

COMPARATIVE ANALYSIS OF TREC AND KREC ASSAYS FOR DIAGNOSIS OF PID IN DIFFERENT COUNTRIES

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Nationwide neonatal screening programs of lymphocyte production using T-cell recombination excision circles (TREC) and kappa-deleting element recombination circle (KREC) have been important tools for the timely diagnosis of primary immunodeficiency (PID). Diagnosis and treatment of congenital defects of the immune system have made significant strides in many countries. However, a significant part of the children with severe immunodeficiency in the first year of life are diagnosed posthumously. Immunodeficiencies are under diagnosed primarily due to the lack of opportunities for early diagnosis and low awareness of these pathologies in doctors and the other healthcare professionals. Therefore, the issue and importance of early SCID detection using newborn screening assays become an essential public health problem. Newborn screening, particularly through TREC and KREC assays, has emerged as a promising avenue for identifying PID in its nascent stages. Early diagnosis not only facilitates prompt and targeted intervention, but also offers the opportunity to provide improved long-term outcomes for individuals facing these complex disorders.

Screening for severe combined immunodeficiency (SCID) was introduced in the Swedish newborn screening program in August 2019, and according to the results from the first year, TREC, KREC and actin beta (ACTB) levels were measured by multiplex qPCR in dried blood spots (DBS) that obtained from 115,786 newborns and children under two years of age. On the basis of low TREC levels, 73 children were requested to undergo further clinical evaluation, resulting in the diagnosis of T-cell lymphopenia in 21 children. The DEPISTREC pilot study in France compared 190,517 infants screened for TREC with a control group of 1,400,000 children. TREC screening

identified three patients with SCID, compared to 28 in the control group. Unfortunately, five children in the control group died of SCID before waiting for HSCT, which could potentially have been prevented by TREC screening. An economic analysis showed that the main cost factors were morbidity and cost per test and demonstrated that routine SCID screening was feasible and effective. In addition, two US states, Wisconsin and Massachusetts, have conducted pilot projects funded by the Center for Disease Control to evaluate the feasibility and effectiveness of newborn screening (NBS) for severe combined immunodeficiency (SCID) using the TREC assay. In Wisconsin, 71,000 infants were screened in 2008, identifying eight infants with T-lymphocytopenia, including one successfully treated with cord blood hematopoietic stem cell transplantation (HSCT). In Massachusetts, 100,597 infants were screened in 2009-2010 where twenty-nine infants with T-lymphocytopenia were identified, one of whom had SCID due to a compound heterozygous mutation in JAK3 and also received successful HSCT from an unrelated donor. After successfully identifying T lymphocytopenia in these experiments, the Advisory Committee on Hereditary Diseases of Newborns and Children of the Health and Human Services recommended that SCID be included in a uniform newborn screening panel.

Therefore, newborn screening based on TREC and KREC assay programs is expected to provide early detection, prevent infections and prompt treatment, eventually improving overall survival. The ability to detect and intervene in the early stages of immunodeficiency diseases not only improves the prognosis for affected individuals but also enhances our understanding of the prevalence and spectrum of PID in the newborn population.