

**UNIVERSITA' DEGLI STUDI DI BARI**  
**CONSIGLIO INTERCLASSE IN BIOLOGIA**

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**VERBALE DELLA SEDUTA DELLA GIUNTA DEL CONSIGLIO  
INTERCLASSE IN BIOLOGIA DEL 6 GIUGNO 2017**

Il giorno 6 giugno alle ore 15, dopo regolare convocazione, si è riunita in via tematica Giunta del Consiglio interclasse in Biologia, per discutere il seguente O.d.G.:

1) Richiesta approvazione progetto Global Thesis

Sono presenti i componenti: prof.ssa N. Archidiacono Coordinatore, prof.ssa MC de Pinto, prof.ssa V. Cavallaro, prof.ssa M. Barile, i sigg. Alessio Cassano, Eleonora De Pasquale rappresentanti degli studenti. Assenti giustificati: la prof.ssa G. Valenti e i sigg. Cassano Alessio, De Pasquale Eleonora rappresentanti degli studenti.

Presiede il Coordinatore, i presenti convengono che le funzioni di segretario siano svolte dalla prof.ssa MC. De Pinto.

Richiesta della studentessa Bitonto Miriana, matricola n.658512, di partecipare al bando "Global Thesis". Relatore Prof.ssa Francesca Antonacci

Il Coordinatore ha precedentemente inviato ai Membri della Giunta di interclasse il bando e i progetti formativi proposti dal relatore. I Membri della Giunta presa visione dei documenti, che costituiscono parte integrante del presente verbale, esprimono parere favorevole all'unanimità, riconoscendo che il periodo eventualmente trascorso presso l'Università autonoma di Barcellona sarà parte integrante dei crediti previsti per lo svolgimento della tesi.

La seduta è tolta alle ore 15,30. Il verbale è approvato seduta stante

Il Segretario

Il Coordinatore

Prof.ssa MC de Pinto

Prof.ssa Nicoletta Archidiacono







## *Premio di studio GLOBAL THESIS*

CO-TUTORSHIP BILATERAL AGREEMENT BETWEEN

UNIVERSITY OF BARI ALDO MORO (*Sending Institution*)

AND

(*Receiving Institution*)

UNIVERSITAT AUTÒNOMA DE BARCELONA

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- WHEREAS** on the basis of this programme, outgoing UNIBA students enrolled in specialization degree courses have the possibility to study abroad, for a minimum of two months;
- WHEREAS** selected students will be admitted to prestigious foreign Universities and research centres for their thesis preparation;
- WHEREAS** the programme offers the opportunity to invite professors from foreign universities to attend the final thesis disputation at the University of Bari Aldo Moro;

THE PARTIES AGREE AS FOLLOWS:

1. The Parties agree to co-operate in the co-tutorship of degree thesis activities for the student as specified in Art. 2. The participation in this programme does not imply a joint academic degree.
2. In respect of the rules in force in their respective countries and Institutions, the Parties agree to organize jointly a co-tutorship of the degree thesis to be prepared by the student MIRIANA BITONTO (name and family name), born in BRINDISI on 02/11/1993 (dd/mm/yyyy) enrolled for the academic year 2016 / 2017 at the University of Bari Aldo Moro, Department/School of BIOSCIENCES, BIOTECHNOLOGY AND BIOPHARMACEUTICAL in the degree programme in CELLULAR AND MOLECULAR BIOLOGY.
3. The student will prepare his/her thesis from 01/10/2017 (dd/mm/yyyy) to 23/12/2017 (dd/mm/yyyy), under the direction of two co-tutors:  
Professor: FRANCESCA ANTONACCI  
of the University of Bari Aldo Moro ( Sending Institution) and  
Professor: MARIO CÀCERES  
of the University/Institution AUTONOMA DE BARCELONA (Receiving Institution),

The thesis activity will concern (short description of thesis activity)

This project aims to create a map of genomic inversions between human and non-human primates, including chimpanzee, gorilla, orangutan and macaque, investigate their functional and evolutionary consequences and their contribution to human disease.

This work will involve 3 steps:

- Identification of inversion through comparison of the net alignments for the most recent builds of human and non-human primate genome assemblies;
- Validation of larger inversions (>500 Kb) through FISH (Fluorescence in situ Hybridization), **at the University of Bari Aldo Moro, Department of Biology.**
- Validation of smaller inversions (<150 Kb) using paired-end sequence data already available for 79 great apes (Javier Prado-Martinez et al., Nature 2013) and through Polymerase Chain Reaction (PCR), **at the Autonomy University of Barcelona, Institution of Biotechnology and Biomedicine.**

The results of this project will provide a valuable tool for clinical and evolutionary studies on human populations, as well as the bases to correct primates reference genomes.

4. The above mentioned co-tutors will each carry out duties of guidance and the overseeing of the student's work. The student will be granted access to facilities, libraries and laboratories.
5. The student - as specified in Art. 2 - will discuss his/her thesis at the University of Bari Aldo Moro in the following language: Italian
6. The student will pay enrolment fees at the University of Bari Aldo Moro only; in principle, no fees are required from the student by the Receiving Institution.
7. The student's accident insurance will be guaranteed by the University of Bari Aldo Moro according to the norms and regulations in force. Additional health insurance coverage, when required, will be provided by the student at his/her own expenses.
8. The duration of this agreement is limited to the period of stay as indicated in Art. 3.
9. This agreement is non-binding and is intended only to provide the general principles and key terms for the co-tutorship of the degree thesis. The Receiving Institution is not committed for direct financial support of this initiative.

<b>Sending Institution:</b>  UNIVERSITY OF BARI ALDO MORO Palazzo Ateneo Piazza Umberto I, n. 1 70121 Bari (Italy)	<b>Receiving Institution:</b>  UNIVERSITAT AUTÒNOMA DE BARCELONA Institut de Biotecnologia i de Biomedivina Carrer de la Vinya s/n 08193 Bellaterra (Cerdanyola del Vallès) Barcelona (Spain)  (please indicate: name, address, postal code)
<b>Thesis tutor's Professor:</b>  FRANCESCA ANTONACCI <hr/> (name and family name)	<b>Thesis tutor's Professor:</b>  MARIO CÀCERES <hr/> (name and family name)
<b>Signature:</b> 	<b>Signature:</b> 
<b>Seal of the Institution:</b> 	<b>Seal of the Institution:</b> 
<b>Date:</b> 30/05/2017	<b>Date:</b> 30/05/2017

Project of: Miriana Bitonto

In title: Genomic inversions in human and non-human primates

### Introduction

In the last few years, next-generation sequencing techniques allowed the discovery and characterization of all kind of variants in the human genome, except for inversion polymorphisms, because these are balanced rearrangements and are difficult to detect and analyze by standard molecular approaches.

Although they are not usually associated with alterations in gene copy number and, thus, do not have a primary effect on phenotype, several of the polymorphic inversions identified to date confer a predisposition to further chromosomal rearrangement in subsequent generations.

From an evolutionary point of view, the inversions have also been proposed to be a direct driving force in speciation because, when present in heterozygous state, they suppress recombination between arrangements, therefore inverted and non-inverted segments can follow independent evolutionary histories and accumulate variation independently, thus creating a genetic barrier to gene flux and contributing to speciation. Moreover, characterization of evolutionary inversion events is important because inversions can affect the expression of genes adjacent to the breakpoints, or directly interrupt genes spanning the breakpoints.

### Objective

The object of this project is the creation of a map of inversions between human and non-human primates through the comparison of net alignments between human and other primates genomes assemblies. Further goal is to determinate the forces responsible of inversions creation, to investigate their worldwide frequency, evolutionary origin and effect on gene expression in primates, and finally the impact of inversions on regions preferentially associated with recurrent rearrangements associated with disease in humans.

### Methods

The discovery and analysis of inversions will involve 3 steps:

- Identification of inversion through comparison of the net alignments for the most recent builds of human and non-human primate genome assemblies, including chimpanzee, gorilla, orangutan and macaque genomes.
- Validation of larger inversions (>500 Kb) through FISH (Fluorescence in situ Hybridization), using BAC or fosmid probes on metaphase and interphase nuclei, **at the University of Bari Aldo Moro, Department of Biology.**
- Validation of smaller inversions (<150 Kb) using paired-end sequence data already available for 79 great apes (Javier Prado-Martinez et al., Nature 2013) and through Polymerase Chain Reaction (PCR), on a set of inversions for which there is pair-end sequencing support **at the Autonomy University of Barcelona, Institution of Biotechnology and Biomedicine.**

This department hosts the necessary equipment and primate DNA samples necessary for this research.

### Expected Results

The proposed project will provide for the first time a comprehensive representation of inversions across human and non-human primate genomes. A complete map of primate inversions will provide important information on the interspecies structural variability that can modify the structure and expression of genes.

Moreover, the results of this project will provide the bases to correct primates reference genomes.

<b>DATE</b>	30/5/2017
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**Part A. Personal Information**

Surname(s)	MARIO	
Forename	CÁCERES AGUILAR	
Social Security, Passport, ID number	46628358-K	
Sex	Male	
Age	44 years	
Researcher numbers	Researcher ID	A-6379-2009
	Open Researcher and Contributor ID (ORCID)	0000-0002-7736-3251

**A.1. Current position**

Post/ Professional Category	ICREA Research Professor / Associate Professor	
UNESCO Code	241007 (Human Genetics)	
Key Words	Genomics, Bioinformatics, Evolution, Humans, Structural variation, Gene expression, Primates	
Name of the University/Institution	Universitat Autònoma de Barcelona	
	Department/Center	Institut de Biotecnologia i de Biomedicina
	Full Address	Edifici MRB, Campus Universitari Bellaterra, Bellaterra (Barcelona), Spain
	Email Address	<a href="mailto:mcaceres@icrea.cat">mcaceres@icrea.cat</a>
	Phone Number	93-5868726
Start date	1/1/2010	

**A.2. Education** (*title, institution, date*)

1995	Universitat Autònoma de Barcelona	<i>First Degree</i>	Biology (Special distinction award)
2000	Universitat Autònoma de Barcelona	<i>PhD</i>	Genetics (Special distinction award)

**A.3. Indicators of Quality in Scientific Production** (*See the instructions*)

Total number of publications	40	1st quartile publications (Q1)	35
Publications within 2 first/last authors	31	1st decile publications (D1)	19
Total number of citations	1584*	Average citations/year (2013-2017)	112.9*
H-index	20*		
Doctoral theses supervised (additional doctoral theses ongoing)	5 (5)	Master theses supervised	11

\* Citations values obtained from Scopus

**Part B. Free Summary of CV** (*Max. of 3.500 characters, including spaces*)

I obtained my PhD at the Universitat Autònoma de Barcelona working on *Drosophila* chromosomal rearrangements (1995-2000). Then I moved to the USA as a postdoc at the Salk Institute for Biological Studies (2001-2003) and Emory University (2003-2006), where my research shifted to the use of novel genomic techniques to compare gene-expression levels in humans and non-human primates. In 2006 I got a Ramón y Cajal position at the Centre for Genomic Regulation in Barcelona, and focused on the identification of genomic changes with potential functional consequences in the human lineage, such as those associated with expression differences and structural variants. Since 2010 I am an ICREA Research Professor and lead the Comparative and Functional Genomics group at the Institut de Biotecnologia i de Biomedicina (IBB) of the UAB. In particular, one of my main research lines is the evolutionary and functional analysis of polymorphic inversions in the human



genome, which aims to investigate the biological significance of these variants at a large scale. To do this my group takes a multidisciplinary approach that combines new genomic methods and bioinformatic analysis of the great wealth of data available, generating results of interest to diverse fields.

As a result of my scientific activity, I have achieved a significant scientific production and co-authored a total of 39 research articles that stand out for their publication in high-quality journals, including some of the most prestigious ones like *Science*, *PNAS* or *Nature Reviews Genetics*. Several of these articles represented significant advances in the respective fields and have received considerable attention, with an average number of 54.6 citations per article. In addition, I have succeeded in securing numerous fellowships and grants to fund my research and I have experience in managing big research projects, including an EMBO Postdoctoral Fellowship, the Salk Institute for Biological Studies Presidents' Club Innovation Grant, two 3-year grants from the Spanish Ministry of Science and Education, a 1.5 million euros ERC Starting Grant, and an ERC Proof of Concept grant. I also have experience in supervising students, with 5 doctoral thesis and 10 master thesis. Finally, I am the coordinator of the Genomics and Proteomics Section of the Catalan Society of Biology and I have been distinguished with the Josep M. Sala-Trepat Award for the scientific trajectory of a young researcher working in the field of gene-expression regulation.

## Part C. Accomplishments (Order by typology)

### C.1. Relevant Publications

Complete list in: [http://scholar.google.es/citations?hl=en&user=qbNYsnoAAAAJ&view\\_op=list\\_works&sortby=pubdate](http://scholar.google.es/citations?hl=en&user=qbNYsnoAAAAJ&view_op=list_works&sortby=pubdate)

- D. Vicente-Salvador, M. Puig, M. Gayà-Vidal, S. Pacheco, C. Giner-Delgado, I. Noguera, D. Izquierdo, A. Martínez-Fundichely, A. Ruiz-Herrera, X. Estivill, C. Aguado, J. I. Lucas-Lledó, and **M. Cáceres**. Detailed analysis of inversions predicted between two human genomes: errors, real polymorphisms, and their origin and population distribution. *Human Molecular Genetics* 26: 567-581 (2017).
- M. Puig, D. Castellano, L. Pantano, C. Giner-Delgado, D. Izquierdo, M. Gayà-Vidal, J. I. Lucas-Lledó, T. Esko, C. Terao, F. Matsuda, and **M. Cáceres**. Functional impact and evolution of a novel human polymorphic inversion that disrupts a gene and creates a fusion transcript. *Plos Genetics* 11: 1-28 (2015).
- M. Puig, S. Casillas, S. Villatoro, and **M. Cáceres**. Human inversions and their functional consequences. *Briefings in Functional Genomics* 14: 369-379 (2015).
- **M. Cáceres**. Structural variants, much ado about nothing? *Briefings in Functional Genomics* 14: 303-304 (2015)
- C. Aguado, M. Gayà-Vidal, S. Villatoro, M. Oliva, D. Izquierdo, C. Giner, V. Montalvo, J. García-González, A. Martínez-Fundichely, L. Capilla, A. Ruiz-Herrera, X. Estivill, M. Puig, and **M. Cáceres**. Validation and genotyping of multiple human polymorphic inversions mediated by inverted repeats reveals a high degree of recurrence. *Plos Genetics* 10: 1-16 (2014).
- J. R. González, A. Cáceres, T. Esko, I. Cusco, M. Puig, M. Esnaola, V. Siroux, E. Bouzigon, R. Nadif, E. Reinmaa, L. Milani, M. Bustamante, D. Jarvis, J. M. Antó, J. Sunyer, F. Demenais, M. Kogevinas, A. Metspalu, **M. Cáceres**, and L. A. Pérez-Jurado. A common 16p11.2 inversion underlies the joint susceptibility to asthma and obesity. *American Journal of Human Genetics* 94: 361-372 (2014).
- J. I. Lucas-Lledó, D. Vicente-Salvador, C. Aguado, and **M. Cáceres**. Population genetic analysis of bi-allelic structural variants from low-coverage sequence data with an expectation-maximization algorithm. *BMC Bioinformatics* 15:163 (2014).
- A. Martínez-Fundichely, S. Casillas, R. Egea, M. Ràmia, A. Barbadilla, L. Pantano, M. Puig, and **M. Cáceres**. InvFEST, a database integrating information of polymorphic inversions in the human genome. *Nucleic Acids Research* 42 (D1): D1027-D1032 (2014).

- J. I. Lucas-Lledó and **M. Cáceres**. On the power and the systematic biases of the detection of chromosomal inversions by paired-end genome sequencing. *PLoS One* 8: e61292, doi:10.1371/journal.pone.0061292 (2013).
- R. Cagliani, F. Guerini, R. Rubio-Acero, F. Baglio, D. Forni, C. Agliardi, L. Griffanti, M. Fumagalli, U. Pozzoli, S. Riva, E. Calabrese, M. Sikora, F. Casals, G. P. Comi, N. Bresolin, **M. Cáceres**, M. Clerici, and M. Sironi. Long-standing balancing selection in the THBS4 gene: influence on sex-specific brain expression and grey matter volumes in Alzheimer's disease. *Human Mutation* 34: 743-753 (2013).
- L. Bassaganyas, E. Riveira-Muñoz, M. García-Aragonés, J. R. González, **M. Cáceres**, Ll. Armengol, and X. Estivill. Worldwide population distribution of the common LCE3C-LCE3B deletion associated with psoriasis and other autoimmune disorders. *BMC Genomics* 14: 261 (2013).
- G. Escaramís, C. Tornador, L. Bassaganyas, R. Rabionet, J. M. C. Tubio, A. Martínez-Fundichely, **M. Cáceres**, M. Gut, S. Ossowski, and X. Estivill. PeSV-Fisher: Identification of somatic and non-somatic structural variants using next generation sequencing data. *PLoS One* 8: e63377 (2013).
- J. Prado-Martínez, I. Hernando-Herraez, B. Lorente-Galdos, M. Dabad, O. Ramírez, C. Baeza-Delgado, C. Morcillo-Suarez, C. Alkan, F. Hormozdiari, E. Rainieri, J. Estelle, M. Fernández-Callejo, M. Valles, L. Ritscher, T. Schöneberg, E. de la Calle-Mustienes, S. Casillas, R. Rubio-Acero, M. Melé, J. Engelken, **M. Cáceres**, J. L. Gómez Skarmeta, M. Gut, J. Bertranpetit, I. G. Gut, T. Abello, E. E. Eichler, I. Mingarro, C. Lalueza-Fox, A. Navarro, and T. Marques-Bonet. The genome sequencing of an albino western gorilla reveals inbreeding in the wild. *BMC Genomics* 14: 363 (2013).
- A. Cáceres, S. S. Sindi, B. J. Raphael, **M. Cáceres**, and J. R. González. Identification of polymorphic inversions from genotypes. *BMC Bioinformatics* 13:28 (2012).
- R. Cagliani, S. Riva, C. Marino, M. Fumagalli, M. G. D'Angelo, V. Riva, G. P. Comi, U. Pozzoli, D. Forni, **M. Cáceres**, N. Bresolin, M. Clerici, and M. Sironi. Variants in SNAP25 are targets of natural selection and influence verbal performances in women. *Cellular and Molecular Life Sciences* 69: 1705-1715 (2012).
- **M. Cáceres**, NISC Comparative Sequencing Program, R. T. Sullivan, and J. W. Thomas. A recurrent inversion on the eutherian X-chromosome. *Proc. Natl. Acad. Sci. U.S.A.* 104:18571-18576 (2007).
- J. A. Calarco\*, Y. Xing\*, **M. Cáceres\***, J. P. Calarco, X. Xiao, Q. Pan, C. Lee, T. M. Preuss, and B. J. Blencowe. Global analysis of alternative splicing differences between humans and chimpanzees. *Genes and Development* 21:2963-2975 (2007).
- T. M. Preuss\*, **M. Cáceres\***, M. C. Oldham, and D. H. Geschwind. Human brain evolution: Insights from microarrays. *Nature Reviews Genetics* 5: 850-860 (2004).
- **M. Cáceres**, J. Lachuer, M. A. Zapala, J. C. Redmond, L. Kudo, D. H. Geschwind, D. J. Lockhart, T. M. Preuss and C. Barlow. Elevated gene expression levels distinguish human from non-human primate brains. *Proc. Natl. Acad. Sci. U.S.A.* 100: 13030-13035 (2003).
- **M. Cáceres**, M. Puig, and A. Ruiz. Molecular characterization of two natural hotspots in the *Drosophila buzzatii* genome induced by transposon insertions. *Genome Research* 11: 1353-1364 (2001).
- **M. Cáceres**, J. M. Ranz, A. Barbadilla, M. Long, and A. Ruiz. Generation of a widespread *Drosophila* inversion by a transposable element. *Science* 285: 415-418 (1999).

\* These authors contributed equally to this work.

Corresponding author.

## C.2. Research Projects and Grants



- Integrative analysis of the functional impact of inversions in genomes and phenotypic traits (BFU2016-77244-R). Research Grant, Ministerio de Economía, Industria y Competitividad (Spain). Duration: 30/12/2016-29/12/2019. Funding: 217,800 € PI: Mario Cáceres.
- Application of genomic inversions as diagnostic markers in precision medicine (IN2DIAG). ERC Proof of Concept Grant, European Research Council (EU). Duration: 1/7/2017-31/12/2018. Funding: 150,000 € PI: Mario Cáceres.
- Understanding genome variation from nucleotides to phenotypes in *Drosophila* and humans (BFU2013-42649-P). Research Grant, Ministerio de Economía y Competitividad (Spain). Duration: 1/1/2014-31/12/2016. Funding: 181,500 € PI: Mario Cáceres and Antonio Barbadilla.
- Research study of inversion genotyping by droplet digital PCR (ddPCR). Bio-Rad reagents research support, Bio-Rad (USA). Duration: 12/05/2015-11/11/2016. Funding: 72,727 € PI: Mario Cáceres.
- Evolutionary and functional analysis of polymorphic inversions in the human genome (INVFEST). ERC Starting Grant, European Research Council (EU). Duration: 1/2/2010-31/10/2015. Funding: 1,475,377 € PI: Mario Cáceres.
- A novel high-throughput tool to genotype human genome inversions for personalized medicine (INGENIHUS). ERC Proof of Concept Grant, European Research Council (EU). Duration: 1/6/2014-31/5/2015. Funding: 149,671 € PI: Mario Cáceres.
- Genomic determinants of gene expression levels in the human brain (BFU2007-60930). Research Grant, Ministerio de Educación y Ciencia (Spain). Duration: 1/10/2007-31/9/2010. Funding: 105,270 € PI: Mario Cáceres.

#### **C.4. Patents and other IPR**

- M. Cáceres, S. Villatoro, and C. Aguado. EU Patent Application EP13382296. An in vitro method of genotyping multiple inversions. Priority date: 23/7/2013. Priority countries: Europe and USA.

#### **C.5. Honors and awards**

- I3 Program Certification, Ministerio de Ciencia e Innovación, Spain (2010).
- Research Accreditation of proven research capabilities by the Agency for the Quality of the University System of Catalonia (AQU Catalunya), Spain (2008).
- Josep M. Sala-Trepas Award for the scientific trajectory of a young researcher working in the field of gene-expression regulation, Societat Catalana de Biologia, Spain (2007).

#### **C.6. Other merits**

- Guest Editor of 'Special Issue: Functional impact of structural variation in the human genome', Briefings in Functional Genomics, Oxford University Press, Oxford (2015)
- Associated Editor for the journal BMC Genomics (2010-present).
- Coordinator of the Genomics and Proteomics Section of the Societat Catalana de Biologia (2011-present).
- Organization of the 4th Bioinformatics and Genomics Symposium of the Societat Catalana de Biologia (20/12/2016). Barcelona, Spain.
- Organization of the XXI Seminario de Genética de Poblaciones y Evolución (3-5/10/2016). Sitges, Spain.
- Organization of the 10th Workshop on Genomics and Proteomics of the Societat Catalana de Biologia (3/10/2014). Barcelona, Spain.

- Organization of the 9th Workshop on Genomics and Proteomics of the Societat Catalana de Biologia (17/12/2013). Barcelona, Spain.
- Member of the Scientific Committee of the I Congrés Internacional de Biologia de Catalunya (CIBICAT) of the Societat Catalana de Biologia (9-12/7/2012). Barcelona, Spain.
- Organization of the Symposium on Structural Evolution of Genomes of the 2012 Annual Meeting of the Society for Molecular Biology and Evolution (23-26/6/2012). Dublin, Ireland
- Organization of the Workshop on Maldi.MS-Imaging for Tissues & Biomedical Proteomics of the Societat Catalana de Biologia (29/11/2011). Barcelona, Spain.
- Organization of the 7th Workshop on Biomedical Genomics and Proteomics of the Societat Catalana de Biologia (17/12/2010). Barcelona, Spain.

Signature:



Dr. Mario Cáceres Aguilar

Bellaterra, June 1<sup>st</sup> 2017