LifeScientist

Telomeres need to last a lifetime

By Susan Williamson | Posted in Genetics on 19 June, 2014

The Short Telomere Syndrome Conference recently held in Sydney brought together international leaders in this field to consider state-of-the art research and what can be done to improve future treatments for patients with these rare and often life-shortening diseases.

One of few meetings to be held on these rare conditions, the conference was convened by Professor Roger Reddel of Children's Medical Research Institute(CMRI), Dr Sharon Savage from the US National Cancer Institute and Dr Pasquale Barbaro from the Children's Hospital Westmead, and provided attendees with an update on clinical and genetic aspects of short telomere syndromes.

"There are four telomere research teams at CMRI, and all of us are primarily focused on cancer," said Reddel in the opening presentation of the meeting. "But a visit from Ian Woollard and his family earlier this year provided a major impetus for us to extend our studies into this condition and to seek the help of our national and international colleagues."

Woollard's son Aaron died in early 2012 of a rare telomere disorder called dyskeratosis congenita. This condition is characterised by skin, mouth and nail abnormalities and over time individuals commonly develop failure of the bone marrow, lungs or liver.

"Few medicos know about short telomere syndromes because they are so rare," Professor Reddel said. "With the support of international colleagues we have brought clinicians together to work towards developing an international consortium to further understand the links between telomeres and disease."

The connection between short telomeres and disease was only discovered about 15 years ago. As the name implies, these syndromes, including dyskeratosis congenita, are caused by abnormally short telomeres - the DNA-protein structures that protect the ends of chromosomes.

Telomeres comprise DNA repeats, TTAGGG, bound by a six-protein complex called shelterin, and with a single-stranded DNA overhang that forms a processing end.

Telomeres shorten with normal replication, and when they become too short cells can no longer divide.

This telomere attrition is partially offset by telomere lengthening processes that occur via the reverse transcription action of the telomerase enzyme. Although telomeres normally shorten as we age, with the right balance between telomere attrition and telomere lengthening, our telomeres last for our lifetime.

Mutations in various components of the telomere protection and lengthening processes have been identified and implicated in causing telomere abnormalities.

Professor Reddel cited a number of genetic mutations that have been identified in the telomerase-directed catalysis of telomere lengthening.

"Mutations occur in the biogenesis of the telomerase complex and in the recruitment of this large molecule to the telomere, although we are still learning about this process," said Reddel, "and in any one of the components in the telomerase complex itself (TERC, TERT and DKC1)."

In addition, one of the shelterin proteins, TINF2, involved in binding the telomere DNA sequence can mutate. These mutations all act either to decrease the level of telomerase enzyme activity or to decrease the telomere protection provided by shelterin, and cause telomeres to shorten at a faster rate.

“Mutations causing accelerated telomere shortening in somatic cells also cause telomere shortening in germ line cells, which means that in families with these mutations the telomeres get shorter from generation to generation. The manifestations of Short Telomere Syndromes therefore get more severe with each successive generation,” Reddel said.

- See more at: http://lifescientist.com.au/content/molecular-biology/news/telomeres-need-to-last-a-lifetime-1056972926#sthash.4JeUrWS0.dpuf