# CV Prof. Massimo Gennarelli

Full Professor of Medical Genetics, Department of Molecular and Translational Medicine, University of Brescia

## Education

November 1987: degree in Biological Sciences - Urbino University
September 1995: PhD in Medical Genetics - University La Sapienza, Rome

## Employment and research experience

1995-1997: Postdoctoral Fellow, University "La Sapienza", Rome
1999-2002: Head of Genetic Unit at IRCCS - Centre S. Giovanni di Dio, FBF, Brescia, Italy
Since 2003: Consultant at IRCCS-Centre S.Giovanni di Dio, FBF, Brescia
2005-2017: Responsible of preclinical studies (Linea 1 Ricerca Corrente) at IRCCS-Centre S.Giovanni di Dio, FBF, Brescia
2002-2016: Associate Professor of Medical Genetics - University of Brescia, Italy
Since 2016: Full Professor of Medical Genetics - University of Brescia, Italy
2020: Director of the Department of Molecular and Translational Medicine, University of Brescia, Italy

## Overview of published work

Author of 250 publications (Scopus, 2022)
Total number of citations: 10010 (Scopus, 2022)
H index: 55 (Scopus, 2022)

## Research activity

Prof. Gennarelli's past research activity includes several international studies on Myotonic Dystrophy type 1 (MD1). These studies were focused mainly on the analysis of the disease-associated variants, on detecting genotype-phenotype correlations and on evaluating the role of somatic mosaicism in disease. Furthermore, detailed analyses were performed to aid definition of the biochemical defect, to understand the preferential segregation of the mutated allele in the families at risk, to identify novel variants in the *DMPK* gene. The published work contributed also to the confirmation of the Northern Euro-Asian origin of the DM1 mutation and to the demonstration of the presence of meiotic drive at the DM1 locus. Altogether, results enabled development of an algorithm for the predictive diagnosis of DM1 based on genotype-phenotype correlations. More recently, Prof. Gennarelli's research activity has been primarily dedicated to the fields of genetics, biochemistry and pharmacogenetics of psychiatric disorders. In recent years, his research group have conducted numerous studies on the identification of molecular (genetic and biochemical) markers predictive of disease onset and treatment response. Specific areas of investigation have included the role of immune system modulators and neurotrophic factors in the

pathogenesis of schizophrenia, major depression, and dementia; and the mechanisms of action involved in pharmacological and non-pharmacological therapy. Several studies entailed case-control association analyses on candidate genes for susceptibility to severe mental disorders, endeavouring to clarify the role of genes linked to neurotransmission- (e.g. glutamate, serotonin, dopamine), cytokine-, and neurotrophic factor-related pathways.
Prof. Gennarelli's group have also worked on the polymorphic variants of genes encoding for cytokines and neurotrophic factors themselves in patients suffering from the sporadic form of Alzheimer disease (AD). These studies have brought evidence of preferential associations between susceptibility to AD and functional polymorphisms of the *BDNF* (Brain Derived Neurotrophic Factor) and *IL10* (interleukin-10) genes. Concerning translational research activities, a noticeable result is represented by the contribution to the creation of guidelines for genetic testing in Myotonic Distrophies (MD1 and MD2), reporting also the long-standing experience in the molecular diagnosis of these conditions. An additional result comes from the recent efforts concerning pharmacogenetics of antipsychotics, antidepressants and mood stabilizers aimed at setting up genetic testing strategies for treatment optimization and personalization in psychiatric diseases (major depressive disorder, schizophrenia, bipolar disorder).

National and international grants (as Unit member – last 5 years)

2021-2023: ERA PerMed 2020 European Research Project, titled "PROMPT - Toward PrecisiOn Medicine for the Prediction of Treatment response in major depressive disorder through stratification of combined clinical and -omics signatures"

2016-2019: Research project of Italian Ministry of Health (RF-2013-02356444) "Neuroplasticity and Alzheimer's disease: integrated approach to identify biological and neurophysiological markers"

National and international grants (as PI – last 5 years)

2018-2021: Research multicentre project of Italian Ministry of Health (RF-2016-02361697) "Towards precision medicine in psychiatry: clinical validation of a combinatorial pharmacogenomic approach"

2016-2018: Research multicentre granted by University of Brescia (REFrACT – Health and Wealth 2015 project) entitled "Analysis of the neurobiological mechanisms underlining treatment resistance to psychotropic drugs in innovative cellular models"

**CV Prof. Massimo Gennarelli**

Professore Ordinario di Genetica Medica, Dipartimento di Medicina Molecolare e Traslazionale, Università degli Studi di Brescia

Formazione

Novembre 1987: Laurea in Scienze Biologiche - Università degli Studi di Urbino
1991-1995: Dottorato di Ricerca in Genetica Medica, Università "La Sapienza", Roma

Esperienza lavorativa e di ricerca

1995-1997: Borsa post dottorato, Università "La Sapienza", Roma
1999-2002: Ricercatore Dirigente, Responsabile Unità Genetica presso l'IRCCS - Centro S. Giovanni di Dio, FBF, Brescia, Italia
Dal 2003: Consulente presso l'IRCCS-Centro S.Giovanni di Dio, FBF, Brescia e responsabile del laboratorio di Genetica
2005-2017: Responsabile degli studi preclinici (Linea 1 Ricerca Corrente) presso l'IRCCS-Centro S.Giovanni di Dio, FBF, Brescia
2002-2016: Professore associato di Genetica Medica-MED/03- Università degli Studi di Brescia, Italia
Dal 2016: Professore Ordinario di Genetica Medica- MED/03 - Università degli Studi di Brescia, Italia
Dal 2020 è Direttore del Dipartimento di Medicina Molecolare e Traslazionale, Università degli Studi di Brescia

Indici relativi alle pubblicazioni

Autore di 250 pubblicazioni (Scopus, 2022)
Numero totale di citazioni: 10010 (Scopus, 2022)
Indice H: 55 (Scopus, 2022)

Attività di ricerca

La precedente attività di ricerca del Prof. Gennarelli comprende diverse pubblicazioni internazionali sulla Distrofia Miotonica di tipo 1 (MD1). Questi studi hanno avuto per oggetto l'analisi della mutazione, le correlazioni genotipo-fenotipo, la valutazione del ruolo del mosaicismo somatico, la definizione del difetto biochimico, la segregazione preferenziale dell'allele mutato nelle famiglie a rischio, l'identificazione di nuove isoforme del gene DM (*DMPK*), la conferma dell'origine Nord-Euroasiatica della mutazione DM valutando il polimorfismo intragenico CTG (3'-UTR) e la dimostrazione dell'esistenza di "drive" meiotico. E' stato inoltre messo a punto un algoritmo per la diagnosi predittiva della DM basato sulla correlazione genotipo-fenotipo. Le analisi quantitative di mRNA nel cervello di pazienti DM hanno consentito di evidenziare la ridotta espressione del gene DMAHP suggerendo un suo possibile ruolo nella patogenesi del ritardo mentale tipico della malattia. L'attività di ricerca più recente del Prof. Gennarelli si è rivolta maggiormente allo studio di aspetti genetici,

biochimici e farmacogenetici delle malattie psichiatriche. Negli ultimi anni sono stati effettuati numerosi studi sull'identificazione di marcatori genetici e biochimici associati con la diagnosi e con la risposta al trattamento. Specifiche aree di studio sono state: il ruolo dei modulatori del sistema immunitario e fattori neurotrofici nei meccanismi eziopatogenetici della schizofrenia, depressione maggiore e demenza; e dei meccanismi d'azione coinvolti nella terapia farmacologica e non per queste patologie. Inoltre, il Prof. Gennarelli e il suo gruppo hanno condotto diversi studi di associazione caso-controllo sui geni candidati per la suscettibilità a gravi disturbi mentali, allo scopo di chiarire il ruolo dei geni coinvolti in alcuni sistemi neurotrasmettitoriali (glutammato, serotonina e dopamina), e in pathway relativi alle citochine e ai fattori neurotrofici. Lo studio di varianti polimorfiche di geni codificanti per citochine e fattori neurotrofici come fattori di suscettibilità è stato esteso alle forme sporadiche di malattia di Alzheimer (AD). Questi studi hanno permesso al Prof. Gennarelli e ai suoi collaboratori di evidenziare associazioni preferenziali di polimorfismi funzionali del gene *BDNF* (Brain Derived Neurotrophic Factor) e dei geni delle citochine con la suscettibilità all'AD. Per quanto riguarda la ricerca traslazionale, un primo importante risultato è rappresentato dalla stesura di linee guida per i test genetici per le Distrofie Miotoniche (MD1 e MD2) che racchiude 10 anni di esperienza nella diagnosi molecolare per queste patologie. Un secondo risultato viene dai recenti studi sulla farmacogenetica degli antipsicotici, antidepressivi e stabilizzanti dell'umore, nell'ottica della messa a punto di test genetici per l'ottimizzazione e personalizzazione del trattamento per le principali patologie psichiatriche (depressione maggiore, schizofrenia, disturbo bipolare).

Progetti Nazionali ed internazionali (come membro di Unità Operativa – ultimi 5 anni)

2021-2023: ERA PerMed 2020. Progetto Europeo dal titolo "PROMPT - Toward PrecisiOn Medicine for the Prediction of Treatment response in major depressive disorder through stratification of combined clinical and -omics signatures"

2016-2019: Ricerca Finalizzata del Ministero della Salute (RF-2013-02356444) dal titolo "Neuroplasticity and Alzheimer's disease: integrated approach to identify biological and neurophysiological markers"

Progetti Nazionali ed internazionali (come Principal Investigator – ultimi 5 anni)

2018-2021: Ricerca Finalizzata del Ministero della Salute (RF-2016-02361697) "Towards precision medicine in psychiatry: clinical validation of a combinatorial pharmacogenomic approach"

2016-2018: Bando di Ateneo "University of Brescia" (REFrACT – Health and Wealth 2015 project) dal titolo "Analysis of the neurobiological mechanisms underlining treatment resistance to psychotropic drugs in innovative cellular models"

Pubblicazioni: Ultimi 5 anni

(1) Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 2022;604(7906):502-508.

(2) Pisanu C, Severino G, De Toma I, Dierssen M, Fusar-Poli P, Gennarelli M, et al. Transcriptional biomarkers of response to pharmacological treatments in severe mental disorders: A systematic review. Eur Neuropsychopharmacol 2022;55:112-157.

(3) Fanelli G, Domschke K, Minelli A, Gennarelli M, Martini P, Bortolomasi M, et al. A meta-analysis of polygenic risk scores for mood disorders, neuroticism, and schizophrenia in antidepressant response. Eur Neuropsychopharmacol 2022;55:86-95.

(4) Mazzarotto F, Argirò A, Zampieri M, Magri C, Giotti I, Boschi B, et al. Investigation on the high recurrence of the ATTRv-causing transthyretin variant Val142Ile in central Italy. Eur J Hum Genet 2022.

(5) Dattilo V, Ulivi S, Minelli A, La Bianca M, Giacopuzzi E, Bortolomasi M, et al. Genome-wide association studies on Northern Italy isolated populations provide further support concerning genetic susceptibility for major depressive disorder. World J Biol Psychiatry 2022.

(6) Gennarelli M, Monteleone P, Minelli A, Monteleone AM, Rossi A, Rocca P, et al. Genome-wide association study detected novel susceptibility genes for social cognition impairment in people with schizophrenia. World J Biol Psychiatry 2022;23(1):46-54.

(7) Concas MP, Minelli A, Aere S, Morgan A, Tesolin P, Gasparini P, et al. Genetic dissection of temperament personality traits in Italian isolates. Genes 2022;13(1).

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(10) Pisanu C, Vitali E, Meloni A, Congiu D, Severino G, Ardau R, et al. Investigating the role of leukocyte telomere length in treatment-resistant depression and in response to electroconvulsive therapy. J Pers Med 2021;11(11).

(11) Maffioletti E, Silva RC, Bortolomasi M, Baune BT, Gennarelli M, Minelli A. Molecular biomarkers of electroconvulsive therapy effects and clinical response: Understanding the present to shape the future. Brain Sci 2021;11(9).

(12) Magri C, Vitali E, Cocco S, Giacopuzzi E, Rinaudo M, Martini P, et al. Whole blood transcriptome characterization of 3xTg-AD mouse and its modulation by transcranial direct current stimulation (TDCs). Int J Mol Sci 2021;22(14).

(13) Enrico P, Delvecchio G, Turtulici N, Pigoni A, Villa FM, Perlini C, et al. Classification of Psychoses Based on Immunological Features: A Machine Learning Study in a Large Cohort of First-Episode and Chronic Patients. Schizophr Bull 2021;47(4):1141-1155.

(14) Zanella I, Zacchi E, Piva S, Filosto M, Beligni G, Alaverdian D, et al. C9orf72 intermediate repeats confer genetic risk for severe covid-19 pneumonia independently of age. Int J Mol Sci 2021;22(13).

(15) Filippini A, Gennarelli M, Russo I. Leucine-rich repeat kinase 2-related functions in GLIA: An update of the last years. Biochem Soc Trans 2021;49(3):1375-1384.

(16) Rampino A, Torretta S, Gelao B, Veneziani F, Iacoviello M, Marakhovskaya A, et al. Evidence of an interaction between FXR1 and GSK3β polymorphisms on levels of Negative Symptoms of Schizophrenia and their response to antipsychotics. Eur Psychiatry 2021;64(1):e39.

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(18) Silva RC, Maffioletti E, Gennarelli M, Baune BT, Minelli A. Biological correlates of early life stressful events in major depressive disorder. Psychoneuroendocrinology 2021;125.

(19) Filippini A, Mutti V, Faustini G, Longhena F, Ramazzina I, Rizzi F, et al. Extracellular clusterin limits the uptake of α-synuclein fibrils by murine and human astrocytes. Glia 2021;69(3):681-696.

(20) Di Maria E, Martini P, Gennarelli M. Naringerin as candidate drug against SARS-CoV-2: The role for TPC2 genomic variants in COVID-19. Pharmacol Res 2021;164.

(21) Shoaib M, Giacopuzzi E, Pain O, Fabbri C, Magri C, Minelli A, et al. Investigating an in silico approach for prioritizing antidepressant drug prescription based on drug-induced expression profiles and predicted gene expression. Pharmacogenomics J 2021;21(1):85-93.

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(24) Bono F, Mutti V, Piovani G, Minelli A, Mingardi J, Guglielmi A, et al. Generation of two human induced pluripotent stem cell lines, UNIBSi012-A and UNIBSi013-A, from two patients with treatment-resistant depression. Stem Cell Res 2020;49.

(25) Mega A, Galluzzi S, Bonvicini C, Fostinelli S, Gennarelli M, Geroldi C, et al. Genetic counselling and testing for inherited dementia: single-centre evaluation of the consensus Italian DIAfN protocol. Alzheimers Res Ther 2020;12(1).

(26) Cupaioli FA, Mosca E, Magri C, Gennarelli M, Moscatelli M, Raggi ME, et al. Assessment of haptoglobin alleles in autism spectrum disorders. Sci Rep 2020;10(1).

(27) Soda T, McLoughlin DM, Clark SR, Oltedal L, Kessler U, Haavik J, et al. International Consortium on the Genetics of Electroconvulsive Therapy and Severe Depressive Disorders (Gen-ECT-ic). Eur Arch Psychiatry Clin Neurosci 2020;270(7):921-932.

(28) Maffioletti E, Minelli A, Tardito D, Gennarelli M. Blues in the brain and beyond: Molecular bases of major depressive disorder and relative pharmacological and non-pharmacological treatments. Genes 2020;11(9):1-24.

(29) Scassellati C, Ciani M, Maj C, Geroldi C, Zanetti O, Gennarelli M, et al. Behavioral and psychological symptoms of dementia (Bpsd): Clinical characterization and genetic correlates in an italian alzheimer's disease cohort. J Pers Med 2020;10(3):1-16.

(30) Maffioletti E, Valsecchi P, Minelli A, Magri C, Bonvicini C, Barlati S, et al. Association study between HTR2A rs6313 polymorphism and early response to risperidone and olanzapine in schizophrenia patients. Drug Dev Res 2020;81(6):754-761.

(31) Dattilo V, Amato R, Perrotti N, Gennarelli M. The Emerging Role of SGK1 (Serum- and Glucocorticoid-Regulated Kinase 1) in Major Depressive Disorder: Hypothesis and Mechanisms. Front Genet 2020;11.

(32) Maffioletti E, Gennarelli M, Magri C, Bocchio-Chiavetto L, Bortolomasi M, Bonvicini C, et al. Genetic determinants of circulating VEGF levels in major depressive disorder and electroconvulsive therapy response. Drug Dev Res 2020;81(5):593-599.

(33) Maj C, Tosato S, Zanardini R, Lasalvia A, Favaro A, Leuci E, et al. Correlations between immune and metabolic serum markers and schizophrenia/bipolar disorder polygenic risk score in first-episode psychosis. Early Intervent Psychiatry 2020;14(4):507-511.

(34) Tosato S, Bonetto C, Tomassi S, Zanardini R, Faravelli C, Bruschi C, et al. Childhood trauma and glucose metabolism in patients with first-episode psychosis. Psychoneuroendocrinology 2020;113.

(35) Maffioletti E, Milanesi E, Ansari A, Zanetti O, Galluzzi S, Geroldi C, et al. miR-146a Plasma Levels Are Not Altered in Alzheimer's Disease but Correlate With Age and Illness Severity. Front Aging Neurosci 2020;11.

(36) Ansari A, Maffioletti E, Milanesi E, Marizzoni M, Frisoni GB, Blin O, et al. miR-146a and miR-181a are involved in the progression of mild cognitive impairment to Alzheimer's disease. Neurobiol Aging 2019;82:102-109.

(37) Maffioletti E, Gennarelli M, Gainelli G, Bocchio-Chiavetto L, Bortolomasi M, Minelli A. BDNF Genotype and Baseline Serum Levels in Relation to Electroconvulsive Therapy Effectiveness in Treatment-Resistant Depressed Patients. J ECT 2019;35(3):189-194.

(38) Filippini A, Gennarelli M, Russo I. α-Synuclein and Glia in Parkinson's Disease: A Beneficial or a Detrimental Duet for the Endo-Lysosomal System? Cell Mol Neurobiol 2019;39(2):161-168.

(39) Vita A, Minelli A, Barlati S, Deste G, Giacopuzzi E, Valsecchi P, et al. Treatment-resistant schizophrenia: Genetic and neuroimaging correlates. Front Pharmacol 2019;10(APR).

(40) Bonvicini C, Scassellati C, Benussi L, Di Maria E, Maj C, Ciani M, et al. Next Generation Sequencing Analysis in Early Onset Dementia Patients. J Alzheimer's Dis 2019;67(1):243-256.

(41) Giacopuzzi E, Gennarelli M, Sacco C, Filippini A, Mingardi J, Magri C, et al. Genome-wide analysis of consistently RNA edited sites in human blood reveals interactions with mRNA processing genes and suggests correlations with cell types and biological variables. BMC Genomics 2018;19(1).

(42) Magri C, Giacopuzzi E, La Via L, Bonini D, Ravasio V, Elhussiny MEA, et al. A novel homozygous mutation in GAD1 gene described in a schizophrenic patient impairs activity and dimerization of GAD67 enzyme. Sci Rep 2018;8(1).

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(44) Minelli A, Magri C, Giacopuzzi E, Gennarelli M. The effect of childhood trauma on blood transcriptome expression in major depressive disorder. J Psychiatr Res 2018;104:50-54.

(45) Bocchio-Chiavetto L, Zanardini R, Tosato S, Ventriglia M, Ferrari C, Bonetto C, et al. Immune and metabolic alterations in first episode psychosis (FEP) patients. Brain Behav Immun 2018;70:315-324.

(46) Bono F, Savoia P, Guglielmi A, Gennarelli M, Piovani G, Sigala S, et al. Role of Dopamine D2/D3 Receptors in Development, Plasticity, and Neuroprotection in Human iPSC-Derived Midbrain Dopaminergic Neurons. Mol Neurobiol 2018;55(2):1054-1067.

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