CURRICULUM VITAE – FRANCISCO JAVIER DE LA CRUZ

Part A. PERSONAL INFORMATION

First name	Francisco Javier		
Family name	de la Cruz Montserrat		
Gender	Male	Birth date (dd/mm/yyyy)	12/09/1958
ID number	36508662A		
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Open Research and Contributor ID (ORCID)		0000-0002-9738-8472	

A.1. Current position

Position	ICREA Research Professor		
Initial date	1-11-2001		
Institution	Vall d'Hebron Institute of Research (VHIR)		
Departament/Center	Clinical and Translational Bioinformatics		
Country	Spain	Teleph. number	636620149
Keywords	Genomics/Proteomics; Next-Generation Sequencing (NGS); Pathological Mutations; In silico methods; Molecular Diagnosis; Clinical and Translational Bioinformatics; Machine Learning		

A.2. Previous positions (research activity interruptions, art. 45.2.c))

Period	Position/Institution/Country/Interruption cause
1997-1999	Post-doctoral/European Bioinformatics Institute-University College London/UK; HFSP fellow
1993-1997	Post-doctoral/National Institutes of Health (NIH)/USA

A.3. Education

PhD, Licensed, Graduate	University/Country	Year
Ph.D. in Biology	Universidad Politécnica de Barcelona	1993

Part B. CV SUMMARY

My interests are devoted to studying the impact of pathogenic mutations and transform the results into clinically useful Artificial Intelligence (AI) models. **Highlights**. We ranked second in the groups' classification at the international challenge for in silico methods, CAGI 5 (2018-2019, BRCA1/2 challenge) and CAGI 6 (2023, ARSA challenge). We won the Best Poster Prize of the Editor of 'Science' in HGM 2018 (Japan). In 2015, we participated in the identification of the glioblastoma signature in cerebro-spinal fluid (De Mattos-Arruda et al., Nature Communications, 6:8839), a project that won the Prize "La Vanguardia de la Ciencia".

Ph.D. Thesis (1990-1993, UPC, Barcelona). I worked in a relationship between atomic areas and free energies (de la Cruz et al., J.Mol.Graphics, 10:96, 1992). During a stay in the lab of van Gunsteren (ETH-Z, Zürich), I shifted toward the study of the structure/function relationship (de la Cruz et al., J. Mol. Biol., 236:1186, 1994).
Fellowships: FPI Generalitat (1990-93, UPC); **EMBO Short Term** (1992, ETH-Z).

Post-doctoral (1993-2000). Two post-doctoral stays: NIH, USA (4 years) and UCL-EBI, UK (3 years). In these stays, I increased my background on structure/function relationship (analog structure comparisons: de la Cruz & Lee, Protein Sci., 5:857, 1996; beta-turn prediction: de la Cruz et al., PNAS, 99:11157, 2002).
Fellowships: Fogarty Fellowship (1993-97, USA); MEC fellowship for doctors (1997); **Human Frontier Science Program (HFSP)** (1997-99, UK).

Present research (2000-Present). Our research aims at understanding/predicting the impact of pathogenic of variants using AI. Our initial approach (Ferrer-Costa et al., J. Mol. Biol. 2002; Proteins, 2004; Bioinformatics, 2005) has been broadly followed (1020+ citations). After joining VHIR (2012) we have designed a novel approach to pathogenicity prediction (Riera et al., Hum. Mut., 2016). This crystallized in the model for BRCA1/2 variants (Padilla et al., Hum. Mut., 2019) that we presented at the international CAGI contest (see above). We have further tested this result to extend it to the clinical genome (Özkan et al., IJMS, 2020). Our expertise is reflected in our collaborations (see below for our international collaborations).
We have worked also in the epigenetic regulation of gene expression, where I would like to single out two of our publications (co-corresponding author in both), one in *PNAS* (Pappa et al., 2019) about DNA damage prevention and the second in *Development* (Estarás et al., 2012) on the regulation of neural development by JMJD3.
Contracts: Reincorporación MEC (2000-2001), **ICREA Research Professor** (2001-Present).
Funding: I addition to the funding listed below, I would like to add the two grants with which I started my career as an independent researcher: BIO2003-09327 (139150 euros) and BIO2006-15557 (157300 euros).

-Academia. (2022-Present). I joined the Universitat Internacional de Catalunya (UIC) in year 2022 as Coordinator of the Specialization in Bioinformatics within the Biomedicine degree. I combine organizational and teaching duties.

-Skills. We have a deep understanding of the molecular basis of hereditary diseases. Technically, we are proficient in the development of AI tools for pathogenicity prediction. We are also proficient in the structural/functional characterization of protein mutations using computational/bioinformatics approaches.
-International collaborations. We have an ongoing collaboration with E. Bhoj (Children's Hospital of Philadelphia) for the clinical characterization of histone H3.3 variants. This work has lead to a high-impact publication (Bryant et al., Science Advances, 2020) in which we leadered the in silico analyses of the whole consortium (137 authors) in a study resulting in the discovery of a new neurodegenerative disorder. We are started a collaboration with the group of K. Avraham (Faculty of Medicine, Tel Aviv) on the analysis and prediction of hearing loss-related genetic variants.
-Scientific responsibilities. I **review for different journals** (Bioinformatics, Human Molecular Genetics, Human Mutation, Plos Computational Biology, etc.). I **review grant proposals** for the ANEP, and intermitently for international agencies (BBSRC-UK, HFSP, EU). I have **co-organized meetings** (2nd Pirepred Scientific Meeting, 2018, Barcelona; Vth meeting of the Catalan Society of Biology, 2017, Barcelona) and **courses** (Course on exome sequencing at Instituto De Investigación Sanitaria Aragón, 2015, and at the Universidad Autónoma de Madrid, 2016).
-Leadership. We have been invitated to participate in the adaptation of the ACMG/AMP guidelines to the ATM gene (Feliubadaló et al., Clinical Chemistry, 2020) and in the report 'Sobre el cribado neonatal en España y en Francia' organized by the Pirepred consortium. Finally, our efforts have been recognized by independent workers in the field (Vihinen, Human Mutation, 2016; Cline et al., Human Mutation, 2019).
-Training researchers. I have supervised 11 Ph.D. theses. The majority of the students work in bioinformatics/computation. Carles Ferrer is Head of Bioinformatics at Fundació Institut d'Investigació Biomèdica (Girona); David Talavera is Lecturer in Genetics/Genomics at

Manchester University; David Piedra is Data Scientist at Barcelona Institute for Global Health; Sergio Lois is Data Scientist at 'Sistemas Genómicos'; etc.

Part C. RELEVANT MERITS *(2019-2023; sorted by typology)*
C.1. Publications *(see end of this document)*
C.2. Congress *(Invited talks only, 2019-2023)*
1.- "From Mutations to Disease Using Computers Only: Is This a Dream?", BIFI2019, 2019, Zaragoza, Opening Lecture/Keynote Speaker.
2.- "BRCA1- and BRCA2-specific in silico tools for variant interpretation in the CAGI 5 ENIGMA challenge" CAGI Workshop, 2019, San Francisco USA. Co-Invited Flash talk.

C.3. Research funding *(2019-2023)*
1. **Reference:** PID2022-142753OB-I00. Title: Avanzando hacia el diagnóstico de precisión a través de la comprensión mecanística de las patologías: de la interpretación de variantes a la identificación del perfil celular. Funding Institution: Ministerio de Ciencia e Innovación, Convocatoria: Proyectos de Generación del Conocimiento. Principal Investigator: Fco. Javier de la Cruz Montserrat. Duration: 1/11/2023-31/11/2025. Amount: 223000 euros. Role: Principal Investigator. Status: awarded
2. **Reference:** TED2021-130342B-I00. Title: Advancing the applicability of artificial intelligence in Genomic Medicine: Integrating performance and interpretability in a new generation of protein variant annotation tools (IAMEDGE). Funding Institution: Ministerio de Ciencia e Innovación. Convocatoria: Proyectos Estratégicos Orientados a la Transición Ecológica y a la Transición Digital (2021). Duration: 1/11/2022-31/11/2024. Amount: 219.650 euros. Role: Principal Investigator. Status: awarded
1. **Reference**: PID2019-111217RB-I00. Title: Una aproximación traslacional a la interpretación de variantes de secuencia en proteínas: integrando impacto molecular, regulación por el entorno genético y coste clínico. Funding Institution: Ministerio de Ciencia e Innovación, Convocatoria: I+D+i 2019 - Retos de la sociedad. Principal Investigator: Fco. Javier de la Cruz Montserrat. Duration: 01/06/2020-31/05/2023. Amount: 133100 euros. Role: Principal Investigator. Status: awarded
2. **Reference**: EFA086/15 – PIREPRED. Title: Network for the interpretation of neonatal screening: from the mutation to the patient. Funding Institution: European Union, Convocatoria: POCTEFA 2014-2020. Principal Investigator: Javier Sancho Sanz. Duration: 01/09/2016-31/08/2020. Amount: Total: 827008 euros. My group: 155214 euros. Role: Principal Investigator. Status: awarded
3. **Reference**: SAF2016-80255-R. Funding Institution: Ministerio de Economía y Competitividad. Convocatoria: I+D+I 2016 - Retos de la Sociedad. Principal Investigator: Fco. Javier de la Cruz Montserrat. Duration: 30/12/2016-29/12/2019. Amount: 96800 euros. Role: Principal Investigator. Status: awarded.

PUBLICATIONS *(2019-2023)*

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- Sheppard SE, Bryant L, Wickramasekara RN, Vaccaro C, Robertson B, Hallgren J, Hulen J, Watson CJ, Faundes V, Duffourd Y, Lee P, Simon MC, **de la Cruz X**, Padilla N, Flores-Mendez M, Akizu N, Smiler J, Pellegrino Da Silva , Li D, March M, Diaz-Rosado A, Peixoto de Barcelos , Choa ZX, Lim CY, Dubourg C, Journel H, Demurger F, Mulhern M, Akman C, Lippa N,

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- Aguirre J, Padilla N, Ozkan S, Riera C, Feliubadalo L, **de la Cruz X** (2023). Choosing Variant Interpretation Tools for Clinical Applications: Context Matters. Int J Mol Sci, 24(14):11872.

- Galano-Frutos JJ, Garcia-Cebollada H, Lopez A, Rosell M, **de la Cruz X**, Fernandez-Recio J, Sancho J (2022). PirePred: An Accurate Online Consensus Tool to Interpret Newborn Screening Related Genetic Variants in Structural Context. J Mol Diagn, 24(4):406-425.

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- Ozkan S, Padilla N, **de la Cruz X** (2021). Towards a New, Endophenotype-Based Strategy for Pathogenicity Prediction in BRCA1 and BRCA2: In Silico Modeling of the Outcome of HDR/SGE Assays for Missense Variants. Int J Mol Sci, 22(12). pii: ijms22126226.

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- Vinas-Gimenez L, Donadeu L, Alsina L, Rincon R, de la Campa EA, Esteve-Sole A, Catala A, Colobran R, **de la Cruz X**, Sayos J, Martinez-Gallo M (2020). Molecular analysis of the novel L243R mutation in STXBP2 reveals impairment of degranulation activity. Int J Hematol, 111(3):440-450.

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