The *sl* rat as a model for human Hirschsprung disease (HSCR)

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Introduction

The spotting lethal (*sl*) rat was first noted 70 years ago, occurring as a spontaneous mutation in the ednrb gene resulting in colonic aganglionosis. It has been useful as a model of a human disease.

In any model it is useful to establish the validity of the model by seeing how well it replicates known features of the human condition. If known features are replicated faithfully, then we can have confidence in the new features demonstrated by the model. Mutations in the human version of the same gene were found in an extended kindred in the United States 25 years ago. We sought to compare the penetrance of the mutation alongside the sex modification of the gene in the rat with the penetrance and sex ratio in the human kindred (Puffenberger et al 1996)

Methods

Spotting lethal rats were bred for a variety of studies over the last 15 years. Breeding was controlled by genotyping the animals. Most (but not all) studies on the rats involved inspecting the gut to determine whether aganglionosis was present. Data on the sex of the animals was also recorded. This rat colony demographic data was retrieved and analysed for the penetrance of the aganglionic phenotype.

Results

Genotype	Gender (M/F)	Enteric Morphology	Number (n=)	Proportion agangl
+/+	M	Aganglionic	1	1.0%
		Normal	86	99.0%
	F	Aganglionic	0	0.0%
		Normal	70	100.0%
sl/+	M	Aganglionic	5	2.6%
		Normal	187	97.4%
	F	Aganglionic	2	1.1%
		Normal	175	98.9%
sl/sl	M	Aganglionic	55	94.8%
		Normal	3	5.2%
	F	Aganglionic	43	89.5%
		Normal	5	10.5%

Figure 1. *sl* mutation penetrance in the rat. Numbers of offspring are close to Mendelian, allowing for pre or early post natal loss in homozygous mutants.

Puffenberger et al 1994			Current paper		
	Heterozygotes	Homozygotes		Heterozygotes	Homozygotes
M	33%	85%	M	3%	95%
F	8%	60%	F	1%	90%
Penetrance of EDNRB mutation W276C.			Penetrance of ednrb 201bp deletion.		

Figure 2. Comparison of penetrance in the rat (right-hand column) and the human (left-hand column).

Discussion

We note that the penetrance figures for the human condition in the kindred reported by Puffenberger result from a two base pair change, whereas the rat condition results from a 201 base pair deletion. In addition, the genetic background of human and rat is considerably different. Allowing for that, in both species the gene acts in a sex modified autosomal recessive fashion. One case reported as aganglionic was in fact homozygous wild-type for the ednrb gene. This genotype would not be expected to be aganglionic. Most likely there has been an error in genotyping or in recordkeeping. Alternatively he may simply be an example of something that happens in humans: that is, he may have suffered a new mutation in one of the several HSCR genes.

Systems studied in the model in this lab:

Proximal gut
Brain
Adrenal **Carotid body**
Facial skeleton
Heart
Urinary tract
Spleen
Blood sugar

Conclusion

- The data parallels the data reported in Puffenberger et al., although the figures for penetrance are not identical. The rat is confirmed as a useful model of Hirschsprung disease.

References : Puffenberger EG, Kauffman ER, Bolk S, Matise TC, Washington SS, Angrist M, Weissenbach J, Garver KL, Mascari M, Ladda R, et al "Identity-by-descent and association mapping of a recessive gene for Hirschsprung disease on human chromosome 13q22." Hum Mol Genet 3(8):1217-1225 (1994)