

BIOGRAPHICAL SKETCH

NAME: Conti, Valerio

POSITION TITLE: Researcher Biologist, Department of Neuroscience and Medical Genetics, Responsible of the Research Operative Unit of Cellular and Morphofunctional Neurobiology, Meyer Children's Hospital IRCCS

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Pisa, Department of Human and Environmental Sciences, University of Pisa, via San Giuseppe, 22, Pisa, Italy	MS	05/2002	Biological Sciences
University of Pisa, Department of Human and Environmental Sciences, University of Pisa, via San Giuseppe, 22, Pisa, Italy	PhD	03/2006	Microbiology and Genetics
University of Florence/ Department of Neuroscience, Meyer Children's Hospital, viale Pieraccini, 24, Florence, Italy	Postgraduate training and board certification	03/2012	Medical Genetics

A. Personal Statement

I am a geneticist and neurobiologist. During my PhD and postgraduate training, I focused on identifying causative variants of neurological conditions (mainly ataxia and epilepsy associated or not with malformations of cortical development) and characterizing their pathophysiological mechanisms at the functional level. In the framework of the PhD thesis preparation and the Postgraduate training, I spent several months at the Pasteur Institute (Paris, France) and the Institut de Neurobiologie de la Méditerranée - INMED (Marseille, France) where under the supervision of Dr Jean Louis Guenet (Pasteur Institute) and Drs. Carlos Cardoso and Alfonso Represa (INMED), I deepened my knowledge of characterizing neurodevelopmental disorders in cellular and animal models. Upon achieving a permanent position at the University Hospital Meyer in 2015, I started characterizing at genetic level cohorts of patients with developmental and epileptic encephalopathy (DEE) and performing in vitro and in vivo functional studies to explore the pathophysiological mechanisms underlying these conditions. In 2022, I was appointed responsible for the Laboratory of Neurobiology of the Neuroscience Department of the University Hospital Meyer. Upon the Meyer Hospital has been recognized as a Research Institute (IRCCS), in 2024, I was appointed responsible for the Cellular and Morphofunctional Neurobiology Research Operative Unit of the Children's Hospital Meyer IRCCS. With my team (two post-doctoral fellows and one PhD student), I started developing protocols to differentiate human induced pluripotent stem cells (hiPSC) reprogrammed from fibroblasts of patients with DEE into cortical neurons and to characterize the effects of specific mutations mainly using confocal immunocytochemistry and patch clamp recordings. We are also working on characterizing, through RNAseq analysis, alterations in the transcriptome of dysplastic brain specimens surgically removed from patients with focal cortical dysplasia (FCD) and drug-resistant epilepsy. I co-authored more than 50 peer-reviews articles and four book chapters. My H-Index is 26.

B. Positions Appointments, and Honors

Positions

06/2002-05/2015: Post-graduate fellowships and research contracts at different institutions (G. Gaslini Institute, Genoa, Stella Maris Foundation, Pisa, and University Hospital Meyer, Florence) awarded within different research projects to perform genetic studies in patients and functional studies in cellular and animal models.

06/2015: University Hospital Meyer, Viale Pieraccini, 24 50139 Florence: Permanent position as Biologist.

02/2022: University Hospital Meyer, viale Pieraccini, 24 50139 Florence: responsible for the Neurobiology laboratory, Department of Neuroscience.

03/2024: Meyer Children's Hospital IRCCS, viale Pieraccini, 24 50139, Florence: Responsible for the Cellular and Morphofunctional Neurobiology Research Operative Unit.

Appointments and Honors

Member of the Editorial Board of *Epilepsia* (2013-2015).

Review editor of *Frontiers Cellular Neuroscience* (2020-).

Topic editor of *Life* (2020-).

Member of the Neuropathology Study Group of the Italian League Against Epilepsy (2024-).

Contributions to Science

My early publications have been devoted to the genetic and functional characterization of spontaneous ataxic mouse models carrying pathogenic variants in the type 1 metabotropic glutamate receptor gene (*GRM1*) and to the demonstration that variants in this gene also cause kidney anomalies. After moving to the Meyer Children's Hospital, I continued to study murine models and demonstrated the functional effects of variants in a novel causative gene of periventricular nodular heterotopia we described (*C6ORF70*, also known as *ERMARD*). Meanwhile, I started characterizing at genetic level cohorts of patients with epilepsy with or without malformations of cortical development, contributing to identifying novel genotype/phenotype correlations for known disease-causing genes (*ARX*, *CHRNA2*, *PRRT2*, and mTOR pathway genes) and to discovering and characterizing at functional level novel causative genes (*RPS6*, *ATP6V1A*, *DMXL2*, and *TMEM63B*). These studies have contributed to better delineating the genotype/phenotype correlations and the pathophysiological mechanisms of some pediatric epilepsy syndromes.

Relevant publications

1. Vetro A, Pelorosso C, Balestrini S, Masi A, Hambleton S, Argilli E, **Conti V**, Giubolini S, Barrick R, Bergant G, Writzl K, Bijlsma EK, Brunet T, Cacheiro P, Mei D, Devlin A, Hoffer MJV, Machol K, Mannaioni G, Sakamoto M, Menezes MP, Courtin T, Sherr E, Parra R, Richardson R, Roscioli T, Scala M, von Stülpnagel C, Smedley D; TMEM63B collaborators; Genomics England Research Consortium; Torella A, Tohyama J, Koichihara R, Hamada K, Ogata K, Suzuki T, Sugie A, vander Smagt JJ, van Gassen K, Valence S, Vittery E, Malone S, Kato M, Matsumoto N, Ratto GM, Guerrini R. Stretch-activated ion channel TMEM63B associates with developmental and epileptic encephalopathies and progressive neurodegeneration. *Am J Hum Genet.* 2023 Aug 3;110(8):1356-1376. doi: 10.1016/j.ajhg.2023.06.008. Epub 2023 Jul 7. PMID: 37421948; PMCID: PMC10432263.
2. Chung C, Yang X, Bae T, Vong KI, Mittal S, Donkels C, Westley Phillips H, Li Z, Marsh APL, Breuss MW, Ball LL, Garcia CAB, George RD, Gu J, Xu M, Barrows C, James KN, Stanley V, Nidhiry AS, Khoury S, Howe G, Riley E, Xu X, Copeland B, Wang Y, Kim SH, Kang HC, Schulze-Bonhage A, Haas CA, Urbach H, Prinz M, Limbrick DD Jr, Gurnett CA, Smyth MD, Sattar S, Nespeca M, Gonda DD, Imai K, Takahashi Y, Chen HH, Tsai JW, **Conti V**, Guerrini R, Devinsky

- O, Silva WA Jr, Machado HR, Mathern GW, Abyzov A, Baldassari S, Baulac S; Focal Cortical Dysplasia Neurogenetics Consortium; Brain Somatic Mosaicism Network; Gleeson JG. Comprehensive multi-omic profiling of somatic mutations in malformations of cortical development. *Nat Genet.* 2023 Feb;55(2):209-220. doi:10.1038/s41588-022-01276-9. Epub 2023 Jan 12. PMID: 36635388; PMCID: PMC9961399.
3. Guerrini R, Mei D, Kerti-Szigeti K, Pepe S, Koenig MK, Von Allmen G, Cho MT, McDonald K, Baker J, Bhambhani V, Powis Z, Rodan L, Nabbout R, Barcia G, Rosenfeld JA, Bacino CA, Mignot C, Power LH, Harris CJ, Marjanovic D, Møller RS, Hammer TB; DDD Study; Keski Filppula R, Vieira P, Hildebrandt C, Sacharow S; Undiagnosed Diseases Network; Maragliano L, Benfenati F, Lachlan K, Benneche A, Petit F, de Sainte Agathe JM, Hallinan B, Si Y, Wentzensen IM, Zou F, Narayanan V, Matsumoto N, Boncristiano A, la Marca G, Kato M, Anderson K, Barba C, Sturiale L, Garozzo D, Bei R; ATP6V1A collaborators; Masuelli L, **Conti V**, Novarino G, Fassio A. Phenotypic and genetic spectrum of ATP6V1A encephalopathy: a disorder of lysosomal homeostasis. *Brain.* 2022 Aug 27;145(8):2687-2703. doi:10.1093/brain/awac145. PMID: 35675510; PMCID: PMC10893886.
 4. Pirozzi F, Berkseth M, Shear R, Gonzalez L, Timms AE, Sulc J, Pao E, Oyama N, Forzano F, **Conti V**, Guerrini R, Doherty ES, Saitta SC, Lockwood CM, Pritchard CC, Dobyns WB, Novotny E, Wright JNN, Saneto RP, Friedman S, Hauptman J, Ojemann J, Kapur RP, Mirzaa GM. Profiling PI3K-AKT-MTOR variants in focal brain malformations reveals new insights for diagnostic care. *Brain.* 2022 Apr 29;145(3):925-938. doi: 10.1093/brain/awab376. Erratum in: *Brain.* 2023 Jan 5;146(1):e7-e8. PMID: 35355055; PMCID: PMC9630661.
 5. Guerrini R, Cavallin M, Pippucci T, Rosati A, Bisulli F, Dimartino P, Barba C, Garbelli R, Buccoliero AM, Tassi L, **Conti V**. Is Focal Cortical Dysplasia/Epilepsy Caused by Somatic MTOR Mutations Always a Unilateral Disorder? *Neurol Genet.* 2020 Dec 8;7(1):e540. doi: 10.1212/NXG.0000000000000540. PMID: 33542949; PMCID: PMC7735020.
 6. Esposito A, Falace A, Wagner M, Gal M, Mei D, **Conti V**, Pisano T, Aprile D, Cerullo MS, De Fusco A, Giovedì S, Seibt A, Magen D, Polster T, Eran A, Stenton SL, Fiorillo C, Ravid S, Mayatepek E, Hafner H, Wortmann S, Levanon EY, Marini C, Mandel H, Benfenati F, Distelmaier F, Fassio A, Guerrini R. Biallelic DMXL2 mutations impair autophagy and cause Ohtahara syndrome with progressive course. *Brain.* 2019 Dec 1;142(12):3876-3891. doi: 10.1093/brain/awz326. Erratum in: *Brain.* 2020 Feb 1;143(2):e16. PMID: 31688942.
 7. Pelorosso C, Watrin F, **Conti V**, Buhler E, Gelot A, Yang X, Mei D, McEvoy-Venneri J, Manent JB, Cetica V, Ball LL, Buccoliero AM, Vinck A, Barba C, Gleeson JG, Guerrini R, Represa A. Somatic double-hit in MTOR and RPS6 in hemimegalencephaly with intractable epilepsy. *Hum Mol Genet.* 2019 Nov 15;28(22):3755-3765. doi: 10.1093/hmg/ddz194. PMID: 31411685; PMCID: PMC6935386.
 8. Kobow K, Ziemann M, Kaipananickal H, Khurana I, Mühlebner A, Feucht M, Hainfellner JA, Czech T, Aronica E, Pieper T, Holthausen H, Kudernatsch M, Hamer H, Kasper BS, Rössler K, **Conti V**, Guerrini R, Coras R, Blümcke I, El-Osta A, Kaspi A. Genomic DNA methylation distinguishes subtypes of human focal cortical dysplasia. *Epilepsia.* 2019 Jun;60(6):1091-1103. doi: 10.1111/epi.14934. Epub 2019 May 10. PMID: 31074842; PMCID: PMC6635741.
 9. Cellini E, Vetro A, **Conti V**, Marini C, Doccini V, Clementella C, Parrini E, Giglio S, Della Monica M, Fichera M, Musumeci SA, Guerrini R. Multiple genomic copy number variants associated with periventricular nodular heterotopia indicate extreme genetic heterogeneity. *Eur J Hum Genet.* 2019 Jun;27(6):909-918. doi: 10.1038/s41431-019-0335-3. Epub 2019 Jan 25. PMID: 30683929; PMCID: PMC6777581.
 10. Baldassari S, Picard F, Verbeek NE, van Kempen M, Brilstra EH, Lesca G, **Conti V**, Guerrini R, Bisulli F, Licchetta L, Pippucci T, Tinuper P, Hirsch E, de Saint Martin A, Chelly J, Rudolf G, Chipaux M, Ferrand-Sorbets S, Dorfmueller G, Sisodiya S, Balestrini S, Schoeler N, Hernandez-Hernandez L, Krithika S, Oegema R, Hagebeuk E, Gunning B, Deckers C, Berghuis B, Wegner I, Niks E, Jansen FE, Braun K, de Jong D, Rubboli G, Talvik I, Sander V, Uldall P, Jacquemont ML, Nava C, Leguern E, Julia S, Gambardella A, d'Orsi G, Crichtiutti G, Faivre L, Darmency V, Benova B, Krsek P, Biraben A, Lebre AS, Jennesson M, Sattar S, Marchal C, Nordli DR Jr, Lindstrom K, Striano P, Lomax LB, Kiss C, Bartolomei F, Lepine AF, Schoonjans AS, Stouffs K, Jansen A, Panagiotakaki E, Ricard-Mousnier B, Thevenon J, de Bellescize J, Catenoix H, Dorn T, Zenker M, Müller-Schlüter K, Brandt C, Krey I, Polster T, Wolff M, Balci M, Rostasy K, Achaz

- G, Zacher P, Becher T, Cloppenborg T, Yuskaitis CJ, Weckhuysen S, Poduri A, Lemke JR, Møller RS, Baulac S. The landscape of epilepsy-related GATOR1 variants. *Genet Med*. 2019Feb;21(2):398-408. doi: 10.1038/s41436-018-0060-2. Epub 2018 Aug 10. Erratum in: *Genet Med*. 2018 Aug 29;: Erratum in: *Genet Med*. 2018 Sep 27;: PMID: 30093711;PMCID: PMC6292495.
11. Fassio A, Esposito A, Kato M, Saitsu H, Mei D, Marini C, **Conti V**, Nakashima M, Okamoto N, Olmez Turker A, Albuz B, Semerci Gündüz CN, Yanagihara K, Belmonte E, Maragliano L, Ramsey K, Balak C, Siniard A, Narayanan V; C4RCD Research Group; Ohba C, Shiina M, Ogata K, Matsumoto N, Benfenati F, Guerrini R. De novomutations of the ATP6V1A gene cause developmental encephalopathy with epilepsy. *Brain*. 2018 Jun 1;141(6):1703-1718. doi: 10.1093/brain/awy092. PMID: 29668857;PMCID: PMC5972584.
 12. Alcantara D, Timms AE, Gripp K, Baker L, Park K, Collins S, Cheng C, Stewart F, Mehta SG, Saggarr A, Sztriha L, Zombor M, Caluseriu O, Mesterman R, Van Allen MI, Jacquinet A, Ygberg S, Bernstein JA, Wenger AM, Guturu H, Bejerano G, Gomez-Ospina N, Lehman A, Alfei E, Pantaleoni C, **Conti V**, Guerrini R, Moog U, Graham JM Jr, Hevner R, Dobyns WB, O'Driscoll M, Mirzaa GM. Mutations of AKT3 are associated with a wide spectrum of developmental disorders including extreme megalencephaly. *Brain*. 2017 Oct 1;140(10):2610-2622. doi: 10.1093/brain/awx203. PMID: 28969385; PMCID: PMC6080423.
 13. Møller RS, Weckhuysen S, Chipaux M, Marsan E, Taly V, Bebin EM, Hiatt SM, Prokop JW, Bowling KM, Mei D, **Conti V**, de la Grange P, Ferrand-Sorbets S, Dorfmueller G, Lambrecq V, Larsen LH, Leguern E, Guerrini R, Rubboli G, Cooper GM, Baulac S. Germline and somatic mutations in the MTOR gene in focalcortical dysplasia and epilepsy. *Neurol Genet*. 2016 Oct 31;2(6):e118. doi:10.1212/NXG.0000000000000118. PMID: 27830187; PMCID: PMC5089441.
 14. Mirzaa GM, Campbell CD, Solovieff N, Goold C, Jansen LA, Menon S, Timms AE, **Conti V**, Biag JD, Adams C, Boyle EA, Collins S, Ishak G, Poliachik S, Girisha KM, Yeung KS, Chung BHY, Rahikkala E, Gunter SA, McDaniel SS, Macmurdo CF, Bernstein JA, Martin B, Leary R, Mahan S, Liu S, Weaver M, Doerschner M, Jhangiani S, Muzny DM, Boerwinkle E, Gibbs RA, Lupski JR, Shendure J, Saneto RP, Novotny EJ, Wilson CJ, Sellers WR, Morrissey M, Hevner RF, Ojemann JG, Guerrini R, Murphy LO, Winckler W, Dobyns WB. Association of MTOR Mutations With Developmental Brain Disorders, Including Megalencephaly, Focal Cortical Dysplasia, and Pigmentary Mosaicism. *JAMA Neurol*. 2016 Jul 1;73(7):836-845. doi:10.1001/jamaneurol.2016.0363. PMID: 27159400; PMCID: PMC4979321.
 15. Mirzaa G, Timms AE, **Conti V**, Boyle EA, Girisha KM, Martin B, Kircher M, Olds C, Juusola J, Collins S, Park K, Carter M, Glass I, Krägeloh-Mann I, Chitayat D, Parikh AS, Bradshaw R, Torti E, Braddock S, Burke L, Ghedia S, Stephan M, Stewart F, Prasad C, Napier M, Saitta S, Straussberg R, Gabbett M, O'Connor BC, Keegan CE, Yin LJ, Lai AHM, Martin N, McKinnon M, Addor MC, Boccuto L, Schwartz CE, Lanoel A, Conway RL, Devriendt K, Tatton-Brown K, Pierpont ME, Painter M, Worgan L, Reggin J, Hennekam R, Tsuchiya K, Pritchard CC, Aracena M, Gripp KW, Cordisco M, Van Esch H, Garavelli L, Curry C, Goriely A, Kayserilli H, Shendure J, Graham J Jr, Guerrini R, Dobyns WB. PIK3CA-associated developmental disorders exhibit distinct classes of mutations with variable expression and tissue distribution. *JCI Insight*. 2016 Jun 16;1(9):e87623. doi:10.1172/jci.insight.87623. PMID: 27631024; PMCID: PMC5019182.
 16. Mirzaa GM, **Conti V**, Timms AE, Smyser CD, Ahmed S, Carter M, Barnett S, Hufnagel RB, Goldstein A, Narumi-Kishimoto Y, Olds C, Collins S, Johnston K, Deleuze JF, Nitschké P, Friend K, Harris C, Goetsch A, Martin B, Boyle EA, Parrini E, Mei D, Tattini L, Slavotinek A, Blair E, Barnett C, Shendure J, Chelly J, Dobyns WB, Guerrini R. Characterisation of mutations of the phosphoinositide-3-kinase regulatory subunit, PIK3R2, in perisylvian polymicrogyria: a next-generation sequencing study. *Lancet Neurol*. 2015Dec;14(12):1182-95. doi: 10.1016/S1474-4422(15)00278-1. Epub 2015 Oct 29. PMID: 26520804; PMCID: PMC4672724.
 17. **Conti V**, Pantaleo M, Barba C, Baroni G, Mei D, Buccoliero AM, Giglio S, Giordano F, Baek ST, Gleeson JG, Guerrini R. Focal dysplasia of the cerebral cortex and infantile spasms associated with somatic 1q21.1-q44 duplication including the AKT3 gene. *Clin Genet*. 2015 Sep;88(3):241-7. doi:10.1111/cge.12476. Epub 2014 Oct 7. PMID: 25091978.
 18. **Conti V**, Aracri P, Chiti L, Brusco S, Mari F, Marini C, Albanese M, Marchi A, Liguori C, Placidi F, Romigi A, Becchetti A, Guerrini R. Nocturnal frontal lobe epilepsy with paroxysmal arousals due to CHRNA2 loss of function. *Neurology*. 2015 Apr 14;84(15):1520-8. doi:

10.1212/WNL.0000000000001471. Epub 2015 Mar 13. PMID: 25770198; PMCID: PMC4408286.

19. Conti V, Carabalona A, Pallesi-Pocachard E, Parrini E, Leventer RJ, Buhler E, McGillivray G, Michel FJ, Striano P, Mei D, Watrin F, Lise S, Pagnamenta AT, Taylor JC, Kini U, Clayton-Smith J, Novara F, Zuffardi O, Dobyns WB, Scheffer IE, Robertson SP, Berkovic SF, Represa A, Keays DA, Cardoso C, Guerrini R. Periventricular heterotopia in 6q terminal deletion syndrome: role of the C6orf70 gene. *Brain*. 2013 Nov;136(Pt 11):3378-94. doi: 10.1093/brain/awt249. Epub 2013 Sep 20. PMID: 24056535.
20. Marini C, **Conti V**, Mei D, Battaglia D, Lettori D, Losito E, Bruccini G, Tortorella G, Guerrini R. PRRT2 mutations in familial infantile seizures, paroxysmal dyskinesia, and hemiplegic migraine. *Neurology*. 2012 Nov 20;79(21):2109-14. doi: 10.1212/WNL.0b013e3182752ca2. Epub 2012 Oct 17. PMID: 23077026; PMCID: PMC3511926.
21. **Conti V**, Marini C, Gana S, Sudi J, Dobyns WB, Guerrini R. Corpus callosum agenesis, severe mental retardation, epilepsy, and dyskinetic quadriplegia due to a novel mutation in the homeodomain of ARX. *Am J Med Genet A*. 2011 Apr;155A(4):892-7. doi: 10.1002/ajmg.a.33923. Epub 2011 Mar 17. PMID: 21416597.
22. **Conti V**, Marini C, Mei D, Falchi M, Ferrari AR, Guerrini R. Contractions in the second polyA tract of ARX are rare, non-pathogenic polymorphisms. *Am J Med Genet A*. 2011 Jan;155A(1):164-7. doi: 10.1002/ajmg.a.33753. Epub 2010 Dec 10. PMID: 21204226.
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24. **Conti V**, Aghaie A, Cilli M, Martin N, Caridi G, Musante L, Candiano G, Castagna M, Fairen A, Ravazzolo R, Guenet JL, Puliti A. *crv4*, a mouse model for human ataxia associated with kyphoscoliosis caused by an mRNA splicing mutation of the metabotropic glutamate receptor 1 (*Grm1*). *Int J Mol Med*. 2006 Oct;18(4):593-600. PMID: 16964410.