

Wistar Han Aryl Hydrocarbon Receptor (AhR)

Background

Genetic testing has confirmed that most Wistar Han rats from Charles River either carry or are homozygous for the mutant aryl hydrocarbon receptor (AhR) allele (See Table 1). This mutation results in an altered response to dioxin and other aromatic hydrocarbons.

Table 1: Mutant allele frequencies for rat stocks and strains tested as of 7 Nov 07.

<u>Group</u>	<u># rats tested</u>	<u>Mutant allele frequency (%)</u>
Wistar Han – Charles River IGS Foundation Colony	20	45
Wistar Han – Charles River Raleigh R07	40	64
Wistar Han – Charles River France B42	10	45
Wistar Han – Charles River France B24	20	15

Information Regarding the Mutation

What is the function of the aryl hydrocarbon receptor (AhR)?

The full function of the receptor is unknown, as is the full implication of the mutation. The receptor binds many aromatic hydrocarbon xenobiotics, including dioxins. Intracellularly, receptor activation is linked to many cell functions, such as the cytochrome oxidase pathway. It has also been speculated to have a role in reproduction.

How much of the AhR function is affected by the mutation?

Unknown, but the effects seem limited. Rats homozygous for the mutant allele have a dramatically increased LD50 for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and PCDD (penta-), but not HCDD (hexa-). Overall, the tissue distribution and excretion of TCDD in rats homozygous for the AhR mutation is similar to that of the Long-Evans rat, which was used as a dioxin-sensitive control strain. Reproductive performance of the Wistar Han rat does not appear affected, nor does there appear to be any effect on lifespan. Other than alterations of some responses to dioxin, no impact has been reported since the trait (mutation) was first described in the literature in 1986.

Are other stocks/strains affected?

We have also detected the mutation, albeit at a lower frequency, in the Wistar and CD stocks. The presence of the mutation in these “old” research strains suggests that it has been present in outbred stocks for many decades. Nonetheless, the mutation has never been reported in

these strains, probably because of the previous lack of a suitable test and the low allele frequency, which means only rare animals would have an increased dioxin LD50.

What does “allele frequency” mean, and how does it predict the percentage of rats affected?

Each rat has two copies (alleles) of each gene. Allele frequency is the percentage of a particular allele out of all alleles combined (for a particular gene). For most genes, including this AhR mutation, the percentage of homozygous animals is the square of the allele frequency. Thus, with an allele frequency of 55%, approximately 30% of rats will be homozygous for the mutation and will have the increased TCDD LD50.

When did this mutation occur in the Charles River Wistar Han?

The mutation was first reported in a Wistar Han colony in Finland in 1986. Although the frequency may vary among different Wistar Han lines, the mutation should be considered part of the genetic diversity that distinguishes current Wistar Han stocks. We have no indication that any Wistar Han stocks lack this mutation.

Are there practical ways to rid affected stocks of the mutation, and if so, what’s involved and what are the risks?

Since the mutation can be identified by PCR, theoretically all homozygous and heterozygous mutants could be identified and culled. However, this would be a *de facto* genetic bottleneck, and it would be a narrow one for stocks such as the Wistar Han where most animals at least carry the mutation. Extensive SNP testing in parallel with the removal of all mutant animals could help maintain much of the current genetic diversity, but the process would potentially be expensive. In addition, it would take several years and there would be no guarantee that the resulting stock would perform the same as the current Wistar Han, which has had the mutation for decades.

What is Charles River planning to do with their Wistar Han, CD, etc?

At this time, we consider this mutation to be of limited impact, although we would like our customers to be aware of it. Given its high prevalence in the Wistar Han and the dangers associated with trying to manipulate gene frequency without affecting other traits (true for all strains), plus our obligation to the research community to provide a consistent animal model, we do not currently intend to try to reduce or eliminate the mutant allele. Discussion with researchers using these rats is important and will help guide us in future decisions.

Reference

Pohjanvirta, R., Wong, J.M.Y., Li, W., Harper, P.A., Tuomisto, J., and Okey, A.B., Point Mutation in Intron Sequence Causes Altered Carboxyl-Terminal Structure in the Aryl Hydrocarbon Receptor of the Most 2,3,7,8-Tetrachlorodibenzo-p-dioxin-Resistant Rat Strain. *Molecular Pharmacology*, 54:86–93 (1998)