A candidate gene approach to understanding the role of the cortisol pathway associated 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).

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
- 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 regression and Bonferroni correction for multiple testing were performed by using software Plink (Purcell et al. 2007)

Results

Frailty outcome | All | Males | Females |
--- | --- | --- | --- |
Robust (0 frailty items present) | 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) | 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) | 96 (3.50%) | 42 (3.30%) | 54 (3.68%) |
Age [years] | 70.5 | 69.5 | 71.2 |
SD | 5.75 | 5.74 | 5.70 |

Demographic results

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

SD: standard deviation

Phenotypes and Genes

- Folly (3 categories) CYP19A1 rs3751592 0.33 intronic OR = 0.80 0.002
- 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 strength item CETP rs9923854 0.11 intronic OR = 1.3 0.017

Conclusion

- 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.

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References