

# Type 2 Diabetic Model

Rat Model with Severe Diabetic Ocular Complications

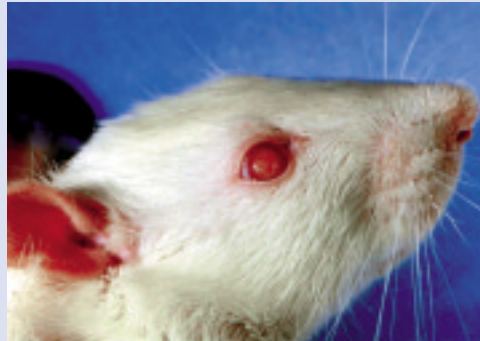
## SDT/Jcl Rats



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## SdT/Jcl Rats



### Background and Origin <sup>1)</sup>

In 1988, twelve-month-old male rats that exhibited polydipsia, polyphagia, polyuria, and glucosuria were found in Sprague-Dawley rats by Shinohara at the Research Laboratories of Torii Pharmaceutical Co., Ltd., Japan. They were mated with normal female rats of the same strain to maintain the disease symptoms and in 1991 several rats were found to exhibit positive urinary glucose earlier (at four to five months of age). An inbred strain of a non-obese type 2 diabetic model was established by repeating this sister-brother mating and the animals obtained were named the Spontaneously Diabetic Torii (SDT) rats in 1997. The SDT rats have diabetic ocular complications such as cataracts, proliferative retinopathy, and neovascularized glaucoma, after exhibiting the primary symptoms of diabetes. Therefore, they are expected to be especially useful for research on diabetic complications and drug development for diabetes. CLEA Japan obtained the strain at F24 from Torii Pharmaceutical Research Laboratories in 1998 and started to distribute the animals as SDT/Jcl rats from 2005 (F47 as of April, 2005).

\*Cover photograph: Appearance of a diabetic male SDT rat ages 35 weeks.

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# SDT/Jcl Rats

## Onset of Diabetes and Clinical Characteristics of SDT rats<sup>1)</sup>

There are sex differences in the onset of diabetes (urinary glucose is 3+ or higher) in SDT rats; glucosuria appears as early as 20 weeks of age and the cumulative incidence of diabetes is 100% at 40 weeks of age in male rats, whereas the symptoms appear after 45 weeks of age and cumulative incidence is only 33% at 65 weeks of age in female rats (Figure-1). The survival rate up to 65 weeks of age is 93% in the male rats and 97% in the female rats. Both the male and female rats can survive with hyperglycemia for a long term without insulin treatment. The male rats start showing hyperglycemia after 20 weeks of age and the blood glucose level reaches 700mg/dl or more at 30 weeks of age (Figure-2). They exhibit hypoinsulinemia by 25 weeks of age and hyperlipidemia with hypertriglyceridemia, as well as increased urea nitrogen, urinary protein excretion, and glycohemoglobin, by 35 weeks of age.

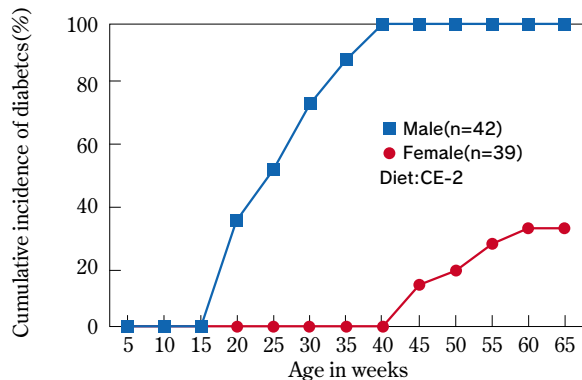


Figure-1. Cumulative incidence of diabetes in SDT rats

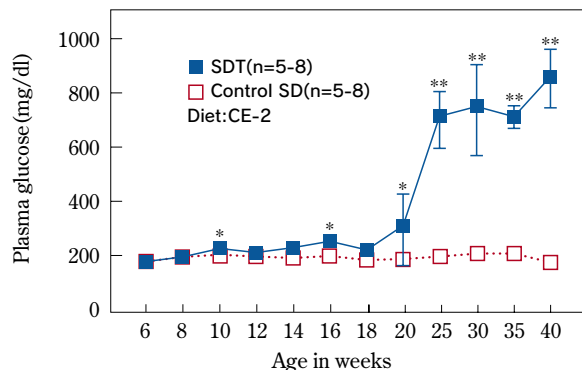


Figure-2. Plasma glucose levels of male SDT rats in non-fasting period (\* $P < 0.05$ , \*\* $P < 0.01$ )

## Body Weight and Body Mass Index (BMI)<sup>1, 2, 4)</sup>

No obesity is observed in male SDT rats and they lose weight after the onset of diabetes (Figure-3). BMI is also lower than that of control rats. And also, no obesity is observed in the female rats.

## Oral Glucose Tolerance Test (OGTT)<sup>1, 2, 4, 5)</sup>

Slight glucose tolerance is first noted in SDT male rats when 12 weeks of age. When 16 weeks of age, the fasting plasma glucose levels in male SDT rats were similar to those in control SD rats. However, the plasma glucose levels at 30, 60 and 120 min after glucose administration in male SDT rats (16w) were significantly ( $P < 0.01$ ) increased compared with those in control SD rats, indicating marked glucose tolerance induced in male 16-week-old SDT rats (Figure-4). In female SDT rats, significant glucose tolerance is observed at 25 weeks of age.

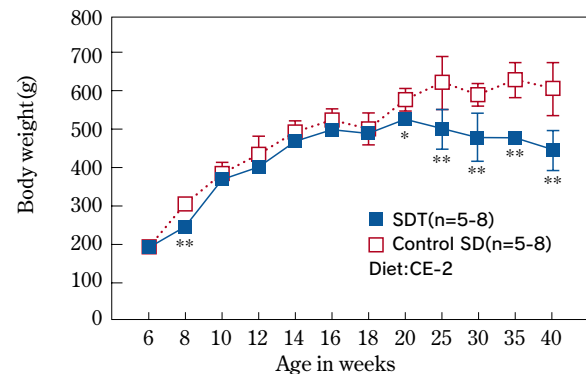


Figure-3. Body weight curves of male SDT rats (\* $P < 0.05$ , \*\* $P < 0.01$ )

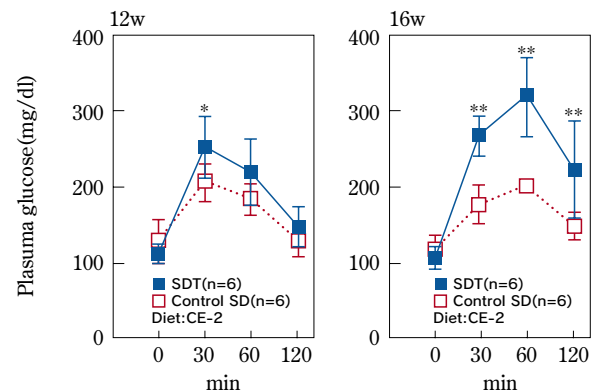


Figure-4. Plasma glucose levels of male SDT rats (12 weeks of age, 16 weeks of age) from OGTT (\* $P < 0.05$ , \*\* $P < 0.01$ )

## Genetic Analysis<sup>3)</sup>

Mating experiments using SDT rats and BN rats (non-diabetic strain) and quantitative trait loci (QTL) analysis using backcrossed offspring (N2) obtained from (BN×SDT)F1×SDT crossing were performed. QTL (*Gisd1*), which is strongly linked to glucose tolerance and weight control, was found on chromosome 1, and QTL (*Gisd2*) and QTL (*Gisd3*), which are strongly linked to glucose tolerance, were found on both chromosome 2 and chromosome X. Furthermore, the onset of diabetes and impaired glucose tolerance of SDT rats is confirmed to be governed by a recessive gene characteristics since a synergistic effect between these three QTLs were found in impaired glucose tolerance.

## Histopathological Examinations of the Pancreas<sup>1, 2, 4, 5)</sup>

Inflammatory cell infiltration probably due to hemorrhaging from capillary vessels in the pancreatic islets and fibrous tissue proliferation are observed in male SDT rats before the onset of diabetes (10 to 20 weeks of age). At around 25 weeks of age, further fibrous tissue proliferation in and around the pancreatic islets and hemosiderin deposition are observed (Figure-5). After 40 weeks of age, the size and number of pancreatic islets are decreased and the islets are partially replaced with connective tissue. Female SDT rats also show similar lesions in the pancreas on and after 16 weeks of age.

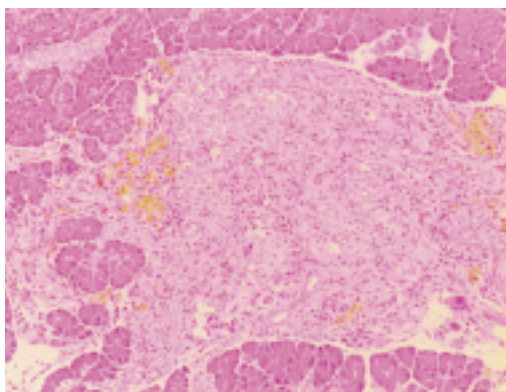


Figure-5.  
Histopathological findings of the pancreas of a male SDT rat (25 weeks of age)

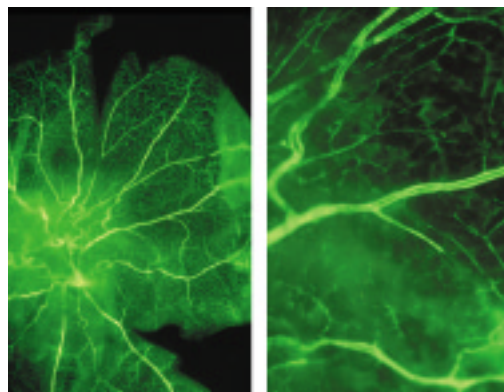


Figure-7.  
Fluorescein angiography findings of the ocular fundus of a male SDT rat (58 weeks of age)

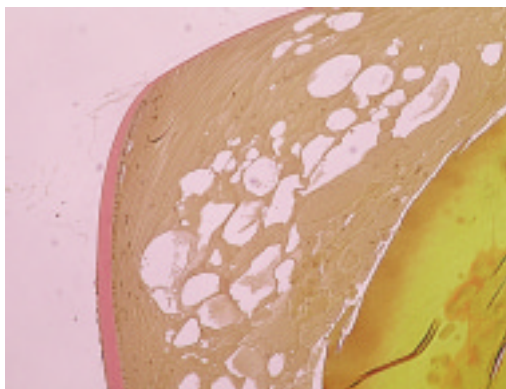


Figure-6.  
Histopathological findings of the lens of a male SDT rat (40 weeks of age)

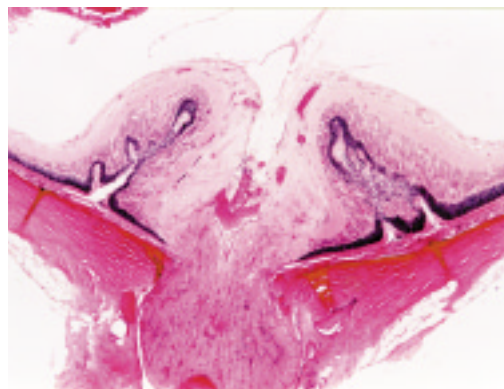


Figure-8.  
Histopathological findings of the retina of a male SDT rat (70 weeks of age)

## Diabetic Ocular Complications<sup>1, 6, 7, 8, 9)</sup>

[Cataracts] Male SDT rats have cataracts on and after 40 weeks of age. Histopathologic changes such as swelling, liquefaction, vacuolation, and disintegration of the lens fibers, and formation of Morgani's globules are observed (Figure-6).

[Retinopathy] In contrast to the development of retinopathy in humans, microaneurysms are rarely observed in capillary vessels in SDT rats. However, male SDT rats (55 weeks of age or older) have pathological changes such as narrowing of the capillary vessels, loss of pericytes, massive fluorescent leakage in fluorescent angiography of the fundus (Figure-7), thickening of the retinal capillary basement membrane, and tractional retinal detachment with fibrous proliferation in the direction of the vitreous cavity, that are similar to human proliferative diabetic retinopathy (Figure-8).

[Neovascular glaucoma (hemorrhagic glaucoma)] Some of the male SDT rats with advanced retinopathy after 77 weeks of age have hemorrhages in the anterior chamber of the eye. This hemorrhaging is associated with fibrous proliferation around the iris (Figure-9).

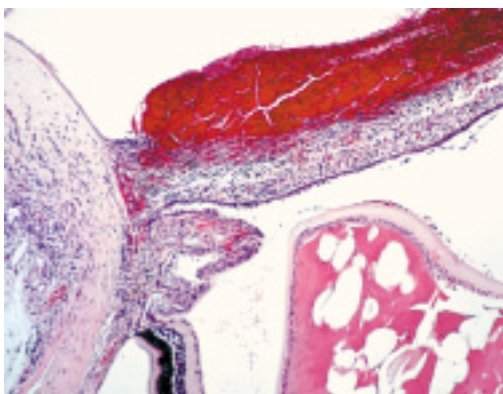


Figure-9.  
Histopathological findings of the iris and surrounding area of a male SDT rat (77 weeks of age)

## References

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### Notes on rearing and handling SDT rats

#### ● Diet and drinking water

In SDT rats, glucosuria appears on ingestion of standard diet for mice and rats. Their diet intake increases (about 1.5 to 2 times that of SD strain rats) and water intake also significantly increases (200 to 400 ml/day and more) with the onset of diabetes. It is, therefore, important to always have sufficient amounts of diet and drinking water.

#### ● Frequent change of bedding and cleaning of cages are recommended

The SDT rats urinate a lot and their bedding easily becomes dirty after onset of diabetes. Therefore, they can easily develop urinary tract infections. In order to avoid such infections, each rat should be reared alone and a large amount of bedding, with frequent replacement, should be used with plastic cage rearing. It is also recommended to change bedding frequently with bracket cage rearing.



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