



# Variabilité génétique et maladies humaines

Rapport Hcéres

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agence d'évaluation de la recherche  
et de l'enseignement supérieur

Department for the evaluation of  
research units

AERES report on unit:

Genetic Variation and Human Diseases

(Variabilité Génétique et Maladies Humaines)

Under the supervision of  
the following institutions  
and research bodies:

Université Paris 7 - Denis Diderot

Institut National de la Santé Et de la Recherche  
Médicale



December 2012



agence d'évaluation de la recherche  
et de l'enseignement supérieur

Research Units Department

President of AERES

**Didier Houssin**

Research Units Department

*Department Head*

**Pierre Glaudes**



## Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.

NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

**Criterion 1 - C1** : Scientific outputs and quality ;

**Criterion 2 - C2** : Academic reputation and appeal ;

**Criterion 3 - C3** : Interactions with the social, economic and cultural environment ;

**Criterion 4 - C4** : Organisation and life of the institution (or of the team) ;

**Criterion 5 - C5** : Involvement in training through research ;

**Criterion 6 - C6** : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report received the following grades:

- Grading table of the unit: **Genetic Variation and Human Diseases**

C1	C2	C3	C4	C5	C6
A+	A+	A	A+	A+	A+



## Evaluation report

Unit name:	Genetic Variation and Human Diseases
Unit acronym:	
Label requested:	UMR
Present no.:	UMR-946
Name of Director (2009-2013):	Ms Florence DEMENAI
Name of Project Leader (2014-2018):	Ms Florence DEMENAI

## Expert committee members

Chair:	Ms Marie-Paule ROTH, INSERM
Experts:	Mr Jacques BENICHO, Rouen University
	Mr Alexis ELBAZ, INSERM (representative of the INSERM CSS9)
	Ms Pascale LE ROY, INRA
	Ms Kristel VAN STEEN, Liège University, Belgium

### Scientific delegate representing the AERES:

Mr Hubert LEVEZIEL

### Representative(s) of the unit's supervising institutions and bodies:

Ms Corinne ALBERTI, Paris Diderot University

Ms Christine GUILLARD, INSERM



## 1 • Introduction

### History and geographical location of the unit

This application is for the renewal of the Inserm and University Paris7 - Denis Diderot support and funding to unit 946 which was created in 2009. The unit occupies 476 m<sup>2</sup> in the Fondation Jean Dausset-CEPH building. The expertise field of this unit is statistical methodology in genetic epidemiology and large-scale studies focused on the genetic epidemiology of asthma and allergy as well as cancers.

### Management team

The unit is managed, as recommended for Inserm units of this size (i.e. single-team laboratories), on a daily basis by the unit Director assisted by an administrative manager. Permanent staff contribute to the organization of information technology resources, health and safety, continuing education, web site maintenance, and scientific animation. A lab management committee, including all permanent staff, is meeting twice a year. From discussions of the visiting committee with the personnel, it appears that there is a general approval of the management of this unit.

### Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
<b>N1:</b> Permanent professors and similar positions	1		
<b>N2:</b> Permanent researchers from Institutions and similar positions	6	5	5
<b>N3:</b> Other permanent staff (without research duties)	4	4	3
<b>N4:</b> Other professors (Emeritus Professor, on-contract Professor, etc.)		1	1
<b>N5:</b> Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	3	4	4
<b>N6:</b> Other contractual staff (without research duties)	3	2	
<b>TOTAL N1 to N6</b>	17	16	13
Percentage of producers	<b>100 %</b>		



<b>Unit workforce</b>	<b>Number as at 30/06/2012</b>	<b>Number as at 01/01/2014</b>
Doctoral students	11	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit*	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	3	2 + 2 (soon HDR candidates)



## 2 • Assessment of the unit

### Strengths and opportunities

The unit has a very strong expertise in genetic epidemiology (one of the top groups in their field worldwide).

The unit demonstrates the capacity to publish in excellent journals.

The unit participates in major national/international consortiums (leader role in many of these) for the diseases of interest.

It develops very good collaboration.

It demonstrates a remarkable success in raising funds, also internationally.

students and post-doctoral fellows are very well supervised.

The unit gathers very knowledgeable engineers with long-term experience in the field.

### Weaknesses and threats

The committee believes that too many projects are coordinated at the same time for the number of permanent researchers in the unit.

So far, there is no scientist with a strong expertise in systems biology in the group.

Identification of theme 1 (statistical methodology in genetic epidemiology) gets lost in theme 2 (genetic epidemiology of asthma and cancers) and very few papers are published in statistical methodology journals.

### Recommendations

Better prioritize the projects to maintain the actual level of scientific production.

Better valorize the statistical developments (for instance by publishing in statistical journals).

Attract a biologist in the unit or increase collaborations with biologists to help developing methods based on biological pathways.

Encourage young researchers to get their HDR and take more responsibilities in order to ensure the long-term future of the unit. This is particularly important since the team will have to identify, within the next five years, a leader able to supervise such a high-profile unit.





### 3 • Detailed assessments

#### Assessment of scientific quality and outputs

Scientific achievements are clearly outstanding, especially when considering the size of the unit. Among 175 publications in peer-reviewed journals, 35 are in journals of IF  $\geq 10$ , including New England Journal of Medicine (3), Nature (2), Nature Genetics (8) and Science (1). Notably, the permanent researchers of the unit have leadership positions on these publications (first or last authors). They have played a major role in genome-wide associations studies (GWAS) of asthma and cancers that resulted in the identification of novel genes and generated new hypotheses regarding the underlying disease mechanisms. Through statistical methods addressing phenotypic heterogeneity and gene-environment interaction, they provided new clues on the effect of a locus identified by an asthma GWAS and its interaction with smoking exposure. They also used family-based strategies, taking into account complex mechanisms, to discover new genes. They developed methods taking into account consanguinity to facilitate gene discovery and uncover new molecular mechanisms, notably in the Taybi-Linder syndrome. Finally, by combining clinical and genetic studies, they characterized molecular mechanisms predisposing to melanoma and renal carcinoma.

#### Assessment of the unit's academic reputation and appeal

The unit is very successful in attracting funding. It is engaged in many collaborations, both national and international. It is partner in 15 national networks (coordinator in 11/15) and in 17 European or international consortiums (coordinator in 5/17 and prominent team leader in 3/15). It is also founding member and coordinator, respectively, of two French "investissement d'avenir" programmes which are highly competitive. Members of the unit have received several awards and contribute to different national and also international scientific councils, i.e. the International Agency for Research on Cancer, the Max Planck Institute of Psychiatry, or the Swiss Cancer League. The head of the unit was President of the International Genetic Epidemiology Society (IGES), the only society that specifically represents the discipline worldwide. Staff members have participated in the organisation of several international meetings and many of them have been invited to give presentations at international conferences.

#### Assessment of the unit's interaction with the social, economic and cultural environment

The unit has contributed to scientific popularization on cancer and asthma through various media, and has edited recommendations for medical practice (i.e., genetic counseling for familial melanoma). Several scientists have developed freely accessible software applications in genetic epidemiology and population genetics. Participation in a patent application (for developing methods and kits for disease diagnosis following the discovery of the responsible gene) and partnership with a few SMEs were also noticed.

#### Assessment of the unit's organisation and life

The visiting committee appreciated the friendly atmosphere despite the work load, and no obvious internal conflict was detected. All resources are shared, including scripts with appropriate documentation. PhD students and post-doctoral fellows appear pleased with the policy regarding publications and presentations at meetings. There are frequent contacts between the students and their advisors. Career plans seem to be discussed with the supervisors on a regular basis and there are frequent exchanges with foreign sites.

#### Assessment of the unit's involvement in training through research

The scientists of this unit are significantly involved in the organisation of the "M2 Génomique et génétique statistique" at the Universities of Paris Sud and of Evry and play a major role in the teaching and training of master and doctoral students in statistical genetics and genetic epidemiology of human diseases. French and foreign post-doctoral fellows are hosted in the unit and very well supervised. Participation in the organization of a European course in Genetic Epidemiology and node leadership in a European training network for PhD students further attest the recognition of this unit at the international level.



### Assessment of the five-year plan and strategy

The questions asked are ambitious and relevant to the fields of genetic epidemiology and statistical genetics. There are several key aims in the research project. The first deals with statistical methodology and aims at developing new methods to account for the complex etiology of multifactorial diseases. These include cutting-edge multi-marker analyses, analyses of gene/environment interactions at the genome-wide level, and meta-analyses taking into account genetic heterogeneity. The more long-term goal is to account for these complex mechanisms and integrate different genome-wide data (genomics, transcriptomics and epigenomics) to identify new genetic determinants of asthma, melanoma and bladder cancer. Members of this unit have access to very large cohorts of patients. They are involved in many national and international consortiums and have secured sufficient funding to develop these research activities. The only concern is that the number of topics this group offers to cover is very high, especially when considering the complexity of the questions asked, the international competition in the field and the comparatively small number of scientists with permanent positions currently in the unit (2 DR, 3 CR, 1 IR, 2 IE). The projects should be better prioritized in order for this unit to maintain its impressive level of scientific production.



## 4 • Conduct of the visit

Visit date: December 13, 2012  
 Start: December 13, 2012, 8:15  
 End: December 13, 2012, 18:00

Visit site:

Address: UMR 946 - IGM Bulding  
 Jean Dausset Foundation / CEPH  
 27 rue Juliette Dodu  
 75010 Paris

### Conduct or programme of visit:

The visit took place on December 13<sup>th</sup>, 2012 and started with a short meeting of the visiting committee with the AERES scientific advisor and a reminder of the roles and procedures of AERES. This was followed by a general presentation by the head of the unit on the history of UMR 946, its functional organization, the staff participating in the project and the general strategy in terms of solving research challenges, teaching, training and getting research funds. Presentations on the different themes, i.e. statistical methodology in genetic epidemiology, genetic epidemiology of asthma, and genetic epidemiology of cancer were given by permanent researchers working on these projects and opened to discussion with the members of the committee. The committee met with local and national representatives (University, CEPH, Inserm) and with research scientists, technicians/engineers and students/post-doctoral fellows. The visit ended with a private meeting of the visiting committee, in the presence of the AERES scientific advisor, to prepare the evaluation report.

The detailed agenda of the site visite was the following :

- 8:15 **Welcome & Closed-door Meeting of Visiting Committee with AERES Scientific Advisor**
- 8:45 **Introduction of Plenary Session: AERES Role & Procedures: AERES Scientific Advisor**
- 9:00 **General Presentation of UMR-946 & Discussion: Director of UMR-946**
- 10:00 *Coffee Break*
- 10:15 **Presentations of Research Themes & Discussion: UMR-946 Research Scientists**
- 12:30 **Closed-door Discussion with Representatives of the Managing Bodies**
- 13:00 *Lunch*
- 14:00 **Parallel meetings with personnel:**  
 Discussion with engineers, technicians, administrative staff  
 Discussion with staff scientists  
 Discussion with students and post-docs
- 14:45 **Discussion with the Director of the unit**
- 15:15 **Closed-door meeting of the Visiting Committee (in presence of AERES Scientific Advisor)**
- 18:00 **End of the visit**



## 5 • Statistics by field: SVE on 10/06/2013

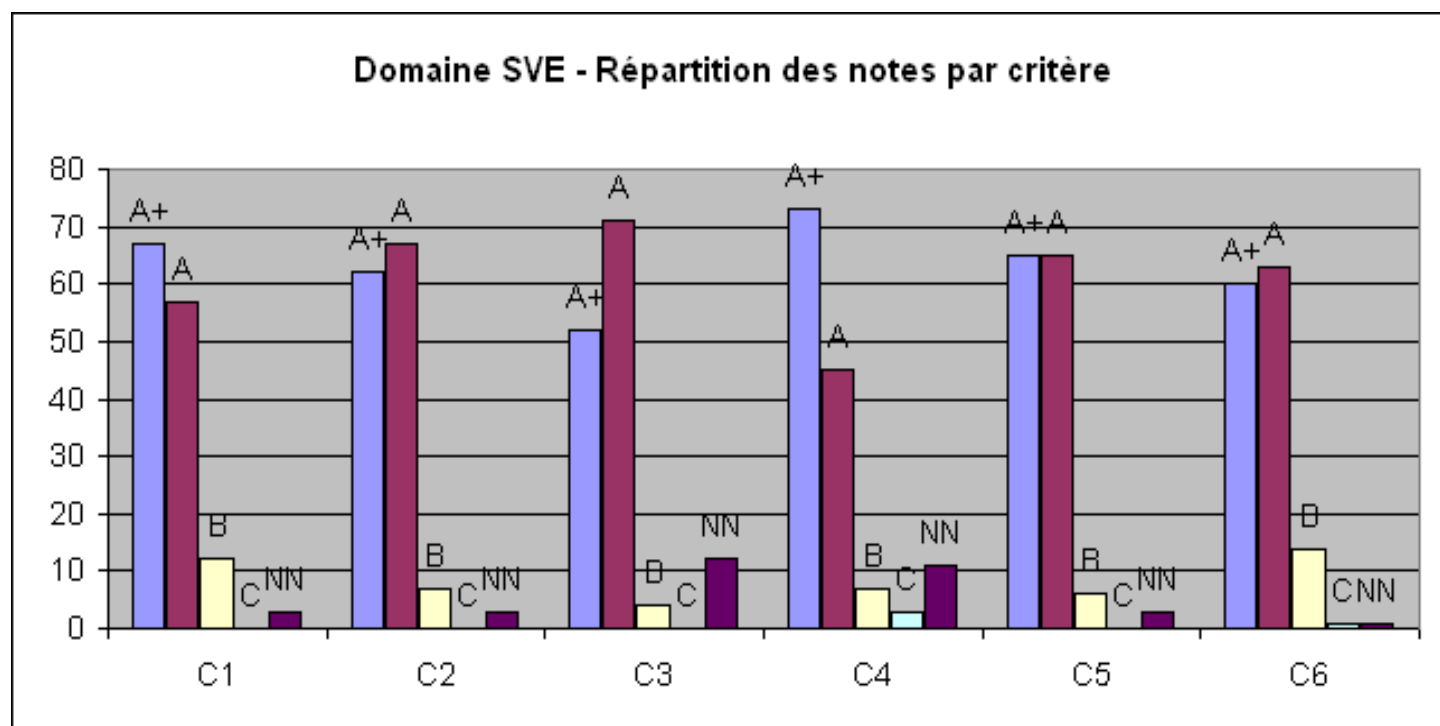
### Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

### Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

### Histogram





## 6 • Supervising bodies' general comments

Le Président

P/VB/RL/NC/YM – 2013 - 074  
Paris, le 12 avril 2013

M. Pierre Glaudes  
Directeur de la section des unités de l'AERES  
20 rue Vivienne  
75002 PARIS

**S2PURI4000636I - VARIABILITÉ GÉNÉTIQUE ET MALADIES HUMAINES -  
0751723R**

Monsieur le Directeur,

Je tiens en premier lieu à remercier les membres du comité de visite de l'AERES pour la production du rapport sur la situation de l'UMR 946 « Variabilité génétique et maladies humaines ».

Le comité a relevé le très bon niveau de publication et l'excellente capacité à obtenir des contrats extérieurs, ce qui est signifiant sur la qualité de cette équipe. Le grand nombre de projets mentionnés par le comité témoigne aussi, comme le précise la directrice Florence Demenais, du dynamisme de cette unité dans les collaborations nationales et internationales. Cette activité traduit le rayonnement de cette unité, ce dont je me réjouis. L'association avec l'INSERM ne peut qu'en être confortée sur le domaine de l'asthme, des maladies allergiques et des cancers, sur lequel l'équipe présente une expertise indéniable.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de toute ma considération.

Vincent Berger

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**Response of UMR-946, Université Paris 7 Denis Diderot-Inserm, to AERES Evaluation Report**

We thank the AERES committee members for their report and their recommendations following the site visit of our unit, UMR-946 Université Paris 7 Denis Diderot-Inserm (“Genetic Variation and Human Diseases”), on 13th December 2012.

We strongly appreciate the positive comments regarding UMR-946 strong expertise in genetic epidemiology (“one of the top groups in their field worldwide”) together with its capacity in publishing in high-impact factor journals, in having a leading role in national and international consortiums, in training students and post-doctoral fellows in a manner particularly appreciated by the committee, in having very knowledgeable engineers with a long-term experience in the field and in generating funding from various sources nationally and internationally.

We would like to comment the remarks of the committee by putting them into perspective within the global strategy of our unit.

Regarding the first comment mentioning that “too many projects are coordinated at the same time for the number of researchers in the unit”, we would like to point out that these projects are conducted by UMR-946 scientists in close collaboration with several groups nationally and internationally both for the development of statistical methodology in genetic epidemiology and large-scale genetic epidemiology studies of asthma, allergic diseases and cancers. Most of these projects have already been undertaken and have received funding from various sources at the national and international levels. We also would like to stress that we are more and more fostering a multidisciplinary and a networking-based approach of our research activities with shared responsibilities with our colleagues, which can greatly facilitate rapid advances in our research programs and maintain our level of scientific production that was noted to be “impressive” by the AERES committee.

Regarding the second comment raised by the committee on “the absence of a scientist with a strong expertise in systems biology in the group”, the systems biology approach in genetic epidemiology is, for us, a new concept that covers multi-dimensional approaches of disease and integration of “omics” data (genomics, transcriptomics, epigenomics...) to progress in the understanding of the complex mechanisms underlying multifactorial diseases, as outlined in our AERES application. We are starting now new programs in this emerging topic with new funding. We are involved in a FP7-Marie Curie program in Machine Learning for Personalized Medicine which allows us recruiting a doctoral student to develop data mining and machine learning methodologies in genetic epidemiology and expanding our links with academic groups and private companies involved in systems biology. On the other hand, we are undertaking a new research project, which integrates genomic data and text-mining approaches, in collaboration with the Data Mining team of the LIPADE laboratory (Paris Descartes University). This program, which has just received funding from the PRES Sorbonne Paris Cité, includes training of post-doctoral fellows and doctoral students.

The integrated approach to complex diseases includes biological components that are developed through tight links with biologists from the Pasteur Institute, the CNRS, French Cancer Institutes (Curie and Gustave Roussy Institutes) and North-American Universities. Functional studies conducted by these teams following gene discovery can accelerate research translation.

Regarding the third comment of the committee underlining that” identification of theme 1 (statistical methodology in genetic epidemiology) gets lost in theme 2 (genetic epidemiology of asthma and cancer), we would like to point out that our work in the past five years has mainly focused on targeted approaches in rare disorders and on large-scale genome-wide studies leading to identification of novel genes and gene-environment interactions in allergic diseases and cancers and has been published in high-impact factor journals. These studies have often included major methodological developments that were included in the disease-oriented publications. Our work has also included comparisons of statistical methods that were carried out on real data rather than on simulated data and we chose to publish in genetic or epidemiological journals to reach a broader readership than usually achieved by pure statistical journals. As mentioned before, the extension of our collaborations to groups involved in methodological developments nationally and internationally will favor expansion of this field with joint publications in statistical methodology journals as well as in general and specialized journals.

Although the youngest researchers do not have yet their HDR (“Habilitation à Diriger des Recherches”), they have been involved in the training of students and are currently co-supervising doctoral students. They are encouraged to get their HDR soon in order to ensure the long-term future of our unit.

Paris, 4th April 2013

A handwritten signature in black ink, appearing to read 'F. Demenais', with a long horizontal stroke extending to the right.

Florence Demenais  
Director of UMR-946