cans are a self-antigen, and so antibodies to such antigens are selected against). When broadly neutralizing antibodies to HIV-1 do arise, they display a number of highly unusual features, including high levels of somatic mutation. These features allow the antibodies to interact with the self-antigen glycan shield and to reach past it to contact foreign peptidic determinants on the HIV-1 spike protein (11). Thus, many of these antibodies recognize a particular combination of self- and foreign antigens, and their development may involve redemption of self-reactive B cells through mutation, as described by Burnett et al. Consistent with a requirement for some level of self-reactivity, broadly neutralizing antibodies to HIV-1 frequently demonstrate cross-reactivity to self-antigens (12). More generally, poly-reactivity was found in 75% of a large collection of human monoclonal antibodies to HIV (13). The notion that some of these antibodies arise from self-reactive precursors is supported by antibody gene knock-in experiments that have demonstrated that B cells that express predicted germline versions of broadly neutralizing antibodies to HIV-1 frequently show precursor cell deletion or absence of allelic exclusion that is indicative of self-reactivity (14, 15). However, when present at high precursor frequencies and challenged with high-affinity multivalent antigen, the knock-in cells can participate in immune responses (14, 15).

The findings of Burnett et al. further our understanding of the biology of B cell energy and provide a framework for thinking about why such cells might be allowed to persist in immune systems despite their self-reactivity. ■

REFERENCES AND NOTES

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shifting cultural norms, rather than increased distance, because of the inconsistent relationship between relatedness and distance. This appears concurrent with popular writing from the time, which led 13 U.S. states to pass cousin marriage prohibitions by the 1880s (7) (although more distant relatedness is in question in Kaplanis et al.). A related study considered 160,000 couples in the Íslendingabók to show that increased couple relatedness (equivalent to third or fourth cousins) is associated with higher fertility that is not explained by socioeconomic influences on number of offspring, and hence is claimed to have a potential biological basis (8).

The main results of Kaplanis et al. involve life span. The resolution of the data set allows them to discern not only that average life span decreased during World War I and World War II, but also that the decrease was larger for individuals of military age. Despite these major events, life span appears to have increased at an almost constant rate of ~4 years per generation since ~1850. They conducted a meticulous study of factors affecting life span, attributing ~7% to gender, birth year, and geography combined. They estimated life span heritability at 16.1 ± 0.4%, lower than most previous studies, although among them, the largest genealogy-based study until now provided a comparable estimate of 15 ± 3% in the Mormon genealogy (9). Kaplanis et al. estimate that an additional ~4% of life span is attributable to dominance (where having a single copy of a genetic variant constitutes the majority of the effect of having two) and none to interaction between different genetic variants.

Despite extensive analyses, Kaplanis et al. only scratch the surface of their resource, which is publicly available, stripped of personal information. It may be interesting to reanalyze life-span factors focused on very high longevity, and revisit other questions previously studied with smaller genealogies. The resource may benefit many disciplines, with unique promise in the combination with genetic data of the same individuals, an opportunity that led to large investments in DTC genetic services by the companies with the largest genealogical websites.

DTC genetic data are not publicly available, but Kaplanis et al. provide an academic version of their resource where individuals can consent to being identified. It can be used on websites to which participants upload their genetic data, as Kaplanis et al. implemented in DNA.Land, which, for example, collates family history of breast cancer and allows users to contribute their genomes to the National Breast Cancer Coalition (10). In a recent study, deCODE genetics highlighted yet again the power of large-scale genealogies with matched genetic data. They reconstructed an ancestor’s genome by mining descendants for inherited genetic fragments, which they tested via unique genealogical analyses (11).

One critical limitation of available crowdsourced data is that the “crowd” is mostly from 15% of the worldwide population that comprises Europe and North America. The overwhelming majority of DTC genetic testing customers are from these regions, as are 85% of the profiles in the Kaplanis et al. study. Partly due to local laws and consent, the potential unleashed by integrating worldwide diversity should provide an incentive to overcome these obstacles. Another shortcoming is the underutilization of the X chromosome by DTC genetic companies for both customer services and medical research (12). Its inclusion via newly developed analytical methods may improve these and, importantly, provide a key step toward closing the gender disparity in disease diagnosis and treatment (12).

The era of precision medicine heralds a greater potential for crowdsourcing, with distinct opportunities when familial, genetic, and medical data are integrated. Funding details of large-scale endeavors such as the U.S. National Institutes of Health All of Us program have put an effective price tag on the recruitment of each participant, their genetic data, and medical records. Recently founded companies, in turn, are attempting to resurrect the option for participants to lease their data to researchers. This may increase the potential for research based on crowdsourced, although not fully crowd-funded, data.

Beyond explosive growth of DTC genetic testing services (of ~16 million current customers, almost two-thirds joined since early 2017), whole-genome sequencing will likely become a cost-effective DTC choice within 2 to 3 years. This will enable tracing, and flagging of potentially harmful, de novo mutations in families and allow crowdsourced genetic research to more substantially advance disease risk prediction, diagnosis, and treatment.

Although many fields make use of crowdsourcing, none is better positioned, since all 7.5 billion of us have a genealogy, DNA, traits, and medical information to share.

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