Resilience to Alzheimer's Disease in Humans with Exceptional Longevity

NIA-AA Symposium
ENABLING PRECISION MEDICINE FOR ALZHEIMER'S DISEASE THROUGH OPEN SCIENCE
July 20, 2018

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Einstein Team


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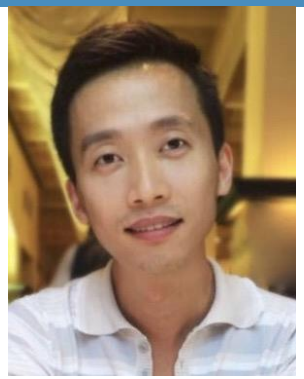
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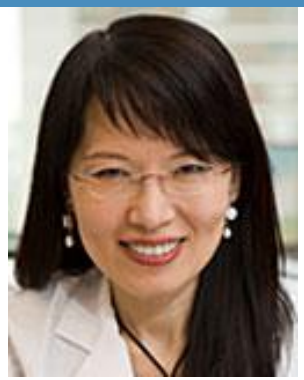
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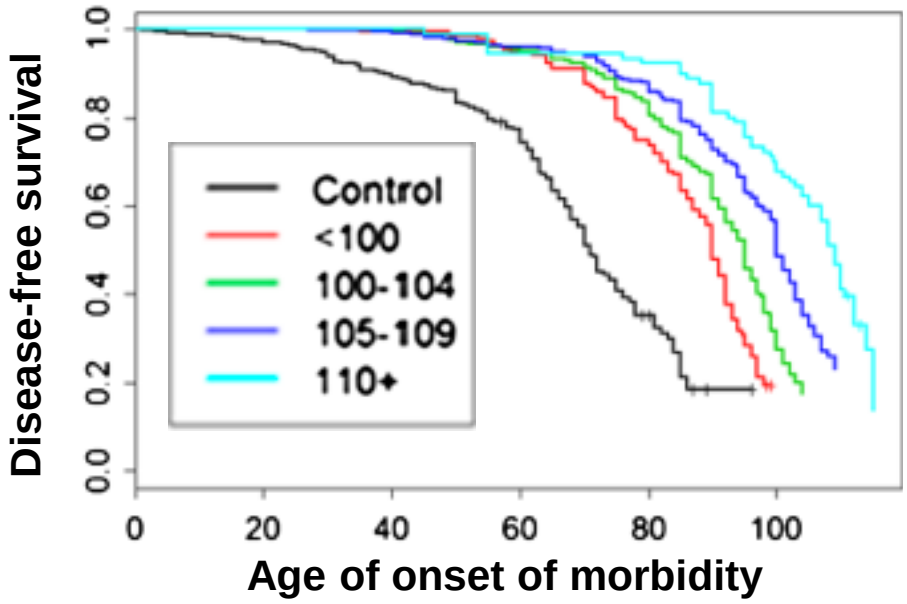
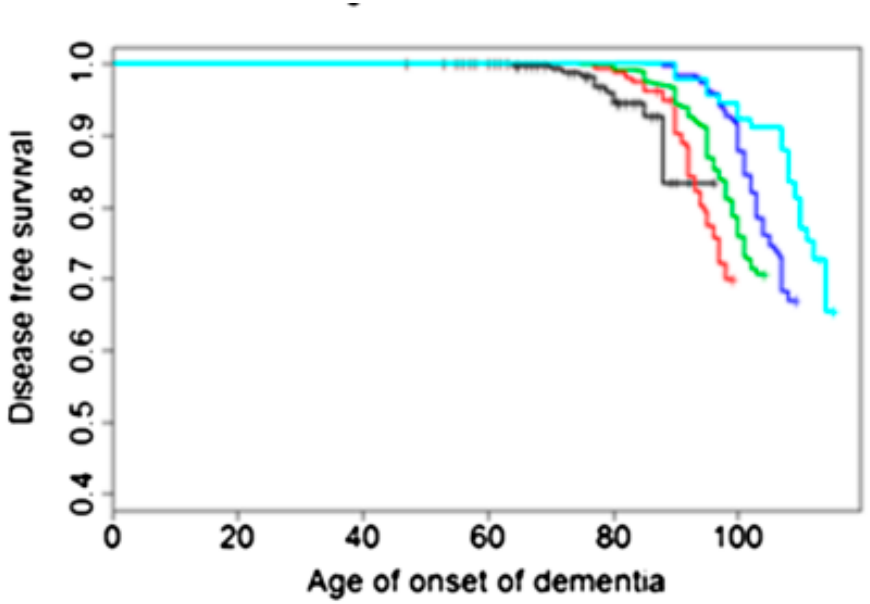
Centenarians delay age-related diseases





Andersen et al. J Gerontol A Biol Sci Med Sci 2012

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Longevity cohorts

Longevity Genes Project

- Families that include centenarians, offspring and their spouses (controls)
- Centenarians: age ≥95 yr
  - Mean lifespan 100
  - Live independently at age 95
  - 1/6,000 in US
- Ashkenazi Jewish
- Northeastern US
- Cross-sectional

LonGenity

- Offspring: centenarian parent
- Controls: no parental longevity
- Ashkenazi Jewish
- Northeastern US
- Longitudinal

Meet our centenarians:
Cover of PLoS Biology April 2006

90 years earlier

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Centenarian lifestyle is not “healthier”

Lifestyle factor	Centenarians n=356 (%)	NHANES I n=1,667 (%)	p-value
Smoked ≥100 cigarettes	29.9	26.2	0.25
Consumed alcohol daily	12.1	11.3	0.80
Regular moderate physical activity	47.0	44.1	0.76
Low-calorie diet	27.3	27.1	0.14
Low-fat diet	35.4	38.5	0.22
Low-salt diet	30.5	30.1	0.67

Rajpathak et al. J Am Geriatr Soc 2011

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Resources from longevity cohorts

Phenotype/Resource	LGP	LonGenity
Centenarians, n (% female)	667 (73)	
Offspring / Controls	559 (53) / 371 (55)	504 (59) / 533 (52)
Frequency of data collection	single time-point	annual (biennial)
Neurocognitive assessments		✔
Physical Assessments	✔	✔
Medical, socioeconomic history	✔	✔
Serum, plasma, whole blood, PBMCs	✔	✔
Genotypes, WES, DNA (banked)	✔	✔
Lymphoblastoid cell-lines	✔	sub-group
Biochemical, lipid, hormonal profiles	✔	✔
Proteomics		✔
Metabolomics	sub-group	sub-group
Brain MRI		sub-group

Approach and Results

- **Identification of candidate resilience genes**
  - compare gene scores between centenarians and controls

- **Characterization of networks of resilience genes**

Identification of candidate resilience genes using WES

- **WES genotype data**
  - 554 centenarians vs. 532 controls
    - 722,205 variants in centenarians and controls
      - 484,762 autosomal rare variants
        (hg38, AAF < 1%)

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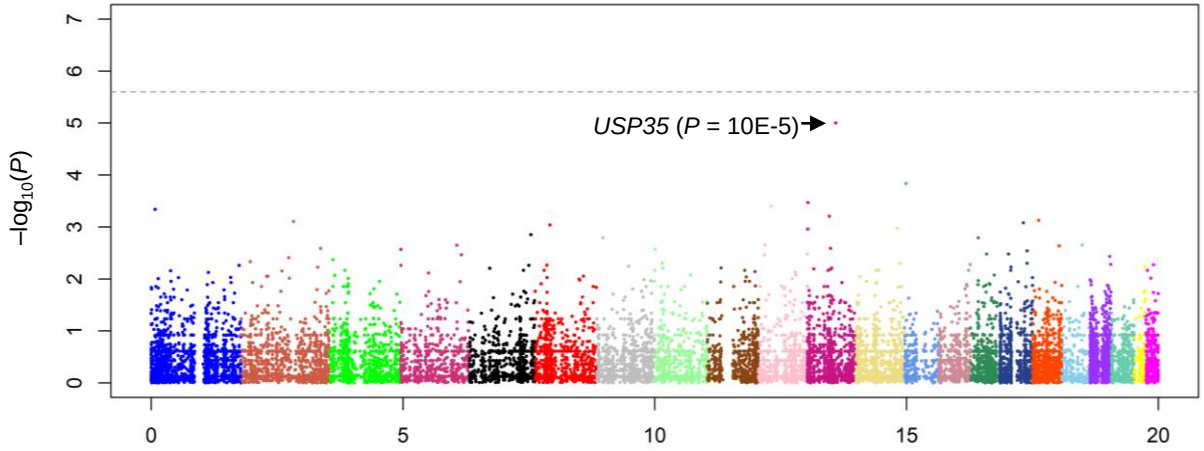
Rare variant association test

- 46,836 autosomal disruptive coding rare variants (CADD>20)
- In protein-coding genes: 14,268



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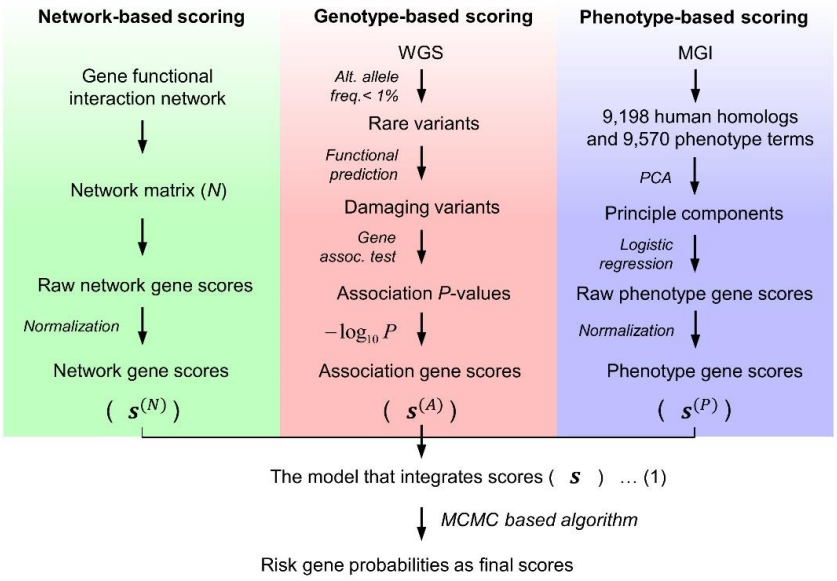
Kircher M. et al. Nature genetics. 2014;46(3):310-315

Integrated Gene Signal Processing (IGSP)

- Data integration for risk gene prediction and prioritization
- Probability estimation based on an integration of:
  - Genetic association: burden test
  - Gene co-functional network: Tasan et al., Nature Methods 2015
  - Gene phenotype network



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Top scoring genes

1. FGF8	11. PLK1	21. COL1A2	31. JAG1	41. COL4A1
2. KALRN	12. GLI3	22. FA2H	32. UTRN	42. PDE3B
3. ADAM22	13. HSD17B4	23. RBM19	33. EHMT1	43. ALDH1A2
4. CACNB2	14. ADRB2	24. TSC2	34. MAPK3	44. SOX9
5. MAPK8IP2	15. USH1C	25. FAT4	35. TP73	45. CHRNA4
6. CLCN6	16. CDH11	26. TREM2	36. FOXD3	46. ROCK2
7. ARHGEF11	17. PTGS2	27. NF1	37. GAA	47. SLIT3
8. HCN2	18. ERCC2	28. ACADL	38. PRKAA2	48. MDFI
9. SCN4A	19. TNKS2	29. KL	39. CAPN3	49. HNF1A
10. ABCA1	20. SCN8A	30. NAT8	40. DOCK2	50. SSTR5

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Candidate genes affected by rare variants for longevity

KEGG pathway enrichment for top 50 genes

Gene Set Name [# Genes (K)]	Description	# Genes in Overlap (k)	k/K	p-value	FDR q-value
KEGG_MAPK_SIGNALING_PATHWAY [267]	MAPK signaling pathway	5		$1.09\ e^{-5}$	$1.36\ e^{-3}$
KEGG_INSULIN_SIGNALING_PATHWAY [137]	Insulin signaling pathway	4		$1.56\ e^{-5}$	$1.36\ e^{-3}$
KEGG_MTOR_SIGNALING_PATHWAY [52]	mTOR signaling pathway	3		$2.58\ e^{-5}$	$1.36\ e^{-3}$
KEGG_PATHWAYS_IN_CANCER [328]	Pathways in cancer	5		$2.92\ e^{-5}$	$1.36\ e^{-3}$
KEGG_FOCAL_ADHESION [201]	Focal adhesion	4		$6.99\ e^{-5}$	$2.6\ e^{-3}$
KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION [86]	Progesterone-mediated oocyte maturation	3		$1.16\ e^{-4}$	$3.61\ e^{-3}$
KEGG_VASCULAR_SMOOTH_MUSCLE_CONTRACTION [115]	Vascular smooth muscle contraction	3		$2.75\ e^{-4}$	$7.3\ e^{-3}$
KEGG_AXON_GUIDANCE [129]	Axon guidance	3		$3.85\ e^{-4}$	$8.94\ e^{-3}$
KEGG_CHEMOKINE_SIGNALING_PATHWAY [190]	Chemokine signaling pathway	3		$1.18\ e^{-3}$	$2.44\ e^{-2}$
KEGG_REGULATION_OF_ACTIN_CYTOSKELETON [216]	Regulation of actin cytoskeleton	3		$1.71\ e^{-3}$	$3.17\ e^{-2}$

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Future Directions: Identify Cognitive Resilience Genes

- Cognitive resilience
  - > Rate of cognitive decline (median f/u 6 years)
  - > Incidence of AD, vascular dementia, MCI
  - > Neuroimaging (Brain MRI, 100 offspring & 100 controls)
    - High-resolution T1-weighted whole head structural imaging
    - FLAIR whole head imaging
    - Susceptibility Weighted Imaging
    - Diffusion Tensor Imaging (DTI)
    - Resting state fMRI
    - 3D Arterial Perfusion Imaging
    - Quantitative T1 Imaging

Future Directions

- Omics
  - Proteomics
  - Metabolomics
- Engineer neuronal cell lines
  - Express cognitive resilience gene(s)
  - Proteomics
  - Metabolomics
  - Test for resilience

Acknowledgements

LGP and LonGenity Study Team

We thank all of our study participants and their families!

NIH National Institute on Aging

GLENN FOUNDATION FOR MEDICAL RESEARCH

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Top genes
(excluded from phenotype based scoring)

CUL2	CDYL2
MIPEP	FMO2
ANKMY2	TESK2
ZIM2	ZNF721
MUC6	
ANAPC1	
CYP2A7	
CLPX	
EXOC3L2	
SEC13	

Associated with AD or healthspan