Strains of origin of the NOD/Scid/Il2Rγ mouse at Jackson Labs

►NOD/ShiLtJ mouse

Appearance
albino
Related Genotype: *A/A Tyr^{c}/Tyr^{c}*

Important Note
This strain is homozygous for *Cdh23^{ahl}*, the age related hearing loss 1 mutation, which on this background results in progressive hearing loss that is already severe by three months of age.

Description
Diabetes in NOD/ShiLtJ mice is characterized by insulitis, a leukocytic infiltrate of the pancreatic islets. Marked decreases in pancreatic insulin content occur in females at about 12 weeks of age and several weeks later in males. Onset of diabetes is marked by moderate glycosuria and by a non-fasting plasma glucose higher than 250 mg/dl. Diabetic mice are hypoinsulinemic and hyperglucagonemic, indicating a selective destruction of pancreatic islet beta cells. Susceptibility to IDDM in NOD/ShiLtJ mice is polygenic, and environment, including housing conditions, health status, and diet, exerts a strong effect on penetrance. NOD/ShiLtJ females are more widely used than males because the onset of IDDM symptoms occurs earlier and with a higher incidence (90-100% by 30 weeks of age). NOD/ShiLtJ males develop IDDM at a frequency of between 40-60% by 30-40 weeks of age. Male mice are useful for certain applications, including pharmaceutical studies, "accelerated transfer" of IDDM, and some *in vitro* studies. The major component of diabetes susceptibility in NOD mice is the unique MHC haplotype (*H2^{g7}* = K^{d}, Aa^{d}, Ab^{g7}, E^{null}, D^{b}). NOD mice also exhibit multiple aberrant immunophenotypes including defective antigen presenting cell immunoregulatory functions, defects in the regulation of theT lymphocyte repertoire, defective NK cell function, defective cytokine production from macrophages (Fan et al., 2004) and impaired wound healing. They also lack hemolytic complement, C5. NOD/ShiLtJ mice also are severely hearing-impaired. A variety of mutations causing immunodeficiencies, targeted mutations in cytokine genes, as well as transgenes affecting immune functions, have been backcrossed into the NOD/ShiLt inbred strain background.

Development
NOD inbred mice originated early on in the inbreeding of the Cataract Shionogi (CTS) strain. These mice were originally outbred Jcl:ICR mice. At F6, the progenitors of the future NOD/Shi mice were inbred on the basis of an elevated fasting blood glucose level in cataract-free mice. At F13, the NOD progenitors were separated from what is now the NON/Shi strain. High fasting blood glucose levels continued to be the basis for selection of the latter strain, while the NOD progenitors at F13 and later were selected on the basis of a normal fasting blood glucose level. In 1974, at F20, a female in the "normoglycemic" line spontaneously developed overt insulin-dependent diabetes mellitus with insulitis (IDDM). Selective breeding of the progeny of this diabetic female produced the nonobese diabetic (NOD) strain. Originally restricted to distribution in Japan, NOD substrains were distributed during the early 1980s to Australia and the United States. NOD and NON strains were imported from a colony in Kyoto, Japan by Dr.

M. Hattori to the Joslin Diabetes Ceneter in Boston in 1984. Breeder pairs from this importation were sent from The Joslin Diabetes Center to Dr. E Leiter at The Jackson Laboratory, and are the source of the production strains NOD/ShiLtJ and NON/ShiLtJ. The current generation of inbreeding is F83.

►The scid defect was bred onto NOD/ShiLtSz by crossing with C.BKa-*Igh*^{b}/IcrSz (C.B-17) to yield NOD.CB17-*Prkdc*^{scid}/J

Appearance
albino
Related Genotype: *A/A Tyr*^{c}/*Tyr*^{c}

Description
Mice homozygous for the severe combined immune deficiency spontaneous mutation (*Prkdc*^{scid}, commonly referred to as *scid*) are characterized by an absence of functional T cells and B cells, lymphopenia, hypogammaglobulinemia, and a normal hematopoietic microenvironment. Normal antigen-presenting cell, myeloid, and NK cell functions are strain dependent. *scid* mice carry a DNA repair defect and a defect in the rearrangement of genes that code for antigen-specific receptors on lymphocytes. Note, they are not Rag-deficient, but lack an enzyme essential for processing V(D)J recombination properly. Most homozygotes have no detectable IgM, IgG1, IgG2a, IgG2b, IgG3, or IgA. Thymus, lymph nodes, and splenic follicles are virtually devoid of lymphocytes. *scid* mice accept allogeneic and xenogeneic grafts making them an ideal model for cell transfer experiments. Some *scid* mice will spontaneously develop partial immune reactivity. *scid* mice that have serum Ig levels greater than 1 ug/ml are considered "leaky." *scid* leakiness is highly strain dependent, increases with age, and is higher in mice housed under non-SPF conditions. In general, *scid* leakiness is high on the C57BL/6J and BALB/cBy genetic backgrounds, low on the C3H/HeJ background, and even lower on the NOD/ShiLtSz background. NOD/ShiLtSz-*Prkdc*^{scid} mice are both insulitis- and diabetes-free throughout life and serve as a diabetes-free control for comparison to NOD/ShiLtJ mice (Stock No. 001976). Thymic lymphomas occur with high frequency, however, and life span typically is limited to only 8.5 months under specific pathogen-free conditions. In addition to being an excellent host for xenografts, NOD.CB17-*Prkdc*^{scid}/J mice may be useful for delineation of the role of T cell subsets in autoimmune diabetes and also as a source for insulitis-free islets.

Development
Prkdc^{scid} occurred spontaneously in a colony of BALB/c-*Igh*^{b} (C.B-17) mice maintained at the Institute for Cancer Research in Philadelphia, PA. The *Prkdc*^{scid} mutation was backcrossed onto the NOD/ShiLtSz background as follows: an NOD/ShiLtSz female was bred to a C.B-17-*Prkdc*^{scid} male; male *Prkdc*^{scid}/+ offspring of the F1/N1 and subsequent generations were mated to NOD/ShiLt females for a total of 10 crosses to NOD/ShiLtSz; at generation N10, *Prkdc*^{scid} was made homozygous by brother-sister inbreeding.

►Then the IL2rg defect was bred in to yield NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ

Appearance
albino

Related Genotype: *A/A Tyr*^{c}/*Tyr*^{c}

Description
The NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ mice, commonly known as NOD scid gamma (NSG), do not express the *Prkdc* gene nor the X-linked *Il2rg* gene. NSG mice are viable, fertile, normal in size and do not display any gross physical or behavioral abnormalities. Histological examination of lymphoid tissues reveals absence of lymphoid cells and some cystic structures in the thymus, an absence of follicles in the spleen and markedly diminished celluarity of lymph nodes. NSG mice are deficient in mature lymphocytes, serum Ig is not detectable and natural killer (NK) cell cytotoxic activity is extremely low. These mice are resistant to lymphoma development even after sublethal irradiation treatment. These mutant mice have been shown to readily support engraftment of human CD34^{+} hematopoietic stem cells and represent a superior, long-lived model suitable for studies employing xenotransplantation strategies. Please note that the NSG carries the true null interleukin-2 receptor gamma chain mutation and should not be confused with other strains that express a truncated interleukin-2 receptor gamma chain as described in: "Modulation of hematopoiesis in mice with a truncated mutant of the interleukin-2 receptor gamma chain" Ohbo K *et al. Blood* 1996. 87:956-67.

View Jackson Lab's Resources for the NSG mouse model, including discussion forum, immunodeficient model comparison, and categorized, up-to-date references.

Development
These double mutant mice were produced by breeding female NOD.CB17-*Prkdc*^{scid}/J (Stock No. 001303) mice with male mice bearing the X-linked B6.129S4-*Il2rg*^{tm1Wjl}/J allele (Stock No. 003174). The resulting male mice heterozygous for the *Prkdc*^{scid} allele and hemizygous for the *Il2rg*^{tm1Wjl} allele were crossed to female NOD.CB17-*Prkdc*^{scid}/J (Stock No. 001303) mice for eight generations. Heterozygotes were interbred to produce mice homozygous for the *Prkdc*^{scid} allele and homozygous (females) or hemizygous (males) for the *Il2rg*^{tm1Wjl} allele.