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Permalink

https://escholarship.org/uc/item/6vk4s1dh

Journal

Movement Disorders, 33(3)

ISSN

0885-3185

Authors

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Publication Date

2018-03-01

DOI

10.1002/mds.27239

Peer reviewed

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Author manuscript

Mov Disord. Author manuscript; available in PMC 2019 March 01.

Published in final edited form as:

Mov Disord. 2018 March ; 33(3): 472–478. doi:10.1002/mds.27239.

Selected Health and Life Style Factors, CAG Status and Phenoconversion in Huntington's Disease

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Authors Roles: 1.Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing of the first draft, B. Review and Critique

CMT: 1.A, B,C; 2.C; 3.A;
SE: 1.B,C; 2.A,B; 3.A,B;
KM: 1.A,B,C; 2.C; 3.B
KB:1.C; 2.C; 3.B;
DO: 2.A,B; 3.B;
IS:1.A,B,C; 2.C; 3.B

Financial Disclosure/Conflict of Interest:

Caroline M. Tanner, Karen Marder, Shirley Eberly, Kevin Biglan, David Oakes and Ira Shoulson have no financial disclosures and no conflicts of interest regarding the manuscript.

Caroline M. Tanner: Regarding the manuscript: None; Other disclosures, past 12 months: Dr. Tanner is an employee of the San Francisco Veterans Affairs Medical Center and the University of California – San Francisco. She receives grants from the Michael J. Fox Foundation, the Parkinson's Disease Foundation, the Department of Defense, Sage Bionetworks and the National Institutes of Health, compensation for serving on Data Monitoring Committees from Biotie Therapeutics, Voyager Therapeutics and Intec Pharma and personal fees for consulting from Neurocrine Biosciences and Adamas Pharmaceuticals.

Karen Marder: Regarding the manuscript: None ; Other disclosures, past 12 months: K. Marder receives research support from, 1UL1 1UL1TR001873-01, NS100600-01, U10 NS077267-06 She receives research support from the Parkinson Disease Foundation, Huntington's Disease Society of America, the Parkinson Study Group, CHDI, and the Michael J. Fox Foundation. She received compensation from Springer SBM LLC for serving on editorial board;

Shirley Eberly: Regarding the manuscript: None; Other disclosures, past 12 months: Support from a grant from Biogen Idec and from the Huntington Study Group on behalf of Auspex Pharmaceuticals (Teva);

Kevin Biglan: Regarding the manuscript: None ; Other disclosures, past 12 months: at the time of manuscript preparation was employed by the University of Rochester, received research funding from the NIH/NINDS, National Parkinson Foundation, Michael J. Fox Foundation, AMC Health, Huntington Disease Society of America and Teva Pharmaceuticals; Contracts for care with the Presbyterian Home of Central New York, The Susquehanna Nursing and Rehailiation Center; consulting support from Teva Pharmaceuticals and is currently employed by Eli Lilly and company;

David Oakes: Regarding the manuscript: None ; Other disclosures, past 12 months: Dr. Oakes is an employee of the University of Rochester. He has received grant support from the NIH, the Department of Defense, TEVA, Prana Biotechnology and Vaccinex Pharmaceuticals and compensation for serving on a Data Monitoring Committee for Voyager Therapeutics and for consulting services to Raptor Pharmaceuticals;Ira Shoulson: Regarding the manuscript: None; Other disclosures, past 12 months: Dr. Shoulson is an employee of Georgetown University. Dr. Shoulson receives grant funds from the Parkinson's Disease Foundation, US Food and Drug Administration, National Institutes of Health (NHGRI, NINDS), and the Michael J. Fox Foundation for Parkinson's Research. Consulting and Advisory Board Membership with honoraria: AZTherapies Inc., Banner Health, Dart Neurosciences, Decibel Therapeutics, Huntington Study Group, JAMA Neurology, Jazz Pharmaceuticals, Lysosomal Therapeutics, Michael J. Fox Foundation, Northwestern University, Oxford Biomedica, Partners Health Care, Sarepta Therapeutics, and the University of California Irvine.

Dr. Shoulson has been a non-executive director of the Prana Biotechnology Ltd Board of Directors (Melbourne, Australia), since May 2014. This position is compensated for director and consulting services but without any equity positions, stock options, or other financial incentives. Dr Shoulson is also founder and principal of Grey Matter Technologies (Sarasota FL) since January 2017.

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Abstract

Background—In Huntington's disease, 60% of variance in onset age is not explained by the *huntingtin* gene mutation [1]. Huntington's disease onset was earlier in caffeine users [2].

Objective—To assess the relationship of life style factors with motor phenoconversion among persons at risk for Huntington's disease.

Methods—Associations of motor phenoconversion and exposure to selected life style and health factors were examined using Cox proportional hazards analyses adjusted for age, gender and repeat length.

Results—Thirty-six of 247 subjects (14.6%) phenoconverted. Mean follow-up was 4.2 years. Greater caffeinated soda use was associated with increased hazard of phenoconversion: moderate use Hazard Ratio 2.26 (95% Confidence Interval 0.59, 8.71), high use Hazard Ratio 4.05 (95% Confidence Interval 1.18, 13.96).

Conclusions—Huntington's disease onset was earlier among consumers of caffeinated soda, but not other caffeinated beverages. This finding may be spurious, or not related to caffeine.

Keywords

Huntington's Disease; Environment; CAG Repeat; Phenoconversion; Caffeine

Introduction

Huntington's disease is a fatal, progressive neurodegenerative disorder resulting from a trinucleotide cytosine-adenine-guanine (CAG) expansion in the *huntingtin* gene (OMIM). Persons with ≥ 37 repeats invariably develop clinical features of Huntington's disease (phenoconversion) during the course of a normal life span, but 30% – 60% of the variability in age at onset remains unexplained [1]. In other chronic neurodegenerative disorders, such as Parkinson's disease and Alzheimer's disease, environmental factors can influence risk, and the interaction of genes and environment is important. Recent reports suggest that environmental factors may modulate neurodegeneration in Huntington's disease [3].

We previously reported analyses of dietary behaviors and phenoconversion in adults at risk for Huntington's disease in PHAROS [4–6]. We now report the relationship of selected life style and health-related behaviors to the onset of Huntington's disease (motor phenoconversion).

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Methods

Study Population

Adults at 50% risk for Huntington's disease who wished to remain unaware of their Huntington's disease genotype but consented to provide a coded DNA sample for CAG analysis were enrolled in PHAROS between 1999 and 2004 and followed prospectively until 2010[6]. Motor phenoconversion was determined by a rater, unaware of genotype, based on the motor component of the Unified Huntington's Disease Rating Scale (UHDRS).

Assessment of Clinical Factors

The UHDRS was administered at baseline and follow-up visits. An investigator's response to UHDRS question #17 that a subject's motor abnormalities "are unequivocal signs of Huntington's disease with ≥99% confidence" for the first time was defined as motor phenoconversion. Depression was assessed using the Beck Depression Inventory administered within +/− 14 days of the environmental survey. Depression was defined as a Beck Depression Inventory >10.

Assessment of Environmental Risk Factors

Information regarding life-long use of tobacco products, caffeine, alcohol, certain medications (non-steroidal anti-inflammatory drugs, corticosteroids and, in women, estrogen preparations) and head injury was collected using validated, closed-response questionnaires completed by the subjects[7,8]. Some subjects completed them at the study baseline and others completed them at a later visit.

Definitions of Exposure Variables

Exposure variables were defined categorically and cumulatively, for the time period prior to phenoconversion, as follows:

1. Tobacco: Ever exposed: subjects who smoked ≥100 cigarettes, ≥50 cigars, ≥50 pipes, or used ≥10 pouches of chewing tobacco or cans of snuff; cumulative exposure was calculated in pack-years, defined as one pack of cigarettes/day for one year.
2. Alcohol: Ever exposed: subjects who consumed alcohol at least once a month for at least six months; cumulative exposure was calculated as grams of alcohol/day times years of use using standard values of alcohol content for each beverage type (http://www.mayoclinic.com/health/alcohol/SC00024), with a standard drink equal to 13.7 grams of pure alcohol.
3. Caffeine: Ever exposed: subjects who consumed ≥ 8 oz. of caffeinated coffee, tea or soda at least once per month for at least six months. For each beverage type, cumulative use was calculated in mg of caffeine/day times years of caffeine use using standard values for caffeine content http://www.mayoclinic.com/health/caffeine/AN01211.

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4. Medications: Ever exposed: Subjects who regularly used nonsteroidal anti-inflammatory drugs, corticosteroids or, in women, estrogen preparations daily for ≥ 2 weeks.

5. Head injury: Subjects who ever had a head injury resulting in loss of consciousness or amnesia for > 5 minutes.

Statistical Methods

Subjects with expanded repeats (CAG ≥ 37) who had not phenoconverted before or at "baseline" were included in these analyses. The "baseline" was the date of survey completion. Cox models to predict time to phenoconversion were run for environmental variables by usage, adjusting for age, gender and CAG repeat length (continuous).

Results

Description of Subjects

247 PHAROS participants with CAG ≥ 37 who completed at least one environmental survey are included. Mean follow-up time after survey completion was 4.2 (SD 1.8) years. Seventy-four percent of subjects were women. Median baseline values for demographic and clinical measures were age: 44, years of education: 16, UHDRS motor score: 3, UHDRS chorea score: 0, symbol digit test score: 54 and Beck depression score: 3.

Phenoconversion in CAG Expanded Group

Thirty-six (14.6%) of the 247 subjects in the CAG expanded group phenoconverted following completion of the environmental survey. Analyses of caffeinated soda showed that history of soda consumption (p=0.05), higher current soda exposure (p=0.0376), and higher cumulative soda exposure (p=0.06) were all significantly associated with phenoconversion, but use of other caffeinated beverages was not associated with phenoconversion (Table 1). Regular use of tobacco or alcohol (Table 2), nonsteroidal anti-inflammatory drugs, corticosteroids or, in women, estrogens (data not shown) were not associated with phenoconversion.

Discussion

Lifestyle behaviors such as caffeine consumption, cigarette smoking and alcohol use were not associated with motor phenoconversion, with one exception. Drinking caffeinated soda, but not other caffeinated beverages, was associated with phenoconversion. Although this association may be spurious in the setting of multiple comparisons, it is interesting to note that Simonin [2], in a retrospective assessment of persons with established Huntington's disease, also reported that caffeine intake was associated with an earlier age at onset. Although caffeine has been associated with lower risk of developing Parkinson's disease in epidemiologic studies,[9,10] in Parkinson's disease patients taking creatine in a clinical trial, caffeine intake was associated with more rapid disease progression, possibly due to a complex interaction with GRIN2A genotype[11,12]. Chronic caffeine intake may reduce adenosine A2A receptor activity[13]. In the 3-NP model of Huntington's disease, A2A receptor antagonism has been associated with worsening of signs [14]. However, no other form

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of caffeine was associated with Huntington's disease risk, nor was a combined caffeine dose associated.

Carbonated soda intake may have adverse health effects independent of caffeine. Sugar containing soda use can increase caloric intake. We previously found increased caloric intake to be associated with higher CAG repeat length and 5 year probability of Huntington's disease onset [5]. Use of carbonated soda is also associated with greater risk of metabolic syndrome and diabetes, conditions associated with increased systemic inflammatory processes that may in turn be associated with neurodegeneration [15,16]. In rats, carbonated soft drink intake causes oxidative stress and alters mRNA expression in dopaminergic and serotonergic pathways [17]. In a community-based investigation of stroke risk factors, diet soda intake was associated with increased risk of vascular events including stroke [18]. Finally, drinking carbonated beverages may result in increased intake of aluminum [19]. Any of these effects, or some combination of these, may plausibly have an adverse effect on the ongoing neurodegenerative processes of Huntington's disease. Replication and laboratory investigation are needed.

No other lifestyle factor assessed in this report was associated with phenoconversion in the PHAROS population, although we previously reported dietary dairy intake and higher caloric intake to be associated with motor phenoconversion [4,5]. In the COHORT HD study, ever smoking cigarettes was associated with greater risk of phenoconversion in 59 persons with intermediate length (36–39 CAGs) repeats[20], but we found no increased risk associated with smoking in our analysis of those with ≥ 37 repeats. More years of education predicted an earlier age at Huntington's disease onset in a retrospective registry-based analysis [21]. However, in our analyses, adjustment for education did not significantly influence the results.

This study has limitations. We collected information on lifelong behavior at a single point in time, without corroboration of participants' reports. Information may have been forgotten, or incorrectly reported. We found few differences in reported exposures when participants with expanded repeats were compared to those without expanded repeats, however, suggesting that reporting was not biased due to "at risk" status. In addition, we collected information on many different factors, and have not made corrections for multiple comparisons. We have chosen to report these for future investigation, recognizing that some of the associations we observed may have been by chance[22].

Strengths of this study include the large sample size, prospective follow up, and collecting data from asymptomatic at-risk persons. Prior reports all used primarily retrospective data collection in persons with established Huntington's disease. In PHAROS, participants were unaware of genotype, an additional strength, suggesting that awareness of risk status was not likely to have caused a behavioral change or a difference in reporting. However, we have not assessed other exposures, such as toxicant chemicals, that may be proposed to modulate Huntington's disease gene expression. Genetic modifiers of Huntington's disease age at onset have been identified in gene association studies, but large populations were required [23]. Future investigations with larger population sizes investigating the individual and

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combined effects of genes and environment on Huntington's disease phenoconversion may provide additional insights.

In summary, in PHAROS, motor phenoconversion was generally not affected by the life style factors that we investigated, although in this and our prior analyses, certain dietary patterns, namely, caffeinated soda use, dairy intake and greater caloric intake were all associated with phenoconversion. Because dietary patterns may be modified, further investigation of these is indicated, and, if verified, could lead to recommendations to delay motor phenoconversion. The considerable amount of the non-CAG variance accounting for age at onset remains unexplained.

Acknowledgments

Funding sources for the study: NIH (HG002449), National Human Genome Research Institute, National Institute of Neurological Disorders and Stroke

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We recognize and thank our committees, consultants and sponsors as well as the PHAROS research participants and their families.

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Table 1

Relationship of Caffeine Use and Phenoconversion among Subjects with CAG ≥ 37

	Median (25th, 75th Percentiles)	Did Not Phenoconvert (N = 211)	Phenoconverted (N = 36)	Hazard Ratio (95% CI)	P-Value
History of Caffeine Use:					
Never/Former		10 (83%)	2 (17%)	1.00	0.48
Current		196 (86%)	33 (14%)	0.59 (0.14, 2.54)	
History of Coffee Use:					
Never		66 (85%)	12 (15%)	1.00	0.12
Former		24 (92%)	2 (8%)	0.21 (0.05, 0.95)	
Current		112 (84%)	21 (16%)	0.67 (0.31, 1.46)	
History of Soda Use:					
Never		40 (91%)	4 (9%)	1.00	0.05
Former		35 (85%)	6 (15%)	2.35 (0.59, 9.42)	
Current		128 (84%)	24 (16%)	4.13 (1.23, 13.84)	
Current Caffeine Exposure: mg caffeine/day					
None	0.0 (0.0, 0.0)	10 (83%)	2 (17%)	1.00	0.25
Moderate	84.2 (33.1, 124.5)	88 (90%)	10 (10%)	0.39 (0.09, 1.83)	
High	450.5 (284.5, 632.1)	78 (81%)	18 (19%)	0.72 (0.16, 3.23)	
Current Coffee Exposure: mg caffeine/day					
None	0 (0, 0)	90 (87%)	14 (13%)	1.00	0.20
Moderate	221.3 (79,0, 221.3)	59 (89%)	7 (11%)	0.67 (0.26, 1.74)	
High	442.5 (442.5, 885.0)	49 (78%)	14 (22%)	1.59 (0.73, 3.46)	
Current Soda Exposure: mg caffeine/day					
None	0 (0,0)	75 (88%)	10 (12%)	1.00	0.0376
Moderate	7.4 (7.4, 22.2)	51 (86%)	8 (14%)	2.13 (0.80, 5.62)	
High	103.5 (51.8, 207.0)	61 (81%)	14 (19%)	3.22 (1.32, 7.90)	
Cumulative Coffee Exposure: mg caffeine/day * years					
None	0 (0, 0)	68 (85%)	12 (15%)	1.00	0.50

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	Median (25th, 75th Percentiles)	Did Not Phenoconvert (N = 211)	Phenoconverted (N = 36)	Hazard Ratio (95% CI)	P-Value
Moderate	2213 (972, 3540)	64 (89%)	8 (11%)	0.56 (0.21, 1.47)	
High	11948 (9293, 19028)	58 (81%)	14 (19%)	0.77 (0.32, 1.87)	
Cumulative Soda Exposure: mg caffeine/day * years					
None	0 (0, 0)	43 (91%)	4 (9%)	1.00	0.06
Moderate	442 (182, 782)	72 (90%)	8 (10%)	2.26 (0.59, 8.71)	
High	2691 (1708, 4192)	63 (80%)	16 (20%)	4.05 (1.18, 13.96)	

Values shown are number (N, %) or medians (25th and 75th percentiles) and hazard ratios (95% confidence intervals). Probability (p) -values are from 2 degree of freedom (df) tests in separate models to predict phenoconversion, adjusted for age at time of environmental survey, gender, and CAG repeat length (continuous); the reference category is never or none. CI =confidence interval.

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Table 2

Relationship of Tobacco Use, Alcohol Use and Phenoconversion among Subjects with CAG ≥ 37

TOBACCO	Median (25th, 75th Percentiles)	Did Not Phenoconvert (N = 211)	Phenoconverted (N = 36)	Hazard Ratio (95% CI)	P-Value
History of Tobacco Use					
Never		105 (85%)	18 (15%)	1.00	0.44
Former		51 (89%)	6 (11%)	0.65 (0.25, 1.66)	
Current		46 (81%)	11 (19%)	1.28 (0.58, 2.86)	
Current Exposure: # Cigarettes/Day					
None	0 (0, 0)	167 (87%)	24 (13%)	1.00	0.35
Current Smoker	12 (5, 20)	29 (78%)	8 (22%)	1.52 (0.64, 3.62)	
Cumulative Exposure: Pack Years					
None	0.0 (0.0, 0.0)	113 (86%)	19 (14%)	1.00	0.64
Current/Past Smoker	9.8 (1.1, 19.0)	77 (87%)	12 (13%)	0.84 (0.39, 1.78)	
ALCOHOL	**Median (25th, 75th Percentiles)**	**Did Not Phenoconvert (N = 211)**	**Phenoconverted (N = 36)**	**Hazard Ratio (95% CI)**	**P-Value**
History of Alcohol Consumption					
Never		45 (82%)	10 (18%)	1.00	0.57
Former		20 (91%)	2 (9%)	0.46 (0.10, 2.18)	
Current		136 (86%)	22 (14%)	1.02 (0.45, 2.29)	
Current Alcohol Exposure: grams alcohol/day					
None	0.0 (0.0, 0.0)	66 (85%)	12 (15%)	1.00	0.61
Moderate	3.1 (1.1, 3.9)	48 (80%)	12 (20%)	1.50 (0.64, 3.53)	
High	18.1 (12.2, 33.0)	56 (92%)	5 (8%)	1.02 (0.34, 3.01)	
Cumulative Beer Exposure: grams alcohol/Day * years					
None	0 (0, 0)	82 (81%)	19 (19%)	1.00	0.99
Moderate	39 (20, 82)	50 (88%)	7 (12%)	1.03 (0.42, 2.55)	
High	369 (235, 822)	51 (91%)	5 (9%)	0.97 (0.30, 3.10)	
Cumulative Wine Exposure: grams alcohol/Day * years					

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TOBACCO	Median (25th, 75th Percentiles)	Did Not Phenoconvert (N = 211)	Phenoconverted (N = 36)	Hazard Ratio (95% CI)	P-Value
None	0 (0, 0)	113 (86%)	18 (14%)	1.00	0.86
Moderate	25 (14, 37)	34 (83%)	7 (17%)	1.28 (0.52, 3.13)	
High	152 (88, 329)	35 (83%)	7 (17%)	1.06 (0.42, 2.69)	
Cumulative Liquor Exposure: grams alcohol/Day * years					
None	0 (0, 0)	121 (86%)	19 (14%)	1.00	0.81
Moderate	23 (11, 36)	34 (85%)	6 (15%)	0.71 (0.24, 2.09)	
High	171 (94, 386)	35 (88%)	5 (13%)	0.85 (0.31, 2.32)	

Values shown are number (N, %) or medians (25th and 75th percentiles) and hazard ratios (95% confidence intervals). Probability (p)-values are from 2 degree of freedom (df) tests in separate models to predict phenoconversion, adjusted for age at time of environmental survey, gender, and CAG repeat length (continuous); the reference category is never or none. CI = confidence interval.