A candidate gene approach to understanding the role of the cortisol pathway associated genes with the Frailty Phenotype in a population sample of older adults from England

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Introduction

- The term frailty refers to an age related, reduced functional reserve and consequent decrease in adaptation (resilience) to any sort of stressors. The overall consequence is that frail elderly are at higher risk for accelerated physical and cognitive decline, disability and death.
- Much research has been focused on distinguishing those with and without frailty. The Frailty Phenotype (FP) is a widely accepted method of five performance related factors for assessing frailty (Fried *et al.* 2001). The outcome categories are: robust, pre-frail and frail.
- The mechanistic pathophysiological pathways of frailty are not known, but higher cortisol/dehydroepiandrosterone-sulphate(DHEAS) ratio in frail individuals is a consistent finding in the literature, indicating the involvement of the cortisol pathway (Collerton *et al*. 2012).

Aims

- To assess the frailty status of individuals over 60 of a population based sample in England, using the Frailty Phenotype and
- To explore possible associations between genetic variants within genes of the cortisol pathway and the Frailty Phenotype

Method

- 3117 participants' with available phenotype and genotype measures were selected from the English Longitudinal Study of Ageing (ELSA) database
- Their frailty status was assessed by using the 5 items of the Frailty Phenotype:
  - Sarcopenia (measured)
  - Exhaustion (self-reported)
  - Low physical activity (self-reported)
  - Slowness (measured)
  - Weakness (measured)
- Phenotypes were:
  - Not frail: positive for 0 items
  - Pre-frail: positive for 1-2 items
  - Frail: positive for 3-5 items
  - Positive for the individual items
- Candidate genes were selected from the ELSA database of genotyped genes, with MAF≥ 0.01 and HWE ≥ 0.005, 198 SNPs in total
- Single marker association analysis by logistic and linear regressions and Bonferroni correction for multiple testing were performed by using software Plink (Purcell *et al.* 2007)

Demographic results

	Males	Females
Number of participants	1438	1679
Age span [years]	60-79	60-79
Average age [years] SD	68.3 5.53	68.3 5.62

SD: standard deviation

Results

Phenotypic results

Frailty outcome	All	Males	Females
Robust (0 frailty items present)			
Number and percentage	1703 (62.13%)	790 (62.26%)	913 (62.02%)
Age [years]	67.4	67.4	67.4
SD	5.36	5.41	5.33
Pre-frail (1-2 frailty items present)			
Number and percentage	942 (34.37%)	437 (34.44%)	505 (34.30%)
Age [years]	69.8	70.0	69.7
SD	5.60	5.43	5.75
Frail (3-5 frailty items present)			
Number and percentage	96 (3.50%)	42 (3.30%)	54 (3.68%)
Age [years]	70.5	69.5	71.2
SD	5.75	5.74	5.70

SD: standard deviation

Association analysis results, most significant p-values for each phenotype analysed

Phenotype	Gene	SNP	MAF	Function	Effect	P value* (uncorrected)
Frailty (3 categories)	*APP*	rs2830029	0.31	intronic	β = -0.04	0.013
Positive for weight loss item	*CETP*	rs820299	0.37	intronic	OR = 0.75	0.004
Positive for exhaustion item	*CETP*	rs11508026	0.44	intronic	OR = 0.82	0.021
Positive for low physical activity item	*APP*	rs2830046	0.28	intronic	OR = 0.71	0.008
Positive for slowness item	*CETP*	rs9923854	0.11	intronic	OR = 1.3	0.017
Positive for weakness item	*CYP19A1*	rs3751592	0.33	intronic	OR = 0.80	0.002

* None of these results remained significant after correction for multiple testing (Bonferroni correction)
APP: Amyloid β precursor protein,
CETP: Cholesteryl ester transfer protein
CYP19A1: Cytochrome 450, family 19, subfamily A, polypeptide 1
SNP: single nucleotid polymorphism
MAF: minor allele frequency

Conclusions

- This study supports the possible role of *APP*, *CETP* and *CYP19A1* genes in frailty, assessed by the Fried method in a population sample of individuals over 60 from England.
- However, these association results were weak and did not survive the Bonferroni corrections.
- Investigating genes involved in the inflammatory pathways, and other approaches, such as pathway analysis with more comprehensive coverage of this genomic area are required in future studies.

References

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