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Mouse Alopecia Areata and Heart Disease: Know Your Mouse!

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To the editor

The proceedings of a recent meeting on alopecia areata (AA) (Bertolini *et al.*, 2012) summarized work using the surgically induced C3H/HeJ mouse model for AA (McElwee *et al.*, 1998), in which investigators found enlarged hearts in affected mice, suggesting an association between AA and cardiac findings. However, the heart lesions described are a well known strain specific disease, not limited to C3H substrains. These lesions have been described by a number of names including epicardial mineralization with fibrosis and dystrophic cardiac calcinosis (Eaton *et al.*, 1978; Frith and Ward, 1988). Crosses between C3H/HeJ and C57BL/6J mice have identified 4 quantitative trait loci (QTLs), designated as Dystrophic Cardiac Calcinosis 1-4 (*Dyscalc1-4*) (Ivandic *et al.*, 2001). Mapping to mouse Chr. 7 (Ivandic *et al.*, 1996), *Dyscalc1* was subsequently identified as being due to non-synonymous single nucleotide polymorphisms in the ATP-binding cassette, sub-family C (CFTR/MRP), member 6 (*Abcc6*) gene (Aherrahrou *et al.*, 2008; Meng *et al.*, 2007). Mutations in the human *ABCC6* gene and targeted mutations in the mouse *Abcc6* gene produce pseudoxanthoma elasticum (PXE) (Gorgels *et al.*, 2005; Klement *et al.*, 2005), a systemic metabolic disease with cutaneous features distinct from AA (Uitto *et al.*, 2010).

In a massive histopathological screening of all organ systems in 31 inbred strains of mice of both genders, dystrophic cardiac calcinosis was diagnosed in 8 strains (Berndt *et al.*, submitted; Sundberg *et al.*, 2011). C3H/HeJ and A/J strains were found to develop both heart lesions (Chase *et al.*, 2009) and AA (McElwee *et al.*, 1999) in the aging study,

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although in both cases more mice with normal skin had heart lesions than those with AA (Table 1a). Three strains were found to develop histologically confirmed AA (MRL/MpJ, SJL/J, and SWR/J) but none of these mice had any type of heart lesion. No correlation was found in a retired breeder study (Table 1b) (Berndt *et al.*, submitted) or in a large mouse cross (C3H/HeJ x C57BL/6J, C3B6F2; Table 1c) generating F2 females for identifying AA eQTLs. Heart lesions varied in severity and location between the strains (Berndt *et al.*, submitted). Genome-wide association mapping determined that none of the QTLs for dystrophic cardiac calcinosis corresponded to genomic regions identified to determine AA.

While it is easy to see clinical correlations between seemingly unrelated diseases in small numbers of mice undergoing experimental manipulation, it is critically important to understand strain specific background lesions. The mineralization and fibrosis phenomena among the inbred strains associated with PXE-like diseases are very complicated. Some are related to each other while others are not. The underlying genetic predisposition can be modified by the genes involved in other diseases. Such appears to be the case for *Abcc6* and PXE (Berndt *et al.*, 2013). As the complex genetics of AA in humans and mice continues to be refined, it is possible that some of the genes involved in development of heart lesions may overlap with those that determine AA, but with technologies currently available using large populations of mice it appears that cardiac mineralization and fibrosis phenotypes are not correlated with AA.

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Abbreviations

AA	alopecia areata
***Abcc6* (mouse gene)**	*ABCC6* (human gene), ATP-binding cassette subfamily C, member 6, gene
Dyscalc1-4	dystrophic cardiac calcinosis 1-4, quantitative trait loci
PXE	pseudoxanthoma elasticum
QTL	quantitative trait loci

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Table 1

Lack of correlation between dystrophic cardiac calcinosis in aging mouse strains and adult onset alopecia areata

There was no correlation between histologically confirmed alopecia areata and dystrophic cardiac calcinosis in 31 inbred strains in an aging histopathology study (a), evaluation of hearts in retired breeders (b), or F2 hybrid study for mapping quantitative trait loci for alopecia areata (c).

Table 1a. There was no correlation between alopecia areata and heart lesions in mouse strains in the 31 strain aging study.

Strain	Total Mice 12 & 20 mo. moribund		Alopecia Areata		Dystrophic Cardiac Calcinosis		Normal Skin		Dystrophic Cardiac Calcinosis	
Gender:	**Fe**	**M**	**Fe**	**M**	**Fe**	**M**	**Fe**	**M**	**Fe**	**M**
A/J	51	46	0	1	0	0	51	45	23	8
C3H/HeJ	28	29	7	3	0	0	21	26	1	3
MRL/MpJ	41	31	2	0	0	0	39	31	0	0
SJL/J	36	10	2	0	0	0	34	10	0	0
SWR/J	24	18	6	0	0	0	18	18	0	0
Total:	**180**	**134**	**17**	**4**	**0**	**0**	**163**	**130**	**24**	**11**

Table 1b. Alopecia areata was not diagnosed in any of the strains in the retired breeder survey.

Strain	Total		Alopecia Areata		Dystrophic Cardiac Calcinosis		Strain	Total		Alopecia Areata		Dystrophic Cardiac Calcinosis	
Gender:	**Fe**	**M**	**Fe**	**M**	**Fe**	**M**	**Gender:**	**Fe**	**M**	**Fe**	**M**	**Fe**	**M**
A/J	10	10	0	0	9	10	DBA/2J	10	10	0	0	10	10
BALB/cJ	10	10	0	0	9	10	FVB/NJ	10	10	0	0	0	0
BALB/cByJ	10	10	0	0	8	10	KK/HlJ	10	10	0	0	10	9
C3H/HeJ	10	10	0	0	10	6	LP/J	10	10	0	0	0	0
C57BL/6J	10	10	0	0	0	1	PWD/PhJ	10	10	0	0	0	0
C57BL/10J	10	10	0	0	7	10	SWR/J	10	10	0	0	0	0
Total:	**60**	**60**	**0**	**0**	**43**	**47**	**Total:**	**60**	**60**	**0**	**0**	**20**	**19**

Table 1c. There was no correlation between alopecia areata and heart disease in an F2 hybrid cross used to investigate the genetics of these diseases (p-value = 0.651 using a Fisher exact test).

Strain	Age Range (d)	Gender	Alopecia Areata	DCC	Normal Skin	DCC
C3B6F2	195–605	Female	191	1	145	4