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Association of exceptional parental longevity and physical function in aging

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Abstract Offspring of parents with exceptional longevity (OPEL), who are more likely to carry longevity-associated genotypes, may age more successfully than offspring of parents with usual survival (OPUS). Maintenance of physical function is a key attribute of successful aging. While many genetic and non-genetic factors interact to determine physical phenotype in aging, examination of the contribution of exceptional parental longevity to physical function in aging is limited. The LonGenity study recruited a relatively genetically homogenous cohort of Ashkenazi Jewish (AJ) adults age 65 and older, who were defined as either OPEL (having at least one parent who lived to age 95 or older) or OPUS (neither parent survived to age 95). Subjective and objective measures of physical function were compared between the two groups, accounting for potential confounders. Of the 893 LonGenity subjects, 365 were OPEL and 528 were OPUS. OPEL had better objective and subjective measures of physical function than OPUS, especially on unipedal stance (p=0.009) and gait speed (p=0.002). Results support the protective role of exceptional parental longevity in preventing decline in physical function, possibly via genetic mechanisms that should be further explored.

Keywords Aging · Genetics · Longevity · Physical Function

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Introduction

Maintenance of physical function is a key component of most definitions of successful aging (Peel et al. 2005; Rowe and Kahn 1998). Good physical function is rated highly among attributes of successful aging in surveys of the general elderly population (Bowling and Dieppe 2005; Rowe and Kahn 1998). Emerging evidence from human and animal studies shows that genetics partially determine exceptional longevity, and associated successful aging phenotypes (Adams et al. 2008; Barzilai et al. 2006; Barzilai et al. 2003; Murabito et al. 2012; Newman et al. 2011). Offspring of parents with exceptional longevity (OPEL) who are more likely to carry longevity-associated genotypes may age more successfully than offspring of parents with usual survival (OPUS) (Barzilai et al. 2006; Barzilai et al. 2003). While many genetic and non-genetic factors (e.g., environment and disease) interact to determine the final physical phenotype in aging, there has been limited examination of the contribution of exceptional parental

longevity to maintenance of physical function in aging (Frederiksen et al. 2002; Newman et al. 2011).

The LonGenity study, established in 2007, recruited a cohort of Ashkenazi Jewish (AJ) adults age 65 and older, who were defined as either OPEL (having at least one parent who lived to age 95 or older) or OPUS (neither parent survived to age 95). Relative genetic homogeneity of the AJ population (Seldin et al. 2006) provides a unique sample for comparisons within the cohort (Barzilai et al. 2006). Our group has identified several biomarkers and candidate mechanisms associated with longevity in a separate cohort of AJ adults not included in this study (Atzmon et al. 2009; Atzmon et al. 2008; Atzmon et al. 2005; Barzilai et al. 2006; Barzilai et al. 2003). In addition, we reported that OPEL have a healthier phenotype than OPUS with lower prevalence of chronic illnesses such as hypertension, diabetes mellitus, heart attacks, and strokes (Atzmon et al. 2004). This is consistent with results from studies of longevity in other cohorts indicating that offspring of centenarians are less susceptible to age-related diseases than those without parents with exceptional longevity (Adams et al. 2008; Terry et al. 2004). Since these risk factors are also implicated in the maintenance of physical function, we hypothesized that OPEL would have better physical function compared to OPUS.

Methods

The goal of the LonGenity study is to identify genotypes associated with longevity and their association with successful aging in AJ seniors. Majority of AJ participants in the LonGenity study were systematically recruited using public records such as voter registration lists. A smaller AJ sample was identified through contacts at synagogues, community organizations, and advertisements in Jewish newspapers (Verghese et al. 2006). Potential participants were contacted by mail and then by telephone to assess interest and eligibility. AJ adults age 65 and above were invited to our research center for participation. Exclusion criterion included diagnosis of dementia, severe visual or hearing impairments as well as having a sibling already enrolled in the study. The eligible sample included 365 OPEL and 528 OPUS participants.

Frailty diagnosis was operationalized using the Cardiovascular Health Study criteria defined as meeting three of more of the following criteria: unintentional weight loss, self-reported exhaustion, weak grip strength (handgrip dynamometer), slow gait speed, and low physical activity (Fried et al. 2001). Presence of depression, diabetes, heart failure, hypertension, myocardial infarction, strokes, Parkinson's disease, chronic obstructive lung disease, and arthritis was used to calculate a summary illness index as previously described (Holtzer et al. 2006; Verghese et al. 2012).

Physical function—subjective: Research assistants interviewed participants at the Aging Research Center at Albert Einstein College of Medicine using validated mobility assessment questionnaires (Verghese et al. 2004). The four physical function related questions examined for this study were: (1) "How far can you walk without a break on level ground?" (abnormal response: ¼ mile or less); (2) "Do you have difficulty walking?" (abnormal response: yes); (3) "Have you ever used a cane or walker?" (abnormal response: yes); and (4) "Do you have difficulty climbing up or down stairs?" (abnormal response: yes) (Verghese et al. 2008). Abnormal responses to the questions were determined based on sampling distributions in our studies, literature review, and clinical experience (Verghese et al. 2004). These questions were reported to be highly reliable, and have been validated against physical performance measures and functional status in older adults (Verghese et al. 2004; Verghese et al. 2008).

Physical function—objective: We selected four established objective clinical markers of physical function focusing on lower extremity to complement our subjective measures. Gait speed is considered a geriatric vital sign, and predicts multiple adverse outcomes in older adults (Studenski et al. 2011; Verghese et al. 2009; Verghese et al. 2007b). As previously described (Verghese et al. 2007b), research assistants measured steady state gait using an 8.5-m long computerized walkway (180×35.5×0.25 in.) with embedded pressure sensors (GAITRite; CIR Systems, PA). Participants were asked to walk at their normal pace in a quiet well-lit hallway wearing comfortable footwear and without any attached monitoring devices. Start and stop points were marked by white lines on the floor, and included four feet from the walkway edge for initial acceleration and terminal deceleration. Based on footfalls recorded on the walkway, the software automatically computes gait parameters such as gait speed (cm/s). The GAITRite system is widely used in clinical and research settings, and

excellent reliability has been reported in our and other centers (Devos et al. 2007; Verghese et al. 2007a; Verghese et al. 2007b). Research assistants also measured time in seconds to climb up three steps, a quick and valid clinical measure for assessing risk of functional decline (Oh-Park et al. 2012). Another physical assessment included unipedal stance, which measures the ability to stand on one foot (maximum 30 s), and is a clinical test of balance that is also a good predictor of falls (Hurvitz et al. 2001; Hurvitz et al. 2000). Lastly, time to get up five times from a chair unassisted was evaluated as a measure of lower extremity strength and balance (Guralnik et al. 2000).

Statistical analysis: Subject characteristics were summarized with descriptive statistics. We used multivariate logistic (categorical) and linear (continuous) regression analysis to test cross-sectional associations of OPEL versus OPUS status with the subjective and objective physical function measures, adjusted for age, gender, years of education, and body mass index (BMI). Results are reported as adjusted mean differences in OPUS and OPEL samples. Odds ratios (OR) (logistic) or beta coefficients (linear) with 95 % confidence intervals (CI) are also reported using OPUS as the reference group. All analyses were performed using SPSS, version 20.

Results

Study population: Table 1 presents subject characteristics. The 365 (40.9 %) OPEL were younger than the 528 (59.1 %) OPUS (75.1 vs. 77.1 years, $p<0.001$), and included a higher proportion of women (59.2 vs. 52.1 %, $p=0.036$). Education was statistically higher in OPEL, though the absolute difference was only 0.5 years. OPEL reported fewer illnesses than OPUS (1.19 vs. 1.45, $p=0.001$). Among individual illnesses, OPUS had significantly higher prevalence of hypertension and strokes. Prevalence of frailty was higher in OPUS than OPEL (12.5 vs. 11.4 %), though the difference was not significant.

Physical function: Table 2 indicates that OPEL reported fewer problems on all subjective physical function questions compared to OPUS, though the differences were only significant for use of an assistive device (OR 0.51, 95 % CI 0.28–0.93) when adjusted for age, sex, education, and BMI.

OPEL also performed better on all objective physical function measures compared to OPUS. Differences were significant for gait velocity ($p=0.004$) and unipedal stance ($p=0.004$), after adjustments for age, sex, education, and BMI. Inclusion of quadratic term in the model to account for possible non-linear age trends did not materially change the results (data not shown). All continuous traits were examined visually and statistically, and met normality assumptions except for unipedal stance. The result remained significant when comparing log transformed unipedal stance values between OPEL and OPUS after adjustments for age, sex, education (0.07, 95 % CI 0.02–0.13, $p=0.007$). OPUS took longer to climb up stairs and perform the chair rise assessment, though differences were not significant in adjusted models.

Figure 1 graphically presents the association of age with the physical function measures by parental longevity. The figures show that at any given age, OPEL have better physical function than OPUS.

Discussion

Overall, the OPEL in the LonGenity cohort had better performance on the four selected subjective and four objective physical function measures compared to OPUS, though differences were significant on few measures. These results are consistent with our hypothesis that persons with long-lived parents may enjoy not only a longer life but one relatively spared from physical functioning declines. Our results are supported by a previous analysis of three Danish population-based studies that reported parental longevity was associated with better physical and cognitive function measures in the adult offspring; almost all the effects were seen solely in the cohort of 70+year-olds (similar to the mean age of the LonGenity cohort), but not among middle-aged or nonagenarian subjects (Frederiksen et al. 2002). While lifestyle factors are important in maintaining physical function in aging, a previous study showed that physical activity, smoking, alcohol consumption, and dietary habits in OPEL did not significantly differ from the general population (Rajpathak et al. 2011). An analysis in the population-based Danish twin registry showed that the effect of genetic factors on functional

Table 1 Subject characteristics of OPUS and OPEL

Description	OPEL (n=365)	OPUS (n=528)	p value
Age, mean±SD	75.04±6.07	77.14±7.04	<0.001
Sex (% female), mean±SD	59.18±0.49	52.20±0.50	0.036
Education (years), mean±SD	17.50±2.97	17.00±2.95	0.013
Grip strength (kg/m2), mean±SD	12.64±11.21	12.45±11.58	0.810
BMI (kg/m^2), mean±SD	27.72±6.03	27.60±4.55	0.753
Summary illness index, mean±SD	1.19±1.05	1.45±1.09	0.001
Depression, n (%)	68 (20)	96 (21)	0.709
Diabetes, n (%)	26 (8)	52 (11)	0.079
Heart failure, n (%)	3 (1)	8 (2)	0.296
Hypertension, n (%)	132 (43)	224 (52)	0.015
Myocardial infarction, n (%)	15 (4)	34 (7)	0.075
Stroke, n (%)	5 (1)	26 (6)	0.002
Parkinson's disease, n (%)	3 (1)	8 (2)	0.298
Chronic obstructive lung disease, n (%)	13 (4)	17 (4)	0.943
Arthritis, n (%)	141 (43)	191 (45)	0.696
[a]Frailty (%)	11.43	12.50	0.793

[a] Meets Cardiovascular Health Study criteria for frailty (3 or more out of 5 features) (Fried et al. 2001)

abilities increases with age and accounts for one third to one half of the variation among women aged 80 years and older (Christensen et al. 2000).

The LonGenity cohort includes a non-disabled, ambulatory, community-dwelling sample, which might have minimized subjective reports of physical limitations overall and between our study groups. However, the differences on all subjective measures between OPUS and OPEL were in the expected direction, with worse performance reported in the OPUS group. A stronger trend was seen with the objective physical function measures, which may be more sensitive to early physical function decline in high functioning adults (Verghese et al. 2012). These results are consistent with conclusions described by Newman and colleagues indicating that continuous measures of physical function, like gait speed, may be sensitive for detecting "rate of aging" and early signs of future disability (Newman et al. 2011). Closer examination of the objective measures showed that age adjusted mean performance for both groups was in the normal range reported in our and other studies indicating the overall high functional status of our cohort (Guralnik et al. 2000; Oh-Park et al. 2010; Oh-Park et al. 2011; Springer et al. 2007). Hence, the group differences seen in this study might be identifying early and mild signs of age-related physical function decline. In particular, the small variance in frailty prevalence along with a strong group difference in gait speed, one of the key criteria of frailty (Fried et al. 2001), indicate support of early signs of decline in physical function in the OPUS group.

The large sample of a relatively genetically homogeneous population and use of validated subjective and objective measures of physical function are strengths of this study; however, limitations are noted. The cross-sectional design does not permit causal inferences. Although previous studies from our group, conducted in a separate cohort of AJ adults, suggest a genetic explanation for phenotypic differences (Atzmon et al. 2005; Barzilai et al. 2006), further mechanistic studies are required. Physical function measures such as gait speed may be linked with specific genotypes via the effect of gene(s) on both brain and peripheral (muscle, nerve, and vasculature) processes. Our studies in other aging cohorts have linked functional polymorphisms in *COMT* and *APOE* genotypes to gait velocity in older adults (Holtzer et al. 2010; Holtzer et al. 2013). While stronger associations with physical function measures might be seen in individuals with both parents with exceptional longevity, we only had 12 such individuals,

Table 2 Subjective and objective physical function measures in OPEL and OPUS adjusted for age, sex, and education years

Subjective physical function measures[a]	OPEL	OPUS	Adjusted odds ratio (95 % CI)	*p* value
Walk≤¼ mile without break, % (SE)	9.4 (1.7)	13.5 (1.5)	0.58 (0.33; 1.02)	0.059
Has difficulty walking, % (SE)	14.5 (2.0)	16.8 (1.7)	0.84 (0.53; 1.32)	0.442
Used a cane or walker, % (SE)	7.5 (1.7)	12.6 (1.4)	0.51 (0.28; 0.93)	0.027
Difficulty climbing up or down stairs, % (SE)	2.98 (2.5)	36.6 (2.1)	0.70 (0.50; 0.99)	0.045
Objective physical function measures[b]			Beta coefficient (95 % CI)	
Gait speed (cm/s), mean (SE)	111.16 (1.18)	106.67 (1.01)	4.49 (1.41; 7.58)	0.004
Stair climb up (s), mean (SE)	1.96 (0.06)	2.08 (0.05)	−0.12 (−0.27; 0.03)	0.110
Unipedal stance (s), mean (SE)	16.94 (0.53)	14.94 (0.44)	2.00 (0.63; 3.36)	0.004
Chair rise (s), mean (SE)	10.70 (0.22)	11.21 (0.19)	−0.51 (−1.07; 0.05)	0.075

[a] Binary logistic regression adjusted for age, sex, education, and BMI

[b] Linear regression adjusted for age, sex, education, and BMI

which was not sufficient to test this hypothesis. The influence of health behaviors such as physical activity, which play an important healthy aging, on longitudinal changes in physical function in OPUS and OPEL should be further studied. We mainly focused on lower extremity subjective and objective measures in this analysis but other physical measures might shed additional light on functional correlates of exceptional parental longevity. The physical function comparisons were adjusted for age, sex, education, and BMI; however, given the higher mean age of OPUS, group differences in disease prevalence should be cautiously interpreted.

Results of this study and others (Atzmon et al. 2005; Frederiksen et al. 2002; Holtzer et al. 2010) provide evidence that variation in late-life physical function and frailty is attributable to both environmental and

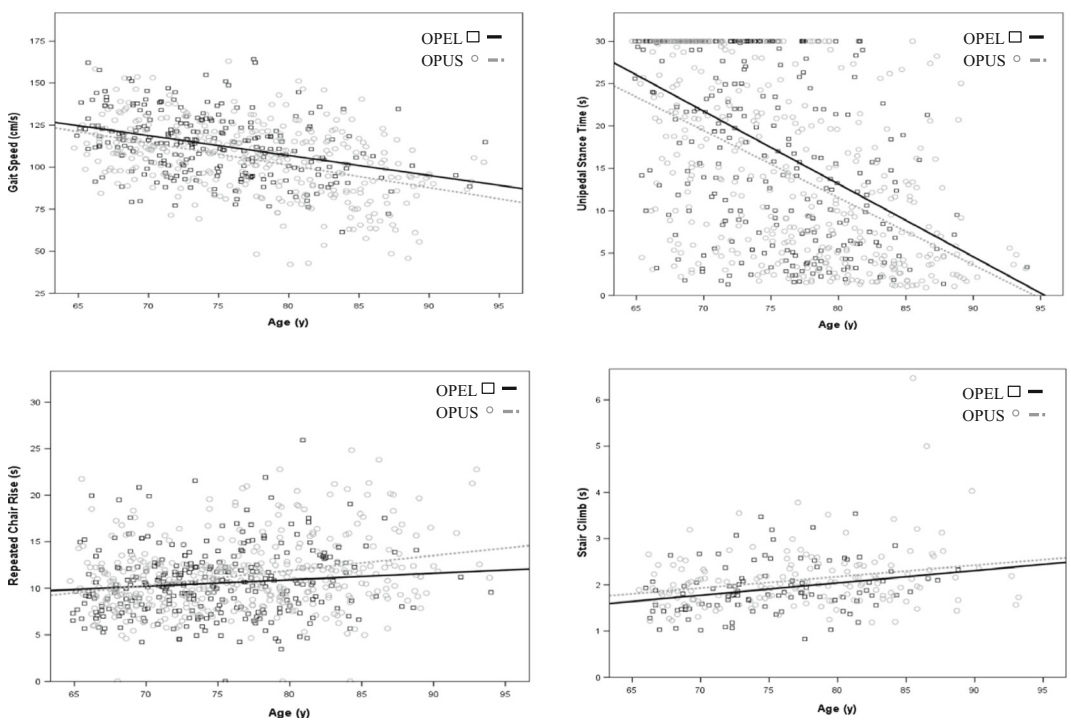

Fig. 1 *Scatter Plots* of quantitative physical function measures for OPEL and OPUS vs. age

genetic factors, and that genetic factors may become increasingly important with aging. Longitudinal studies of physical function and the effect of parental longevity are necessary to validate results of this study and provide important clues of the genetic factors that mediate aging and susceptibility to frailty and functional decline.

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