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Anomalous (Preduodenal) Portal Vein: Autosomal Recessive Mutation in AKR/J Mice

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Background and Purpose: **Anomalous (preduodenal) portal vein was found in AKR/J mice. It is a rare congenital malformation in humans, and to the authors' knowledge, has never been reported in laboratory animals. Morphology, clinical signs of disease, and heritability of this anomaly were examined.**

Methods: **Fifty-three strains of inbred mice (6,026 mice) in our mouse colony were examined for preduodenal portal vein and its association with clinical signs of disease (vomiting or abdominal pain) and other anomalies. Heritability also was tested by use of cross-backcross matings of AKR/J mice with clinically normal PT mice.**

Results: **The portal vein was found at the ventral side of the duodenum in most (98%) AKR/J mice, whereas it ran at the dorsal side of the duodenum in 52 other inbred mouse strains in our mouse colony. Clinical signs of disease and other congenital anomalies were not detected in this strain of mice, although position has a high association with other congenital anomalies in humans. Heritability testing of this anomaly in AKR/J mice indicated single autosomal recessive inheritance.**

Conclusions: **Preduodenal portal vein found in AKR/J mice is a single autosomal recessive mutation, but is not associated with clinical signs of disease and other congenital malformations.**

The preduodenal portal vein, which runs at the ventral side of the duodenum is a rare congenital anomaly in humans. The theory to account for development of a preduodenal portal vein was put forth by His in 1885 (1), and an example of this anomaly in a pig embryo was reported by Begg in 1912 (2). The first case report in humans was made by Knight in 1921 (3), who found this anomaly in a dissecting-room cadaver. Since then, many cases have been reported in children and adults, as well as during surgery (4-6). It is found sporadically during investigations of epigastric pain or other symptoms, such as vomiting or jaundice. This anomaly has high association with other congenital anomalies, such as malrotation; situs inversus; pancreatic, duodenal, biliary system, and splenic anomalies; and dextrocardia. However, to the authors' knowledge, heritability of this anomaly is unknown.

In experimental animals, the authors first found this anomaly in the inbred mouse strain AKR/J. In the study reported here, preduodenal portal vein and its association with clinical signs of disease and other congenital anomalies were examined in AKR/J and 52 inbred strains of mice maintained in our department, and heritability of preduodenal portal vein also was examined.

Materials and Methods

Animals: Pedigreed mouse strain AKR/J at F_{164} was provided by the Jackson Laboratory, Bar Harbor, Maine in 1985. A tester stock of mouse strain PT which has seven recessive marker genes (*a; b; p, c^{ch}; d*, *se; s*) on chromosomes 2, 4, 7, 9, and 14 was also kindly provided to T. Nomura by Drs. M. F. Lyon and A. G. Searle of Medical Research Council, Harwell, UK in 1978. The other 51 pedigreed strains of mice (Table 1) studied were derived from stocks originating at other sites between 1978 and 1987.

All mouse stocks maintained in the Department of Radiation Biology were examined every day and were euthanatized by rapid CO_2 inhalation at about 12 months of age, except for mice used for life-span and short-term experiments. All dead or euthanatized mice were necropsied and doubly examined independently by two pathologists, and macroscopic lesions were submit-

Table 1. Frequency of preduodenal portal vein and associated anomalies and signs of disease in various inbred mouse strains necropsied from October 1993 to December 1995 in the Department of Radiation Biology

Strains	Generation	No. of mice	Preduodenal portal vein (%)	Other anomalies (%)*	Vomiting** (%)
AKR /J	$F_{188\sim192}$	49***	48 (98.0)	0	0
RSV/Le	$F_{86\sim96}$	89	3 (3.4)	0	0
C57BL/6J-*fz*	$N_7F_{14\sim20}$	44	1 (2.3)	0	0
C3H/HeJ	$F_{195\sim204}$	136	0	0	0
C3H/HeJ-*md*	$F_{147\sim155}$	48	0	0	0
C3HeB/FeJ-*a/a*	$N_7F_{79\sim89}$	54	0	0	0
C57BL/6J	$F_{161\sim165}$	110	0	0	0
C.B17	$F_{38+21\sim+29}$	343	0	0	0
CL/Fr	$F_{40+33\sim+43}$	66	0	0	0
DBA/2J	$F_{179\sim185}$	37	0	0	0
HRS/J	$F_{94\sim98}$	120	0	0	0
HT	$F_{27\sim30}$	103	0	0	0
LT/Sv-3	$F_{131\sim137}$	115	0	16 (13.9)	0
MSM/MS	$F_{46+2\sim+6}$	255	0	0	0
MWT/Le	$F_{100\sim106}$	47	0	0	0
N5	$F_{43\sim46}$	221	0	0	0
PT	$F_{38\sim43}$	95	0	0	0
STX/Le	$F_{81\sim88}$	190*	0	0	60 (31.6)
101/H	$F_{28\sim33}$	119*	0	1 (0.8)	44 (37.0)
BXH-8	$F_{84\sim90}$	88	0	0	79 (89.9)
Others+		3697	0	2 (0.05)	0

*Renal anomalies (13 cystic kidneys and 3 hemirenal defects) in LT/sv-3 mice, hypogenesis of left atrium and ventricle in 101/H mice, cystic kidney in C57BL/6J-p^{un} mice, and hydrocephaly in BXH/11 mice.
Some anomalies observed sporadically in mice (*e.g.*, imperforate hymen and kinky tail) were not included.
** All vomiting mice had large esophageal dilatation.
*** 38 AKR/J mice died of thymic lymphoma within the age of 12 months.
+ BALB/cByJ, BXH-2, BXH-3, BXH-4. BXH-6, BXH-7, BXH-9, BXH-10, BXH-11, BXH-12, BXH-14, BXH-19, C3-101-A^W/A-*Ta/O*, C.B17-*scid*, C3H/HeJ-*scid*, C57BL/6J-*scid*, C57BL/6J-*bg^J-scid*, C57BL/6J-PL-*thy-1^a/Cy*, C57BL/6J-*bg^J*, C57BL/6J-*b*, C57BL/6J-*c^{ch}*, C57BL/6J-*dse*, C57BL/6J-*p*, C57BL/6J-*pa*, C57BL/6J-*pe*, C57BL/6J-p^{un}, C57BL/6J-p^{un}/ *, C57BL/6J-*s*, C57BL/10J, Mus spretus, N5/3513, N5/3566, and RF/J mice.

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ted for pathologic examination. Although the preduodenal portal vein was described in the necropsy records of AKR/J and a few strains in our mouse colony, we were unaware of this congenital anomaly in humans until 1993. Consequently, an examination of morphology and clinical signs of disease, especially vomiting, abdominal pain, or jaundice, was carried out carefully in AKR/J ($F_{188-192}$) and 52 other mouse strains (Table 1) during the same period, from 1993 to 1995, to avoid unexpected bias.

All mice were maintained by brother-sister inbreeding under complete barrier (specific-pathogen-free [SPF]) husbandry, with lights on from 4 AM to 6 PM at 23 ± 1°C and 50 to 70% humidity. Mice were fed autoclaved mouse diet CRF-1 (Charles River Japan, Kanagawa, Japan), and acidified, chlorinated, filtered (by Millipore) water was available ad libitum. All animal experiments were carried out in the barrier section of the Institute of Experimental Animal Sciences, Osaka University, following the Osaka University Guidelines for Animal Experimentation.

Examination for clinical signs of disease: To find the vomiting mice, pastes of vomited foods on the cage wall were examined every day, because it is commonly observed on the cage wall of a mouse with esophageal dilatation (achalasia) (7). To detect abdominal pain, mice were examined carefully to see whether they had spontaneous abdominal constrictions similar to those associated with acetic acid-induced abdominal constriction (writhing) test (8).

Heritability testing: To analyze the inheritance of preduodenal portal vein, male and female AKR/J (12 weeks old, weighing 24 to 25 g) were mated with female and male PT mice (12 weeks old, weighing 23 to 26 g), respectively. The F_1 mice derived from PT and AKR/J parents were back-crossed to AKR/J mice, and their progeny were necropsied at 3 to 4 weeks of age to examine the anomaly. The F_1 mice and their parents also were euthanatized to examine the portal vein anomaly.

Analysis of data: Statistical analysis was carried out by use of the SPSS system (SPSS Inc., Chicago, Ill.).

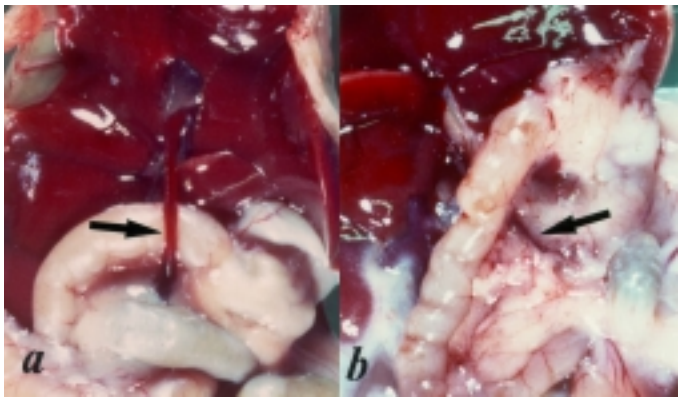

Figure 1. Preduodenal portal vein in AKR/J mouse (a) and normal portal vein in PT mouse (b). Arrows indicate portal veins.

Results

In 48 of 49 AKR/J mice (98%), the portal vein was found at the ventral side of the duodenum (Fig. 1a), whereas it was observed at the dorsal side of the duodenum (Fig. 1b) in PT and 51 other inbred mouse strains in our mouse colony, with a few exceptions in RSV/Le and C57BL/6J-*fz* mice (Table 1). In RSV/Le mice, anomalous preduodenal portal vein was found in 2 of 38 RSV/Le-*Va*/+ (circling) mice, and one was found in 51 RSV- +/+ (non-circling) mice. The difference was not significant ($P = 0.39$, by use of Fisher's exact test). Types of congenital malformations associated with preduodenal portal vein in humans were not detected in AKR/J mice, whereas renal, cardiac, and cerebral anomalies were found in other strains (Table 1). Clinical signs of disease (vomiting, abdominal pain, or jaundice) were not detected in AKR/J mice; however, vomiting was observed in HT, 101/H, STX/Le and BXH-8 mice, which developed large esophageal dilatation.

All but one of 21 F_1 animals of AKR/J and PT had normal portal vein location, irrespective of the sex of their parents (Table 2), indicating autosomal recessive inheritance. Among 20 litters derived from the back cross of (PT × AKR) F_1 to AKR/J, 89 of 183 progeny (48.6 %) had preduodenal portal vein, while 94 had a normal portal vein position. The segregation ratio of abnormal to normal portal vein position indicates that this anomaly is determined by a single autsomal recessive gene. Although data are not shown, chromosomal linkage was not detected by the mating with a tester strain PT.

Discussion

In humans, the preduodenal portal vein has high association with other congenital anomalies, such as malrotation; situs inversus; pancreatic, duodenal, biliary system, and splenic anomalies; and dextrocardia (4-6). In contrast, these anomalies were not associated in AKR/J and other inbred strains of mice. Only one cardiac anomaly was observed during the experimental period from 1993 to 1995 (Table 1). Even in the historical necropsy records from 1978 to 1999 in our Department, we found situs inversus in 3 of 3,646 N5 and one of 231 BXH-14 mice, cardiac anomaly (double outlet) in one of 625 BXH-6 mice, biliary system anomaly (choledochal cyst showing jaundice) in one of 1570 LT/Sv mice, and Meckel's diverticulum in one of 631 C3HeR/FeJ-*a*/*a* and one of 525 C57BL/6J-*p*

Table 2. Frequency of preduodenal and normal portal veins in AKR/J, PT, their F_1, and progeny of [PT × AKR] F_1 × AKR mice

Parents and their progeny	No. of mice	Male	Female	Preduodenal position			Normal position		
				Total (%)	Male (%)	Female (%)	Total (%)	Male (%)	Female (%)
AKR /J	49 (10)*	25	24	48 (98.0)	24 (96.0)	24 (100)	1 (2.0)	1 (4.0)	0 (0.0)
PT	95 (20)	46	49	0 (0.0)	0 (0.0)	0 (0.00)	95 (100)	46 (100)	49 (100)
PT × AKR] F_1	7 (1)	3	4	0 (0.0)	0 (0.0)	0 (0.00)	7 (100)	3 (100)	4 (100)
[AKR × PT] F_1	14 (3)	9	5	1 (7.1)	1 (11.1)	0 (0.0)	13 (92.9)	8 (88.9)	5 (100)
Progeny of [PT × AKR] F_1 × AKR/J	183 (20)	88	95	89 (48.6)	37 (42.0)	52 (54.7)	94 (51.40)	51 (58.0)	43 (45.3)

*Numbers in parentheses indicate litter numbers.

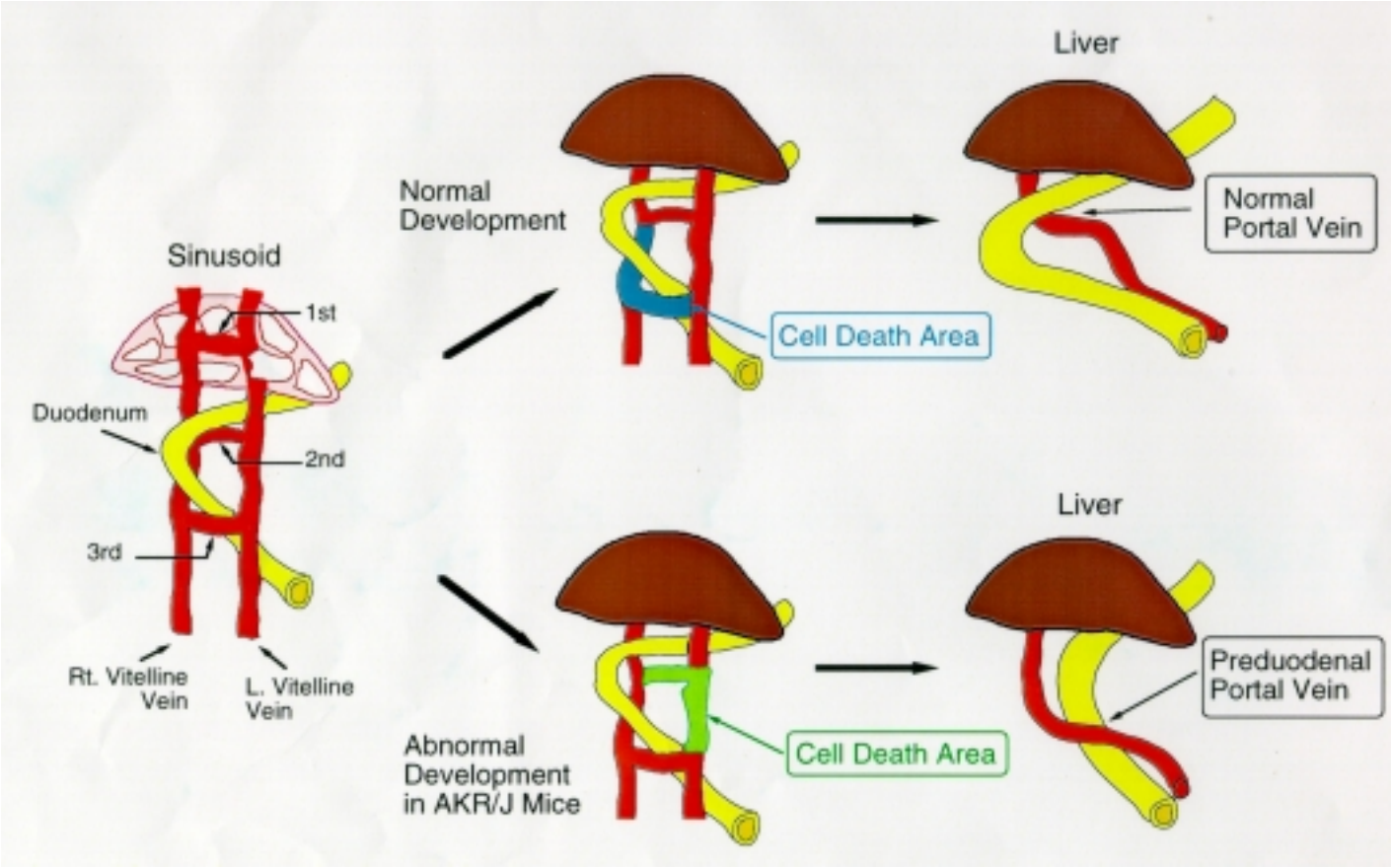

Figure 2. Scheme for the development of normal and anomalous (preduodenal) portal vein.

mice. Consequently, AKR/J mice specifically develop preduodenal portal vein.

Heritability analysis (Table 2) indicated single autosomal recessive inheritance of the preduodenal portal vein in AKR/J mice. In humans, however, it seems too rare to determine exact heritability.

The developmental mechanism of the preduodenal portal vein has been described by several investigators (1, 4, 9). The duodenum runs between the first and second and between the second and third bridges of right and left vitellin veins in the early-stage human embryo (5 weeks) (Fig. 2; left). From 6 to 10 weeks of embryonic age, the third bridge and a part of the right vitelline vein are programmed to disappear (Fig. 2; upper middle, blue color) and normal portal vein develops. On the other hand, the second bridge and a part of left vitelline vein (Fig. 2; lower middle, green color) disappear instead of the third bridge and right vitelline vein in affected humans and AKR/J mice, and the anomalous (preduodenal) portal vein develops. The developmental anomaly of the portal vein in AKR/J mice may be caused by the difference in the area of the vitelline and bridging veins, which is destined to die genetically. Recently, it was reported that some knockout mice develop asymmetric defects (10, 11) with pathologic changes similar to the congenital malformations associated with the preduodenal portal vein in humans. Though association with preduodenal portal vein has not been reported, a similar mechanism might be involved at the molecular level.

Acknowledgments

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