Werner Syndrome and Diabetes: Opportunities for Precision Medicine

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The precision diagnosis of diabetes is an increasingly important part of understanding the full spectrum of disease heterogeneity, and several groups have recently outlined current and future roles for precision medicine approaches in diabetes (1–4). Patients with monogenic or syndromic diabetes are often misdiagnosed as having type 1 or type 2 diabetes (5,6), so it remains a pressing question how patients with atypical presentations of diabetes should be evaluated and what role precision medicine should have in their care. This exact question is raised in the thought-provoking case report presented by Spira et al. (7) in this issue of *Diabetes Care*, who describe a patient found to have a previously unidentified variant in the *WRN* gene, which is associated with Werner syndrome (WS) as well as diabetes, insulin resistance, and hirsutism.

WS is an autosomal-recessive progeroid syndrome with cardinal features including accelerated aging, short stature, bilateral cataracts, and skin atrophy. It is also associated with diabetes, hypogonadism, osteoporosis, atherosclerotic disease, cancer, voice changes, and flat feet, among other findings (8). Biallelic loss-of-function variants in the *WRN* gene, which produces a highly conserved RecQ helicase with exonuclease activity performing key aspects of DNA maintenance and repair, have been identified as the underlying genetic changes causing WS (9). Management of WS is typically limited to addressing manifestations of the disease, and there is currently no targeted treatment that addresses the cumulative changes brought about by loss of functioning *WRN* gene product and accumulated DNA damage (10).

The patient described by Spira et al. (7) is a 24-year-old woman found to have hyperglycemia and laboratory testing consistent with new diabetes as well as hirsutism, significant insulin resistance, and preserved C-peptide levels. She underwent targeted next-generation genetic sequencing, which ruled out other causes, including monogenic diabetes as well as both type A and type B insulin resistance syndromes. However, sequencing did show a previously unrecognized homozygous variant in the canonical splice site of intron 4 in *WRN* causing a frameshift mutation, which the authors confirmed by RT-PCR amplification, showing deletion of 11 nucleotides with a premature stop codon in exon 5. Interestingly, other than cataracts, the other cardinal signs of WS were missing in this patient, and she ultimately did not meet definitive criteria for the diagnosis of WS. Given the possibility for alternative splicing with partial expression of WRN protein, as noted in prior studies of a similar genetic variant at the same site (11), future analysis of protein expression could provide further evidence of the pathogenicity of this variant. She was treated with low-dose metformin and lifestyle modifications, and she had significant improvement in her glycemic targets.

About 55% of patients with WS present with diabetes (12). There are also prior descriptions of insulin resistance, accumulated visceral fat, and low BMI (13–14). There is thought to be benefit in treatment with medications addressing insulin resistance, such as thiazolidine derivatives, as well as metformin (12,15–17). Case reports have linked WS to partial lipodystrophy with insulin resistance (14,18) as well as laminopathies (19,20), although none of these are part of the diagnostic criteria for the condition. It is also known that some of the less typical manifestations of WS may be part of the initial presentation, even before progeria, as demonstrated in this case (21). In describing their approach to this patient, the authors add to our knowledge of the spectrum of metabolic consequences of WS and highlight the heterogeneity of syndromic forms of diabetes. The long-term outcomes of specific treatments for metabolic conditions associated with WS remain to be seen and merit future work.

Equally pressing is the need for a framework for thinking about how to approach diabetes in patients with other syndromic conditions and equivocal genetic testing. Here, we have a patient with a likely pathogenic variant of the syndrome who did not meet clinical criteria for definitive diagnosis. This represents an opportunity to connect our clinical assessment of the patient to our growing knowledge of the underlying genomic landscape, which aids not only in understanding subtleties regarding diagnosis of the syndrome but also in appropriate precision treatment. For example, is metformin the best treatment for this patient, or would other medications better

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address the etiology of her diabetes and insulin resistance, such as pioglitazone or even metreleptin? This patient presented with normal leptin levels at any rate, although others have reported on the use of metreleptin for improvement of metabolic markers in WS (14). Furthermore, we do not yet have data for WS suggesting that the clinical phenotype changes with different *WRN* mutations (10), although both follicular and papillary thyroid cancer may be more closely associated with specific genetic variants of *WRN* (22).

How can this connection between genotype and phenotype be achieved? The International Registry of Werner Syndrome (https://dlmp.uw.edu/research-center/werner/registry) provides a vital means by which this can be facilitated for WS, and the information gathered through such registries will provide data that could strengthen genotype-phenotype correlation and help guide future precision treatments for these patients. For atypical diabetes, the Rare and Atypical Diabetes Network (RADIANT) study (https://www.atypicaldiabetesnetwork.org) is a collaborative clinical study funded by the National Institute of Diabetes and Digestive and Kidney Diseases. RADIANT team members span 14 institutions and screen eligible participants for atypical diabetes in stages, proceeding to whole-genome, RNA, and mitochondrial sequencing as well as metabolomics as indicated. The RADIANT team has recently reported their findings at 3 years, including six new monogenic gene variants and several phenotypic clusters undergoing additional study (23).

As clinical registries and ambitious studies such as RADIANT provide larger, more complete data sets on combining both genotypic and phenotypic data for atypical and syndromic diabetes, we may soon be able to develop more precise classifications and treatment to better help patients like the one in this report.

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