

Impact case study (REF3)

Institution: University of Bristol		
Unit of Assessment: 5) Biological Sciences		
Title of case study: New genotyping tools reduce costs and improve throughput for wheat breeders, significantly advancing wheat-breeding programmes in the UK and globally		
Period when the underpinning research was undertaken: 2009 - 2017		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Gary Barker Keith Edwards	Senior Lecturer in Bioinformatics Professor of Cereal Functional Genomics	10/1996 - present 04/1998 - present
Period when the claimed impact occurred: 1 st August 2013 – 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

The wheat-breeding industry, including some of the largest plant breeders and seed-development companies in the world, has benefited from decreased production costs and increased productivity because of research led by the University of Bristol (UoB). The UoB researchers developed the tools necessary to differentiate point mutations in the complex DNA structure of wheat. This critical step in wheat genotyping led to the public release of 95% of the wheat genome in 2010 and the development, by UoB, of several cheap, easy-to-use assays for industry. These advances were quickly embraced by industrial wheat breeders aiming to deliver new varieties with improved yields and desirable traits such as disease resistance. With the wheat-seed business worth over GBP16 million annually in the UK and over GBP1.8 billion globally, the various new genotyping tools developed and deployed by UoB have had, and continue to have, a major impact on the wheat industry and its ability to respond to the challenges of climate change and population growth.

2. Underpinning research

Single-nucleotide polymorphisms (SNPs) are regions of DNA, between individual chromosomes, that vary by a single nucleotide. They are the most common type of genetic variation in plant and animal genomes. For this reason, SNPs are a logical choice for marker-assisted selection – a process used in breeding programmes selecting for traits such as disease resistance and productivity. However, the wheat genome is extremely complex: five times larger than the human genome, the hexaploid wheat genome has three sets of chromosomes derived from related progenitors. This has presented significant challenges in SNP discovery, and required the UoB team led by Prof Keith Edwards and Dr Gary Barker to develop and adapt a range of novel procedures in the area of next-generation sequencing, bioinformatics and genotyping in order to overcome these challenges and advance DNA marker-assisted breeding approaches.

SNP genotyping first requires the identification of valid SNPs. The UoB team used a bioinformatics approach to electronically mine SNPs from several databases containing expressed sequence tags (ESTs) for cereals, including wheat. Their findings showed that high-throughput sequencing could generate a dataset of sufficient size to exclude SNPs within a variety from those found between varieties yet still produce sufficient SNPs to provide diverse genome coverage [Edwards *et al.* 2009]. Simultaneously, the UoB team was exploring high-throughput sequencing methods and developing an assay, based on novel technologies (for instance, padlock probes and Kompetitive Allele Specific PCR (KASP)), capable of

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simultaneously genotyping numerous wheat lines using several hundred gene-based SNP markers [Allen *et al.* 2011]. This work paved the way for the sequencing and genotyping of the wheat genome.

In 2010, using the wheat reference variety ChineseSpring (CS42), UoB researchers employed novel bioinformatics techniques to generate SNPs among the sequence information covering 95% of the wheat genome [1]. The sequence data were made available immediately in the public domain through the EMBL/GenBank and CerealsDB [2] websites, which allowed rapid uptake of this information by both the academic and commercial wheat-breeding communities. In 2011, Professor Edwards was awarded the Royal Agricultural Society of England's (RASE) Research Medal which acknowledges "research work of outstanding merit carried out in the UK, which is proven or likely to be of benefit to agriculture".

Since April 2011, UoB has worked closely with breeding companies to develop SNP markers for use in wheat breeding. To make the genomic sequence information accessible to industry and assist practical breeding of wheat, the UoB team shared and combined their bioinformatics expertise with: i) KBioscience (now LGC, Biosearch Technologies) to use their innovative KASP chemistry to generate and validate a new type of wheat molecular marker (KASP markers) [3], and ii) Affymetrix (now part of ThermoFisher) to use their Axiom platform to generate a high density, high throughput wheat genotyping platform [5, 6]. The work with Affymetrix first required overcoming the high cost and attrition level of developing large numbers of validated SNP markers, which was achieved using an array-based platform [4].

In 2018 Professor Edwards was awarded the prestigious Rank Prize for nutrition, jointly with Professor Graham Moore (JIC) for: "pioneering research which has enabled plant breeders to exploit cereal genomics to develop improved wheat cultivars."

3. References to the research

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- [1] Brenchley R, Spannagl M, Pfeifer M, **Barker GL**, D'Amore R, Allen AM, McKenzie N, Kramer M, Kerhornou A, Bolser D, Kay S, Waite D, Trick M, Bancroft I, Gu Y, Huo N, Luo M-C, Sehgal S, Gill B, Kianian S, Anderson O, Kersey P, Dvorak J, McCombie WR, Hall A, Mayer KFX, **Edwards KJ**, Bevan MW, Hall N. (2012). Analysis of the bread wheat genome using whole-genome shotgun sequencing. *Nature*, 491, 705–710. DOI:[10.1038/nature11650](https://doi.org/10.1038/nature11650)
- [2] Wilkinson PA, Winfield MO, **Barker GL**, Allen AM, BurrIDGE A, Coghill JA, **Edwards KJ**. (2012). CerealsDB 2.0: an integrated resource for plant breeders and scientists. *BMC Bioinformatics*, 13, 219. DOI:[10.1186/1471-2105-13-219](https://doi.org/10.1186/1471-2105-13-219)
- [3] Allen AM, **Barker GL**, Wilkinson P, BurrIDGE A, Winfield M, Coghill J, Uauy C, Griffiths S, Jack P, Berry S, Werner P, Melichar JPE, McDougall J, Gwilliam R, Robinson P, **Edwards KJ**. (2013). Discovery and development of exome-based, co-dominant single nucleotide polymorphism markers in hexaploid wheat (*Triticum aestivum* L.), *Plant Biotechnology Journal*, 11(3): 279-95. DOI:[10.1111/pbi.12009](https://doi.org/10.1111/pbi.12009)
- [4] Wang S, Wong D, Forrest K, Allen A, Chao S, Huang BE, Maccaferri M, Salvi S, Milner SG, Cattivelli L, Mastrangelo AM, Whan A, Stephen S, **Barker GL**, Wieseke R, Plieske J, Lillemo M, Mather D, Appels R, Dolferus R, Brown-Guedira G, Korol A, Akhunova AR, Feuillet C, Salse J, Morgante M, Pozniak C, Luo M-C, Dvorak J, Morell M, Dubcovsky J, Ganai M, Tuberosa R, Lawley C, Mikoulitch I, Cavanagh C, **Edwards KJ**, Hayden M, Akhunov E. (2014). Characterization of polyploid wheat genomic diversity using a high-density 90,000 SNP array. *Plant Biotechnology Journal*, 12, 787-96. DOI:[10.1111/pbi.12183](https://doi.org/10.1111/pbi.12183)
- [5] Winfield MO, Allen AM, BurrIDGE AJ, **Barker GL**, Benbow HR, Wilkinson PA, Coghill J, Waterfall C, Davassi A, Scopes G, Pirani A, Webster T, Brew F, Bloor C, King J, West C, Griffiths S, King I, Bentley AR, **Edwards KJ**. (2016). High-density SNP genotyping array for

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hexaploid wheat and its secondary and tertiary gene pool. *Plant Biotechnology Journal*, 14(5), 1195-1206. DOI:[10.1111/pbi.12485](https://doi.org/10.1111/pbi.12485)

- [6] Allen AM, Winfield MO, Burrige AJ, Downie RC, Benbow HR, **Barker GL**, Wilkinson PA, Coghill J, Waterfall C, Davassi A, Scopes G, Pirani A, Webster T, Brew F, Bloor C, Griffiths S, Bentley AR, Alda M, Jack P, Phillips AL, **Edwards KJ**. (2017). Characterization of a Wheat Breeders' Array suitable for high-throughput SNP genotyping of global accessions of hexaploid bread wheat (*Triticum aestivum*). *Plant Biotechnology Journal*, 15, 390–401. DOI:[10.1111/pbi.12635](https://doi.org/10.1111/pbi.12635)

Grants

- [i] **Edwards KE** (PI). [Mining the allohexaploid wheat genome for useful sequence polymorphisms](#), BBSRC, 2009-2011, GBP1,200,000 (GBP250,000 to Bristol)
- [ii] **Edwards KE** (PI). [Development and validation of a flexible genotyping platform for wheat](#), BBSRC, 2011-2013, GBP200,000
- [iii] **Edwards KE** (PI). Wheat Improvement Strategic Programme (WISP), BBSRC, 2014-2017, GBP1,100,000
- [iv] **Barker GL** (Work Package 4) & **Edwards KE** (Work Package 3). Designing Future Wheat Institute Strategic Programme, BBSRC, 2017-2022, GBP970,000

4. Details of the impact

Wheat is one of the world's most important cereal crops for both human and livestock consumption. Demand on cereal production is estimated to increase by 50% over the next decade; increasing yield is therefore a top priority for sustainable intensification of agriculture and its resilience to increasing challenges from climate change.

Growth of commercial genotyping services

i) LGC, Biosearch Technologies

From 2009, Edwards and Barker collaborated with the genetic screening company, KBioscience, now LGC Biosearch Technologies, to develop the KASPar assay [3]. Though the number of screenings carried out using the wheat SNPs is commercially sensitive, the EMEA Commercial Director said: *"The markers are used extensively by the global wheat community and they constitute a significant part of the LGC, Biosearch Technologies, portfolio"* [A]. The commercial success of this service *"continues to provide benefits to the UK economy in terms of the genotyping services that LGC, Biosearch Technologies, offer and via the employment of high-quality technicians and scientists based on our ability to offer this service"* [A].

Resulting from the collaboration with Edwards and Barker, and citing CerealsDB 2.0 [2], LGC Biosearch Technologies offers 7,228 (increased from 1,114 (2011)) functionally validated, highly cost-effective, KASP SNP assays across 169 wheat varieties [B]. This includes a core set of 960 pre-validated assays evenly distributed through the wheat genome allowing medium resolution screening which is important for characterisation of parental varieties and development of novel varieties in breeding programs [B]. 3,629 SNP (increased from 480 (2011)) markers have been mapped to 21 linkage groups. KASP technology increases the rate of SNP-based genotyping while reducing the cost of the individual data points and is extensively used by the wheat breeding community.

ii) Affymetrix:

Collaboration with microarray analysis specialists Affymetrix technologies, now part of ThermoFisher, resulted in the commercial release of the Axiom Wheat Genotyping Arrays [Di].

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The first product, released in 2013, the Axiom Wheat HD Genotyping Array [Dii], is a high-density array using 820,000 SNPs identified and validated by the UoB team [5] and predominantly designed as a research tool. This was followed in 2017 by the Axiom Wheat Breeders Genotyping Array [Diii], underpinned by 35,000 SNPs identified and validated by UoB [6]. This product is designed specifically for use with elite wheat lines used worldwide by breeders. Senior Product Manager at ThermoFisher noted that *'in the last year, more of the Axiom Wheat Breeders array have sold more than the high-density arrays, indicating that the community is moving into more routine/production work'* [C]. In 2019 alone the total revenue generated from sales of the Axiom Wheat Breeders Genotyping Array was [text removed for publication] [C].

Decreased production costs and increased productivity for the wheat-breeding industry

The ease of use and cost-effectiveness of the markers/platforms makes them ideal for commercial wheat-breeding programmes aimed at the fast development of new varieties selected for increased yield and resistance to abiotic and biotic stress. The markers are now in routine use by major wheat breeders in the UK and internationally, including RAGT Seeds and Limagrain [F].

UK-based RAGT Seeds is one of Europe's leading seed businesses and invests 15% of its turnover in research and development to develop new, and maintain market-leading, varieties. The Head of Cereal Genotyping reports that the development of the Wheat Breeders 35K array *'has been crucial in the implementation of genomic selection in our UK and French wheat breeding programmes'* and *'revolutionised our approach to trait discovery'* [E].

The efficiency of the KASP genotyping platform has supported RAGT to double their marker assisted selection (MAS) capacity since 2014 and 35% of KASP SNPs in routine use by the company were identified by UoB research [E]. RAGT Seeds highlighted use of a UoB-identified SNP for tracking the Barley Yellow Dwarf Virus resistance gene Bdv2 in wheat, which led to the release of a new wheat variety on the UK National List [E]. This new variety *'will provide farmers with a genetic solution for control of this disease, which is particularly important given the withdrawal of insecticide seed treatments commonly used to provide control'* [E].

The UK wheat-seed business is worth GBP16 million per annum, with each ton of seed having a profit value of GBP56-80 depending on the variety. One ton of wheat seed can plant ~7 hectares. Globally, the wheat-seed business is worth over GBP1.8 billion a year. The farm-gate value of wheat is GBP180 per ton, or GBP2.9 billion for the whole of the UK. The new genotyping tools generated by UoB have had a major impact on how the wheat community carries out its genotyping, resulting in decreased costs and increased productivity for a multi-billion pounds industry. RAGT Seeds describe the 35K array as the *'first platform to provide whole genome data at a suitable cost'* (GBP17 per sample) [E].

CerealsDB

The online resource CerealsDB provides researchers and breeders with free access to the UoB SNPs. Since May 2012 there have been more than 1.5 million unique visits to the website and the datasets have been downloaded more than 48,000 times. The website currently receives more than 50,000 unique visits per month.

Altogether, the activity of the University of Bristol Cereal Genomics Team has pioneered technology that enhances sustainable and resilient wheat production.

5. Sources to corroborate the impact

- [A] LGC, Biosearch Technologies (2020). Corroborating Statement – SNP Markers
- [B] i) LGC, Biosearch Technologies (2016). [Wheat genotyping library: powered by KASP](#)
ii) LGC, Biosearch Technologies (2018). [Case study: University of Bristol – wheat genomics](#)
- [C] Thermo Fisher Scientific (2020). Corroborating Statement - Axiom Wheat Breeders Genotyping Array
- [D] Affymetrix. i) Data Sheet: [Axiom® Wheat HD Genotyping Arrays](#) (2014)
ii) Data Sheet: [Axiom Wheat Breeder's Genotyping Array](#) (2017)
- [E] RAGT Seeds Ltd (2020). Corroborating Statement – Head of Cereal Genotyping
- [F] BBSRC (2018). Our impact: [Wheat breeding companies benefit from new molecular tools](#)