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Irving Kahn, the oldest trader on Wall Street, is remarkably active despite being over 100 years of age — and scientists hope many more will match him.

CENTENARIANS

Great expectations

Scientists are searching for a genetic blueprint that will enable humans to stay healthy and vital well into their old age.

BY MICHAEL EISENSTEIN

On any weekday morning, you might catch Irving Kahn heading into his office in Manhattan, where he works as an investor and financial analyst — seemingly unremarkable, except for the fact that he has been in the business more or less continuously since 1928.

The 106-year-old Kahn is one of many who have managed to live well into their eleventh decade with mental faculties intact and in surprisingly good health — and researchers into ageing have taken notice. Thomas Perls, a gerontologist at Boston University in Massachusetts and director of the New England Centenarian study, recalls an early encounter with two centenarians that challenged his expectation that the remarkably old would be remarkably unhealthy. While he was training at a rehabilitation centre, Perls saw one centenarian "out and about playing piano for everybody", while another — a retired tailor — "was in occupational therapy mending people's clothes and teaching other people how to sew".

But the data increasingly suggest that people who reach such ripe old ages are getting a biological helping hand (see 'Disease delay and genetics'). For example, recent research from Perls supports a hypothesis known as 'compression of morbidity', in which individuals whose lifespan is considerably longer than average (at least 100 years old) tend to stay healthy for longer, with delayed onset of age-associated diseases such as cancer and cardiovascular disease[1]. "These diseases don't appear until roughly the last 5% of their lives," says Perls. If this is the case, exploring extreme longevity could provide insights into the foundations of many common diseases — and into new weapons with which to fight them.

ARMOUR AGAINST AGEING

Much of the seminal work in assessing genetic contributions to healthy ageing in the general population has been done in Scandinavia, where political peace and a strong societal infrastructure have minimized the external forces that prematurely shorten life elsewhere. "Over the past 100 years, we've basically had 'laboratory conditions' for humans," jokes Kaare Christensen, a genetic epidemiologist specializing in human ageing at the University of Southern Denmark in Odense. From studies of fraternal and identical twins, Christensen has found that roughly 25% of longevity is attributable to hereditary factors[2]. Furthermore, he suspects there is a clear age dependency for this genetic contribution. "Before age 60, genetic factors are not that important in the cohorts that we have studied," says Christensen, "but after age 60 their impact increases, and seems to get strongest at the very highest ages." In other words, a healthy lifestyle and environment are the key determinants of whether most people will reach their seventh decade, but after that it's increasingly down to their genes.

However, a healthy lifestyle might not be mandatory for everybody. Many specialists in ageing now believe that the extremely old possess beneficial genetic variants that protect

them against the vicissitudes of ageing throughout life. It is only beyond a certain age — as the health of less-fortunate people begins to decline — that these variants become apparent.

Gerontologist Nir Barzilai of the Albert Einstein College of Medicine in New York is among the leading researchers in this field. He has been tracking a large cohort of Ashkenazi Jews for many years in an effort to understand what sets the extremely old apart from their peers. "We have 2,500 people between the ages of 60 and 112, including nearly 600 people over 95," says Barzilai. His aim is to identify genomic variants that are more common in the oldest cohort than in those who achieve only an average lifespan. "Most genotypes do not change in frequency because they're not involved in lifespan," he says. "Therefore, those genotypes that do change are either going down in frequency because they're killing people or going up because they are promoting longevity."

One might expect these 'longevity genotypes' to be perfectly attuned for health — devoid of variants associated with increased disease risk. But several studies have shown that this is not the case. For example, the Leiden Longevity Study found that the genomes of nonagenarians were as likely to contain common risk factors for cancer, diabetes and other diseases as were the genomes of a young, control population[3]. This suggests that other variants in the longevity genome are somehow insulating their possessors against the effects of these potentially harmful genes — an effect that Christensen has also observed in family studies. "In Denmark, we have seen that children of the long-lived have about 25% lower cancer risk compared with other people." For Barzilai, patterns like this suggest that the genomes of the extremely old might provide clinical researchers with a guide for understanding how health deteriorates over time. "What really controls our ageing rate," he says, "are protective mechanisms and protective genes."

THE HUNT IS ON

For most diseases with a heritable component, the search for contributory genes takes the form of a genome-wide association study (GWAS). This is essentially a fishing expedition for individual variations — single nucleotide polymorphisms (SNPs) — that are statistically more or less common in individuals with a trait of interest than in a control population. However, to avoid overloading researchers with false-positive results, a high bar is set for designating hits. Furthermore, it can be nearly impossible to discover factors that are rare or exert only a modest effect on their own, as these might appear as noise in a large study population. "It's highly unlikely that there's a single genetic variant or even a handful of genetic variants that have a powerful enough influence to pop up in a GWAS and be independently associated with longevity," says Perls.

To sidestep this problem, Perls and his colleague at Boston University, Paola Sebastiani, performed a different kind of GWAS. They focused not on individual SNPs but on groups of SNPs, seeking variants with weak individual effects that seem to act synergistically in long-lived individuals. These SNP groups might then reveal dependencies in the genome — clusters of variants that must occur together — that establish a protective biological environment that favours an extended lifespan. Perls and Sebastiani uncovered a number of such 'fingerprints', but their 2010 paper was retracted from *Science* a year later owing to technical mistakes that called their analysis into question. The team partnered with genetic epidemiologists at Yale University in New Haven, Connecticut, to address these issues, and re-published their research in *PLoS ONE*[4] in 2012. Perls concedes that the retraction cast an unfortunate cloud over the study, but he stands by his team's discovery: a collection of 281 SNPs linked to at least 130 genes that seem to be notably enriched in centenarians. "Here's a bunch of variants that together are probably influencing one another and interacting with the environment to have an important impact on living to these most extreme ages," says Perls, adding that "the accuracy of the model became greater and greater with subjects of older and older ages".

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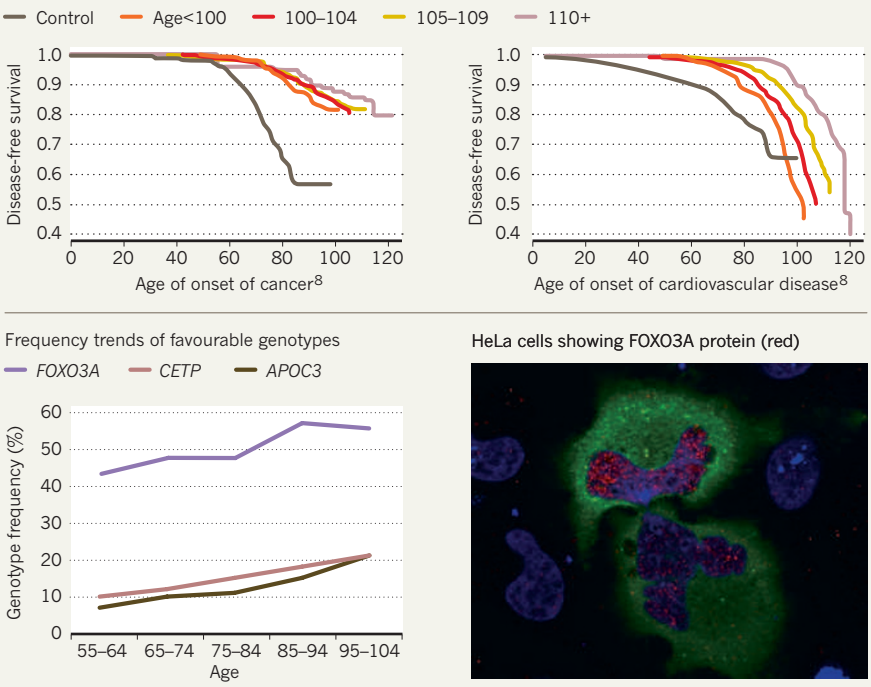
Several genes identified in this study have also cropped up in research in animal models. Indeed, data from animal studies have generally been more effective in uncovering human genetic variations associated with healthy ageing than GWAS. One of the associations that has been most heavily replicated in humans is a variant of the apolipoprotein E (APOE) gene known as *E4*, which is linked not with longevity but with frailty[5] — understandable given that this variant greatly increases the risk of both Alzheimer's disease and cardiovascular problems. However, some see it purely as a risk factor for disease and are reluctant to call it a true 'ageing gene'. With regards to the latter, variations in a gene encoding a regulatory factor called forkhead box O3A (*FOXO3A*) — the human counterpart of *daf-16*, a gene that modulates lifespan in worms — have been repeatedly linked to longevity in diverse populations of humans[6]. "It has been replicated in Han Chinese, Japanese, Ashkenazi Jews, southern Europeans and Germans," says Stefan Schreiber, director of the Research Group for Healthy Ageing at Christian Albrechts University in Kiel, Germany. "This means that the origin of the genetic variant must be very old." *FOXO3A* is part of a set of signalling pathways that govern growth and metabolic activity. In research that further supports the importance of metabolic pathways in ageing, Barzilai has found similar results in his Ashkenazi cohort. In particular, he has identified variants in genes encoding two proteins involved in lipid metabolism that reduce the levels of functional cholesterol esterase transport protein (CETP) and apolipoprotein C3

DISEASE DELAY AND GENETICS

Long-lived individuals show apparent compression of morbidity, with delayed onset of age-related diseases.



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(APOC3)[7]. "They seem to behave like longevity genes — these variants go from 8–10% frequency in a population of 60-year-olds to about 20% in centenarians," says Barzilai.

Studies of centenarians are fraught with difficulties, however. For example, there is the issue of control groups: centenarians have experienced environmental and lifestyle changes that will not necessarily be matched in modern-day populations. "If you're studying centenarians born in 1910, ideally you'd want a cohort of individuals who were also born in 1910 and died at age 50, and there's little or no DNA available to do those studies," says Nicholas Schork, a bioinformatician at the Scripps Research Institute in San Diego, California. On the other hand, dramatic improvements in contemporary medical care and diet mean that would-be control cohorts might harbour secret centenarians — lucky individuals with 'normal' genotypes who reach a ripe old age today, but who would have probably died younger in harder times. "The bet is that only a small number of control individuals will live to a very old age," says Perls, "but there may be more people than were once thought who can live to 100."

SUPER-OLD, SUPER-HEALTHY

Researchers are devising craftier strategies for tracking down biological factors that support very long life. Schreiber's team is among those beginning to focus on 'supercentenarians' — those rare individuals who reach 110 years of age. "We're starting with the most extreme and deploying all of our genomic and genetic tools to really dive deep," says Schreiber. He notes that he has successfully used this type of approach for Crohn's disease: by focusing on children who developed the disease at an unusually early age he has uncovered several causative genetic factors.

Another approach is to bank on the compression of morbidity model and focus on individuals in their 80s or 90s who are 'biologically young'. Schork is involved with the Wellderly study at Scripps, which works along these lines. "If somebody is 80 years old and as fit as a 50-year-old, studying them could shed light on what allows people to live to old age," he says.

As with GWAS, the difficulty in finding longevity gene candidates across populations might in part be a result of scientists casting their nets too wide. Given that most of the benefits of longevity genes are likely to kick in well after our child-rearing days, these variants probably lack the evolutionary momentum to spread, existing only as 'family heirlooms' that are passed from parent to child. There is certainly anecdotal evidence of this — all three of Kahn's siblings, for example, also lived past the age of 100. Accordingly, several research groups and collaborative efforts such as the multinational Long Life Family Study, backed by the US National Institute on Aging (NIA) in Bethesda, Maryland, are attempting to get a better handle on this relationship. "We're looking at longevity-enriched families; for control persons we are using their spouses," says Christensen, one of the study's investigators. "We've performed GWAS on these individuals, and now we are moving on to sequencing."

People who enjoy good health in old age may have a genetic advantage.

As sequencing technology becomes cheaper and more powerful, it is likely to become an essential tool in the field. "I don't think there will be major progress until we can analyse and interpret the whole-genome sequences of our centenarians," says Schork. Barzilai has long been interested in this approach: a grant proposal from his group to perform whole-genome sequencing on centenarians didn't find traction with the US National Institutes of Health (NIH) but ultimately became the foundation for the Archon Genomics X PRIZE. This competition will award US$10 million to the genome-sequencing team that can deliver the fastest, best and cheapest sequences for Archon's cohort of centenarian volunteers, termed the '100 over 100'. This effort has continued to benefit from input from both Barzilai and Perls, and both scientists see it as a good start. "One hundred people is not a large enough sample size," says Perls, "but it is a fantastic step in the right direction."

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Still, Barzilai cautions against thinking of genetic analysis as an end in itself. He would like to see how genetic variants translate into physiological effects, such as shifts in a person's metabolic profile that directly reflect the state of their health. "Measure something in the blood, and then tell us if it's relevant," he says. He notes that although there might be numerous variations in different genes, they could all lead to the same life-extending result. "All our findings have had a relationship to a phenotype," says Barzilai. "With CETP, the CETP levels were low. With APOC3, the APOC3 levels were low. And with both of them there were changes in cholesterol levels." He further notes that although *FOXO3* variations have been linked to longevity in several genetic studies, their physiological impact has yet to be demonstrated.

Fortunately, there are a handful of other prospective, longitudinal studies of ageing-related health that can provide phenotypic data with which to compare genotypic findings. These include two osteoporosis studies that have been running at the University of California, San Francisco, since 2000, one focusing on men and the other on women. "Large numbers of those cohorts have passed away because they've reached their 70s and 80s," says Perls. "But they happen to be about the same birth cohort as the children of our centenarians, the vast majority of whom are still alive."

Despite all these leads, researchers in both Europe and the United States are hampered by a lack of funding for longevity research. For example, the NIA-backed Longevity Consortium, which has supported many genetic studies of human ageing, is running on a limited and dwindling budget, says Schork. On the other hand, the field has strong support from NIH director Francis Collins. Collins is a driving force behind the NIH's new Geroscience Interest Group, which envisages ageing as a primary link between many diseases. According to this perspective, understanding ageing might indicate a point of attack for treating or preventing conditions that have otherwise proven difficult to conquer, such as Alzheimer's and cardiovascular disease (see 'Live long and prosper', page S18). "You have many more genetic susceptibilities within you than you will have diseases — and the mechanisms that either make a disease manifest or protect you are therefore of extreme importance," says Schreiber. "Studying longevity is one way into this." ■

Michael Eisenstein *is a freelance science writer based in Philadelphia, Pennsylvania.*

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