Göteborg, 2023

Thymus dysfunction in the 22q11 deletion syndrome

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssal Tallen, Drottning Silvias Barnsjukhus, Fredagen den 5e maj, klockan 09.00

av Jenny Lingman Framme

Fakultetsopponent:
Professor Andrew Gennery
Newcastle University, Storbritannien

Avhandlingen baseras på följande delarbeten

I. **Lingman Framme J**, Borte S, von Döbeln U, Hammarström L, Óskarsdóttir S. Retrospective analysis of TREC based newborn screening results and clinical phenotypes in infants with the 22q11 deletion syndrome. J Clin Immunol. 2014 May; 34(4): 514-9.

II. **Framme JL**, Lundqvist C, Lundell AC, van Schouwenburg PA, Lemarquis AL, Thörn K, Lindgren S, Gudmundsdottir J, Lundberg V, Degerman S, Zetterström RH, Borte S, Hammarström L, Telemo E, Hultdin M, van der Burg M, Fasth A, Óskarsdóttir S, Ekwall O. Long-Term Follow-Up of Newborns with 22q11 Deletion Syndrome and Low TRECs. J Clin Immunol. 2022 Apr; 42(3): 618-633.

III. **Lingman Framme J**, Hennings V, Lundell A-C, Thörn K, Lundqvist C, Lindgren S, Lundberg V, Telemo E, Fasth A, Óskarsdóttir S, Ekwall O. Proteome wide autoantibody profiling in the 22q11.2 deletion syndrome. In manuscript.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

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Thymus dysfunction in the 22q11 deletion syndrome

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Avdelningen för pediatrik, Institutionen för kliniska vetenskaper, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2023.

Abstract

Introduction: The 22q11.2 deletion syndrome (22q11DS) is associated with heterogeneous clinical findings, including T-cell immunodeficiency resulting from thymus hypoplasia. Newborn screening programs based on the quantification of T-cell receptor excision circles (TRECs) identify infants with severe combined immunodeficiency, as well as a number of infants with 22q11DS.
Aim: To study the outcome of TRECs at birth in infants with 22q11DS, and to investigate if low numbers of TRECs are predictive of persistent thymus dysfunction in individuals with 22q11DS.
Methods: TRECs were retrospectively quantified by PCR using the original newborn screening cards from 48 infants with 22q11DS (Paper I). A follow-up of individuals with low numbers of TRECs (22q11Low, N=10), normal numbers of TRECs (22q11Normal, N=10) and matched healthy controls (N=10), was performed, including quantification of TRECs, flow cytometry for characterization of lymphocyte subsets, deep sequencing of T-cell receptor repertoires, and PCR for assessment of telomere lengths (Paper II). High-density arrays were used for autoantibody profiling (Paper III).
Results: A considerable proportion of infants with 22q11DS had abnormal numbers of TRECs at birth (Paper I). At follow-up (median age 16 years), the 22q11Low group had lower TRECs, lower proportions of naïve T cells, aberrant T-cell receptor repertoires (Paper II) and more autoantibodies (Paper III), as compared to the 22q11Normal group and to healthy controls. Many autoantibody specificities were shared between the two 22q11DS groups.
Conclusion: Newborn screening with TRECs identifies a subpopulation of infants with 22q11DS, in whom low numbers of TRECs at birth are associated with long-term immune aberrations, necessitating follow-up.

Keywords: 22q11.2 deletion syndrome, TREC, thymus

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