BIOGRAPHICAL SKETCH

NAME: Elisabetta Flex

POSITION TITLE: PhD

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University “Sapienza”, Rome, Italy	Master Degree (Biology)	1999	Virology
University “Tor Vergata”, Rome, Italy	Research Fellow	1999-2000	Human genetics
Institute “CSS-Mendel”, Rome, Italy	PhD Student	2001-2004	Human genetics
University “Sapienza”, Rome, Italy	PhD	2005	Medical genetics

A. Personal Statement

ORCID ID: 0000-0002-6802-1356
SCOPUS ID: 6603088723

In the last decade, my scientific activity has been directed to understanding the disease mechanisms underlying human genetic disorders affecting development and growth, and molecular processes contributing to hematological malignancies. In particular, my research has contributed to the identification of novel disease-genes implicated in RASopathies (*i.e NRAS, RRAS, RRAS2, MAPK1*), as well as to the understanding the molecular and cellular mechanisms underlying these disorders, with particular attention to LEOPARD and Noonan syndromes. My work also contributed to the identification and functional characterization of disease genes involved in severe unrecognized rare disorders characterized by multiple malformations, early-onset neurodegeneration, defects of neurodevelopment, and premature aging *(i.e., ATP6V1B2, KCNH1, TBCD, TBCE, HIST1H1E, VPS4A, KIF5B*). Actually, my research activity is aimed at defining the metabolic profile of Costello and cardiofaciocutaneous syndromes (CFC), two developmental disorders clinically related to Noonan syndrome, and to understanding the mechanisms underlying several issues characterizing these condition as poor growth, muscle-skeletal anomalies and reduced bone mineral density.
I have extensive expertise in functional genomics and for my research activity I use a broad variety of experimental approaches utilizing both patients’ derived cell lines and transduced/transfected cellular models.

B. Positions, Scientific Appointments, and Honors

2005-2009 Post-Doctoral research fellow, Department of Cell Biology and Neurosciences, Istituto Superiore di Sanità, Rome, Italy.

2010-2016 In staff-scientist, Department of Hematology, Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy.

2017-present In staff-scientist, Group leader of the Functional Genomics Unit, Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy.

2019 – present Member, Editorial Board, Frontiers in Genetics (section “Genetic Disorders”).
2016 – present Member, Italian Society of Human Genetics (SIGU).

C. Contributions to Science

Most important publications (A co-first authorship; B co-last authorship; * corresponding author).

1. Melo US, Jatzlau J, Prada-Medina CA, **Flex E**, Hartmann S, Ali S, Schöpflin R, Bernardini L, Ciolfi A, Moeinzadeh MH, Klever MK, Altay A, Vallecillo-García P, Carpentieri G, Delledonne M, Ort MJ, Schwestka M, Ferrero GB, Tartaglia M, Brusco A, Gossen M, Strunk D, Geißler S, Mundlos S, Stricker S, Knaus P, Giorgio E, Spielmann M. 1. Enhancer hijacking at the ARHGAP36 locus is associated with connective tissue to bone transformation. Nat Commun. 2023 Apr 11;14(1):2034. doi: 10.1038/s41467-023-37585-8.
2. **Flex E^{A*}**, Albadri SA, Radio FC, Cecchetti S, Lauri A, Priolo M, Kissopoulos M, Carpentieri G, Fasano G, Venditti M, Magliocca V, Bellacchio E, Welch CL, Colombo PC, Kochav SM, Chang R, Barrick R, Trivisano M, Micalizzi A, Borghi R, Messina E, Mancini C, Pizzi S, De Santis F, Rosello M, Specchio N, Compagnucci C, McWalter K, Chung WK, Del Bene F, Tartaglia M*. Dominantly acting KIF5B variants with pleiotropic cellular consequences cause variable clinical phenotypes. Hum Mol Genet. 2023 Jan 13;32(3):473-488.
3. Rodger C^{A}, **Flex E^{A}**, Allison RJ, Sanchis-Juan A, Hasenahuer MA, Cecchetti S, French CE, Edgar JR, Carpentieri G, Ciolfi A, Pantaleoni F, Bruselles A; Genomics England Research Consortium, Onesimo R, Zampino G, Marcon F, Siniscalchi E, Lees M, Krishnakumar D, McCann E, Yosifova D, Jarvis J, Kruer MC, Marks W, Campbell J, Allen LE, Gustincich S, Raymond FL, Tartaglia M, Reid E. De Novo VPS4A Mutations Cause Multisystem Disease with Abnormal Neurodevelopment. Am J Hum Genet. 2020 Dec 3;107(6):1129-1148.
4. **Flex E^{A}**, Martinelli S^{A}, Van Dijck A, Ciolfi A, Cecchetti S, Coluzzi E, Pannone L, Andreoli C, Radio FC, Pizzi S, Carpentieri G, Bruselles A, Catanzaro G, Pedace L, Miele E, Carcarino E, Ge X, Chijiwa C, Lewis MES, Meuwissen M, Kenis S, Van der Aa N, Larson A, Brown K, Wasserstein MP, Skotko BG, Begtrup A, Person R, Karayiorgou M, Roos JL, Van Gassen KL, Koopmans M, Bijlsma EK, Santen GWE, Barge-Schaapveld DQCM, Ruivenkamp CAL, Hoffer MJV, Lalani SR, Streff H, Craigen WJ, Graham BH, van den Elzen APM, Kamphuis DJ, Õunap K, Reinson K, Pajusalu S, Wojcik MH, Viberti C, Di Gaetano C, Bertini E, Petrucci S, De Luca A, Rota R, Ferretti E, Matullo G, Dallapiccola B, Sgura A, Walkiewicz M, Kooy RF, Tartaglia M. Aberrant Function of the C-Terminal Tail of HIST1H1E Accelerates Cellular Senescence and Causes Premature Aging. Am J Hum Genet. 2019 Sep 5;105(3):493-508.
5. **Flex E^{A}**, Niceta M^{A}, Cecchetti S, Thiffault I, Au MG, Capuano A, Piermarini E, Ivanova AA, Francis JW, Chillemi G, Chandramouli B, Carpentieri G, Haaxma CA, Ciolfi A, Pizzi S, Douglas GV, Levine K, Sferra A, Dentici ML, Pfundt RR, Le Pichon JB, Farrow E, Baas F, Piemonte F, Dallapiccola B, Graham JM Jr, Saunders CJ, Bertini E, Kahn RA, Koolen DA, Tartaglia M. Biallelic Mutations in TBCD, Encoding the Tubulin Folding Cofactor D, Perturb Microtubule Dynamics and Cause Early-Onset Encephalopathy. Am J Hum Genet. 2016 Oct 6;99(4):962-973.
6. **Flex E**, Petrangeli V, Stella L, Chiaretti S, Hornakova T, Knoops L, Ariola C, Fodale V, Clappier E, Paoloni F, Martinelli S, Fragale A, Sanchez M, Tavolaro S, Messina M, Cazzaniga G, Camera A, Pizzolo G, Tornesello A, Vignetti M, Battistini A, Cavé H, Gelb BD, Renauld JC, Biondi A, Constantinescu SN, Foà R, Tartaglia M. Somatically acquired JAK1 mutations in adult acute lymphoblastic leukemia. J Exp Med. 2008 Apr 14;205(4):751-8.

Relevant publications related to RASopathies
(A co-first authorship; B co-last authorship; * corresponding author).

1. Leoni C, Massese M, Gervasoni J, Primiano A, Giorgio V, Onesimo R, Kuczynska E, Rigante D, Persichilli S, Carpentieri G, **Flex E**, Pastorino R, Tartaglia M, Zampino G. Metabolic profiling of Costello syndrome: Insights from a single-center cohort. Eur J Med Genet. 2022 Mar;65(3):104439. doi: 10.1016/j.ejmg.2022.104439. Epub 2022 Jan 29.
2. Carpentieri G, Leoni C, Pietraforte D, Cecchetti S, Iorio E, Belardo A, Pietrucci D, Di Nottia M, Pajalunga D, Megiorni F, Mercurio L, Tatti M, Camero S, Marchese C, Rizza T, Tirelli V, Onesimo R, Carrozzo R, Rinalducci

S, Chillemi G, Zampino G, Tartaglia M[B*], **Flex E**[B*]. Hyperactive HRAS dysregulates energetic metabolism in fibroblasts from patients with Costello syndrome via enhanced production of reactive oxidizing species. Hum Mol Genet. 2022 Feb 21;31(4):561-575.

3. Leoni C, Massese M, Gervasoni J, Primiano A, Giorgio V, Onesimo R, Kuczynska E, Rigante D, Persichilli S, Carpentieri G, **Flex E**, Pastorino R, Tartaglia M, Zampino G. Metabolic profiling of Costello syndrome: Insights from a single-center cohort. Eur J Med Genet. 2022 Mar;65(3):104439. doi: 10.1016/j.ejmg.2022.104439.
4. Leoni C, Bisanti C, Viscogliosi G, Onesimo R, Massese M, Giorgio V, Corbo F, Acampora A, Cipolla C, **Flex E**, Dell'Atti C, Rigante D, Tartaglia M, Zampino G. Bone tissue homeostasis and risk of fractures in Costello syndrome: A 4-year follow-up study. Am J Med Genet A. 2022 Feb;188(2):422-430.
5. Leoni C, Viscogliosi G, Onesimo R, Bisanti C, Massese M, Giorgio V, Corbo F, Tedesco M, Acampora A, Cipolla C, Dell'Atti C, **Flex E**, Gervasoni J, Primiano A, Rigante D, Tartaglia M, Zampino G. Characterization of bone homeostasis in individuals affected by cardio-facio-cutaneous syndrome. Am J Med Genet A. 2022 Feb;188(2):414-421.
6. Leoni C, Romeo DM, Pelliccioni M, Di Già M, Onesimo R, Giorgio V, **Flex E**, Tedesco M, Tartaglia M, Rigante D, Valassina A, Zampino G. Musculo-skeletal phenotype of Costello syndrome and cardio-facio-cutaneous syndrome: insights on the functional assessment status. Orphanet J Rare Dis. 2021 Jan 22;16(1):43.
7. Bobone S, Pannone L, Biondi B, Solman M, **Flex E**, Canale VC, Calligari P, De Faveri C, Gandini T, Quercioli A, Torini G, Venditti M, Lauri A, Fasano G, Hoeksma J, Santucci V, Cattani G, Bocedi A, Carpentieri G, Tirelli V, Sanchez M, Peggion C, Formaggio F, den Hertog J, Martinelli S, Bocchinfuso G, Tartaglia M, Stella L. Targeting Oncogenic Src Homology 2 Domain-Containing Phosphatase 2 (SHP2) by Inhibiting Its Protein-Protein Interactions. J Med Chem. 2021 Nov 11;64(21):15973-15990.
8. Motta M, Pannone L, Pantaleoni F, Bocchinfuso G, Radio FC, Cecchetti S, Ciolfi A, Di Rocco M, Elting MW, Brilstra EH, Boni S, Mazzanti L, Tamburrino F, Walsh L, Payne K, Fernández-Jaén A, Ganapathi M, Chung WK, Grange DK, Dave-Wala A, Reshmi SC, Bartholomew DW, Mouhlas D, Carpentieri G, Bruselles A, Pizzi S, Bellacchio E, Piceci-Sparascio F, Lißewski C, Brinkmann J, Waclaw RR, Waisfisz Q, van Gassen K, Wentzensen IM, Morrow MM, Álvarez S, Martínez-García M, De Luca A, Memo L, Zampino G, Rossi C, Seri M, Gelb BD, Zenker M, Dallapiccola B, Stella L, Prada CE, Martinelli SB, Flex EB, Tartaglia MB. Enhanced MAPK1 Function Causes a Neurodevelopmental Disorder within the RASopathy Clinical Spectrum. Am J Hum Genet. 2020 Sep 3;107(3):499-513.
9. Martinelli S, Pannone L, Lissewski C, Brinkmann J, Flex E, Schanze D, Calligari P, Anselmi M, Pantaleoni F, Canale VC, Radio FC, Ioannides A, Rahner N, Schanze I, Josifova D, Bocchinfuso G, Ryten M, Stella L, Tartaglia M, Zenker M. Pathogenic PTPN11 variants involving the poly-glutamine Gln255 -Gln256 -Gln257 stretch highlight the relevance of helix B in SHP2's functional regulation. Hum Mutat. 2020 Jun;41(6):1171-1182.
10. Capri Y[A], **Flex E**[**A**], Krumbach OHF, Carpentieri G, Cecchetti S, Lißewski C, Rezaei Adariani S, Schanze D, Brinkmann J, Piard J, Pantaleoni F, Lepri FR, Goh ES, Chong K, Stieglitz E, Meyer J, Kuechler A, Bramswig NC, Sacharow S, Strullu M, Vial Y, Vignal C, Kensah G, Cuturilo G, Kazemein Jasemi NS, Dvorsky R, Monaghan KG, Vincent LM, Cavé H, Verloes A, Ahmadian MR, Tartaglia M, Zenker M. Activating Mutations of RRAS2 Are a Rare Cause of Noonan Syndrome. Am J Hum Genet. 2019 Jun 6;104(6):1223-1232.
11. Pantaleoni F, Lev D, Cirstea IC, Motta M, Lepri FR, Bottero L, Cecchetti S, Linger I, Paolacci S, **Flex E**, Novelli A, Carè A, Ahmadian MR, Stellacci E, Tartaglia M. Aberrant HRAS transcript processing underlies a distinctive phenotype within the RASopathy clinical spectrum. Hum Mutat. 2017 Jul;38(7):798-804.
12. Altmüller F, Lissewski C, Bertola D, **Flex E**, Stark Z, Spranger S, Baynam G, Buscarilli M, Dyack S, Gillis J, Yntema HG, Pantaleoni F, van Loon RL, MacKay S, Mina K, Schanze I, Tan TY, Walsh M, White SM, Niewisch MR, García-Miñaúr S, Plaza D, Ahmadian MR, Cavé H, Tartaglia M, Zenker M. Genotype and phenotype spectrum of NRAS germline variants. Eur J Hum Genet. 2017 Jun;25(7):823-831.
13. **Flex E**[**A**], Jaiswal M[A], Pantaleoni F, Martinelli S, Strullu M, Fansa EK, Caye A, De Luca A, Lepri F, Dvorsky R, Pannone L, Paolacci S, Zhang SC, Fodale V, Bocchinfuso G, Rossi C, Burkitt-Wright EM, Farrotti A, Stellacci E, Cecchetti S, Ferese R, Bottero L, Castro S, Fenneteau O, Brethon B, Sanchez M, Roberts AE, Yntema HG, Van Der Burgt I, Cianci P, Bondeson ML, Cristina Digilio M, Zampino G, Kerr B, Aoki Y, Loh ML, Palleschi A, Di Schiavi E, Carè A, Selicorni A, Dallapiccola B, Cirstea IC, Stella L, Zenker M, Gelb BD,

Cavé H, Ahmadian MR, Tartaglia M. Activating mutations in RRAS underlie a phenotype within the RASopathy spectrum and contribute to leukaemogenesis. Hum Mol Genet. 2014 Aug 15;23(16):4315-27.

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