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Medically actionable pathogenic variants in a population of 13,131 healthy elderly individuals

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Authors' contributions

PL and RS conceived the study; I.W, E.S and J.J.M directed the research; J.J.M, R.L.W, A.M.M, A.M.T, M.R.N and C.M.R directed the ASPREE trial; J.R, M.R, M.S, Y.C.W, R.C, B.A.T, D.D.B, P.A.J contributed to genetic analysis and variant curation; P.G, A.M.T, J.E.L, R.W and F.A.M contributed to the design and conduct of the ASPREE trial; R.L.W, J.P, E.J.P, S.G.O, W.P.A, T.J.L, R.L.W, and J.J.M contributed to collection of biospecimens; R.S, R.C, D.S, T.A, M.S, Y.C.W and E.S contributed to panel design, DNA sequencing and variant calling; D.S, M.R and J.R contributed to the preparation of genetic data; D.D.B, F.A.M, P.A.J and I.W contributed to clinical interpretation of genetic variants; P.L wrote the manuscript, with editing from J.T, R.S, I.W and J.J.M. All authors reviewed the manuscript.

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Declaration of interests

None

Ethics committee approval

This work was approved by the Alfred Hospital Human Research Ethics Committee (Project 390/15) in accordance with the National Statement on Ethical Conduct in Human Research (2007).

Data and code availability

Data and code can be provided upon reasonable request from the corresponding author.

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Abstract

Purpose: To measure the prevalence of medically actionable pathogenic variants (PVs) among a population of healthy elderly individuals.

Methods: We used targeted sequencing to detect ‘pathogenic’ or ‘likely pathogenic’ variants in 55 genes associated with autosomal dominant medically actionable conditions, among a population of 13,131 individuals aged 70 or older (mean age 75 years) enrolled in the ASPirin in Reducing Events in the Elderly (ASPREE) trial. Participants had no previous diagnosis or current symptoms of cardiovascular disease, physical disability or dementia, and no current diagnosis of life-threatening cancer. Variant curation followed ACMG/AMP standards.

Results: One in 75 (1.3%) healthy elderly individuals carried a PV. This was lower than rates reported from population-based studies, which have ranged from 1.8% to 3.4%. We detected 20 PV carriers for Lynch syndrome (*MSH6/MLH1/MSH2/PMS2*) and 13 for familial hypercholesterolemia (*LDLR/APOB/PCSK9*). Among 7056 female participants, we detected 15 *BRCA1/BRCA2* PV carriers (1 in 470 females). We detected 86 carriers of PVs in lower-penetrance genes associated with inherited cardiac disorders.

Conclusion: Medically actionable PVs are carried in a healthy elderly population. Our findings raise questions about the actionability of lower-penetrance genes, especially when PVs are detected in the absence of symptoms and/or family history of disease.

Keywords

Pathogenic variants; medical actionability; penetrance; genetic testing; healthy elderly

INTRODUCTION

The American College of Medical Genetics and Genomics (ACMG) has published a list of 59 genes relating to ‘medically actionable’ conditions, intended to promote the standardised reporting of information from clinical sequencing (1). The ACMG’s recommendations do not extend to standardised reporting of research findings (2). However, recently some research groups have used the gene list as a guide for identifying medically actionable findings, including from research and in population-based DNA screening of asymptomatic adults (3–5). Of these 59 genes, 55 are associated with autosomal dominant conditions, where single variants confer disease predisposition.

The prevalence of PV carriers for genes associated with autosomal dominant medically actionable conditions, using the ACMG59™ list as a guide, has recently been estimated

from population-based studies at between 1 in 53 (1.8%) to 1 in 29 (3.4%) (4, 6, 7). However, the prevalence of these PVs among healthy older individuals is unknown. Measuring PV frequencies in healthy older populations, as well as population-based studies, may improve understanding of gene penetrance, help overcome historic clinical ascertainment bias, and help determine the relative survival risk conferred by PVs during middle years of life. Healthy elderly populations may also provide new insights into the role of protective alleles in modifying gene penetrance.

Here, we measured PV frequencies in a population of 13,131 healthy elderly individuals from Australia enrolled in the ASPREE clinical trial (8), aged 70 years and older, without cardiovascular disease, dementia, physical disability, or life-threating cancer diagnoses. We report the frequency of pathogenic variants in medically actionable genes among this uniquely ascertained population.

MATERIALS AND METHODS:

Study Population

All participants were enrolled in the ASPirin in Reducing Events in the Elderly (ASPREE) study, a randomized, placebo-controlled trial for daily low-dose aspirin. Study design (9), recruitment (10), baseline characteristics (11) and outcomes (8) have been published previously. Genetic analysis was conducted on 13,131 samples from Australian participants aged 70 years or older who met ASPREE trial entry criteria at enrolment (11). Participants had no previous diagnosis or current symptoms of atherothrombotic cardiovascular disease, physical disability or dementia, and no current diagnosis of life-threatening cancer at enrolment (ASPREE eligibility criteria in Supplementary Appendix).

DNA Sequencing and Variant Analysis

A custom sequencing panel of 762 genes was designed, which included 59 genes on the ACMG59™ Secondary Findings list (1). Following standard protocols, DNA was extracted and sequenced using the Thermo Fisher Scientific S5TM XL system, to average 200X depth (see Supplementary Appendix). Variants with ‘pathogenic’ or ‘likely pathogenic’ annotation (12) and/or high-confidence predicted loss-of-function in coding regions (13) were curated following ACMG/AMP Standards and Guidelines for the Interpretation of Sequence Variants (14), including review by two or more laboratory scientists and a clinical geneticist. Analysis was restricted to single nucleotide variants and small insertions/deletions. Variants of uncertain significance or conflicting interpretations of pathogenicity were excluded.

Ethics Statement

This work was approved by the Alfred Hospital Human Research Ethics Committee (Project 390/15) in accordance with the National Statement on Ethical Conduct in Human Research (2007). Informed consent was obtained from all study participants.

RESULTS:

Characteristics of the 13,131 sequenced participants are shown in Table 1 and include low rates of obesity and smoking, and no personal history of cardiovascular events or dementia at enrolment (11). Most participants were white/Caucasian and 54% were female. Age at enrolment ranged between 70-74 years (60%), 75-79 (26%) and >80 years (14%).

Among 13,131 participants, DNA sequencing and variant analysis identified 172 different 'pathogenic' or 'likely pathogenic' sequence variants meeting ACMG/AMP guidelines (14) in 59 genes associated with medically actionable conditions. Of the PVs detected, 129 were in genes associated with autosomal dominant conditions, detected in 176 participants. This corresponded to a PV carrier rate of 1 in 75 healthy elderly participants (N=176/13,131 or 1.3%). We validated a representative sample of 10% of these 129 variants by Sanger sequencing (N=14), with 100% concordance. The highest number of PVs found in any one dominant gene was N=22 (*BRCA2* and *KCNQ1*) (Table 2 and Table S1).

We found that overall, the carrier rate for PVs in genes associated with autosomal dominant medically actionable conditions was lower in the healthy elderly (1 in 75 or 13 per 1000) than the UK Biobank (1 in 50 or 20 per 1000, unpublished data) and other population-based studies, which have reported carrier rates between 1 in 53 (1.8%) and 1 in 29 (3.4%) (4, 6, 7).

We detected 15 female *BRCA1* or *BRCA2* PV carriers among 7056 female ASPREE participants (0.2% or 2 per 1000). We detected 13 PV carriers for familial hypercholesterolemia genes (*LDLR*, *APOB*, *PCSK9*) and 20 carriers for Lynch syndrome genes (*MSH6, MLH1, MSH2, PMS2*). Additionally, we detected 86 PV carriers for genes associated with inherited cardiac disorders, including Romano-Ward, Brugada and Long QT syndrome (N=39), hypertrophic and dilated cardiomyopathy (N=25) and arrhythmogenic right-ventricular cardiomyopathy (N=22).

We found no individuals carrying two or more variants in genes associated with autosomal recessive conditions (homozygotes or compound heterozygotes). However, we found two individuals carrying multiple PVs in genes associated with different autosomal dominant conditions (*PMS2+KCNQ1* and *MYBPC3+LDLR* respectively).

DISCUSSION

In this study, we report the prevalence of pathogenic variants (PVs) in genes associated with autosomal dominant medically actionable conditions, among a population of 13,131 healthy elderly individuals. The observed PV carrier rate was 1 in 75 participants, in a population of individuals aged 70 years and older without prior history or current symptoms of atherothrombotic cardiovascular disease, physical disability or dementia, or current diagnosis of life-threatening cancer (11). Compared with published population-based studies (4, 6, 7), lower PV frequencies were observed in mismatch-repair genes associated with Lynch syndrome and lipid-metabolism genes associated with familial hypercholesterolemia. However, PVs in other genes with lower penetrance on the ACMG list were found at equivalent frequencies to population-based studies (4, 6, 7). Our findings raise questions

about the medically actionability of these lower penetrance genes, especially when PVs are detected in the absence of symptoms and/or family history of disease.

Strengths of the study include the unique ascertainment, enabling a rare opportunity for a population study of clinically significant genetic variation in >10,000 healthy older individuals. Other strengths include the depth of sequencing and stringency of variant curation, ensuring high confidence PV calls. Limitations include ASPREE PV carriers potentially having a personal history of indicated disease prior to enrolment, including personal history of cancer (not an exclusion criterion of the study, unlike prior cardiovascular events). Other limitations include a sequencing assay not capable of detecting large structural variants, including those in *MSH2* and other mismatch repair genes. The strict variant curation criteria may also have resulted in an under-estimation of PV carriers in ASPREE. Differences in variant curation likely account for some variability in rare PV frequencies reported between different studies.

We detected 176 carriers of PVs in genes associated with autosomal dominant medically actionable conditions in the healthy elderly ASPREE population (13 per 1000 participants). This relatively high rate of PV detection raises a clinically relevant question of whether there is an indicative age at which some PV carriers for dominant conditions outlive their genetic risk; that is, whether there is an age at which population risk and genetic risk for carriers of PVs converge and become equal. Previous studies suggest the majority of clinical risk attributed to PVs in genes associated with autosomal dominant conditions diminishes by age 70, especially for cancer (15, 16). The diminishing risk conferred by PVs beyond age 70 could also have implications for predictive clinical testing of older individuals, and decisions around the return of genetic results to elderly research participants (17). However, that would not necessarily preclude older individuals from gaining benefits from genetic testing as it becomes more widespread, especially those with a family history of a disease.

In conclusion, PVs in genes associated with medically actionable conditions are carried by individuals in a healthy elderly population, often in the absence of indicated disease phenotypes. Further study of healthy elderly populations may provide an opportunity to identify protective alleles that may decrease the disease-causing effect of otherwise highly penetrant pathogenic variants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.
Characteristics of Sequenced Participants at Enrolment.

Sequenced participants were enrolled in the ASPREE clinical trial, aged 70 years and older, without cardiovascular disease, dementia, physical disability, or life-threating cancer diagnoses. Most were white/ Caucasian and 54% were female. Participants with personal cancer history were not excluded, other than those with cancer diagnoses deemed likely to cause death within five years.

	ASPREE N=13,131 (mean age 75 years)
Female sex – no. (%)	7056 (54)
Age in years – no. (%) 70-74 yr 75-79 yr ≥80 yr	 7,894 (60) 3,406 (26) 1,831 (14)
Race or ethnic group [a] – no. (%) White/Caucasian Other	 12,953 (99) 178 (1)
Obese (BMI≥30 kg/m^2) [b] (%)	28
Current smoking (%)	4
Heart, stroke or vascular disease [c] (%)	0
Personal cancer history (%)	20
Breast cancer history (%)	4
Colorectal cancer history (%)	3

[a] Self-report.

[b] Obese was defined as body-mass index (weight in kilograms divided by the square of the height in meters) of ≥30.

[c] Baseline Characteristics of Participants in the ASPREE (ASPirin in Reducing Events in the Elderly) Study (11)

Table 2.

Pathogenic Variants in Genes Associated with Autosomal Dominant Medically Actionable Conditions in a Population of 13,131 Healthy Elderly Individuals.

We sequenced 13,131 individuals aged 70 or older (mean age 75 years) enrolled in the ASRPEE trial. Variant curation following ACMG/AMP Standards and Guidelines for the Interpretation of Sequence Variants (14), including review by two or more laboratory scientists and a clinical geneticist.

	Healthy Elderly (ASPREE) N=13,131		
Mean age – yrs (1st-3rd quartiles)	75 (72 to 77)		
Female sex – %	54		
Gene groups	**No. of carriers**	**Carriers per 1000**[b]	**Carriers % of total**[c]
Medically actionable genes[a] Autosomal dominant (N=55)	176	13	1.34%
Hereditary breast and ovarian cancer *BRCA1* *BRCA2* *BRCA1* or *BRCA2* females	 11 22 15	 1 1.5 2	 0.08% 0.17% 0.11%
Lynch syndrome *PMS2* *MSH6, MLH1, MSH2*	 12 8	 1 0.5	 0.09% 0.06%
Familial hypercholesterolemia (*pathogenic*) *LDLR, APOB, PCSK9*	 13	 1	 0.10%
Romano-Ward long QT syndrome types 1,2, 3, Brugada *KCNQ1* *KCNH2, SCN5A*	 22 17	 1.5 1.5	 0.17% 0.13%
Hypertrophic cardiomyopathy, Dilated cardiomyopathy *MYBPC3* *MYH7, MYH11, LMNA, MYL3, TNNT2, TNNI3, GLA, MYL2*	 15 10	 1 1	 0.11% 0.08%
Arrhythmogenic right-ventricular cardiomyopathy *PKP2* *DSC2, DSG2, DSP, TMEM43*	 12 10	 1 1	 0.09% 0.08%
Hereditary paraganglioma-pheochromocytoma syndrome *SDHB, SDHC, SDHD*	 5	 0.5	 0.04%

[a] Genes defined by the American College of Medical Genetics (ACMG) as medically actionable for reporting of secondary findings from clinical sequencing (1).

[b] Carrier rate per 1000 has been rounded to the nearest 0.5

[c] Carrier rate % of total has been rounded to the nearest 0.01