

## ALLERGY, GENETICS

# LACTASE VARIANTS IN EUROPE - ANY CONNECTION TO ALLERGY?

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I will present this poster next Monday in San Francisco at the Annual Conference of the American Thoracic Society.

### Allergy and the farming environment: Do genes play a role?

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## INTRODUCTION

The farming environment has been found in several studies to protect a subset of children from allergy. Factors discussed so far include such diverse events as:

- $\Phi$ PS: Inhalation of barn dust
- $\Phi$ pusky: contact and dog ownership
- $\Phi$ Trichin: or other parasite infection
- $\Phi$ Chlamydia: contact
- $\Phi$ drinking unpasteurized milk
- $\Phi$ avoiding vitamin D supplements

These studies usually assume that there is no genetic difference of rural population and those of cities although there is preliminary evidence that such differences might exist. A previous study detected 20 de novo SNPs in Finnish farming population and unrelated SLE subjects (Vartiainen et al. 2006, 26, 265).

We now tested if there is any evidence of population stratification in European farming populations or even local-level differentiation could lead to false-positive or false-negative associations results.

## METHODS

We have shown earlier in 6221 randomly selected adults 20 to 44 years of age participating in the European Community Respiratory Health Survey (ECRHS) that living on a farm in childhood was associated with a reduced risk of single sensitization to adulthood.

We have now further refined the history of being raised in a farm or in a city and analyzed the -11390C variant in the lactase gene (*LC7*) in a subset of

The 207-11950 CT/TT genotype is known to be under positive selection giving an advantage to clonal larvae and may therefore relate to milk drinking.



## RESULTS

ECT-11949 CT/TT prevalence shows a large variation across farms (FIG. 3) which closely resembles the observed distribution of cattle (FIG. 2) but not that of allergy.

There was a clear rural-city gradient in the  $\Delta CT$  -1999 CT/TT genotype in the total sample.

404 JK (farm)  
405 JK (rural/village)  
474 JK (rural, PoLi 15.1 (3.7))

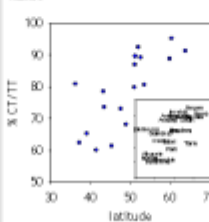
An exact test of Hardy-Weinberg equilibrium showed no departure of 2C7-12110 genotypes to be in (p=0.579). However, in the rural/village (p=0.34<sup>2</sup> 10-7) and city group (p=0.34<sup>2</sup> 10-7).

This effect is not due to stratification by latitude as it may be found in the South (Albania) and the North of Europe (Bergen). On a single center level, however, effects are generally weaker, probably due to an intraspecific regional sampling (Table 2).

ECT -1040 status was neither associated with atrophic rhinitis (Table 1) nor grain restriction even after adjustment for various confounder and inclusion of interaction term.

		est. (95% CI) for change in risk		P
stroke and death				
age	est.			
stroke	0.70	0.68	0.72	<0.001
death	0.80	0.78	0.84	<0.001
CC	est.			
CHD/HT	0.44	0.40	0.47	<0.001

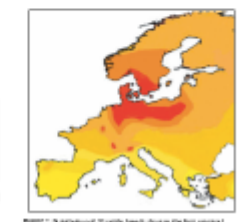
TABLE IV. Alloy solubility (C77-177C) as a function of alloy weight percent carbon (wt. %).



**FIGURE 1.** Frequency of the LCP-CHD association in patients with psoriasis (n = 109).

State	Non- voting U.S. citizens	U.S. citizens not in U.S.	U.S. citizens in U.S.	Total
Alabama	2 117	1 546	56 766	60 429
Alaska	1 000	1 546	56 766	60 429
Arizona	2 117	1 546	56 766	60 429
Arkansas	1 000	1 546	56 766	60 429
California	1 000	1 546	56 766	60 429
Colorado	1 000	1 546	56 766	60 429
Connecticut	1 000	1 546	56 766	60 429
Delaware	1 000	1 546	56 766	60 429
District of Columbia	1 000	1 546	56 766	60 429
Florida	1 000	1 546	56 766	60 429
Georgia	1 000	1 546	56 766	60 429
Hawaii	1 000	1 546	56 766	60 429
Idaho	1 000	1 546	56 766	60 429
Illinois	1 000	1 546	56 766	60 429
Indiana	1 000	1 546	56 766	60 429
Iowa	1 000	1 546	56 766	60 429
Kansas	1 000	1 546	56 766	60 429
Kentucky	1 000	1 546	56 766	60 429
Louisiana	1 000	1 546	56 766	60 429
Maine	1 000	1 546	56 766	60 429
Maryland	1 000	1 546	56 766	60 429
Massachusetts	1 000	1 546	56 766	60 429
Michigan	1 000	1 546	56 766	60 429
Minnesota	1 000	1 546	56 766	60 429
Mississippi	1 000	1 546	56 766	60 429
Missouri	1 000	1 546	56 766	60 429
Montana	1 000	1 546	56 766	60 429
Nebraska	1 000	1 546	56 766	60 429
Nevada	1 000	1 546	56 766	60 429
New Hampshire	1 000	1 546	56 766	60 429
New Jersey	1 000	1 546	56 766	60 429
New Mexico	1 000	1 546	56 766	60 429
New York	1 000	1 546	56 766	60 429
North Carolina	1 000	1 546	56 766	60 429
North Dakota	1 000	1 546	56 766	60 429
Ohio	1 000	1 546	56 766	60 429
Oklahoma	1 000	1 546	56 766	60 429
Oregon	1 000	1 546	56 766	60 429
Pennsylvania	1 000	1 546	56 766	60 429
Rhode Island	1 000	1 546	56 766	60 429
South Carolina	1 000	1 546	56 766	60 429
South Dakota	1 000	1 546	56 766	60 429
Tennessee	1 000	1 546	56 766	60 429
Texas	1 000	1 546	56 766	60 429
Vermont	1 000	1 546	56 766	60 429
Virginia	1 000	1 546	56 766	60 429
Washington	1 000	1 546	56 766	60 429
West Virginia	1 000	1 546	56 766	60 429
Wisconsin	1 000	1 546	56 766	60 429
Wyoming	1 000	1 546	56 766	60 429

TABLE 2. Generation of ICT-EPH contact liquidity and flow based measures.

[illegible]

The significance of the farming effect dropped after including LCT + F2010 (statist in a regression model (probably due to collinearity); the effect size of being raised on a farm was more or less identical when analysed in both LCT + F2010 groups.

## SUMMARY

European farmers represent by their demands a unique population that has conserved certain skills. Genetic studies of the farming populations need to control for stratification to avoid erroneous efforts.

The ability of lactose digestion is unlikely to explain the lower allergy rates of children raised on a farm.

## TAKE HOME

Genetic differences may be involved in the protective effect of living in a farming environment.

We thank all participating individuals for their help and knowledge of the work of the Steering Committee and the World Network studies.

- [illegible]

abridged / revised version

The farming environment has been found in several studies to protect a subset of children from allergy. Factors discussed so far include such diverse events like LPS inhalation of barn dust, poultry contact or dog ownership, Trichiuris or other parasite infection, Acinetobacter contact, drinking unpasteurized milk or avoiding vitamin D prophylaxis. These studies usually assume that there is no genetic difference of rural population and close-by cities although there is preliminary evidence that such differences might exist. A previous study described LD decay in Scottish farming populations and unrelated U.K. subjects (AJHG 2005; 76:763 ). We now tested if there is any evidence of population stratification in European farming populations as even low-level differentiation could lead to false-positive or false-negative association results.

## METHODS

We have shown earlier in 6251 randomly selected adults 20 to 44 years of age participating in the European Community Respiratory Health Survey (ECRHS) that living on a farm in childhood was associated with a reduced risk of atopic sensitization in adulthood. We now refined the history of being raised on a farm or in a city and analyzed the  $\epsilon$ -T13910C variant in the lactase gene LCT in a subset of 5350 individuals. The LCT -13910 CT/TT genotype is known to be under positive selection giving an advantage to digest lactose and may therefore relate to milk drinking.

## RESULTS

LCT  $\epsilon$ -13910 CT/TT prevalence shows a large variation across Europe (FIG.1) which closely resembles the ancestral distribution of cattle (FIG.2) but not that of allergy. There was a clear rural-city gradient of the LCT -13910 CT/TT genotype in the total sample, dropping from 84.8% (farm), 80.2% rural/village) to 74.9% (city,  $P=1.15 \times 10^{-5}$ ). An exact test of Hardy-Weinberg equilibrium showed no departure of LCT  $\epsilon$ -13910 genotypes in farm ( $p=0.539$ ), however in the rural/village ( $p=4.14 \times 10^{-7}$ ) and city group ( $4.96 \times 10^{-7}$ ). LCT  $\epsilon$ -13910 status was neither associated with allergic rhinitis (Table 1) nor grass sensitization even after adjustment for various confounder and inclusion of interaction terms.

