Curriculum vitae. Alfredo Brusco

Personal information

Nationality: Italian

Place / date of birth: Biella / August, 28th 1968

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Current / past positions

Positions

1996: Fellowship at the "San Giovanni Battista" Turin Hospital to study genetics of Duchenne Muscular Dystrophy
1997-2000: Assistant researcher in Medical Genetics, Dept. Genetics Biology and Biochemistry, Turin, Italy
2000-2016: Assistant Professor in Medical Genetics, Dept. Medical Sciences, Turin, Italy
2000-now: Molecular Biology Laboratory Scientist, Medical Genetics unit "Città della Salute e della Scienza" University Hospital
July 2012-now: Chief of the Molecular Genetics laboratory, Medical Genetics unit.
2016-now: Associate Professor in Medical Genetics, Dept. Medical Sciences, Turin, Italy

Education

1991, Bs.C degree in Biological Sciences 110/110 with first class honours (thesis entitled "Evolution of IgG constant genes in Primates")
1997, University of Torino, Philosophical Doctorate in Human Genetics
(Thesis entitled "Genetic instability and allotypic polymorphisms of the immunoglobulin heavy chain constant genes (IGHC)")
1989-96 Short training visits at the "Istitut fur Immunologie" (Basel, Switzerland), and the "Guy' s Hospital" (London). I attended courses and congresses among which the "7th course of the European school of medical genetics" and the "GASLINI-IARC course in cancer genetics" (International School of Paediatric Sciences, Genova, Italy & International Agency for Research on Cancer, Lion, France).
2018, National Abilitation to Full Professor in Medical Genetics

Main research activity

Main achievements in research activities.

My early research focused on immunogenetics. As graduate and Ph.D. student, I investigated genetic variability at the Immunoglobulin Heavy chain Constant (IgHC) region, demonstrating the presence of a high percentage of single and multiple gene deletions/duplications and triplications in the human population and studied the evolution of the IgHC cluster in Primates. I defined the genetic basis of allotypic variation for IgG2 and IgG4 subclasses. These studies were recognized by an award of the Italian Society of Human Genetics (SIGU 1996) and by the publication of the results in significant international journals (e.g., J. Immunology).

After my Ph.D., my interests moved to the field of Medical Genetics. I started collaborations with important national and international groups in the field of neurological and neurodegenerative diseases with two specific aims: 1. Develop and set up diagnostic tests in the field of neurodegenerative diseases, with a peculiar focus on hereditary ataxias; 2. Identify genetic causes of hereditary ataxias. Since 1991, I was in charge of the day-to-day running of my research group, which included from three to nine persons, including Ph.D. and post-doc students.

A number of important step-changing results were obtained in the diagnostic field recognized by international publication in high impact journals (e.g., Neurology, Archives of Neurology). Among them the demonstration that a form of tremor-ataxia (FXTAS) is frequent in males >50yr with an unknown cause of ataxia, and that rare forms of cerebellar degeneration and cognitive impairment (Gerstmann-Straussler-Sheinker) are present among patients diagnosed with sporadic ataxia. I developed new

genetic tests for mutation screening in Fragile-X syndrome, ataxia telangiectasia, and in other hereditary ataxias that are now routinely used worldwide (STR-PCR for Friedreich ataxia, SCA10, and SCA12).

I contributed to strategic collaborative works to identify genes involved in autosomal dominant spinocerebellar ataxia (SCA) such as *AFG3L2* (SCA28, Nature Genetics 2006), *ELOVL5* (SCA38, AJHG 2014), and *CACNA1G* (SCA40, AJHG 2015). We further studied mutational spectrum, genotype-phenotype correlation and pathogenic mechanisms of SCA28 and SCA38. The characterization of pathogenic mechanism related SCA28 lead us to develop and characterize a knockin animal model to study the phenotype and identify potential therapeutic targets. This work led to study mitochondrial bioenergetics, dynamics, and autophagy pathways. On the other hand, the work on SCA38 is leading to the study of the role of long chain fatty acids in the cerebellum, and the role of mutant ELOVL5 protein in the ER-Golgi stress response.

My position within the Genetics Unit of the most important Hospital in the Piedmont region (4.5 million people), has allowed me to work on several other research program and gain expertise in the broad field of Medical Genetics. One of these projects allowed the discovery of a novel gene involved in an autosomal recessive disease associated to arterial calcifications, which also had international highlight in the media (New England Journal of Medicine, 2011).

My expertise allowed defining and characterizing mutation spectrum in several genetic diseases and identifying variant phenotypes associated to known disease genes (TSC, Alport, ATM, SCA12, MLC1, CFTR, DBA, CLN5, etc), and uncommon mutational mechanisms including uncommon splicing defect (MLC1, ATM) and RNA transcription cis-ruption (THOC2 involved in intellectual disability). I recently worked to characterize regulatory position effects in Autosomal Dominant Leukodystrophy (ADLD)(2014, 2015), where we recently described a mutation acting on a transcriptional activation domain boundary.

My diagnostic duties allowed me to apply array-CGH analysis on sporadic and familial cases with intellectual disability, multiple congenital malformations and foetal anomalies whose results have been recently described in Molecular Cytogenetics and Cytogenetic and Genome Research. I started a large collaboration on Autistic Spectrum Disorders and Intellectual Disabilities with an International collaboration led by the Mount Sinai Hospital in New York, with the aim to exome sequence >500 Trios and identify genetic variants causative of these diseases. I also apply exome sequencing to identify new causative genes in neurodegenerative and neurodevelopmental disorders.

Finally, I am working on translational approaches to Mendelian disorders following several routes: 1) the role of glucocorticoids in therapies for neurodegenerative disorders (Ataxia Telangiectasia); 2) studying allele-specific siRNA as therapeutic approaches in ADLD and SCA1; 3) searching for new drugs able to downregulate LMNB1 in ADLD, using high throughput drug screening.

Presently my group is composed of eight members, working in different fields from mutation analysis to pathogenic mechanisms, to array-CGH screening of patients with cognitive impairment and to exome sequencing of relevant families with unknown genetic diseases. We focus on neurodevelopmental defects, hereditary ataxias and autosomal dominant leukodystrophy, for which we are creating a worldwide network of research and clinical laboratories.

Research Performance

- *Research Performance*
- *Publications: 146 publications in I.F. international journals, citations 2564, H-index: 29 (WOS); over 40 oral presentations at National and International meetings and as invited speaker/ professor.*
- *Scientific organizing committee of ESHG 2018, SIGU 2017, and other national meetings on Genetics*
- *ORCID: http://orcid.org/0000-0002-8318-7231*
- Abstracts to congresses: over 240.

Academic experience.

1997-2000 Teaching activity in the course: “Molecular Biology for Biomedical technicians” (University of Torino).

2000-now Assistant Professor in Medical Genetics at the Department of Genetics, Biology and Biochemistry, Medical Genetics Unit – University of Torino. Courses: Medical Genetics for Biotecnologists (50 h), "Molecular diagnostic techniques I (16 h) and II (8 h)" at the School of Specialization in Medical Genetics, "Medical Genetics" (8h) for Psychiatrists, Medical genetics for nurses (9 h), Medical Genetics for Paediatric Nurses (20 h), Medical Genetics for Neuropsychiatrists and Paediatricians..
From 2000 teaching duties at the PhD School in Biomedical Sciences and Medical Oncology.

Diagnostic activity
2000-now Reference biologist for diagnostic activity in the field of hereditary ataxias, autosomal dominant leukoencephalopathies, Medical Genetics Unit, "San Giovanni Battista Hospital", Turin, Italy, 200 tests/yr.
Supervisor of the sequencing diagnostics facility, same location.
2009-now Supervisor of the array CGH screening in intellectual disability, ASDs, same location, 800 tests/yr.

Memberships
From 2002, Member of the American Society of Human Genetics (ASHG)
From 2009, Member of the Italian Society of Human Genetics (SIGU)
2011-2018, Coordinator of the Regional Unit of the Italian Society of Human Genetics (SIGU)
From 2012, Member of the European Society of Human Genetics (ESHG)
Scientific committee of the Italian Association for Ataxic Syndromes (AISA)
Scientific Committee of the National Association for Ataxia Telangiectasia (AT)(from2018)
Review Editor for Frontiers in Aging Neuroscience
Review Editor for Neurogenetics
Review Editor in Frontiers in Genetics - Genetic Disorders
From 2018 Gruppo di Studio Neurogenetica Clinica e Malattie Rare (Società Italiana Neurologia)

Others
In the last ten years, I served as referee for the following journals: American Journal of Medical Genetics, Annals of Neurology, BMC Genetics, Clinica Chimica Acta, Clinical Genetics, GeneReviews, European Journal of Human Genetics, European Journal of Medical Genetics, European Journal of Neurology, Human Genetics, Human Molecular Genetics, Journal of the Neurological Sciences, Neuroepidemiology, Neurology, Translational Neurodegeneration.
I served as referee for the following organizations/institutions: Ataxia UK (UK, 2006); Fondazione Mariani (Italy, 2006); AFM (France 2008); European Leukodystrophy Association (France, 2009); AFM – SPCS (2010).
I organized the "1° International meeting of Ataxia Telangiectasia Associations" Torino September 26-27th 2008.

National and International Collaborators
Present collaborators in active projects include: Giovanni Stevanin, Alexis Brice, Alexandra Durr (INSERM, Paris, France), Richard Gatti (UCLA, Los Angeles), Laura Ranum (University of Florida, College of Medicine), Annalisa Buffo (Neuroscience Institute Turin, Italy), Laura Gasparini (IIT, Genoa Italy), Odile Boesplung-Tanguy (Hopital Salpetriere, Paris, France), Russell Margolis (Baltimore, USA), Marco Tartaglia (ISS, Rome, Italy), Barbara Borroni (Dept. Neurology, Brescia, Italy), Giuseppe Gasparre, Marco Seri (University of Bologna, Italy), Giorgio Casari (San Raffaele Scientific Institute, Milan), Enrico Bertini (University of Rome, Italy).

Torino, 09 April, 2019

Alfredo Brusco