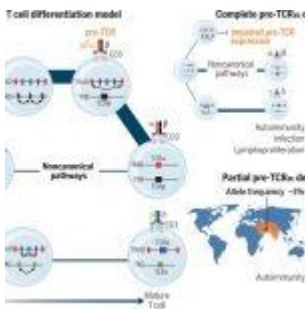
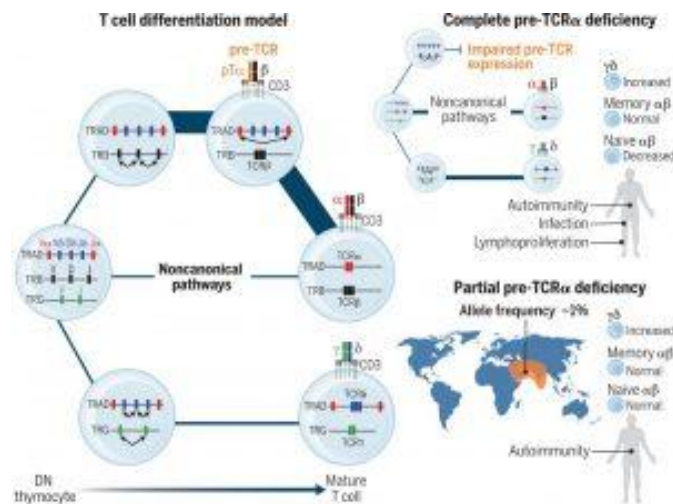


# Does pre-TCR $\alpha$ deficiency have any effect on human beings?



In animal models, particularly those carried out in mice, pre-TCR $\alpha$  chains have been identified as essential to the development of  $\alpha\beta$  T-cells in mice. In a recent study, researchers aimed to establish this in humans, something that has not been done (Figure 1).



**Figure 1: Functional  $\alpha\beta$  T cells and late-onset immunological conditions in humans with complete or partial inherited pre-TCR $\alpha$  deficiency. Although complete pre-TCR $\alpha$  deficiency is very rare, partial pre-TCR $\alpha$  deficiency is common in South Asia and the Middle East, affecting about 1 in 4000**

*individuals. DN, double-negative. [Figure created with BioRender.com.]*

Loss of pre-TCR $\alpha$  in mice can cause up to a 95% decrease in the number of  $\alpha\beta$  [T-cell](#) precursors. Mice with very few TCR $\alpha\beta$  cells detected in the lymph nodes do remain healthy however, they fail to be challenged with pathogens.

To determine whether inherited pre-TCR $\alpha$  deficiency has any effect in human beings, 10 patients with rare biallelic loss-of-function PTCRA variants were looked at in this study. 6 out of the 10 patients were found to remain irrelative of their age while the remaining 4 reported having infections or some form of autoimmunity that began between the ages of 13 and 25. All patients had low  $\alpha\beta$  [T-cell](#) counts from the childhood, however their memory  $\alpha\beta$  [T-cell](#) counts were normal.

The two most common PTCRA variants that are linked to partial pre-TCR $\alpha$  deficiency in homozygotes were identified to occur very rarely; the p.Tyr76Cys PTCRA variant was found to be homozygous in about 1 in 73,000 individuals from Africa while the p.Asp51Ala variant was homozygous in about 1 in 4000 people from the Middle East and South Asia. Altogether, this has led Materna and colleagues to conclude that a complete inherited pre-TCR $\alpha$  deficiency is not only rare in human beings but also not very severe since individuals are able to reach adulthood without very extreme signs of underlying immune-pathophysiology.

**Journal article: Materna, M., et al., 2024. [The immunopathological landscape of human pre-TCR \$\alpha\$  deficiency: From rare to common variants.](#) *Science*.**

*Summary by Vanessa Mwebaza Muwanga*