

## Possible Japanese Racial Predisposition for Particular Tumors in Edwards Syndrome

Motoi Nishi

Motoi Nishi, Department of Fundamental Health Sciences, Health Sciences University of Hokkaido, 061-0293 Tobetsu 1757, Hokkaido, Japan

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Correspondence to: Motoi Nishi, Department of Fundamental Health Sciences, Health Sciences University of Hokkaido, 061-0293 Tobetsu 1757, Hokkaido, Japan.

Email: [motoi@hoku-iryo-u.ac.jp](mailto:motoi@hoku-iryo-u.ac.jp)

Telephone: +81-(0)133-23-1211

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### ABSTRACT

It is known that a case with trisomy 18 (T18) develops hepatoblastoma (HB) or Wilms tumor (WT). But are there any differences among districts in the frequency of developing them? In this report, based on articles and abstracts, frequency of HB is compared between Japan and the USA. Using key words of "T18", "HB", "WT", "leukemia", etc., articles and abstracts reporting cases with T18 and malignant neoplasms were gathered from the Pubmed as well as the Iqaku Chuo Zassi (Japanese Central Journal of Medicine), which is a searching tool for medical articles written in Japanese and English. In Japan, a total of 21 cases with HB and only 1 case with WT were reported. In the USA, however, 5 cases with HB and 8 cases with WT in T18 cases were reported. Long survival periods lead to increased chances to develop HB. Infant mortality of Japan is the lowest in the world, being less than half of that of the USA. Several authors reported survival rates of T18 cases in general. Survival rates of Japanese cases were longer than those in western countries. The general incidence of WT in Japan is about half of that in the USA. These facts might partially explain why HB cases are frequent and WT ones are less frequent in T18 cases in Japan. Considering the number of live births of the USA and that of

Japan, the frequency of HB cases in Japan is too high to be explained only by publication bias. There may be some racial differences that promote HB and suppress WT in Japanese T18 cases.

**Key words:** Edwards syndrome; Hepatoblastoma; Japan; USA; Wilms tumor

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### INTRODUCTION

Congenital chromosomal disorders are sometimes accompanied by malignant diseases. For example, it is well known that persons with Down syndrome have an increased risk of leukemia. Employing articles and abstracts, we reported a tumor profile in those with Edwards syndrome, or trisomy 18 (T18), and they are at high risk for several malignant tumors such as hepatoblastoma (HB) or Wilms tumor (WT), etc<sup>[1]</sup>. At the same time, however, it was noted that there were regional differences (Japan vs the USA) in the frequency of developing them.

The mortalities of adulthood malignancies (gastric cancer, breast cancer, etc.) are different between Japan and the USA<sup>[2]</sup>. These differences seem to be dependent mainly on the differences in lifestyle, but part of them might be attributable to racial factors. In this report, based on these articles and abstracts, the frequencies of HB in Japan and the USA are compared.

### NUMBER OF CASES REPORTED

In this article, the same references employed in our previous article<sup>[1]</sup> are used. Using the key words "trisomy 18", "malignancy", "hepatoblastoma", "Wilms tumor", "leukemia", "neuroblastoma", and so on, articles and abstracts reporting patients with trisomy 18 and malignant neoplasms were gathered from "Pubmed" and

“*Igaku Chuo Zasshi* (Japanese Central Journal of Medicine)”, which is a search tool for medical articles written in Japanese and English without limitation of date.

In Japan, a total of 7 cases with HB were reported in journal articles<sup>[3-15]</sup>. Among them, there are 2 mosaic cases. In congress abstracts a total of 14 cases were reported<sup>[16-33]</sup> (Table 1; these 14 cases are arranged according to our previous report<sup>[1]</sup>). Among them there are no mosaic cases, and many females. In summary, a total of 21 cases with HB were reported in Japan. Since only one leukemia case<sup>[34]</sup> and one case with WT<sup>[35]</sup> were reported (Table 2), HB accounts for most of the malignancies in those with T18 in Japan.

In the USA, 5 cases of HB in persons with T18 were reported in journal articles<sup>[36-40]</sup> (Table 3), and 8 cases of WT<sup>[41-46]</sup> were reported (Table 4). The case reported in Slovenia<sup>[47]</sup> and the 2 cases reported in Singapore<sup>[48]</sup> were excluded, since they belonged neither to Japan nor to the USA.

“Pubmed” does not include abstracts alone. But even when the numbers of journal articles are compared, Japanese with T18 develop HB more frequently than WT (Table 5).

## FACTORS SHOWING NO LARGE DIFFERENCE BETWEEN THE CASES OF JAPAN AND THE USA

The distribution of age at diagnosis of both groups is similar. Most of them were discovered at 0 or 1 year of age (18 out of the 21 cases in Japan and 3/5 in the USA; Table 6;  $p > 0.10$ , chi-square test).

In the HB cases of Japan and those of the USA, there are several factors showing no large difference. There are more female cases both in Japan (17/21) and in the USA (4/5) (Table 7;  $p > 0.10$ , chi-square test).

There are only a small number of cases whose clinical stage of HB was confirmed, but no large difference was found in this, either (Table 8).

## GENERAL SURVIVAL RATES OF PATIENTS WITH T18

What are the general survival rates of patients with T18? Several authors have reported them and, evidently, the 1-year-survival rates for Japanese (6-25%)<sup>[49-51]</sup> are longer than those for westerners (4-8%)<sup>[52-54]</sup> (Table 9). Six-month-survival rates of Japanese cases are longer, too (12-50% vs 5-9%; Table 10). One-month-survival rates of Japanese patients are longer, as well (39-83% vs 11-39%; Table 11). There may be a tendency for many patients with T18 in western countries to die within a short period of time after their birth.

## INFANT MORTALITY

There is a difference in infant mortality between Japan and the USA. The present infant mortality of Japan is the lowest in the world (2.3 per 1,000 live births), being less than half of that of the USA (6.1)<sup>[55]</sup> (Table 12). This might lead to the high survival rates of patients with T18, and long survival leads to increased chances to develop HB. That is, the low infant mortality rate might be one of the factors that explain why HB is frequent in Japanese T18 cases.

## WILMS TUMOR

Then, why do Japanese T18 cases rarely develop WT? Are there any differences in the general incidences of WT?

**Table 1** Reported T18 cases with HB in Japan.

| Year                         | Author(first) | Karyotype     | Sex |
|------------------------------|---------------|---------------|-----|
| Journal articles (7 cases)   |               |               |     |
| 1983                         | Abe           | 47XX+18       | F   |
| 1992                         | Tanaka        | 47XX+18, 46XX | F   |
| 1992                         | Ariwa         | 47XX+18       | F   |
| 1997                         | Hamada        | 47XX+18       | F   |
| 2001                         | Maruyama      | 47XX+18       | F   |
| 2004                         | Takahashi     | 47XX+18,46XX  | F   |
| 2012                         | Uekusa        | 47XY+18       | M   |
| Congress abstracts (14cases) |               |               |     |
| 1999                         | Yokoyama      | 47XX+18       | F   |
| 1999                         | Suzuki,R      | 47XX+18       | F   |
| 1999                         | Hino          | 47XY+18       | M   |
| 2000                         | Uemura        | 47XX+18       | F   |
| 2000                         | Matsuoka      | 47XX+18       | F   |
| 2000                         | Nishimura     | 47XX+18       | F   |
| 2004                         | Takagi        | 47X?+18       | ?   |
| 2004                         | Ito           | 47XX+18       | F   |
| 2006                         | Watanabe      | 47XX+18       | F   |
| 2006                         | Nishi         | 47XX+18       | F   |
| 2006                         | Ogawa         | 47XX+18       | F   |
| 2009                         | Ishibashi     | 47XX+18       | F   |
| 2009                         | Kunitaka      | 47X?+18       | ?   |
| 2012                         | Sugitate      | 47XX+18       | F   |

**Table 2** Reported T18 cases with leukemia or WT in Japan.

| Year | Author(first) | Karyotype     | Sex | Malignancy |
|------|---------------|---------------|-----|------------|
| 2005 | Tateishi      | 47XX+18       | F   | leukemia   |
| 1992 | Suzuki, Y     | 47XY+18, 46XY | M   | WT         |

**Table 3** Reported T18 cases with HB in the USA (journal articles).

| Year | Author(first) | Karyotype    | Sex |
|------|---------------|--------------|-----|
| 1987 | Dasouski      | 47XX+18      | F   |
| 1989 | Mamlök        | 47XX+18      | F   |
| 1996 | Bove          | 47XX+18      | F   |
| 2011 | Fernandez     | 47XY+18,46XY | M   |
| 2012 | Pereira       | 47XX+18,46XX | F   |

**Table 4** Reported T18 cases with WT in the USA (journal articles).

| Year | Author(first) | Karyotype | Sex |
|------|---------------|-----------|-----|
| 1969 | Geiser        | 47XX+18   | M   |
| 1981 | Karayalcin    | 47XY+18   | F   |
| 1990 | Sheng         | 47XX+18   | M   |
| 1995 | Olson         | 47XX+18   | F   |
|      |               | 47XX+18   | F   |
|      |               | 47XX+18   | F   |
|      |               | 47XX+18   | F   |
| 2003 | Anderson      | 47XX+18   | F   |

**Table 5** Number of HB and WT in the T18 cases.

| Region | HB     | WT    |
|--------|--------|-------|
| Japan  | 21(7*) | 1(0*) |
| USA    | 5      | 8     |

\*Number of cases reported in journal articles.

**Table 6** Age at diagnosis of HB in the T18 cases.

| Age (year) | Japan | USA |
|------------|-------|-----|
| 0          | 16    | 2   |
| 1          | 2     | 1   |
| 2          | 2     | 1   |
| 10         | 0     | 1   |
| Unknown    | 1     | 0   |
| Total      | 21    | 5   |

**Table 7** Number of males and females in the T18 cases with HB.

| Sex     | Japan | USA |
|---------|-------|-----|
| Male    | 2     | 1   |
| Female  | 17    | 4   |
| Unknown | 2     | 0   |

**Table 8** Clinical stage of HB in the T18 cases

| Stage | Japan | USA |
|-------|-------|-----|
| I     | 3     | 2   |
| II    | 1     | 0   |
| III   | 1     | 0   |
| IV    | 1(?)  | 1   |

**Table 9** 1-year-survival rates of T18.

| Author(first)     | Area       | Period    | n   | rate |
|-------------------|------------|-----------|-----|------|
| Japan             |            |           |     |      |
| Kosho             | Nagano     | 1994-2003 | 24  | 25%  |
| Kondo             | Nagoya     | 2000-2009 | 77  | 19%  |
| Imataka           | Japan      | 1997-2003 | 179 | 9%   |
| Iwami             | Osaka      | 1994-2004 | 18  | 6%   |
| Iwami             | Osaka      | 2004-2009 | 12  | 17%  |
| Western countries |            |           |     |      |
| Rasmussen         | Atlanta    | 1968-1999 | 114 | 8%   |
| Root              | Utah       | 1979-1988 | 64  | 5%   |
| Carter            | Queensland | -1985     | 43  | 4%   |

**Table 10** 6-month-survival rates of T18.

| Author(first)     | Area       | Period    | n   | rate |
|-------------------|------------|-----------|-----|------|
| Japan             |            |           |     |      |
| Imataka           | Japan      | 1997-2003 | 179 | 18%  |
| Iwami             | Osaka      | 1994-2004 | 18  | 12%  |
| Iwami             | Osaka      | 2004-2009 | 12  | 50%  |
| Western countries |            |           |     |      |
| Root              | Utah       | 1979-1988 | 64  | 9%   |
| Carter            | Queensland | -1985     | 43  | 5%   |

**Table 11** 1-month-survival rates of T18.

| Author(first)     | Area    | Period    | n   | rate |
|-------------------|---------|-----------|-----|------|
| Japan             |         |           |     |      |
| Kosho             | Nagano  | 1994-2003 | 24  | 83%  |
| Kondo             | Nagoya  | 2000-2009 | 77  | 67%  |
| Imataka           | Japan   | 1997-2003 | 179 | 44%  |
| Iwami             | Osaka   | 1994-2004 | 18  | 39%  |
| Iwami             | Osaka   | 2004-2009 | 12  | 83%  |
| Western countries |         |           |     |      |
| Rasmussen         | Atlanta | 1968-1999 | 114 | 39%  |

**Table 12** Infant mortality (per 1,000 live births).

| Region | 1990 | 2010 |
|--------|------|------|
| Japan  | 4.6  | 2.3  |
| USA    | 9.2  | 6.1  |

**Table 13** Annual incidence of WT based on Registries

| Area     | Incidence |
|----------|-----------|
| Hokkaido | 3.1       |
| USA      | 7.6       |

Hokkaido Prefecture is the northernmost main island of Japan. Since 1969, a nationwide program of childhood cancer registration (the Japan Children’s Cancer Registry) has been conducted<sup>[56]</sup>. The Hokkaido Children’s Cancer Registry is its branch. The registration rate in Hokkaido is at least 90% because there are only 5 hospitals that can treat children’s malignancies there, and therefore registration can be done with ease. On the other hand, the rate of the Japan Children’s Cancer Registry is about 40-50%. According to the Japan Children’s Cancer Registry, from 1969 to 2014, only 5 T18 cases were registered, and all of them had HB.

The incidence of WT in Hokkaido is about 3.1 (0-14 years of age, 1969-2012, per million). But that in the USA is 7.6<sup>[57]</sup>. Thus, there is a large difference in the incidence of WT between Japan and the USA (Table 13). This difference might partly explain why there are a small number of cases with WT in T18 in Japan.

### STATISTICAL ESTIMATION BASED ON THE NUMBER OF LIVE BIRTHS

However, differences in survival rates of those with HB or the general incidences of WT cannot be the final explanation. In the USA, the number of live births in 2012 was 3,952,841 and that of Japan in 2013 was 1,029,816<sup>[58]</sup>. Therefore, its ratio is about 1: 0.25 (the USA: Japan). If there is no difference in incidence of a tumor between the 2 countries, its number in Japan is a quarter of that in the USA. Since the number of the cases with WT in Japan is 1, the expected number of the cases in the USA is 4. Because its observed number in the USA is 8, its chi-square value is 4 ( $p < 0.05$ ). On the other hand, the expected number of the cases with HB in Japan is 1.25, since the number of the cases in the USA is 5. Since the observed numbers in Japan are 7 (journal articles only) and 21 (total), its chi-square values are 26.45 ( $p < 0.01$ ) and 312.05 ( $p < 0.01$ ), respectively. Thus, in any case, the number of cases with HB in Japan is significantly large. In addition, Matsuoka<sup>[22]</sup> reported that out of 43 autopsied cases with T18, 3 ones had HB. There are likely to be some racial differences in the case of T18. For example, genes in Japanese patients with T18 might promote HB and suppress WT.

According to the previous reports concerning the tumor profile in Down’s syndrome (0-14 years of age), leukemia constituted 93% (27 cases out of 29) in Japan<sup>[59]</sup>, and 97% (31/32) in Denmark<sup>[60]</sup>. This difference is small, which brings out the high incidence of cases with HB in T18 in Japan.

### CONCLUSIONS

Between Japan and the USA, there are no large differences in the characteristics (age, sex and clinical stage) of T18 cases with HB. But the differences in frequency of HB and WT between Japan and the USA are too large to be explained only by publication bias. There

may be some racial differences that promote HB and suppress WT in Japanese T18 cases.

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**Peer reviewer:** Naveen Kumar Vishvakarma