biology and its perturbation in disease. Further deepening this understanding will accelerate the transition to genomic medicine (clinical care based on genomic information). But significant change rarely comes

quickly. Although genomics has already begun to improve diagnostics and treatments in a few circumstances, profound improvements in the effectiveness of healthcare cannot realistically be expected for many years (Fig. 2). Achieving such progress will depend not only on research, but also on new policies, practices and other developments. We have illustrated the kinds of achievements that can be anticipated with a few examples (Box 2) where a confluence of need and opportunities should lead to major accomplishments in genomic medicine in the coming decade. Similarly, we note three cross-cutting areas that are broadly relevant and fundamental across the entire spectrum of genomics and genomic medicine: bioinformatics and computational biology (Box 3), education and training (Box 4), and genomics and society (Box 5).

Understanding the biology of genomes

Substantial progress in understanding the structure of genomes has revealed much about the complexity of genome biology. Continued acquisition of basic knowledge about genome structure and function will be needed to illuminate further those complexities (Fig. 2). The contribution of genomics will include more comprehensive sets (catalogues) of data and new research tools, which will enhance the capabilities of all researchers to reveal fundamental principles of biology.

Comprehensive catalogues of genomic data

Comprehensive genomic catalogues have been uniquely valuable and widely used. There is a compelling need to improve existing catalogues and to generate new ones, such as complete collections of genetic variation, functional genomic elements, RNAs, proteins, and other biological molecules, for both human and model organisms.

Genomic studies of the genes and pathways associated with disease-related traits require comprehensive catalogues of genetic variation, which provide both genetic markers for association studies and variants for identifying candidate genes. Developing a detailed catalogue of variation in the human genome has been an international effort that began with The SNP Consortium²⁰ and the International HapMap Project²¹ (<http://hapmap.ncbi.nlm.nih.gov>), and is ongoing with the 1000 Genomes Project²² (<http://www.1000genomes.org>).

Over the past decade, these catalogues have been critical in the discovery of the specific genes for roughly 3,000 Mendelian (monogenic) diseases

Figure 1 | Genomic achievements since the Human Genome Project (see accompanying rollfold).

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²Lists of participants and their affiliations appear at the end of the paper.

Consequences for understanding relation of genomics to translation

Mapping and sequencing projects	Sequence production	Resource production and use
PiGMaP/ELWW USDA intra-mural USDA extra-mural Sino-Danish Swine Genome Sequencing Consortium	What is being sequenced? By whom? When? Where? How? For what intended purpose? For what incidental purpose(s)?	Production, circulation and use of: DNA samples DNA probes Primers Non-sequence data Clones (e.g. from BAC libraries)

Ongoing work

Further empirical work concerning history of pig genomics – international and non-project dimensions

Development of quantitative data and network visualisations – community structure, relationship of producers and users of data

Pig genomics and *biomedical* translation

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Interviewees

Providers of archival materials and data

TRANSGENE project team

Perspectives on Genetics and Genomics group

European Union Horizon 2020 programme



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