nature genetics

25 more years

This month, to celebrate a quarter century of excellence in genetics, we are highlighting selections from the past work we have published. We will then publish a number of forward-looking Perspectives in the coming months to examine and chart the future directions of our field. In parallel, we will also consult researchers for their answers to current questions of interest to the genetics and genomics community for discussion throughout the year.

This journal—the first sister title to *Nature* itself—was first published this month in 1992. To give a sense of the over 5,000 research articles we have been privileged to host since that time, the editors will take turns in selecting an article from our archive every day this month on the Free Association blog. Some highlights selected by the editorial team start the celebration here.

At the beginning of an adventure, there is always a map. Augustine Kong, Kari Stefansson and colleagues (*Nat. Genet.* **31**, 241–247, 2002) used 5,136 microsatellite markers to genotype 869 individuals in 146 Icelandic families, creating the highest-resolution linkage map of the human genome to date, locating over 2 million polymorphic single-nucleotide markers (SNPs) on this map, and stimulating revision of the draft human genome sequence to resolve remaining discrepancies between the linkage and physical assembly versions of the human map. Then there are treasures to be unearthed. Stephen Scherer, Charles Lee and colleagues (*Nat. Genet.* **36**, 949–951, 2004) used array-based comparative genomic hybridization (aCGH) to identify over 200 large copy number variants in the human genome, many of which involve the coding regions of genes and many of which are common in human populations.

Methods and standards have always moved the field forward in significant steps. In 1995, Eric Lander and Leonid Kruglyak (*Nat. Genet.* **11**, 241–247, 1995) set standards for complex disease mapping, pointing out that an LOD score of 3 had served the monogenic linkage field well and that the equivalent false-positive rate of 5% would be appropriate for genome-wide markers in a range of experimental designs employing allele sharing and QTL mapping methods. These standards informed the association mapping era, emphasizing the need for replication as well as genome-wide correction for multiple testing, for both genome-wide markers and candidate loci. Alkes Price and colleagues (*Nat. Genet.* **38**, 904–909, 2006) introduced an important strategy for control that enabled genome-wide association studies with the EIGENSTRAT approach to assign statistical significance to each axis of variation in a principal-components analysis of population-specific allele frequency. This strategy provides a way to assign regional ancestry to genotypes and to correct for false-positive results arising from frequency differences between cases and controls among thousands of genome-wide markers. Sarah Ng, Kati Buckingham and colleagues (*Nat. Genet.* **42**, 30–35, 2010) were first to use the new technology of whole-exome sequencing to identify a new monogenic disorder. *DHODH* mutations cause Miller syndrome, in which a genetic pyrimidine biosynthesis defect underlying a developmental dysmorphology resembles an environmental birth defect syndrome that occurs as a result of maternal methotrexate exposure.

A number of remarkable discoveries became the model for new directions in genomics. For example, Huda Zoghbi and colleagues identified mutations in the X-linked gene *MECP2* as the cause of the neurodevelopmental disorder Rett syndrome (*Nat. Genet.* **23**, 185–188, 1999), pointing to the importance of this methyl-CpG DNA-binding protein connecting genome to epigenome and regulating gene expression in the developing brain. Bing Ren and colleagues (*Nat. Genet.* **39**, 311–318, 2007) were able to distinguish promoter elements enriched in the H3K4me3 chromatin mark from enhancers bearing monomethylated H3K4me1. This permitted correct prediction of regulatory elements as well as the annotation of functional elements across the genome. In an article that reoriented the journal toward the agricultural roots of genetics, Hong-Xuan Lin and colleagues (*Nat. Genet.* **37**, 1141–1146, 2005) identified *SKC1* variants influencing sodium and potassium homeostasis that confer a salt tolerance quantitative trait on rice.

Other examples demonstrated the remarkable directional effects of natural selection on the human population, leaving us wishing that there were more such examples to make the power of genetics easier to explain to the public. In one of these cases, population variants were found—exceptionally—both to be relatively common and to exert a large effect on a trait. Irwin McLean and colleagues (*Nat. Genet.* **38**, 441–446, 2006) identified two loss-of-function *FLG* (filaggrin) variants carried by about 9% of people of European origin, accounting for a large proportion of atopic dermatitis and a subset of asthma associated with atopic dermatitis. In another study, Sarah Tishkoff and colleagues identified independent origins for and strong positive selection on *LCT* (lactase) persistence alleles in East African pastoralist populations (*Nat. Genet.* **39**, 31–40, 2007). Thus, under the strong pressure of animal domestication and milk consumption, peoples in Europe and Africa have recently convergently evolved the ability to digest lactose into adulthood.

With this solid beginning—and with far too many excellent papers to mention in just one month—we are excited to face the next 25 years of genomics research! ■