

# Preface

When Victor Neel termed type 2 diabetes (T2D) “the geneticist’s nightmare,” (Neel 1962) it was already evident that T2D harbored a familial component; yet its polygenic genetic architecture, the inherent limitations in the techniques available at the time, and the strong (and growing!) influence of environmental determinants made genetic discovery an arduous task. In the 50 years since then, the public health impact of T2D has only skyrocketed, fueled by the changes in modern lifestyle increasingly adopted by developing societies and the expansion of caloric superabundance.

As a result, T2D and its complications represent one of the most serious challenges to public health in the twenty-first century. We live in the midst of a worldwide pandemic that threatens to undermine the significant gains we have made against cardiovascular disease over the last few decades. Despite its status as one of the oldest known endocrinopathies, the availability of a molecular therapy since 1920, and the existence of over a dozen drug classes approved for the management of the disease, we are largely unable to cure it and are losing the population battle in both the developed and developing worlds.

The population and healthcare costs are enormous and only expected to rise. Stoked by the snowballing obesity epidemic, diabetes affects over 29 million Americans, with more than 80 million at high risk. People with Asian, African, and American indigenous ancestry experience a higher risk, with the worldwide prevalence of diabetes expected to hit 500 million by 2030. In the USA alone, diabetes and its complications account for \$245 billion annually. With its concomitant life-threatening complications of cardiovascular disease, renal failure, visual loss, and peripheral vascular disease, T2D can undermine the global economy, with a disproportionate burden on underprivileged groups and low- and middle-income countries.

At the crux of our lack of clinical effectiveness lies our incomplete understanding of its pathogenesis, evolution, and metabolic consequences. Definite causal triggers, the interplay between various risk factors, and specific mechanisms that underlie long-term complications remain largely unknown. Thus, T2D has become the quintessential complex disease, with substantial genetic and environmental

components, significant variation in prevalence across ethnic groups, pathophysiological heterogeneity, multiple treatment modalities, and poorly defined interactions with related metabolic phenotypes.

In the midst of many significant advances, key questions remain unanswered: Why do people develop T2D? Why do incidence rates differ across populations drawn from around the world? What causes beta cells to fail? How does obesity influence T2D risk? Can medications be designed that cure, rather than treat, diabetes? If more than one medication is needed, what is the best sequence or combination for specific subgroups?

These pressing questions also represent tantalizing opportunities. Our growing understanding of pathophysiology, the invention and deployment of global technologies that query specific areas of the biological space, and our improved ability to focus on the human as the targeted model system have placed the field of diabetes investigation on the verge of momentous discovery. However, among all valid experimental approaches employed in humans, only two can consistently bypass correlative associations and firmly establish causal inference. Beyond expensive and focused clinical trials, *the genetic method* is unique in ensuring that the exposure of interest (genotype) precedes phenotype, that it is conferred on individuals on a randomized basis at the time of conception, and that it is not in turn affected by the disease process or its treatment. Thus, it can serve as a powerful approach to dissect the nosology of T2D, illuminate its pathogenesis, and identify therapeutic targets through mechanistic insight.

In this volume, we have endeavored to take a contemporary snapshot of a rapidly moving field. In the time passed since Neel's initial cautionary statement, the scientific community has developed methods to measure global genomic variation with great precision, together with the statistical concepts and related analytical techniques that allow us to draw rigorous conclusions. Investigators have coalesced to advance knowledge in a collaborative fashion where needed, introducing appealing notions on the sociology of team science.

All of these ideas are illustrated in this book. The amount of novel information collected here, most of which was simply undreamed of just a decade ago, is staggering. At the same time, and reflecting the dizzying pace of discovery, nascent findings that have emerged most recently may not be fully captured in these chapters, making this reading all the more exciting. Finally, the organization of this work was intended to mirror the collaborative atmosphere that pervades our field, in that every chapter is authored by two or more investigators who hail from different research groups and yet complement each other in style, insight, and perspective.

The initial section, containing seven chapters, centers on fundamental genetic discovery. The initial overview provides a helpful historical viewpoint that will help the nongenetic reader take stock of the chronological evolution of the research enterprise in this area. From the proven effectiveness of genome-wide association studies (GWAS), subsequent contributions touch on the challenges that follow initial associations, the extension of this method to less accessible phenotypes,

and the arrival of next-generation sequencing as the harbinger of discovery focused on rare genetic variation.

The second section expands beyond genetics and illustrates how other data sources can inform initial genetic findings. Leveraging population diversity, correlating genetic associations with physiological measurements, learning from genetic variants that have strong phenotypic effects, and incorporating other key influences such as the modulation of gene expression, environmental factors, and our microbial commensals all help place genetic findings in focus and can lead to additional insight.

The third section makes a fundamental point: genetic association, however robust, is only the beginning of a laborious process. Convincing association signals notwithstanding, in most cases the specific DNA sequences that cause the molecular phenotype have not been identified. Indeed, the polymorphisms identified thus far merely signal genomic regions—at times hundreds of kilobases away from known genes—where an association has been found, but do not necessarily represent the causal variants: further fine-mapping and functional studies must be carried out before the true contribution of these loci to T2D can be accurately assessed. Thus, while we can rapidly and systematically uncover new associations, genetic studies do not circumvent the process of refining the associated loci to find the precise “causal” DNA sequences (causal in the sense of having a direct impact on RNA and/or protein quality or quantity that contributes to the diabetic phenotype). Indeed, variants may exert their molecular effects at remote sites even when they are relatively close to other uninvolved genes. Thus, loci identified by GWAS require in-depth sequencing and functional studies of the cellular and molecular effects of genes in that region. Six successful vignettes are described in this section, illustrating the progress we have made in just a few years.

The final section, comprising seven chapters, attempts to bring our current state of knowledge closer to the clinic, acknowledging both its potential and its limitations. It includes chapters on prediction, interaction of genetic variants with drugs or nutrients, and approaches to prevention or to the inference of causality for clinical relevant questions where randomized clinical trials have not produced conclusive answers or cannot be carried out. The epilogue, authored by a trio of long-standing collaborators who have set the pace for our field and whom many of us consider inspiring mentors, paints a realistic but hopeful vision of the future.

This book would not have been possible without the prescience of Andrea Pillmann at Springer in making the initial suggestion that we undertake this initiative, and without Jutta Lindenborn’s patience in managing the editorial process. Over the years I have been fortunate to count on the professionalism and support of a superb publisher such as Springer in a variety of editorial projects, and this was no exception. I am most thankful to so many of my colleagues and friends who took time out of their busy professional lives to share their thoughts through eminently readable and informative chapters. Naturally not everyone who should or could have contributed was able to do so, but we have benefited from their wisdom as well, as this book largely reflects the collective body of knowledge garnered by the community over the past decade. Our remembrance goes to those luminaries

and pioneers who are no longer with us, such as Alan Permutt, Steve Elbein, and Linda Kao. And finally our mind rests in the smart, competent, and energized trainees we have the pleasure of working with, as they represent the bright future for our field: theirs will be the next edition in this fascinating journey of discovery, as we materialize our heartfelt commitment to ameliorate world suffering by improving human health.

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## Reference

Neel JV (1962) Diabetes mellitus: a “thrifty” genotype rendered detrimental by “progress”? *Am J Hum Genet* 14:353–362

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