

RESEARCH ARTICLE

Does arterial hypertension influence the onset of Huntington's disease?

Leire Valcárcel-Ocete¹, Asier Fullaondo¹, Gorka Alkorta-Aranburu², María García-Barcina³, Raymund A. C. Roos⁴, Lena E. Hjermind⁵, Carsten Saft⁶, Marina Frontali⁷, Ralf Reilmann⁸, Hugh Rickards⁹, The REGISTRY investigators of the European Huntington's Disease Network (EHDN)[¶], Ana M. Zubiaga¹, Ana Aguirre^{1*}

1 Department of Genetics, Physical Anthropology and Animal Physiology, University of the Basque Country (UPV/EHU), Leioa, Spain, **2** Human Genetics, University of Navarra, Navarra, Spain, **3** Genetics Unit, Basurto University Hospital, OSI Bilbao Basurto, Bilbao, Spain, **4** Department of Neurology, Leiden University Medical Centre (LUMC), Leiden, The Netherlands, **5** Danish Dementia Research Centre, Neurogenetics Clinic, Department of Neurology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, **6** Huntington-Zentrum (NRW) Bochum, St. Josef-Hospital, Bochum, Germany, **7** Institute of Experimental Medicine, CNR, Rome, Italy, **8** George-Huntington Institute and Institute for Clinical Radiology, University of Muenster, and Dept. of Neurodegenerative Diseases and Hertie Institute of Clinical Brain Research, University of Tuebingen, Germany, **9** Department of Neurology, University of Birmingham, Birmingham, United Kingdom

¶ Membership of the REGISTRY investigators of the European Huntington's Disease Network is provided in the Acknowledgments.

* ana.aguirre@ehu.eus



OPEN ACCESS

Citation: Valcárcel-Ocete L, Fullaondo A, Alkorta-Aranburu G, García-Barcina M, Roos RAC, Hjermind LE, et al. (2018) Does arterial hypertension influence the onset of Huntington's disease? PLoS ONE 13(5): e0197975. <https://doi.org/10.1371/journal.pone.0197975>

Editor: David Blum, Centre de Recherche Jean-Pierre Aubert, FRANCE

Received: May 31, 2017

Accepted: May 13, 2018

Published: May 23, 2018

Copyright: © 2018 Valcárcel-Ocete et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This study was funded by Basque Government Department of Industry grants (Saiotek PE08UN78 and University-Company Program 09+ UEGV096/C01), by the Basque Government Department of Education (IT634-13) and by the University of the Basque Country UPV/EHU (UFI11/20). No funding bodies had any role in

Abstract

Huntington's disease (HD) age of onset (AO) is mainly determined by the length of the CAG repeat expansion in the *huntingtin* gene. The remaining AO variability has been attributed to other little-known factors. A factor that has been associated with other neurodegenerative diseases is arterial hypertension (AHT). The aim of this study is to evaluate the contribution of AHT to the AO of HD. We used data from a cohort of 630 European HD patients with adult onset collected by the REGISTRY project of the European Huntington's Disease Network. Multiple linear regression and ANOVA, controlling for the CAG repeat number of the expanded allele (CAGexp) of each patient, were performed to assess the association between the AHT condition and the AO of the motor symptoms (mAO). The results showed a significant association between AHT and mAO, especially when we only considered the patients diagnosed with AHT prior to manifesting any HD signs (pre-HD AHT). Remarkably, despite the low number of cases, those patients developed motor symptoms 5–8 years later than normotensive patients in the most frequent CAGexp range (40–44). AHT is an age-related condition and consequently, the age of the patient at the time of data collection could be a confounder variable. However, given that most pre-HD AHT patients included in our study had started treatment with antihypertensive drugs prior to the onset of HD, and that antihypertensive drugs have been suggested to confer a neuroprotective effect in other neurodegenerative diseases, raises the interest in elucidating the impact of AHT and/or AHT treatment in HD age of onset in further studies. A confirmation of our results in a larger sample set would open the possibility to significantly improve HD management.

study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Huntington's disease (OMIM: 143100) AO is mainly (about 60%) determined by the length of the CAG repeat expansion (CAGexp) in the *HTT* gene. The remaining variability has been attributed to genetic and little-explored environmental factors [1]. Arterial Hypertension (AHT) is a risk factor for numerous diseases with controversial effect on neurodegenerative diseases [2]. The impact of AHT on HD has not been examined to date. The aim of this study was to explore whether AHT could be an AO modifier factor for HD.

Methods

European Huntington's Disease Network's (EHDN) REGISTRY project provided data on 1,011 HD individuals. For this study, we gathered information on mAO [3], sex and age at the time of data collection of 630 European adult-onset HD patients with CAGexp ranging between 40 and 50, with known AHT status (86 hypertensives vs. 544 normotensives) and with AHT onset date available in the REGISTRY dataset. The 40–50 CAGexp range was selected to avoid the inclusion of juvenile-onset HD cases and thus, the introduction of errors in the regression analysis [3–5]. Furthermore, 40–50 CAGexp was the repeat range of hypertensive patients in our sample. Consequently, comparisons were performed between hypertensives and normotensives exhibiting equivalent CAGexp distribution. Ethical approval and written informed consents for each participant were obtained by the EHDN from the local ethics committees (<http://www.euro-hd.net/html/registry>), in compliance with the Declaration of Helsinki, the International Conference on Harmonisation—Good Clinical Practice (CH-GCP), and local regulations. Specific ethical approval of the study was obtained from the Clinical Research Ethics Committee of the Basque Country (CEIC- Euskadi), the Human Research Ethics Committee of the University of the Basque Country (CEISH) and the EHDN Scientific Bioethical Advisory Committee (SBAC). Multiple linear regression and ANCOVA tests were used to analyze the relationship between mAO and AHT, using CAGexp value as a covariate in each regression. Kolmogorov-Smirnov (K-S) test was used to compare CAGexp and mAO distributions between normotensive and hypertensive patients, while Mann-Whitney *U* test was used, in the same way, to compare the medians (SPSS ver.23.0; SPSS Inc.).

Results

In patients with CAGexp ranging between 40 and 50, AHT explains HD mAO variability significantly (regression analysis $P = 0.016$, Table 1; ANCOVA test $P = 0.004$). Remarkably, mAO in HD patients with AHT was manifested on average 7 years later than in normotensives (52.5 vs. 45 years, $P < 0.0001$), suggesting that AHT is associated with the appearance of motor symptoms at a later age. A significant association between AHT and a higher mAO was still detected in patients who manifested AHT before HD symptoms (pre-HD AHT patients) ($P = 0.024$, Table 1). Despite the limited number of patients ($N = 28$), we detected that the mAO median value was 10 years higher in pre-HD AHT patients than in normotensive patients.

Differences in CAGexp distribution among pre-HD AHT and normotensive patients were detected (K-S test $P < 0.0001$), probably due to sample size differences. Thus, we focused on HD patients carrying the most frequent CAGexp alleles (ranging from 40 to 44). In this case, the CAGexp allele distribution did not now differ between hypertensives and normotensives ($P = 0.266$, K-S test). However, the association between AHT and mAO ($P = 0.020$, Table 1) and the differences in the mAO distribution ($P = 0.011$, K-S test) remained significant. Remarkably, pre-HD AHT developed motor symptoms 6 years later than normotensives on

Table 1. Multiple regression analyses and descriptive statistics for mAO.

Model	N	Adjusted R ²	P-value	Groups	N	Motor AO		
						Median	Mann-Whitney U test (P)	Kolmogorov-Smirnov test (P)
<i>HTT</i> CAGexp + AHT (40–50 CAGexp range)	630	0.592	0.016	With AHT	86	52.5	<0.0001	<0.0001
				Normotensive	544	45		
<i>HTT</i> CAGexp + Pre-HD AHT (40–50 CAGexp range)	572	0.604	0.024	Pre-HD AHT	28	55.5	<0.0001	<0.0001
				Normotensive	544	45		
<i>HTT</i> CAGexp + Pre-HD AHT (40–44 CAGexp range)	384	0.340	0.020	Pre-HD AHT	27	56	0.002	0.011
				Normotensive	357	50		

<https://doi.org/10.1371/journal.pone.0197975.t001>

average (56 vs. 50 years, $P = 0.002$). Interestingly, the tendency of pre-HD AHT patients to manifest HD at higher mAOs relative to normotensives was detected for each CAGexp repeat number, except for the 41 CAGexp allele and the median difference ranged between 5 and 8 years (Fig 1).

Discussion

AHT, the most prevalent cardiovascular disorder in developed countries, has been associated with neuronal disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD) [6–8], suggesting that it may affect the neurodegeneration process. Our study is the first exploring the impact of AHT on HD and the first revealing an association between AHT and mAO.

According to our results, patients with AHT show the HD symptoms later (median of 7.5 years) than normotensive patients. These differences are more evident (median of 10.5 years) in the analysis that only takes into account patients that exhibited AHT before HD onset (pre-HD AHT patients). The results of the pre-HD AHT individuals are particularly relevant, since having manifested AHT before HD onset is a requirement for the examined variable to be considered a mAO modifying factor. The results after normalization of ratings to CAGexp values between 40 to 44 in pre-HD AHT and in normotensive patients indicate that the pre-HD AHT patients show motor symptoms between 5 and 8 years later than normotensive patients with the same CAGexp, suggesting that AHT may be an AO modifier. This effect is remarkably longer than those reported for any genetic modifier in HD [9].

The mechanism underlying this observation is presently unknown. In fact, although AHT has been related with other neurodegenerative diseases, its effect is presently unclear. AHT has been associated with a reduced risk of Parkinson's disease [6], but has also been considered a risk factor [7]. In AD, the relationship is also controversial [2], but most of the reviewed literature has noted that AHT is a strong risk factor [8], while antihypertensive drugs reduce the risk of AD [8,10]. Interestingly, most pre-HD AHT patients included in this study had started treatment with antihypertensive drugs prior to the onset of HD. Antihypertensive drugs have been suggested to confer a neuroprotective effect not only in AD [8,10], but also in PD [11], and they might also play a role in the later mAO shown by HD patients in our study.

The mechanism underlying this observation is presently unknown. In fact, although AHT has been related with other neurodegenerative diseases, its effect is presently unclear. AHT has been associated with a reduced risk of Parkinson's disease [6] but has also been considered a risk factor [7]. In AD, the relationship is also controversial [2], but most of the reviewed literature has noted that AHT is a strong risk factor [8] while antihypertensive drugs reduce the risk of AD [8,10]. Interestingly, most pre-HD AHT patients included in this study had started treatment with antihypertensive drugs prior to the onset of HD. Antihypertensive drugs have

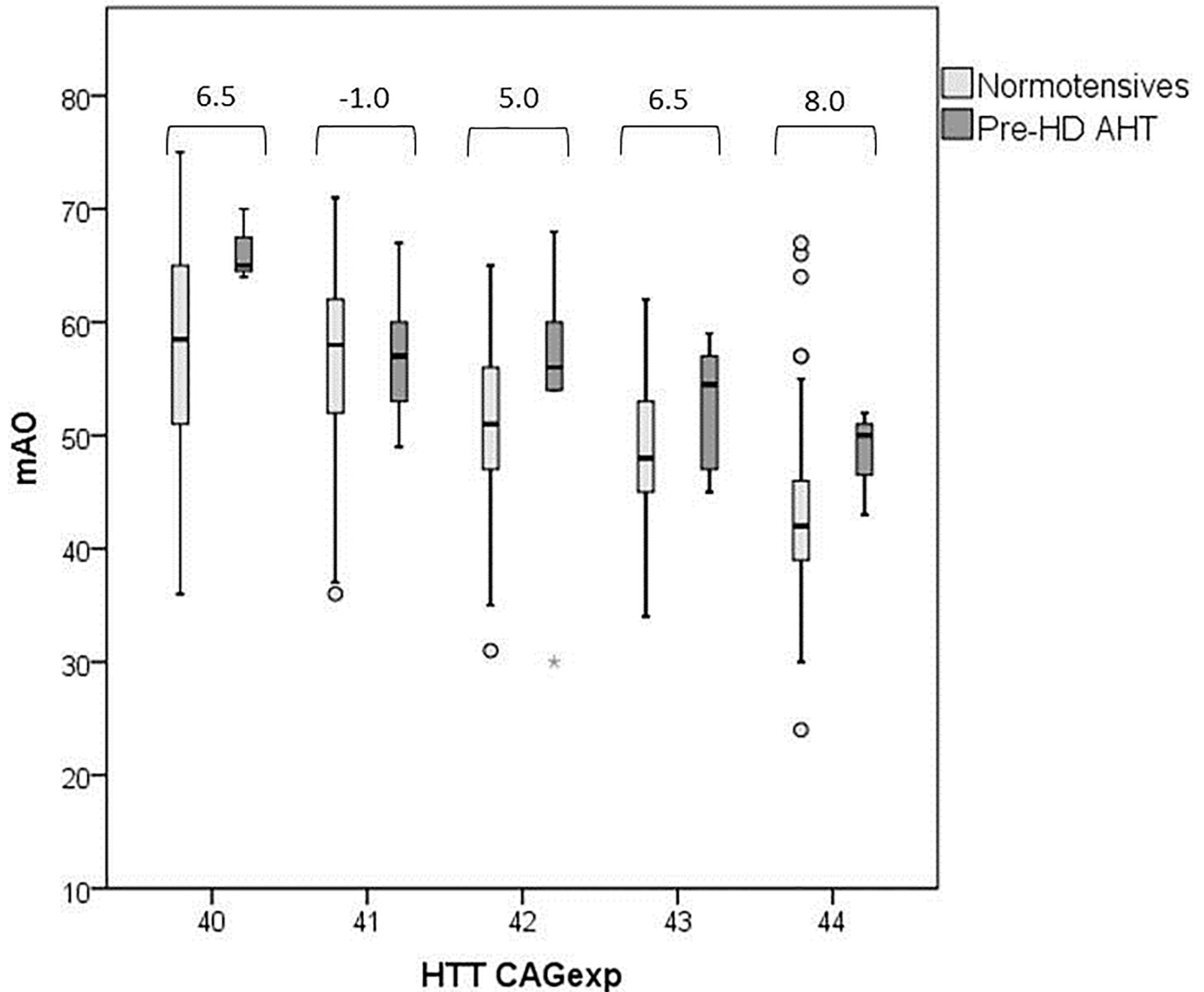


Fig 1. Variance in mAO for each CAGexp allele (40–44 range) in normotensives and in pre-HD AHT patients. Numbers above the square brackets are the difference in median years between Pre-HD AHT and normotensives for each CAGexp allele.

<https://doi.org/10.1371/journal.pone.0197975.g001>

been suggested to confer a neuroprotective effect, not only in AD [8,10], but also in PD [11], and they might also play a role in the later mAO shown by HD patients in our study.

Unfortunately, the high variability in the antihypertensive treatment types, changes in medication and incomplete medical records of our HD patient cohort have hampered our understanding of the impact of antihypertensive drugs in HD mAO. An additional limitation is that the prevalence of AHT increases with age [12], which means that a later onset HD patient is more likely to be recorded with a history of AHT, than an earlier onset participant. We have observed that the age of the participant at the time of data collection is correlated with mAO, as well as, with AHT. Thus, although age does not explain the mAO variability, it could have an influence in the observed relationship between mAO and AHT, leading to a spurious

association. On the other hand, the mAO and AHT onset data suggest that the pre-HD AHT condition is not necessarily related to later onset ages: 1) the median age of AHT onset in pre-HD AHT cases is 45.5 years, which is similar to the mAO median in normotensives patients (45 years); 2) the majority of pre-HD AHT patients (71%) showed motor symptoms at < 60 years and there were no pre-HD AHT cases with late-onset mAO (>70 years); 3) the effect of AHT in mAO is detected in ranges of CAG (40–44) in which juvenile and late HD cases (extreme cases that could bias the result) are not manifested. Notwithstanding this evidence, we cannot rule out the possible influence that age of patients at the time of data collection could have on the pre-HD AHT condition and, consequently, on the observed association.

In spite of the caveats, given the lack of current treatment options for HD, we consider that the findings of our study merits to be reported considering the accessibility to AHT treatments and the potential impact of these drugs (or the AHT condition) in the onset of HD. We believe that the role of AHT and/or its treatment should be further examined in other HD cohorts such as ENROLL-HD and possibly in pre-clinical models.

Supporting information

S1 Dataset. 630 European adult-onset HD patient dataset. Age: patient's age at the time of data collection; Sex: M (male) and F (female); CAGexp: CAG number repeat in expanded allele; mAO: motor onset, age of the first motor symptoms; AHT condition: normotensive (patient without arterial hypertension record), with AHT (patient with arterial hypertension records) and pre-HD AHT (patient with arterial hypertension records who manifested hypertension before HD symptoms). (PDF)

Acknowledgments

We thank all EHDN REGISTRY Study Group investigators for collecting the data and all participating REGISTRY patients for their time and efforts. The investigators of the European Huntington's Disease Network are:

Registry Steering committee: Anne-Catherine Bachoud-Lévi, Anna-Rita Bentivoglio, Ida Biunno, Raphael M. Bonelli, Jean-Marc Burgunder, Stephen B. Dunnett, Joaquim J. Ferreira, Jan Frich, Joe Giuliano, Olivia J. Handley, Arvid Heiberg, Sergey Illarioshkin, Torsten Illmann, Jiri Klempir, G. Bernhard Landwehrmeyer, Jamie Levey, Tim McLean, Maria Ramos-Arroyo, Jørgen E. Nielsen, Susana Pro Koivisto, Markku Päivärinta, Sven Pålhagen, Oliver Quarrell, Raymund A.C. Roos, Carsten Saft, Ana Rojo Sebastián, Sarah J. Tabrizi, Wim Vandenberghe, Christine Verellen-Dumoulin, Tereza Uhrova, Jan Wahlström, Jacek Zaremba.

Language coordinators: Katrin Barth, Monica Bascuñana Garde, Reineke Bos, Adrien Come, Leonor Correia Guedes, Vieira da Silva, Daniel Ecker, Ana Maria Finisterra, Ruth Fullam, Olivia J Handley, Carina Hvalstedt, Christine Held, Kerstin Koppers, Matilde Laurà, Asunción Martínez Descals, Saul Martinez-Horta, Tiago Mestre, Sara Minster, Daniela Monza, Martin Oehmen, Helene Padiou, Laurent Paterski, Nadia Peppia, Susana Pro Koivisto, Niini Røren (formerly Heinonen), Pavla Šašinková, Jenny Townhill, Patricia Trigo Cubillo, Marleen R van Walsem, Marie-Noelle Witjes-Ané, Daniel Zielonka, Eugeniusz Zielonka, Paola Zinzi.

AUSTRIA

Graz (Medizinische Universitäts Graz, Psychiatrie): Raphael M. Bonelli, Karen Hecht, Brigitte Herranhof, Anna Holl (formerly Hödl), Hans-Peter Kapfhammer, Michael Koppitz,

Sabine Lilek, Markus Magnet, Nicole Müller, Daniela Otti, Annamaria Painold, Karin Reisinger, Monika Scheibl, Helmut Schöggel, Jasmin Ullah; **Innsbruck (Universitätsklinik Innsbruck, Neurologie)**: Eva-Maria Braunwarth, Florian Brugger, Lisa Buratti, Eva-Maria Hametner, Caroline Hepperger, Christiane Holas, Anna Hotter, Anna Hussl, Barbara Larcher, Philipp Mahlkecht, Christoph Müller, Michael Nocker, Bernadette Pinter, Werner Poewe, Eva-Magdalena Reiter, Klaus Seppi, Fabienne Sprenger, Gregor Wenning.

BELGIUM

Charleroi (Institut de Pathologie et de Génétique (IPG)): Cécile Minet, Pascale Ribaï, Dominique Van Paemel, Christine Verellen-Dumoulin; **Leuven (Universitair Ziekenhuis Gasthuisberg)**: Andrea Boogaerts, Wim Vandenberghe, Dimphna van Reijen.

CZECH REPUBLIC

Prague (Extrapyramidové centrum, Neurologická klinika, 1. LF UK a VFN): Jiří Klempíř, Veronika Majerová, Jan Roth.

DENMARK

Copenhagen University Hospital (Rigshospitalet, Memory clinic): Lis Hasholt, Lena E. Hjermand, Oda Jacobsen, Jørgen E. Nielsen, Anne Nørremølle, Lisbeth Regeur, Sven Asger Sørensen, Jette Stockholm, Ida Unmack Larsen, Christina Vangsted-Hansen, Tua Vinther-Jensen.

FINLAND

Oulu (Dep. of Neurology): Jaana Åman, Jaakko Ignatius, Mikko Kärppä; **Oulu (Dep. of Medical Genetics)**: Aki Mustonen, Outi Kajula, Jukka Moilanen; **Tampere (Terveystalo Health-care Service Centre)**: Maire Santala; **Turku-Suvituuli (Rehabilitation Centre Suvituuli)**: Pia Eklund, Heli Hiivola, Hannele Hyppönen, Kirsti Martikainen, Katri Tuuha.

FRANCE

Angers (Centre de référence des maladies neurogénétique- CHU d'Angers): Philippe Allain, Dominique Bonneau, Marie Bost, Bénédicte Gohier, Marie-Anne Guérid, Audrey Olivier, Julie Prouzet, Adriana Prundean, Clarisse Scherer-Gagou, Christophe Verny.

GERMANY

Aachen (Universitätsklinikum Aachen, Neurologische Klinik): Christoph Michael Kosinski, Eva Milkereit, Daniela Probst, Kathrin Reetz, Christian Sass, Johannes Schiefer, Christiane Schlangen, Cornelius J. Werner; **Berlin (Universitätsmedizin Berlin, Klinik und Poliklinik für Neurologie)**: Markus Beuth, Harald Gelderblom, Josef Priller, Harald Prüß, Eike Spruth, Silvia Thiel; **Bochum (Huntington-Zentrum (NRW) Bochum im St. Josef-Hospital)**: Jürgen Andrich, Gisa Ellrichmann, Lennard Herrmann, Rainer Hoffmann, Barbara Kaminski, Peter Kraus, Christian Prehn, Carsten Saft, Stephan Salmen, Christiane Stamm, Katrin Straßburger; **Dinslaken (Reha Zentrum in Dinslaken im Gesundheitszentrums Lang)**: Herwig Lange, Robert Maiwald; **Dresden (Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Klinik und Poliklinik für Neurologie)**: Ulrike Hunger, Matthias Löhle, Antonia Maass, Simone Schmidt, Alexander Storch, Annett Wolz, Martin Wolz; **Freiburg (Universitätsklinik Freiburg, Neurologie)**: Philipp Capetian, Johann Lambeck, Birgit Zucker; **Hamburg**

(Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Neurologie): Kai Boelmans, Christos Ganos, Walburgis Heinicke, Ute Hidding, Jan Lewerenz, Alexander Münchau, Michael Orth, Jenny Schmalfeld, Lars Stubbe, Simone Zittel; **Hannover (Neurologische Klinik mit Klinischer Neurophysiologie, Medizinische Hochschule Hannover):** Gabriele Diercks, Dirk Dressler, Flverly Francis, Sabine Gayde-Stephan, Heike Gorzolla, Bianca Kramer, Rebecca Minschke, Christoph Schrader, Pawel Tacik; **Itzehoe (Schwerpunktpraxis Huntington, Neurologie und Psychiatrie):** Michael Ribbat; **München (Huntington-Ambulanz im Neuro-Kopfzentrum—Klinikum rechts der Isar der Neurologischen Klinik und Poliklinik der Technischen Universität München):** Antje Lüsebrink, Mark Mühlau, Alexander Peinemann, Michael Städtler, Adolf Weindl, Juliane Winkelmann, Cornelia Ziegler; **Münster (George-Huntington-Institute):** Natalie Bechtel, Heike Beckmann, Stefan Bohlen, Eva Hölzner, Herwig Lange, Ralf Reilmann, Stefanie Rohm, Silke Rumpf, Christian Sass, Sigrun Schepers; **Taufkirchen (Isar-Amper-Klinikum—Klinik Taufkirchen (Vils)):** Michael Bachmeier, Antonie Beister, Matthias Dose, Kathrin Hammer, Gabriele Leythaeuser, Ralf Marquard, Tina Raab, Caroline Schrenk, Michele Schuierer, Alexandra Wiedemann; **Ulm (Universitätsklinikum Ulm, Neurologie):** Katrin Barth, Andrea Buck, Julia Connemann, Daniel Ecker, Carolin Geitner, Christine Held, Andrea Kesse, Bernhard Landwehrmeyer, Franziska Lezius, Jan Lewerenz, Solveig Nepper, Anke Niess, Michael Orth, Ariane Schneider, Daniela Schwenk, Sigurd Süßmuth, Sonja Trautmann, Patrick Weydt.

ITALY

Bari (Neurophysiopathology of Pain Unit, Basic Medical, Neuroscience and Sensory System Department, University of Bari): Claudia Cormio, Olimpia Difruscolo, Vittorio Sciruicchio, Claudia Serpino, Marina de Tommaso; **Bologna (DIBINEM—Alma Mater Studiorum—Università di Bologna, IRCCS Istituto delle Scienze Neurologiche di Bologna):** Sabina Capellari, Pietro Cortelli, Roberto Gallassi, Roberto Poda, Giovanni Rizzo, Cesa Scaglione; **Florence (Department of Neuroscience, University of Florence & Careggi University Hospital):** Elisabetta Bertini, Elena Ghelli, Andrea Ginestroni, Francesca Massaro, Claudia Mechi, Marco Paganini, Silvia Piacentini, Silvia Pradella, Anna Maria Romoli, Sandro Sorbi; **Genova (Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova):** Giovanni Abbruzzese, Monica Bandettini di Poggio, Emilio Di Maria, Giovanna Ferrandes, Paola Mandich, Roberta Marchese; **Milan (SODS Genetica delle Malattie Neurodegenerative e Metaboliche & U.O. Neurologia, Fondazione IRCCS Istituto Neurologico Carlo Besta):** Alberto Albanese, Stefano Di Donato+, Daniela Di Bella, Antonio Elia, Cinzia Gellera, Silvia Genitrini, Caterina Mariotti, Daniela Monza, Lorenzo Nanetti, Dominga Paridi, Paola Soliveri, Chiara Tomasello; **Naples (Department of Neurosciences and Reproductive and Odontostomatological Sciences, Federico II University of Naples):** Giuseppe De Michele, Luigi Di Maio, Carlo Rinaldi, Cinzia Valeria Russo, Elena Salvatore, Tecla Tucci; **Pozzilli (IS) (IRCCS Neuromed):** Milena Cannella, Valentina Codella, Francesca De Gregorio, Annunziata De Nicola, Tiziana Martino, Maria Simonelli, Ferdinando Squitieri; **Rome (LIRH Foundation):** Ferdinando Squitieri; **Rome (Department of Neurology, Università Cattolica del Sacro Cuore; National Research Council of Italy, Institute of Translational Pharmacology & Institute of Cognitive Sciences and Technologies):** Anna Rita Bentivoglio, Claudio Catalli, Raffaella Di Giacopo, Alfonso Fasano, Marina Frontali, Arianna Guidubaldi, Tamara Ialongo, Gioia Jacopini, Giovanna Loria, Anna Modoni, Carla Piano, Chiara Piccininni, Davide Quaranta, Silvia Romano, Francesco Soleti, Maria Spadaro, Paola Zinzi.

NETHERLANDS

Enschede (Medisch Spectrum Twente): Monique S.E. van Hout, Jeroen P.P. van Vugt, A. Marit de Weert; **Leiden (Leiden University Medical Centre (LUMC)):** Reineke Bos, Eve M. Dumas, Ellen P. 't Hart, Caroline Jugens, Anne Kampstra, Raymund A.C. Roos, Marie-Noëlle Witjes-Ané, Simon J.A. van den Bogaard; **Nijmegen (Universitair Medisch Centrum St. Radboud, Neurology):** Berry Kremer, Carla Verstappen.

NORWAY

Bergen (Haukeland University Hospital, Dept of Medical Genetics and Olaviken Psychiatric Hospital): Ellen Økland Blinkenberg. (NKS Olaviken's HD clinic): Erik Hauge, Hilde Tyvoll; **Oslo University Hospital (Dept. of Medical Genetics, Dept. of Neurology, Dept. of Neurorehabilitation):** Olaf Aaserud, Kathrine Bjørgo, Nancy Borgeød, Elisabeth Dramstad, Madeleine Fannemel, Jan C. Frich, Per F. Gørvell, Arvid Heiberg, Lars Retterstøl, Oddveig Røsby, Alma Sikiric, Bodil Stokke, Marleen van Walsem, Ragnhild Wehus; **Trondheim (St. Olavs Hospital):** Inga Bjørnevoll, Sigrid Botne Sando.

POLAND

Gdansk (St. Adalbert Hospital, Gdansk, Medical University of Gdansk, Neurological and Psychiatric Nursing Dpt.): Artur Dziadkiewicz, Emilia Sitek, Jaroslaw Slawek, Witold Soltan; **Katowice (Medical University of Silesia, Katowice):** Magdalena Błaszczuk, Magdalena Boczarska-Jedynak, Ewelina Ciach-Wysocka, Barbara Jasińska-Myga, Gabriela Kłodowska-Duda, Grzegorz Opala, Daniel Stempel; **Krakow (Krakowska Akademia Neurologii):** Krzysztof Banaszkiwicz, Dorota Boćwińska, Kamila Bojakowska-Jaremek, Małgorzata Dec, Małgorzata Krawczyk, Monika Rudzińska, Elżbieta Szczygieł, Magdalena Wójcik, Anna Wasielewska; **Poznan (Poznan University of Medical Sciences, Poland):** Anna Bryl, Anna Ciesielska, Aneta Klimberg, Jerzy Marcinkowski, Husam Samara, Justyna Sempołowicz, Daniel Zielonka; **Warsaw-MU (Medical University of Warsaw, Neurology):** Anna Gogol (formerly Kalbarczyk), Zygmunt Jamrozik, Piotr Janik, Hubert Kwiecinski; **Warsaw-IPiN (Institute of Psychiatry and Neurology Dep. of Genetics, First Dep. of Neurology):** Jakub Antczak, Katarzyna Jachinska, Wioletta Krysa, Maryla Rakowicz, Danuta Ryglewicz, Iwona Stępnia, Anna Sułek, Grzegorz Witkowski, Jacek Zaremba, Elzbieta Zdzienicka, Karolina Ziara-Jakutowicz.

PORTUGAL

Coimbra (Hospital Universitário de Coimbra): Cristina Januário, Filipa Júlio; **Lisbon (Hospital de Santa Maria, Clinical Pharmacology Unit, Instituto de Medicina Molecular):** Leonor Correia Guedes, Tiago Mestre, Tiago Mendes, Maria Finisterra, Anabela Valadas, Miguel Coelho, Joaquim J Ferreira; **Porto (Hospital de São João):** Miguel Gago, João Massano, Carlos Andrade, Andreia Costa, Maria Rosalia Guerra, Joana Guimarães, Joana Meireles, Ana Monteiro, Carolina Garrett.

SPAIN

Badajoz (Hospital Infanta Cristina): Carmen Durán Herrera, Patrocinio Garcia Moreno; **Barcelona-Bellvitge (Hospital Universitari de Bellvitge):** Jordi Bas, Núria Busquets, Matilde Calopa, Serge Jaumà Classen, Nadia Rodríguez Dedichá; **Barcelona-Hospital Mútua de Terrassa:** Miquel Aguilar Barbera, Ana Rojo Sebastián, Sonia Arribas Pardo, Dolors Badenes Guia, Noemi Calzado, Laura Casas Hernanz, Judit López Catena, Pilar Quiléz Ferrer, Gemma Tome Carruesco; **Barcelona-Merced (Hospital Mare de Deu de La Merced):** Misericordia

Floriach Robert, Cèlia Mareca Viladrich, Elvira Roca, Jesús Miguel Ruiz Idiago, Antonio Villa Riballo; **Burgos (Servicio de Neurología Hospital General Yagüe)**: Esther Cubo, Natividad Mariscal; **Fuenlabrada (Hospital Universitario)**: Fernando Alonso-Frech; **Granada (Hospital Universitario San Cecilio, Neurología)**: Francisco Barrero, Blas Morales; **Madrid-Clínico (Hospital Clínico Universitario San Carlos)**: María del Mar Fenollar, Rocío García-Ramos García, Purificación Pin Quiroga, Clara Villanueva; **Madrid RYC (Hospital Ramón y Cajal, Neurología)**: Mónica Bascañana, Marta Fatás Ventura, Juan García Caldentey, Guillermo García Ribas, Justo García de Yébenes, José Luis López-Sendón Moreno, Christine Schwarz, Patricia Trigo Cubillo; **Madrid FJD (Madrid-Fundación Jiménez Díaz)**: Pedro José García Ruíz, Ana García, Juan García Caldentey, Rosa Guerrero López, Antonio Herranz Bárcenas, Asunción Martínez-Descals, Noelia Rodríguez Martínez, María José Sainz Artiga, Vicenta Sánchez, Angel Martínez Pueyo; **Murcia (Hospital Universitario Virgen de la Arrixaca)**: Carmen Antúnez Almagro, Lorenza Fortuna, Salvadora Manzanares, Juan Marín Muñoz, María Martirio Antequera Torres, Fuensanta Noguera Perea, Laura Vivancos; **Palma de Mallorca (Hospital Universitario Son Espases)**: Aranzazú Gorospe, María José Torres Rodríguez, Inés Legarda Ramirez, Penelope Navas Arques, Monica Rodriguez Lopera, Barbara Vives Pastor; **Valencia (Hospital la Fe)**: María Bosca, Juan Andrés Burguera, Francisco Castera Brugada Carmen Peiró Vilaplana, Pilar Solís, Begoña Jeweinat Figuerola, Paloma Millan Palanca.

SWEDEN

Stockholm Karolinska University Hospital: Elisabeth Björnsson, Martin Paucar, Sven Pålhaugen, Per Svenningsson, Tina Wallden; **Umeå (Umeå University Hospital)**: Ghada Loutfi, Carina Olofsson, Eva-Lena Stattin, Laila Westman, Birgitta Wikström.

SWITZERLAND

Bern (Swiss HD Zentrum): Jean-Marc Burgunder, Yanik Stebler, **Bern (Zentrum für Bewegungsstörungen, Neurologische Klinik und Poliklinik, Universität Bern)**: Alain Kaelin, Irene Romero, Michael Schüpbach, Sabine Weber Zaugg.

U.K.

Aberdeen (NHS Grampian Clinical Genetics Centre & University of Aberdeen): Roisin Jack, Kirsty Matheson, Zosia Miedzybrodzka, Daniela Rae, Sheila A Simpson, Fiona Summers, Alexandra Ure; **Birmingham (The Barberrry Centre, Dept of Psychiatry)**: Shahbana Akhtar, Jenny Crooks, Adrienne Curtis, Jenny de Souza (Keylock), Hugh Rickards, Jan Wright; **Cambridge (Cambridge Centre for Brain Repair, Forvie Site)**: Roger A. Barker, Anna Gerrtiz (nee Di Pietro), Kate Fisher, Anna Goodman, Susan Hill, Ann Kershaw, Sarah Mason, Nicole Paterson, Lucy Raymond, Rachel Swain; **Cardiff (Schools of Medicine and Biosciences, Cardiff University)**: Jonathan Bisson, Monica Busse, Cynthia Butcher, Catherine Clenaghan, Stephen Dunnett, Ruth Fullam, Olivia Handley, Alis Hughes, Sarah Hunt, Lesley Jones, Una Jones, Hanan Khalil, Sara Minster, Michael Owen, Kathleen Price, Anne Rosser, Jenny Townhill; **Fife (Scottish Huntington's Association Whytman's Brae Hospital)**: Peter Brockie, Jillian Foster, Nicola Johns, Sue McKenzie, Jean Rothery, Gareth Thomas, Shona Yates; **Glasgow (Glasgow HD Management Clinic, Southern General Hospital)**: Catherine Deith, Stuart Ritchie; **Gloucester (Department of Neurology Gloucestershire Royal Hospital)**: Liz Burrows, Amy Fletcher, Alison Harding, Fiona Laver, Mark Silva, Aileen Thomson; **Leeds (Chapel Allerton Hospital, Department of Clinical Genetics)**: Carol Chu, Stephanie Hamer, Emma Hobson, Stuart Jamieson, Alison Kraus, Ivana Markova, Ashok Raman, Jean Toscano, Sue Wild, Pam Yardumian; **London (St. Georges-Hospital)**: Michael Patton, Maria Peterson,

Sarah Rose; **London (Guy's Hospital)**: Thomasin Andrews, Andrew Dougherty, Charlotte Golding, Fred Kavalier, Hana Laing, Alison Lashwood, Dene Robertson, Deborah Ruddy, Anna Whaite; **London (The National Hospital for Neurology and Neurosurgery)**: Thomasin Andrews, Stefania Bruno, Elvina Chu, Karen Doherty, Charlotte Golding, Nayana Lahiri, Marianne Novak, Aakta Patel, Elisabeth Rosser, Sarah Tabrizi, Rachel Taylor, Thomas Warner, Edward Wild; **Manchester (Genetic Medicine, University of Manchester, Manchester Academic Health Sciences Centre and Central Manchester University Hospitals NHS Foundation Trust)**: Natalie Arran, Jenny Callaghan, David Craufurd, Ruth Fullam, Marianne Hare, Liz Howard, Susan Huson, Liz Johnson, Mary Jones, Helen Murphy, Emma Oughton, Lucy Partington-Jones, Dawn Rogers, Andrea Sollom, Julie Snowden, Cheryl Stopford, Jennifer Thompson, Iris Trender-Gerhard, Nichola Verstraelen (formerly Ritchie), Leann Westmoreland; **Oxford (Oxford University Hospitals NHS Trust, Dept. of Neurosciences, University of Oxford)**: Andrea H Nemeth, Gill Siuda; **Sheffield (The Royal Hallamshire Hospital–Sheffield Children's Hospital)**: Oliver Bandmann, Alyson Bradbury, Helen Fairtlough, Kay Fillingham, Isabella Foustanos, Paul Gill, Mbombe Kazoka, Kirsty O'Donovan, Oliver Quarrell, Nadia Peppia, Katherine Tidswell.

Author Contributions

Conceptualization: Leire Valcárcel-Ocete, Ana Aguirre.

Data curation: Leire Valcárcel-Ocete.

Formal analysis: Leire Valcárcel-Ocete.

Funding acquisition: Ana M. Zubiaga, Ana Aguirre.

Investigation: Leire Valcárcel-Ocete, Raymund A. C. Roos, Lena E. Hjermand, Carsten Saft, Marina Frontali, Ralf Reilmann, Hugh Rickards, Ana Aguirre.

Methodology: Leire Valcárcel-Ocete, Asier Fullaondo, Gorka Alkorta-Aranburu, Ana Aguirre.

Project administration: Leire Valcárcel-Ocete, Ana Aguirre.

Resources: María García-Barcina, Raymund A. C. Roos, Lena E. Hjermand, Carsten Saft, Marina Frontali, Ralf Reilmann, Hugh Rickards, Ana Aguirre.

Software: Leire Valcárcel-Ocete, Asier Fullaondo, Gorka Alkorta-Aranburu, Ana Aguirre.

Supervision: Asier Fullaondo, Ana M. Zubiaga, Ana Aguirre.

Validation: Leire Valcárcel-Ocete.

Visualization: Leire Valcárcel-Ocete, Ana Aguirre.

Writing – original draft: Leire Valcárcel-Ocete, Ana Aguirre.

Writing – review & editing: Leire Valcárcel-Ocete, Asier Fullaondo, Gorka Alkorta-Aranburu, María García-Barcina, Raymund A. C. Roos, Lena E. Hjermand, Carsten Saft, Marina Frontali, Ralf Reilmann, Hugh Rickards, Ana M. Zubiaga, Ana Aguirre.

References

1. Wexler NS, Lorimer J, Porter J, Gomez F, Moskowitz C, Shackell E, et al. Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. *Proc Natl Acad Sci USA*. 2004; 101:3498–3503. <https://doi.org/10.1073/pnas.0308679101> PMID: 14993615

2. Yuan M, Chen SJ, Li XL, Xu LJ. Blood Pressure and the Risk of Alzheimer's Disease: Is There a Link? *Am J Alzheimers Dis Other Dement*. 2016; 31:97–8. <https://doi.org/10.1177/1533317515587086> PMID: [26006793](https://pubmed.ncbi.nlm.nih.gov/26006793/)
3. Valcárcel-Ocete L, Alkorta-Aranburu G, Iriondo M, Fullaondo A, García-Barcina M, Fernández-García JM, et al. Exploring Genetic Factors Involved in Huntington Disease Age of Onset: E2F2 as a New Potential Modifier Gene. *PLoS One*. 2015; 10:e0131573. <https://doi.org/10.1371/journal.pone.0131573> PMID: [26148071](https://pubmed.ncbi.nlm.nih.gov/26148071/)
4. Ramos EM, Latourelle JC, Lee JH, Gillis T, Mysore JS, Squitieri F, et al. Population stratification may bias analysis of PGC1- α as a modifier of age at Huntington's disease motor onset. *Human Genet*. 2012; 131:1833–1840
5. Lee JM, Ramos EM, Lee JH, Gillis T, Mysore JS, Hayden MR et al., CAG repeat expansion in Huntington's disease determines age at onset in a fully dominant fashion. *Neurology*. 2012; 78:690–695. <https://doi.org/10.1212/WNL.0b013e318249f683> PMID: [22323755](https://pubmed.ncbi.nlm.nih.gov/22323755/)
6. Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, et al.: Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Ann Neurol*. 2012; 72: 893–901. <https://doi.org/10.1002/ana.23687> PMID: [23071076](https://pubmed.ncbi.nlm.nih.gov/23071076/)
7. Qiu C, Hu G, Kivipelto M, Laatikainen T, Antikainen R, Fratiglioni L, et al. Association of blood pressure and hypertension with the risk of Parkinson disease: the National FINRISK Study. *Hypertension*. 2011; 57:1094–1100. <https://doi.org/10.1161/HYPERTENSIONAHA.111.171249> PMID: [21536985](https://pubmed.ncbi.nlm.nih.gov/21536985/)
8. Murray IV, Proza JF, Sohrabji F, Lawler JM. Vascular and metabolic dysfunction in Alzheimer's disease: a review. *Exp Biol Med (Maywood)*. 2011; 236: 772–782.
9. Gusella JF & MacDonald ME. Huntington's disease: the case for genetic modifiers. *Genome Med*. 2009; 8:80.
10. Duron E, Rigaud AS, Dubail D, Mehrabian S, Latour F, Seux ML, et al. Effects of antihypertensive therapy on cognitive decline in Alzheimer's disease. *Am J Hypertens*. 2009, 22:1020–1024. <https://doi.org/10.1038/ajh.2009.119> PMID: [19590498](https://pubmed.ncbi.nlm.nih.gov/19590498/)
11. Becker C, Jick SS, Meier CR. Use of antihypertensives and the risk of Parkinson disease. *Neurology*. 2008, 70:1438–1444. <https://doi.org/10.1212/01.wnl.0000303818.38960.44> PMID: [18256367](https://pubmed.ncbi.nlm.nih.gov/18256367/)
12. Bielecka-Dabrowa A, Aronow WS, Rysz J, Banach M. The Rise and Fall of Hypertension: Lessons Learned from Eastern Europe. *Curr Cardiovasc Risk Rep*. 2011, 5: 174–179. <https://doi.org/10.1007/s12170-010-0152-2> PMID: [21475621](https://pubmed.ncbi.nlm.nih.gov/21475621/)