Cracking beer's genetic code

A team of researchers in Belgium have been busy sequencing the DNA of brewers' yeast. Their modest aim? To breed a new generation of yeasts capable of producing beers that have previously only been dreamt of

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Imagine ales with a richness of flavour you never before imagined, lagers that can be brewed warm, or a Trappist-style beer that would never put you over the limit. It may sound like indulgent fantasy, but such beers could soon become cold, wet reality, thanks to a Belgian lab which is analysing the DNA of hundreds of species of brewing yeast. The research promises, for the first time, to reveal how the tiniest differences in DNA affect the flavours, strengths and qualities of beers they produce and to make possible the creation of new yeasts which will produce beers with flavours and properties never seen or tasted before.

The research is being led by Dr Kevin Verstrepen at the University of Leuven and the VIB research institute, who has dedicated most of his working life to the study of these tiny, unsung heroes of brewing. Together with the help of US-based White Labs, his lab (fittingly named The Verstrepen Lab) has embarked on the first ever project to systematically sequence the DNA of 220 species of brewers' yeast. Their work has enabled them to put together a brewing yeast 'family tree', which depicts the different species of yeast used around the world and shows how they are related - an exciting prospect in itself for anyone interested in how the organisms have spread and bred throughout history. However, it is the further possibilities of the project that will set beer lovers everywhere salivating.

"Farmers, since ancient times, have been selecting the best crops and best livestock and have been breeding them. And breeding in farming sounds very old-fashioned, but we forget its immense power - we have a three, four, six hundred even thousand per cent gain in yield," Verstrepen says. "It's amazing how much we've been able, over thousands of years, to make crops and livestock better. But with microbes we're lagging behind." This discrepancy is something that he and his team are putting right, using the information gained from the sequencing programme to selectively and accurately breed yeast, to generate novel variants able to produce innovative new beers.

It's not hard to understand why yeast has remained untamed. It wasn't discovered until 1680, when the Dutch naturalist Antonie van Leeuwenhoek first spied them at the end of his microscope. It wasn't until the 19th century that the first pure yeast culture, *Saccharomyces carlsbergensis*, was identified in Carlsberg's laboratories, and time had marched on to the 20th century before pure yeast cultures were widely used in breweries. As Verstrepen puts it, "It's easy to put a big bull and a cow that gives lots of milk together, and hope that the next cows will produce even more milk. With yeast, it's a bit more difficult because you can't see it."

With sophisticated microscopes and detailed genetic blueprints, however, naked-eye invisibility is no longer a problem. Armed with their data from the sequencing project, Verstrepen's team are now able to identify even the tiniest genetic variations in a yeast and to link these to specific characteristics in the beer it produces. This means that they can not only select with precision the yeasts they want to breed together, but that they can also track the yeasts' offspring to see which have the right combination of mutations to give the beer they want to create. And if the team have thousands of years of catching up to do, they do have one big advantage over ancient farmers: yeast breeds very quickly, reproducing every two hours, meaning a new cross can be developed within just two weeks.

How many are there?

Together with White Labs, the Verstrepen Lab has sequenced and analysed 220 yeast genomes, which Dr Verstrepen believes to represent around 80% of the yeast currently being used in brewing across the world. Quantifying yeast is, however, a tricky business, since it is not always clear where one strain of yeast ends and another begins. "In principle every brewery can have their own yeast, but of course many are related," Verstrepen explains. "Actually, it's quite silly sometimes because, bigger breweries especially, they guard their yeast as if it were gold in Fort Knox or something. But then what we sometimes see is that multiple breweries are using pretty much the same yeast, or almost – often it's almost like an identical twin of the yeast of the competing brewery."

The results have been eye-opening, particularly in the area of flavour - the team have already developed a yeast which, Verstrepen says, produces 50 per cent more flavours than even the most flavoursome example previously available, giving an extraordinarily aromatic beer. (One of the perks of the job is that the team get to sample each of the beers they make, every day, just before lunch.) Another area of focus is alcohol yield, or, more specifically, creating new yeasts which are able to produce and withstand higher levels of alcohol. Their motivation is not to create novelty 'party' beers, but to aid the bioethanol industry and high gravity brewing, where stronger than normal beer is brewed, to be later watered down to a more standard level of alcohol. If it sounds a bit depressing to dilute beer with water, Verstrepen points out that the practice is not only cheaper, but much kinder to the environment, requiring smaller volumes of beer to be brewed and therefore resulting in lower energy demands and less environmental impact. Other characteristics that can and are being honed are flocculation - the degree to which yeast clumps together and falls to the bottom of the brew after fermentation, making a brewer's life much easier - and the temperature profile at which a yeast works.

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One beer style the team have been looking at more closely is lager. Lager yeast is actually a hybrid - rather like a mule - of ale-producing yeast and another species *Eubayanus*, which thrives in colder conditions. Previous sequencing projects have shown that there are only two different kinds of this yeast, meaning the process of cross-breeding which has been necessary to ultimately produce lager has only happened twice in history. What nature has only managed to do twice over thousands of years, however, Verstrepen's team can now do as often as they like. "So what we're now doing is we're making way more [lager yeasts]. We have hundreds of different beer yeasts in our collection and we now have a few different of this other species, *Eubayanus*, so we can make a whole collection - around 150 so far - of completely new lager yeasts. And we can see that their properties are really different from the two archetypes that are used now," Verstrepen explains. These include differences in flavour, in flocculation and in the optimum temperature at which the yeast operates. "Lager yeasts traditionally are fermented at lower temperatures, but we can see that we can go even lower than what's out there, and we can also go higher. So we have ➤

Flavour genes from a raspberry could be implanted into a yeast, to give a raspberry flavoured beer

Verstrepen and his team are awaiting adventurous brewers willing to rise to the challenge of experimenting with genetically modified yeasts

lager yeasts that actually do better at somewhat higher temperatures, which could also be interesting because then fermentation goes a little bit quicker." He adds: "Pretty much everything can vary beyond what's already out there now for lager yeasts." It's both amazing and brilliantly simple. ("If you're a geneticist or if you know about the history of agriculture, it's almost weird that people haven't done this before.")

But there are limits to this side of the research. Researchers can only work with DNA that is already present within the yeast and, because of this, although they can intensify characteristics, they can't introduce new properties. Where the research is limitless, it also becomes more controversial - with the introduction of genetically modified yeast.

Unlike the cross-breeding programme, which simply recreates the naturally occurring process of sexual reproduction, GM research involves directly altering the DNA of an organism, bypassing nature altogether. It can be divided into two areas. The first is to recreate the natural breeding process but, rather than leaving nature to mix up the 'parental' DNA, to transfer the genes between organisms directly. The end result of the hybridisation is essentially the same, since the DNA used is taken from the same naturally available gene pool, but the process is much quicker, more accurate, and the results dramatic. In one experiment, carried out for Belgian television, the Verstrepen Lab engineered and tasted a GM yeast which produced 100 times - not 100 per cent, but 100 times - more of one specific flavour compound. Verstrepen concedes that it didn't taste much like beer, but it was interesting. There are several yeasts genetically modified in this way stored in the lab freezer. They are available for use by any adventurous brewers, although there have been no takers yet. "If anyone ever wants to use them and gets the right paperwork done to receive formal approval from the food safety authorities, we'd be happy to supply them, because we think they're completely safe and quite fun to use. Of course, brewers are interested, but they're too afraid to use them, because they're afraid that part of their audience would have a negative reaction."

The second, more exciting and ethically questionable prospect is to mix genes from across the plant and animal kingdoms. One example would be to take 'flavour' genes from a raspberry and implant them into a yeast, to give a raspberry flavoured beer. It may sound far-fetched, but Verstrepen insists it can be done. A little further in the future lies the creation of yeasts with man-made DNA – yeasts which are 100 per cent custom designed. Here, the DNA is designed on a computer and then inserted into a yeast cell from which the original DNA has been taken out. It is, Verstrepen admits, "a little scary" and something about which he has "serious concerns". "I'm not saying this is something we should start doing to make beer with, but it's technology which is getting there. So far they've made viruses, they've made bacteria, and yeast is next. It's extremely expensive and takes a lot of people to get this done," he says. "But probably in ten or twenty years it's going to be cheap and easy. So these things are coming to us."

But for now, his sights and those of his team are set firmly on the more humble, and, arguably, more worthy mission of making interesting, tasty new beers. And doesn't the future for brewers and beer lovers look exciting even without genetic engineering? "Yeah, exactly. And [regarding GM] you always have to ask yourself, do we really need this, and do we really want this? There will always be a market for traditional beers. But, on the other hand, we also don't have to be too restricted and old-fashioned, and it could be nice to expand our palate a little bit, and to be a little bit more adventurous – as long as it's completely safe. But for many of the things we're doing that's pretty much guaranteed." ■

"Like an anti-drinking campaign for geneticists"

Among the insights gained from the Verstrepen Lab's research is the revelation of just what a strange creature beer yeast is. "The genomes are a complete mess. You could almost use it in an anti-drinking campaign for geneticists." One peculiarity is that there has been a lot of inter-species crossing. Pilsner and lager yeast are one example already well known, but Verstrepen's team have discovered others. Another is that yeast genomes are riddled with chromosomal disorders. Just as humans typically have two pairs of 23 chromosomes, so yeasts should each have two pairs of 16. In humans, the condition Down syndrome is caused by the existence of just one extra chromosome; in Verstrepen's samples, almost every yeast had either three or four extra copies, or was missing a chromosome or parts of a chromosome. And interestingly, this prevalence of disorders is not seen anywhere near to the same degree in yeast used in wine making or in baking. "[Brewers' yeasts] are quite amazing. The level to which they show these disorders is quite unexpected," says Verstrepen. "They're some of the most weird and complex genomes that we've seen."