BIOGRAPHICAL SKETCH June 2025

NAME	POSITION TITLE
Ioannis Zaganas, MD, PhD Tel: +302810394643, +302810394617 Email: zaganas@uoc.gr, johnzag@yahoo.com	Associate Professor of Neurology, Neurology / Neurogenetics Laboratory, Medical School, University of Crete / **Neurology Department, University Hospital of Heraklion, Stavrakia Voutes 71500 Heraklion, Crete, Greece**

EDUCATION / TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
University of Crete, Heraklion, Crete, Greece	MD	1997	Medicine
University of Crete, Heraklion, Crete, Greece	Ph. D.	2005	Neuroscience
Prefecture of Heraklion, Crete, Greece	Neurology Certification	2008	Neurology

A. PERSONAL STATEMENT

Neurodegenerative disorders, and especially Alzheimer's disease, as well as Rare Neurogenetic Disorders, have been the focus of my clinical, educational, and research activities for at least 25 years.

On *clinical grounds*, I have been running the Memory Clinic of the University Hospital of Heraklion, Crete, Greece, since its establishment in 2007, following patients with cognitive disorders and offering them access to research projects. Also, I have been diagnosicng and treating patients with rare neurogenetic diseases, including spinal muscular atrophy, hereditary amyloidosis, Huntington's disease, hereditary ataxias, muscular dystrophies etc.

On *educational grounds*, I have been teaching 4th and 5th year medical students at the University of Crete, as well as postgraduate students, on dementia and neurogenetic disease related topics since 2014. Since July 2022, I have been organizing two highly successful summer schools entitled "Dementia for Medical Students" and "TTR Amyloidosis", respectively, with participation of medical students from Belgium, Cyprus, Germany, Italy, India, Poland, Romania, and the UK. Also, I have been teaching in 5 postgraduate programs (Molecular Basis of Human Disease, Neurosciences, Molecular Medicine, Bioethics, Emergency and Intensive Pediatric Care of the University of Crete, and Neurodegenerative Disorders of the Aristotle University of Thessaloniki). Recently, I organized a very successful Erasmus Blended Intensive Program on Cognitive Disorders in Crete, with the participation of students and faculty from Coimbra, Valencia, Istanbul and Sofia. I serve as the Scientific Coordinator for the International Student Exchanges of the University of Crete and Chairman of the Ethics Committee of the University Hospital of Heraklion.

Finally, the focus of my *research* is on the epidemiology, genetic basis, and molecular mechanisms of neurodegeneration, especially in relation to Alzheimer's disease and other dementias, as well as the etiology and pathophysiology of rare neurogenetic disorders. Specifically, I am interested in:

a) Dissecting the role of genetic factors, as found using whole exome sequencing and other genetic analysis strategies, in the pathophysiology of Alzheimer's disease and other dementias, as well as other neural and non-neural phenotypes (e.g. Mathioudakis et al, *Neurobiology of Aging*, 2022, PMID: 36117051). In this respect, I have been a co-investigator in the National Network for Neurodegenerative disorders Research based on Precision medicine, a multidisciplinary research network funded by the Greek state.

b) Establishing procedures for the use of whole exome sequencing and other next generation sequencing techniques in the diagnostic investigation of neurogenetic diseases, including inherited dementias (e.g. Bourbouli et al, *Brain Sci*, 2021, PMID: 34573259). In this context, I have been participating in the SOLVE RD project, an international project aimed at deciphering the genetic basis of rare diseases. Also, this project is continued in the context of a

HORIZON program (ERDERA; European Rare Disease Research Alliance), in which my laboratory has been included as a partner.

c) Studying the role of environmental factors on the onset and progression of dementia and other neurological disorders (e.g. Zaganas et al, *Am J Alzheimers Dis Other Demen*, 2019, PMID: 30259758)

d) Understanding the functional properties and role of glutamate dehydrogenase, a key enzyme in glutamate metabolism and glutamate-induced neurodegeneration (e.g. Dimovasili et al, *J Neurochem*, 2021, PMID: 33421122; Litso et al, Biomolecules, 2023, PMID: 38254622)

B. POSITIONS, SCIENTIFIC APPOINTMENTS, AND HONORS:

2022-today	**Chairman of the Institutional Review Board of the University Hospital of Heraklion, Crete** (member of the Board since 2016)
2016-today	**Coordinator of the International Exchanges Committee** of the University of Crete, Medical School (in charge of Erasmus and other Student Exchanges)
2024-today	**Associate Professor of Neurology** Medical School, University of Crete, Greece
2020 – today	**Member, Hellenic Initiative Against Alzheimer's Disease** (Basic and Clinical Science groups)
2018 – 2022	Evaluator / Member of the MODIP-Quality Assurance Unit of the University of Crete
2014-2023	**Assistant Professor of Neurology** Medical School, University of Crete, Greece
2013 – 2013	**Teaching and Research Faculty Member (PD407)** Medical School, University of Crete, Greece
2011 – 2013	**Post-Doctoral Researcher** Medical School, University of Crete, Greece
2011 – 2011	**Invited scientist** Neuro-metabolism Unit, Department of Drug Design and Pharmacology, University of Copenhagen, Denmark
2010 – 2011	**Neurology Consultant** Neurology Department, University Hospital of Heraklion, Crete, Greece
2009 – 2010	**Teaching and Research Faculty Member (PD407)** Medical School, University of Crete, Greece
2008 – today	**Member of the Greek Neurological Society** (Participating in Dementia and Neurogenetics branches)
2008 – 2009	**Teaching and Research Faculty Member (PD407)** Medical School, University of Crete, Greece
2004 – 2008	**Neurology Resident** Neurology Department, University Hospital of Heraklion, Crete, Greece
2004 – 2005	**Post-Doctoral Researcher on Genetics and Neurobiology of Alzheimer's disease** Mount Sinai School of Medicine, Department of Psychiatry, New York, USA (partly through Scholarship by the Alexandros Onassis Foundation)
2000 – 2001	**Psychiatry Resident** Neurology Department, University Hospital of Heraklion, Crete, Greece
1999 – 2005	**PhD Candidate** "Glutamate dehydrogenase in the biology of the mammalian nervous system" Medical School, University of Crete, Greece
1999 – 1999	**Internal Medicine Resident** Neurology Department, University Hospital of Heraklion, Crete, Greece
1997 – 1999	**Rural Medical Service** Kastelli Health Center, Crete, Greece
1997	**Permit to practice medicine (Heraklion Prefecture): 16554 (4/9/1997)**
1997 – today	**Member of the Medical Association of Heraklion, Crete**

1991 – 1997	**Medical Student** Medical School, University of Crete, Greece

C. CONTRIBUTION TO SCIENCE

My contribution to science has been in the field of neurodegenerative and neurogenetic disorders, and is reflected in 88 peer reviewed PubMed indexed publications, that can be found at:
https://pubmed.ncbi.nlm.nih.gov/?term=Zaganas+I+NOT+Fotidis&sort=date
These publications have drawn 1,793 citations (h-index 24) in Scopus (accessed June 20th, 2025):
https://www.scopus.com/pages/citationOverview?authorsIds=6506306253&origin=AuthorNamesList
and 2,552 in Google Scholar (h-index 29)

Specifically, I have contributed to research endeavors on the:

I. **Study of epidemiological and biological factors affecting dementia occurrence**

The Cretan Aging Cohort has been established through a grant partially funded by the European Union and I have been a co-investigator in this project, participating in the epidemiological studies and directing all genetic analyses as part of this project. The study describing this cohort (Zaganas et al, 2019) showed that both MCI and dementia were common in the aged population of Crete (32.4% and 10.8%, respectively) and were partly associated with the low educational status due to World War II. Furthermore, studies on this cohort have shed light on the role of inflammation and sleep in neurodegenerative disorders such as AD (Basta et al, 2021; 2022; Antypa et al, 2022)

1) **I. V. Zaganas**, P. Simos, M. Basta, S. Kapetanaki, S. Panagiotakis, I. Koutentaki, N. Fountoulakis, A. Bertsias, G. Duijker, C. Tziraki, N. Scarmeas, A. Plaitakis, D. Boumpas, C. Lionis and A. N. Vgontzas. The Cretan Aging Cohort: Cohort Description and Burden of Dementia and Mild Cognitive Impairment. *Am J Alzheimers Dis Other Demen*, 34: 23-33, 2019.
2) Basta M, **Zaganas I**, Simos P, Koutentaki E, Dimovasili C, Mathioudakis L, Bourbouli M, Panagiotakis S, Kapetanaki S, Vgontzas A. Apolipoprotein E ε4 (APOE ε4) Allele is Associated with Long Sleep Duration Among Elderly with Cognitive Impairment. *J Alzheimer's Dis* 79:763-771, 2021.
3) M. Basta, A. N. Vgontzas, J. Fernandez-Mendoza, D. Antypa, Y. Li, **I. Zaganas**, S. Panagiotakis, E. Karagkouni and P. Simos. Basal Cortisol Levels Are Increased in Patients with Mild Cognitive Impairment: Role of Insomnia and Short Sleep Duration. J Alzheimers Dis, 87: 933-944,2022.
4) Antypa D, Basta M, Vgontzas A, **Zaganas I**, Panagiotakis S, Vogiatzi E, Kokosali E, Simos P.The association of basal cortisol levels with episodic memory in older adults is mediated by executive function. Neurobiol Learn Mem. 2022 Apr; 190:107600.

II. **Genetic basis of neurodegenerative diseases, including Alzheimer's disease**

Since 2001 I have been working on the genetic basis of neurodegenerative disorders. Recently, my laboratory (Neurogenetics Laboratory, Medical School, University of Crete) has worked on the elucidation of the genetic background of Frontotemporal Dementia (FTD), Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's disease (AD). Through this research, an especially important role for TDP-43 (the protein product of the *TARDBP* gene) across these 3 neurodegenerative disorders has emerged since causative variants in the *TARDBP* gene have been found in patients with AD, patients with FTD/ALS and patients with ALS. Of note, in another project of our laboratory (Cretan Brain Bank, a tissue bank from deceased patients with AD), we have found TDP43 deposits in 9 out of 10 patients histopathologically examined.

Selected publications:

1. L. Mathioudakis, C. Dimovasili, M. Bourbouli, H. Latsoudis, E. Kokosali, G. Gouna, E. Vogiatzi, M. Basta, S. Kapetanaki, S. Panagiotakis, A. Kanterakis, D. Boumpas, C. Lionis, A. Plaitakis, P. Simos, A. Vgontzas, D. Kafetzopoulos and **I. Zaganas**. Study of Alzheimer's disease- and frontotemporal

dementia-associated genes in the Cretan Aging Cohort. *Neurobiol Aging*, 2022.

2. M. Bourbouli, G. P. Paraskevas, M. Rentzos, L. Mathioudakis, V. Zouvelou, A. Bougea, A. Tychalas, V. K. Kimiskidis, V. Constantinides, S. Zafeiris, M. Tzagournissakis, G. Papadimas, G. Karadima, G. Koutsis, C. Kroupis, C. Kartanou, E. Kapaki and **I. Zaganas**. Genotyping and Plasma/Cerebrospinal Fluid Profiling of a Cohort of Frontotemporal Dementia-Amyotrophic Lateral Sclerosis Patients. *Brain Sci*, 11: 2021.

III. Genetic basis of rare neurogenetic disorders

The laboratory I am directing (Neurology/Neurogenetics Laboratory, Medical School, University of Crete, Greece), has been working extensively in unraveling the genetic basis of neurogenetic disorders, including transthyretin related amyloidosis (Tzagournissakis et al, 2022), epilepsy (Zaganas et al, 2021), myopathies (Zaganas et al, 2020) and polyneuropathies (Michaelidou et al, 2020).

1) M. Tzagournissakis, E. Foukarakis, D. Samonakis, M. Tsilimbaris, K. Michaelidou, L. Mathioudakis, A. Marinis, E. Giannakoudakis, C. Spanaki, I. Skoula, S. Erimaki, G. Amoiridis, G. Koutsis, S. Koukouraki, K. Stylianou, A. Plaitakis, P. D. Mitsias and **I. Zaganas**. High Hereditary Transthyretin-Related Amyloidosis Prevalence in Crete: Genetic Heterogeneity and Distinct Phenotypes. *Neurol Genet*, 8: e200013, 2022.
2) **I. Zaganas**, P. Vorgia, M. Spilioti, L. Mathioudakis, M. Raissaki, S. Ilia, M. Giorgi, I. Skoula, G. Chinitrakis, K. Michaelidou, E. Paraskevoulakos, O. Grafakou, C. Kariniotaki, T. Psyllou, S. Zafeiris, M. Tzardi, G. Briassoulis, A. Dinopoulos, P. Mitsias and A. Evangeliou. Genetic cause of epilepsy in a Greek cohort of children and young adults with heterogeneous epilepsy syndromes. *Epilepsy Behav Rep*, 16: 100477, 2021.
3) **I. Zaganas**, V. Mastorodemos, M. Spilioti, L. Mathioudakis, H. Latsoudis, K. Michaelidou, D. Kotzamani, K. Notas, K. Dimitrakopoulos, I. Skoula, S. Ioannidis, E. Klothaki, S. Erimaki, G. Stavropoulos, V. Vassilikos, G. Amoiridis, G. Efthimiadis, A. Evangeliou and P. Mitsias. Genetic cause of heterogeneous inherited myopathies in a cohort of Greek patients. Mol Genet Metab Rep, 25: 100682, 2020.
4) K. Michaelidou, I. Tsiverdis, S. Erimaki, D. Papadimitriou, G. Amoiridis, A. Papadimitriou, P. Mitsias and **I. Zaganas**. Whole exome sequencing establishes diagnosis of Charcot-Marie-Tooth 4J, 1C, and X1 subtypes. Mol Genet Genomic Med, 8: e1141, 2020.

In this respect, my laboratory has been participating in the SOLVE-RD Consortium since 2022, a project aimed to decipher the genetic bases of rare genetic diseases. In this context, there have been two recent publications from this Consortium with the participation of my Laboratory (and more in preparation):

1) Yaldiz B, Kucuk E, Hampstead J, Hofste T, Pfundt R, Corominas Galbany J, Rinne T, Yntema HG, Hoischen A, Nelen M, Gilissen C; **Solve-RD consortium**. Twist exome capture allows for lower average sequence coverage in clinical exome sequencing. Hum Genomics, 17: 39, 2023.
2) Denommé-Pichon AS, Matalonga L, de Boer E, Jackson A, Benetti E, Banka S, Bruel AL, Ciolfi A, Clayton-Smith J, Dallapiccola B, Duffourd Y, Ellwanger K, Fallerini C, Gilissen C, Graessner H, Haack TB, Havlovicova M, Hoischen A, Jean-Marçais N, Kleefstra T, López-Martín E, Macek M, Mencarelli MA, Moutton S, Pfundt R, Pizzi S, Posada M, Radio FC, Renieri A, Rooryck C, Ryba L, Safraou H, Schwarz M, Tartaglia M, Thauvin-Robinet C, Thevenon J, Tran Mau-Them F, Trimouille A, Votypka P, de Vries BBA, Willemsen MH, Zurek B, Verloes A, Philippe C; Solve-RD DITF-ITHACA; Solve-RD SNV-indel Working Group; **Solve-RD Consortia**; Orphanomix Group; Vitobello A, Vissers LELM, Faivre L. A Solve-RD ClinVar-based reanalysis of 1522 index cases from ERN-ITHACA reveals common pitfalls and misinterpretations in exome sequencing. Genet Med, 25: 1000182023, 2023.

IV. Structure function relationships and role of human glutamate dehydrogenases in health and disease

Glutamate dehydrogenase (GDH) is essential for the metabolism of glutamate, the major mammalian excitatory neurotransmitter involved in multiple functions, including human cognition. The enzyme plays a crucial role in cancer and neurodegenerative diseases. While most mammals possess a single housekeeping gene (*GLUD1*), humans and non-human apes have acquired a second GLUD2 gene that arose in their common ancestor through *GLUD1* duplication. The human GDH2 (hGDH2) enzyme, encoded by the *GLUD2* gene, has a unique tissue expression pattern and a functional profile enabling enhanced function under the intense excitatory transmission required for memory consolidation. My studies have shed light on the role of specific amino acid substitutions on the emergence of the novel properties of hGDH2 that led to its persistence through evolution (Zaganas and Plaitakis, 2002). Also, my group has provided insights on the localization and metabolic role of human glutamate dehydrogenases (Nissen et al, 2017; Mathioudakis et al, 2019). Finally, we have solved for the first time the crystal structure of hGDH2 (Dimovassili et al, 2021) and provided insights in its structural evolution in the primate lineage.

1) I. Litso, A. Plaitakis, VE. Fadouloglou, M. Providaki, M. Kokkinidis, **I. Zaganas**. Structural Evolution of Primate Glutamate Dehydrogenase 2 as Revealed by In Silico Predictions and Experimentally Determined Structures. Biomolecules, 14: 22, 2023.
2) C. Dimovasili, V. E. Fadouloglou, A. Kefala, M. Providaki, D. Kotsifaki, K. Kanavouras, I. Sarrou, A. Plaitakis, **I. Zaganas** and M. Kokkinidis. Crystal structure of glutamate dehydrogenase 2, a positively selected novel human enzyme involved in brain biology and cancer pathophysiology. J Neurochem, 157: 802-815, 2021.
3) L. Mathioudakis, M. Bourbouli, E. Daklada, S. Kargatzi, K. Michaelidou and **I. Zaganas**. Localization of Human Glutamate Dehydrogenases Provides Insights into Their Metabolic Role and Their Involvement in Disease Processes. Neurochem Res, 44: 170-187, 2019.
4) J. D. Nissen, K. Lykke, J. Bryk, M. H. Stridh, **I. Zaganas**, D. M. Skytt, A. Schousboe, L. K. Bak, W. Enard, S. Pääbo and H. S. Waagepetersen. Expression of the human isoform of glutamate dehydrogenase, hGDH2, augments TCA cycle capacity and oxidative metabolism of glutamate during glucose deprivation in astrocytes. Glia, 65: 474-488, 2017.
5) **I. Zaganas**, A. Plaitakis. Single amino acid substitution (G456A) in the vicinity of the GTP binding domain of human housekeeping glutamate dehydrogenase markedly attenuates GTP inhibition and abolishes the cooperative behaviour of the enzyme. J Biol Chem 277: 26422-28, 2002.

D. Research Support.

Active

1) European Rare Disease Research Alliance (ERDERA). Principal Investigator.
2) INGENIUM Research Group proposals: INGENIUM Rare Neurogenetic Disease Initiative. Principal Investigator.
3) *"Εθνικό δίκτυο έρευνας για την ανάδειξη της γενετικής βάσης των νευροεκφυλιστικών νόσων Alzheimer και Parkinson, την ανίχνευση αξιόπιστων βιοδεικτών και την ανάπτυξη καινοτόμων υπολογιστικών τεχνολογιών και θεραπευτικών στρατηγικών στη βάση της ιατρικής ακρίβειας". TAEDR-0535850. Co-Investigator.*
4) "*Next Generation Sequencing in patients with neurological and other disorders*" (Code 4106, 10/7/2014-30/06/2024- through this program WES has been performed in >300 patients and other genetic tests in >150 patients). Principal Investigator.
5) "*Basic, epidemiological, genetic and clinical research in neurological disorders*" (Code 4313, 01/04/2015-31/12/2024). Principal Investigator.

6) "*Novel Clinical trials in neurological disorders*" (Code 10771, 30/11/2020-30/6/2036). Principal Investigator.
7) "Educational Activities in Neurology" (Code 11085, 19/4/2022-31/12/2025). Principal Investigator.
8) "Structural and Biochemical Properties of Human Glutamate Dehydrogenases and their mechanisms of regulation" (Code 11337, 23/3/2023-30/11/2025). Principal Investigator.

Completed

1) "National Network for Neurodegenerative disorders Research based on Precision medicine" (Greek National funds). Co-Investigator.
2) "*MDND-Mitochondrial dysfunction in neurodegenerative diseases*" (Grant Code 377226, 2013-2015, European Union/European Social Fund and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework). Co-Investigator.
3) "*MNSAD-Multidisciplinary network for the study of Alzheimer's Disease*" (Grant Code 377299, 2013-2015, European Union/European Social Fund and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework, budget 520.207,20). Co-Investigator.
4) "*Biomarkers-Correlation study of biomarkers and genetic changes of patients with neurological disorders*" (Code 4323, 13/05/2015-15/05/2021). Principal Investigator.
5) "*Clinical trials in neurological disorders*" (Code 4393, 3/11/2015-30/9/2022, industry-funded). Principal Investigator.
6) "*Structural studies on human glutamate dehydrogenase iso-enzymes*" (Code 4374, 10/9/2015-09/09/2017, University of Crete Intramural Grants). Principal Investigator.
7) "*Specific inactivation of GLUD1 and GLUD2 genes from human cell lines using the CRISP / Cas9 system*" (Code 4435, 28/01/2016-27/07/2017, University of Crete Intramural Grants). Principal Investigator.
8) "Characterization and functional study of *EPHA1* gene, in a family with late-onset Alzheimer's disease". (Code 4971, 1/1/2018-18/12/2018, University of Crete Intramural Grants). Principal Investigator.

E. Clinical Trials Acting as Principal Investigator

	Study Code	Medicinal Product	Disease	Sponsor	Phase	Date
1	**KAR-032**	KarXT	Psychosis in Alzheimer's Disease	Karuna Therapeutics	III	2024
2	**TEG4001**	Inotersen	Hereditary Transthyretin-Mediated Amyloid Polyneuropathy	Aksea	IV	2022
2	**M09AX10**	Risdiplam	Spinal Muscular Atrophy type 1 and 2	Roche	Pre-Approval Access / Compassionate Use Program	2021

3	***ION-682884-CS3***	ION-682884	Hereditary Transthyretin-Mediated Amyloid Polyneuropathy	Ionis	III	2020
4	***AB09004***	Masitinib	Alzheimer	AB Science	III	2016-2019
5	***CENA713D2409***	Rivastigmine TTS	Alzheimer	NOVARTIS	IV	2015-2018