Learning to Find Needles in Haystacks: Fellowship for Advanced Genomics in Rare Diseases

By Jason W. An, MD, MSc, FRCPC

Fifty. That's the number of new autoinflammatory diseases discovered in the past decade. The invention of and rapid developments in genomic sequencing technologies have revolutionized our ability to make molecular diagnoses and ushered in an unprecedented era of precision medicine in rheumatology.

With the introduction of the Genome-wide Sequencing Ontario (GSO) program in April 2021, genetic testing that was previously sent out internationally can now be performed locally in the province. As more genetic studies are performed, we as rheumatologists will have to be prepared to address complex questions. Referring colleagues may inquire on "What is the significance of this heterozygous variant of uncertain significance in the *MEFV* gene, in my patient with unexplained fevers?" Similarly, our patients may ask "Does this *TNFRSF1A* pathogenic variant mean I have tumor necrosis factor receptor-associated periodic Syndrome (TRAPS), and what are the risks of my children developing inflammatory disease?" We will need to read genetic reports that describe a variant's population frequencies, conservation, and in silico prediction scores — and interpret them to manage patients. How are we to make sense of all this information, which we were never taught in medical school or residency? How do we keep up with these rapid advancements in immunology and genetics?

"Finding needles in haystacks is the essence of rare disease medicine."

In 2019, the Department of Clinical and Metabolic Genetics at The Hospital for Sick Children launched the Fellowship for Advanced Genomics in Rare Diseases. Funded by the Canadian Gene Cure Advanced Therapies for Rare Disease (Can-GARD), the fellowship had two aims: First, to promote education and literacy in genetics across all fields of medicine; and second, to equip newly graduated specialists to proficiently manage patients with rare genetic conditions within their own specialty.

As a rheumatologist with an interest in genetically driven inflammatory conditions, I was fortunate to graduate from this unique program in rare diseases. By attending pediatric and adult clinics in genetics, metabolomics, autoinflammation and immunology, I learned approaches to investigating complex genetic conditions. Training in the molecular laboratory taught me the intricacies of analyzing genomic data. Just as it is important to know whether anti-nuclear antibodies were assayed with immunofluorescence or ELISA, it is important to understand the different genetic sequencing technologies with their strengths and limitations in order to interpret the results, counsel patients, and inform management. Indeed, finding needles in haystacks is the essence of rare disease medicine.

The Rare Diseases Fellowship was eye opening and highlighted the discrepancy between the importance of genetic literacy in our future practices and the lack of genetics education in our current residency programs. As genetic testing continues to develop at a rapid pace and becomes increasingly integrated into rheumatology practice, we will need to place greater emphasis on genetics education at all levels, from medical school to subspecialty fellowship training.

The skills I learned in this fellowship will indeed be important as a new staff rheumatologist at St. Michael's Hospital in Toronto. With the continued mentorship of Dr. Ron Laxer and collaborations with the rheumatology-genetics research team at SickKids, we aim to establish a clinic for the investigation and management of adult patients with recurrent fevers and undifferentiated systemic inflammation.

Gone are the days when every recurrent fever syndrome was labelled as Familial Mediterranean Fever (FMF) or "atypical FMF." As we find more needles in the haystack, the 50 monogenic diseases discovered in the past decade may prove to be just the tip of the iceberg.

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