PRIMEVIEW

SCIDs AND RELATED DISORDERS

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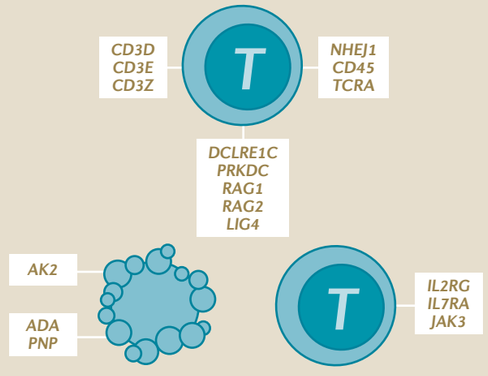
Severe combined immunodeficiencies (SCIDs) and combined immunodeficiencies (CIDs) comprise a group of monogenic diseases in which T lymphocyte development or functioning is intrinsically impaired. Depending on the cause, B cells and natural killer cells can also be affected. Patients are immunocompromised and susceptible to recurrent infections, which result in early lethality unless immune function is restored.

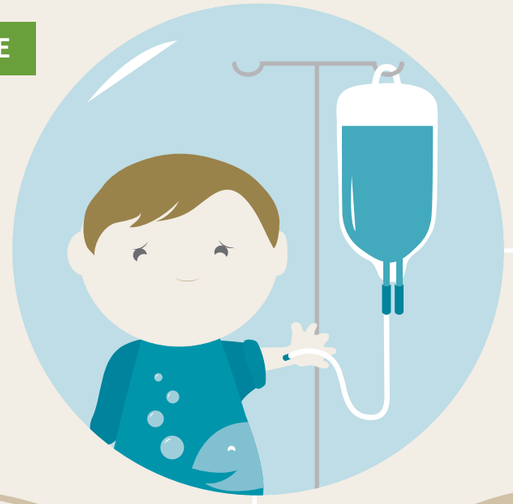
MECHANISMS

Typical SCID is characterized by a complete lack of functional endogenous T cells owing to mutations in genes encoding proteins that are involved T cell differentiation. Impaired pathways range from apoptosis of haematopoietic stem cells (HSCs) and lymphoid precursors to defects in the common γ-chain subunit that is present in many interleukin receptors. Hypomorphic mutations — allowing residual protein expression — in any of these genes lead to atypical SCID. In addition, mutations in several other genes have been described that permit T cells to survive but impair function; these conditions are classified as CID. The exact phenotype — lymphocyte abnormalities and the involvement of extra-haematopoietic tissues — depends on the specific mutation.



QUALITY OF LIFE

SCID used to be lethal in infancy



Addressing issues such as the stability of immune reconstitution and extra-haematopoietic co-morbidities has become crucial

Advances in management and diagnosis have greatly improved survival of patients with SCID

Most patients still experience complications, and premature mortality still remains an issue

EPIDEMIOLOGY

SCID has an incidence of 1 per 58,000 births, although values might vary depending on the population. 80% of all individuals with SCID can be traced back to mutations in genes that are known to be associated with typical SCID, of which mutations in *IL2RG* (as in X-linked SCID) and *RAG1* are the most common.

PREVENTION

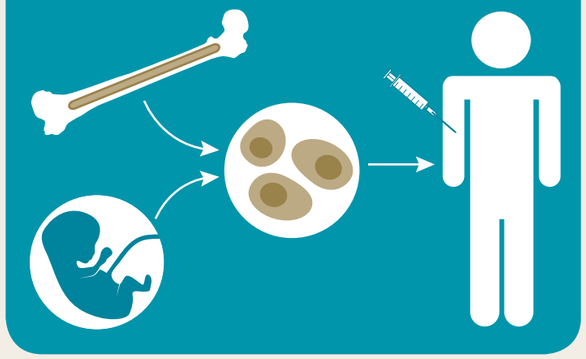
The outcomes and survival of patients with SCID greatly improve when patients are diagnosed and treated early, before complications develop. SCID newborn screening was first implemented in 2010 in the United States. Since then, a few countries have followed and more have initiated pilot programmes.

DIAGNOSIS

Endogenous T cell production is measured by quantifying specific DNA fragments — T cell receptor excision circles (TRECs). This test can be performed on dried blood spots collected from heel pricks and is used to screen newborns. Further classification of the SCID types involves lymphocyte phenotyping by flow cytometry, the evaluation of T cell functioning and other molecular techniques to identify the specific mutation.

MANAGMENT

SCID leads to early-onset immune dysfunction characterized by recurrent infections, including opportunistic attack by microorganisms such as fungi, viruses and bacteria. The only definite treatment option is to restore immunity. HSC transplantation to replace the defective cells is successful in >90% of patients, but success depends on a good donor match, the presence of active infections, the type of SCID and the age of the patient. Accordingly, genetic modification of diseased, autologous HSCs through *ex vivo* gene therapy has emerged as an attractive alternative. Second-generation retroviral vectors with less genotoxicity have been used to correct mutations in *IL2RG* and *ADA*; *ADA* mutations can also be addressed with enzyme replacement therapy.



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