

Stress, Inflammation, and Genetics of Human Longevity: Project update

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Project Outline

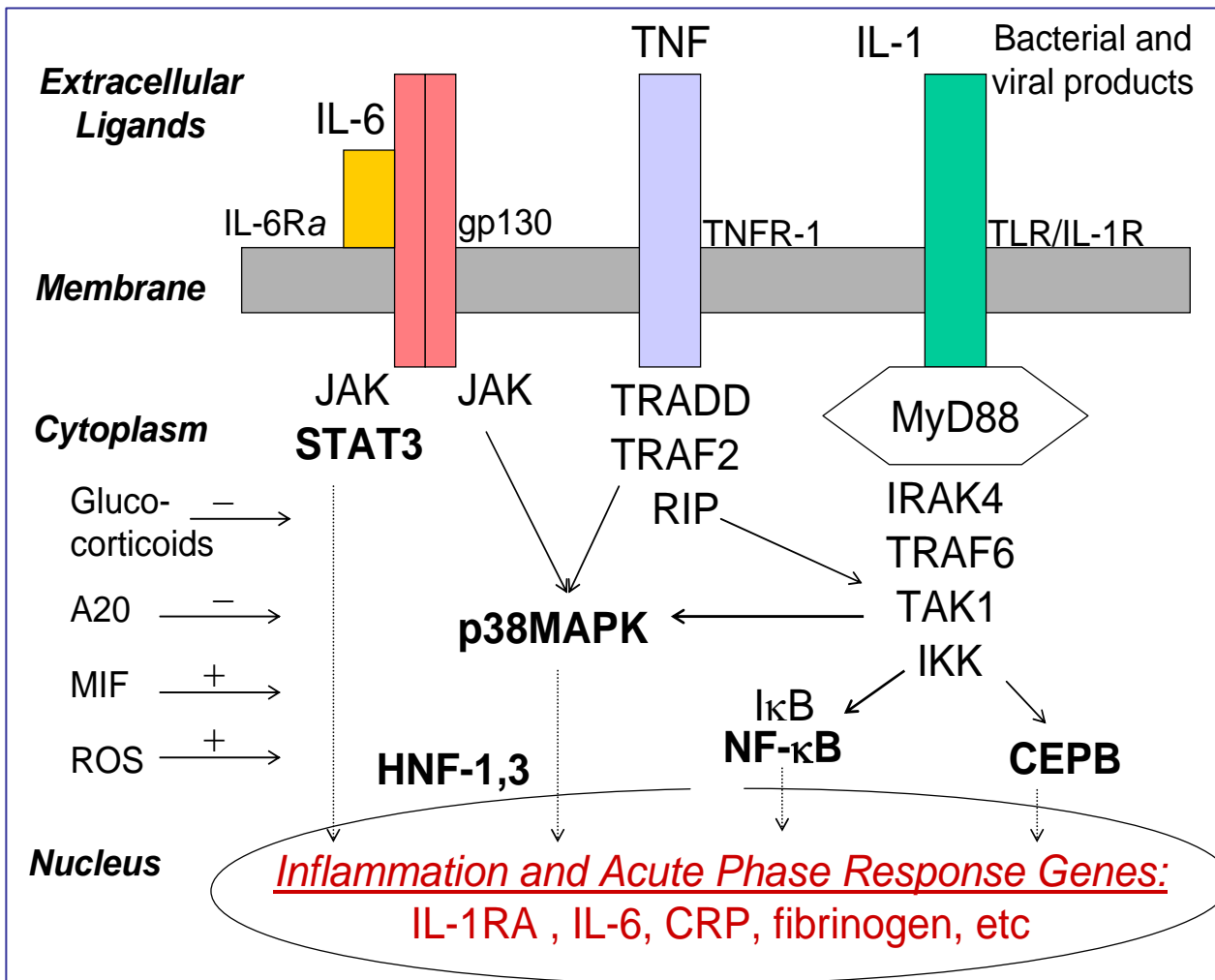
- Cardiovascular Health Study (CHS) cohort description
- Longevity candidate gene associations
 - Single locus results
 - Genetic interaction/multi-locus results
- Biomarkers and intermediate phenotypes
- Replication efforts

Cardiovascular Health Study



- Population-based cohort study
 - 5,888 men & women
 - mean baseline age = 73 (range 65 – 98)
- Recruitment sites
 - North Carolina, Pittsburgh, Maryland, Sacramento
- Current longevity genetic study
 - 5,142 participants
 - 4,352 whites + 790 African-Americans

Candidate inflammation gene pathways



- 1,508 SNPs
- 132 genes
- Includes other aging- and CVD-related genes

Aging and longevity phenotypes



- All-cause and cause-specific mortality during 15 yrs follow-up (>3,000 deaths)
- “Years of healthy life (YHL)”
- Other related traits
 - Inflammation biomarkers
 - Subclinical vascular disease
 - Co-morbid conditions
 - Physical and cognitive function; “frailty”

Summary of candidate gene associations and all-cause mortality in CHS*

	<i>Whites</i> (N=4,352)	<i>African-Americans</i> (N=790)
Common SNPs	711	1,069
# significant genes ($p \leq 0.05$)	10 (8%)	8 (7%)
# significant SNPs ($p \leq 0.05$)	44 (6%)	85 (8%)

*Adjusted for baseline age, sex, and clinic

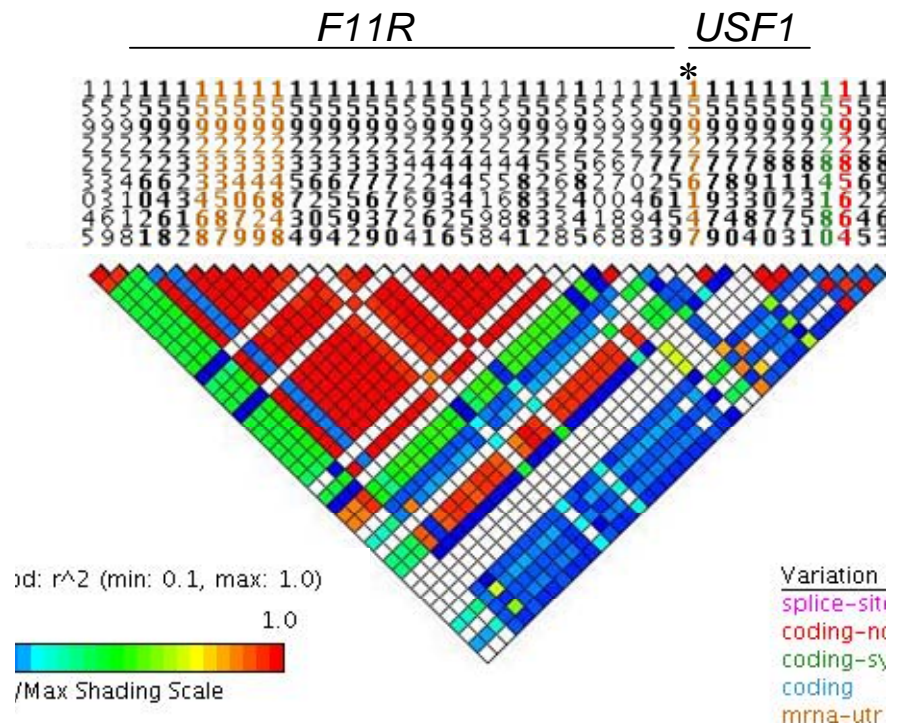
Top longevity associations in CHS whites

<i>Gene</i>	<i>SNP</i>	<i>Function</i>	<i>Bayes Factor</i>	<i>P-value</i>
USF-1 transcription factor	<i>rs2073655</i>	intron	90.4	0.0004
Toll-like receptor 10	<i>rs10856838</i>	3' UTR	14.9	0.001
Coagulation factor 10	<i>rs3213005</i>	intron	18.7	0.003
	<i>rs3093229</i>	5' flanking	9.9	0.004
PolyADP ribose polymerase-1	<i>rs1805415</i>	exon (silent)	10.8	0.004
Glucocorticoid receptor	<i>rs6877893</i>	intron	9.7	0.006
	<i>rs10482682</i>	intron	4.9	0.01

USF1 and other replication efforts

- *USF1*, *MIF* and *PROCR* not associated with longevity in SOF
- Other replication efforts in progress
 - Health ABC,
 - Framingham,
 - centenarians

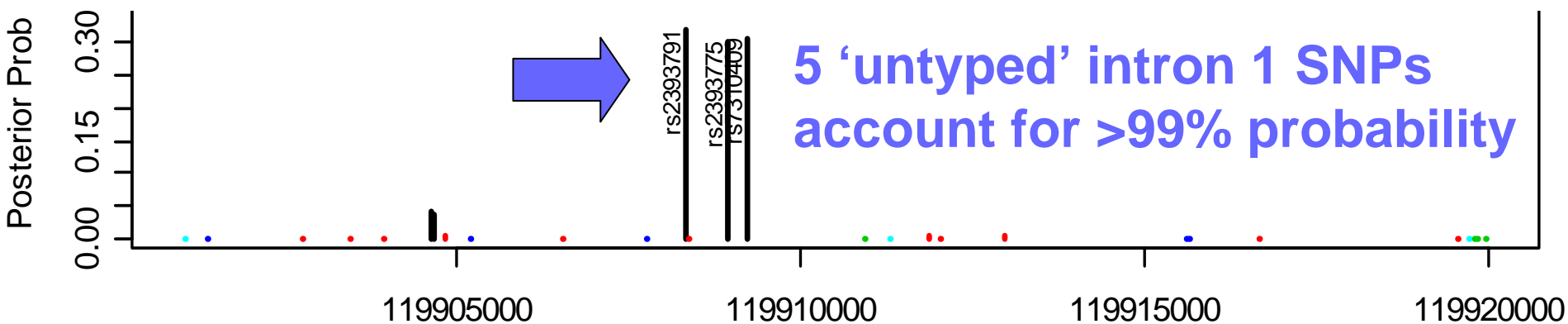
- *USF1* allele increases mortality risk by 30-80%
 - (Komulainen et al, *PLoS Genet* e69, 2006)



Reiner et al, *ATVB* 27:2736, 2007

HNF-1 α (*TCF1*) gene and C-reactive protein: combined evidence from CHS and PARC

*Bayes Factor = 10^{16} for TCF1 – CRP
phenotype association in CHS + PARC*



- HNF-1 α regulates *CRP* gene expression under basal and inflammatory conditions
- HNF-1 α mutations also cause diabetes (MODY)

Top longevity associations in CHS African-Americans

Gene	SNP	Function	Bayes Factor	P-value
IL-1RA (<i>IL1RN</i>)	<i>rs315919</i>	Intron	38.9	0.001
	<i>rs3213448</i>	intron	6.3	0.004
VCAM-1	<i>rs3783613</i>	Gly413Ala	26.5	0.002
	<i>rs3819950</i>	intron	4.4	0.017
IL-10	<i>rs3024498</i>	3' UTR	7.1	0.008
	<i>rs1878672</i>	intron	2.0	0.044
HNF1 α (<i>TCF1</i>)	<i>rs1169286</i>	intron	4.8	0.009
	<i>rs1169288</i>	Ile27Leu	3.3	0.027

IL-1 receptor antagonist (IL-1RA): regulator of inflammatory response

- Common *IL1RN* variants associated with
 - IL-1RA production in response to innate immunity agonist
 - multiple inflammation biomarker phenotypes in young and older white adults (Reiner *et al*, submitted)
- *IL1RN* variant associated with increased mortality and higher plasma cystatin C levels in African-Americans

Longevity phenotype multi-locus association analyses

- Gene x gene interaction
 - Sp1 and NF κ B in whites ($p=1 \times 10^{-7}$)
- Gene x environment interaction
 - Logic regression in progress (Kooperberg *et al*)
- Generalized AMOVA (Nievergelt & Schork)
 - Years of life: not significant
 - Years of healthy life: $p<0.01$; attenuated by adjustment for ancestry

Summary of CHS longevity project on inflammation genes

- *USF1* associated with mortality risk in European-American older adults
- Transcription factors (*USF-1*, *HNF1 α* , *PARP-1*) may link inflammation to various aging-related pathways
- Multi-locus effects and genetic interactions (YHL > YOL?)

Future directions

- Replication in other cohorts
- Larger set of candidate genes available soon in CHS through NHLBI CARE, GWAS, dbGaP, etc.
- Combining evidence across studies
- Fine-mapping and further characterization of 'causal' variants
- Integration of other available phenotypic data on co-morbidities, frailty; biomarkers

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UW and PARC

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Selected baseline CHS variables and risk of mortality during follow-up (n=3,425)*

Predictor	HR	Std. Err.	Z	— log P
Age (per year)	1.1	0.01	19.0	76
Cystatin C	1.4	0.03	11.3	26
Interleukin-6	1.2	0.03	5.4	7
White blood count	1.1	0.02	3.6	3
C-reactive protein	1.1	0.03	1.9	1.2
Fibrinogen	1.0	0.03	0.9	0.4

*adjusted for race, gender, recruitment site, smoking, BMI, HDL, hypertension, diabetes, CVD status

Multi-locus association analysis of longevity phenotypes in CHS African-Americans

Variable	Marginal Tests			Conditional Tests		
	Statistic	<i>P</i>	PVE	Statistic	<i>P</i>	PVE
African	18.7	0.001*	0.0239	18.7	0.001*	0.0239
YHL	1.6	0.001*	0.0021	1.2	0.10	0.0015
YOL	1.5	0.005*	0.0019	1.1	0.23	0.0014
Clinic	1.1	0.07	0.0044	1.1	0.24	0.0041
CRP	1.2	0.09	0.0016	1.2	0.055*	0.0016
BMI	1.0	0.4	0.0013	1.1	0.17	0.0015
Sex	0.9	0.7	0.0012	1.0	0.57	0.0012
Age	0.8	0.9	0.0011	0.8	0.87	0.001