APPEL A PROJETS COHORTES / CALL FOR PROPOSALS

2010

Acronyme du projet / Acronym

GENHI EN SANTE

DOCUMENT SCIENTIFIQUE B / SCIENTIFIC SUBMISSION FORM B

Acronyme du projet/ Acronym of the project	**GénHi En Santé**	
Titre du projet en français	Génétique, Histoire, Environnement et Santé	
Project title in English	Genetics, History, Environment and Health	
Coordinateur du projet/ Project's coordinator	Nom (Name): Hervé LE MAREC Etablissement (Institution) / Hôpital (Hospital): CHU de Nantes Laboratoire (laboratory): Institut du thorax/Inserm UMR_S915	
Affiliation(s) du partenaire coordinateur de projet/ Organization of the coordinating partner	Laboratoire(s)/Etablissement(s)/Hôpital (Laboratory/Institution(s)/ Hospital) Institut du thorax Inserm UMR_S915	Tutelle(s) /Research organization reference Inserm
Type de cohorte / Type of cohort	☑ Population générale / general population ☑ patients	☑ circonscrite au territoire national (french area only) □ formant la composante nationale de cohortes multinationales (part of multinational cohort)
Principal thématique (Main topic)	Genetic and environmental epidemiology	
Durée (Duration)	10 years	
Aide demandée / Requested funding	€	

Affiliations des partenaires au projet/Organization of the partner(s)

Préciser : - Laboratoire(s) / Etablissement(s)/ Hôpital… (Laboratory/Institution(s)/Hospital…) & tutelle(s) (Research organization reference)
- Entreprise(s) (company) / Secteur(s) d'activité (activity field) / Effectif (Staff size)

P1 - Inserm UMR915 / Institut du thorax P2 - Inserm U613 P3 - CHU de Nantes P4 - Etablissement Français du Sang P5 - Inserm UMR707 / UPMC Paris 6 P6 - CHU de Brest	P7 - CHU de Rennes *A8 - Institut Pasteur* *A9 – Inserm UMR 946* *A10 – ARS/ORS des Pays-de-la-Loire* *A11 – ARS/ORS de Bretagne*

RESUME / SUMMARY

Efficient healthcare strategies should include prevention policies against chronic and ageing pathologies – those which have the strongest medical and economical impact. However, preventing disease require prior identification of both collective and individual disease risk factors.
From a genetic perspective, genome-wide association studies (GWAS) are based on the 'common variant/common disease' hypothesis and mostly applied to large - and somewhat heterogeneous - cohorts. Despite great successes in discovering new biological pathways involved in common diseases, GWAS have not identified genetic risk factors with strong effect and have only explained a small fraction of the expected heritability for most conditions. There is increasing evidence that 'common diseases' are rather groups of rare pathologies sharing the same phenotypic characteristics globally, but resulting locally from different combinations of rare genetic variants and local environment factors. A large fraction of rare variants - those of recent origin - are concentrated in particular geographical areas, where they can be carried by individuals who also share some specific environmental conditions. In this context, future genetic investigations will require homogenous cohorts comprising patients with common diseases as well as unaffected individuals from the same geographical locations.
While extensive efforts have been focused recently on the genetics of common disease, the precise role of environmental factors to many chronic or ageing conditions is still largely unknown. In contrary to global environmental conditions such as climate change, most environmental factors result from local features, such as geology, industrial activity, agriculture or social habits. Our knowledge about daily local environments surrounding people remains limited. In consequence, it is extremely difficult to differentiate the role of environmental vs. genetic factors and - most importantly - to understand how their combination influences disease risk. There is an urgent need for new approaches to answer the societal demand and develop targeted preventive strategies.
So we propose to implement in western France a new model for translational research, named « GénHi En Santé », which will set up unprecedented national resources to develop basic research based on gene-environment interaction discovery. GénHi En Santé can be seen as an integrated survey of genetic and environmental factors influencing chronic conditions during lifetime. It is designed as a multidisciplinary network gathering specialists in anthropology, epidemiology, genetics, environmental sciences and clinical practice. Our common goal is to promote better adapted prevention and care strategies for chronic and ageing pathologies. To reach this goal, we propose to work on four complementary objectives: investigate the natural history of chronic conditions; decipher the fine genetic structure of regional populations in France; address the effect of environmental factors on chronic conditions; design new deciding tools for health care strategies in regions. Integrating such diverse medical and scientific investigations will broaden significantly our knowledge on gene-environment interactions causing both occurrence and worsening of chronic pathologies.
Firstly, we aim to better understand the molecular mechanisms by which chronic conditions occur and worsen with time. To achieve this objective, we will recruit groups of patients born in the same geographical area and affected by the same chronic condition, but at variable disease stages. Selecting patients from the same geographical areas will allow us to apply new genetic screening strategies by considering disease models with founder effects and relatively low environmental variability. Describing disease phenotypes at different stages will enable us to reconstitute the natural history of chronic pathologies and to describe the chronology of events underlying disease worsening. For the first phase of the project, we have selected four chronic conditions, for which clinicians in Nantes, Brest and Rennes have already accumulated knowledge and expertise for several years. For each condition, up to 1,000 patients (and relatives) will be recruited in restricted geographical areas showing high disease frequency. For the second phase of the project, additional chronic pathologies will be selected following the outcomes of the epidemiological investigations performed in parallel.
Secondly, we will start sampling 24,000 individuals from France, covering every region and taking into consideration detailed ethnological and historical data. We will use the logistics from EFS (the

national blood agency), the only infrastructure in France able to collect blood from 10,000 donors each day across the country - even in the most remote rural municipalities. In GénHi En Santé, as a pilot study, we plan to recruit 4,000 healthy individuals from western France by covering every regional territories but recruiting more particularly relevant subpopulations from an anthropological perspective. This cohort is essential to improve our knowledge on the genetic structure and stratification of historical French populations and will also serve as a major biological resource in GénHi En Santé as well as in many other future studies in medical, population and evolutionary genetics.

Thirdly, we believe that, as for genetics, regional epidemiology will create new conditions to get deeper insight into environmental exposures modulating disease expression. This discipline is just emerging: one major long-term objective in GenHi En Santé is to characterize the heterogeneous distribution of diseases and relate it to variable environmental exposure.We will start by organizing a strategic conference of experts in spatial epidemiology and environmental sciences. This conference will guide GénHi En Santé in identifying new actors in environmental epidemiology and setting up new research programs in collaboration with them. As a pilot investigation, we propose to investigate the effect of air pollutants on chronic respiratory diseases, which are paradigm examples of pathologies due to gene/environment interactions. GénHi En Santé will provide a unique opportunity to identify those interactions by recruiting groups of individuals in restricted geographical area, where we will be able to apply epidemiological models involving founder effect and restricted environmental variability.

Fourthly, we aim at building new integrated strategies involving epidemiologists, statisticians and geographical analysts from our regional health agencies and observatories. By sharing information from National Health System databases, these specialists in health management will help us in identifying spatial disease clusters for current pathologies of interest as well as new pathologies displaying strong spatial clustering patterns. Together with them, our experts in genetic epidemiology will develop or optimize methods in statistical genetics, according to which patient recruitment will be adjusted. This unprecedented collaboration will eventually provide decision makers with new tools to adjust health policies, in particular primary and secondary prevention strategies.

At last but not least, the cohorts created by GénHi en Santé will promote the development of innovative research projects, through tight collaborations between epidemiologists, anthropologists, population geneticists, biostatisticians and clinical experts. We propose in particular to build a new Laboratory of Excellence in western France, aiming to optimize translational research based on the exceptional biological resources provided by GénHi en Santé. By this way, Génhi en Santé will eventually lead to more targeted - or even personalised - therapeutic strategies.

1. ENVIRONNEMENT, CONTEXTE ET POSITIONNEMENT DU PROJET DE COHORTE / ENVIRONMENT, CONTEXT AND POSITIONING OF THE COHORT PROJECT

Many common human diseases, including chronic and ageing conditions, cluster in families and seem to be influenced by both genetic and environmental factors. However, the identification of genetic variants contributing to these 'complex diseases' has been laborious so far (Altshuler, 2008). Before 1980, very few human genes had been identified as disease loci. In the 1980s, following the emergence of recombinant DNA technology, new approaches such as familial linkage analysis led to the identification of many gene mutations associated with disease. However, genetic discoveries involved mostly Mendelian diseases, where damaging mutations in one or both alleles of a single gene are sufficient in most patients to cause the pathology. Those 'monogenic' conditions, caused by rare genetic variants exhibiting strong effect, high penetrance and relatively weak environmental modulation, have been - and are still - prototypes for the application of medical research from patient to bench, then bench to bedside (Antonarakis and Beckmann, 2006).

Since the mid-nineties, the human genome project has made a new generation of resources available, including physical maps, clones and gene sequence annotations. The discovery of extensive genetic variation between apparently normal human individuals has overturned our vision of our own genome: there is no unique human genome, but each human individual carries a combination of genetic variations that make his/her genome unique. The architecture of the human genome reflects the evolution of our species. Our genome is shaped by ancient polymorphisms shared between human ethnical groups and accounting for approximately 90% of its variation. These variations have been assessed comprehensively by international research projects (International HapMap consortium, 2005; Redon, 2006).

Detailed maps of single nucleotide as well as copy number polymorphisms (respectively SNPs and CNPs) have been published (International HapMap consortium, 2007; Conrad, 2009) and have led - and are still leading - to the development of new technologies allowing the detection in a high-throughput manner genetic markers or variations in the genomes of thousands of individuals. This new era in human genetics - symbolised by the success of genome-wide association studies (GWAS) on complex diseases such as coronary artery disease, rheumatoid arthritis or type-2 diabetes (WTCCC, 2007) - is still under way but has already produced some major breakthroughs (reviewed in Manolio, 2010).

However, GWAS have been designed following the 'common disease / common variant' hypothesis, according to which common diseases are partly attributable to ancient allelic variants carried by human individuals with a minor allele frequency of more than 5% (Manolio, 2010). Many investigators expected these studies to find only a subset of variants associated with disease risks (Pritchard, 2001; Terwilliger, 2002; Bodmer, 2008). Indeed, except for few conditions such as age-related macular degeneration (Maller, 2006), most common variants identified by GWAS as disease risk factors confer relatively small increments in risk (1.1 to 1.5-fold) and explain only small proportions of heritability (Manolio, 2009). In addition, despite huge research investments, the translational impact of GWAS has been notably weak so far (Collins, 2010).

Although most described genetic variants are ancient and shared between humans, the vast majority of allelic variants causing disease are recent and rare (Bodmer, 2008). New genetic mutations arise constantly in human populations and generate a wide spectrum of phenotypic traits and diseases (McClellan, 2010). Contemplating our more recent history, although the European population have long been regarded as homogeneous, more detailed surveys on the genetic structure of European subpopulations have shown an unexpected heterogeneity in terms of allelic variant frequencies, with genetic differentiation between countries, regions and even villages (Novembre, 2008; Heath, 2008; Nelis, 2009; O'Dushlaine, 2010).

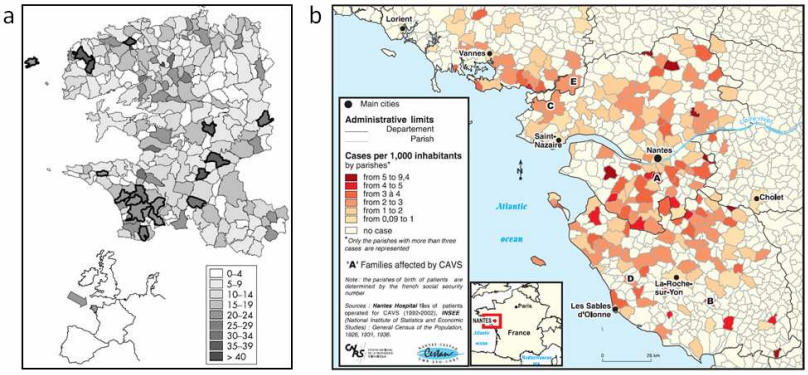


Figure 1: Heterogeneous geographic distribution and familial aggregation of patients with aortic valve stenosis in western France.

(a) *Map of Finistère, France. Ratios are the number of patients originating from each commune who underwent aortic valve replacement for aortic valve stenosis for each 10 000 inhabitants living in the communes in 1926 (Le Gal, 2005).* ***(b)*** *Map of the repartition of operated CAVS in the western part of France. Disease frequency was calculated for each parish by comparing the number of native cases of operated CAVS to the population living in the village. Population was estimated from the mean of the censuses performed in 1926, 1931, and 1936. The letters represent parishes in which familial aggregation of the disease has been identified (Probst, 2006).*

In parallel, epidemiologic investigations have shown that common diseases do not affect human populations homogenously, but are rather distributed in spatial clusters across territories. This heterogeneity can be attributed to environmental differences or exposures but also to genetic differences between distinct sedentary populations, each of them being characterised by a set of specific common ancestors (Peltonen, 2000). As an example, we have recently shown heterogeneous geographic distribution and familial segregation of Calcific Aortic Valve Stenosis in the western part of France, strongly suggesting the involvement of founder genetic mutations conferring high risk for this late-onset disease (Figure 1).

Here we hypothesise that the proportion of heritability which is still missing after GWAS can be largely explained by rare genetic variants conferring high disease risk but not detectable using current genotyping assays. These rare variants are concentrated in particular geographical areas, where they are carried by individuals who also share specific environmental conditions. Following this model, common diseases should be considered as groups of rare pathologies sharing the same phenotypic characteristics worldwide, but resulting locally from different combinations of rare genetic variants and local environment factors (McClellan, 2010).

Because GWAS have been mostly applied on large cohorts and have been focusing on frequent human DNA polymorphisms, they have not been successful in identifying such rare and localized genetic factors. In order to start addressing the 'common disease / rare variant' hypothesis which is increasingly recognized by clinical geneticists, one need to optimize patient recruiting strategies by taking into account our recent knowledge on human population stratification.

With the development of next generation sequencing technologies, screening for rare genetic variants genome-wide has become possible, allowing direct detection of those allelic variants that have not been described yet in human populations. The complete sequences from several single genomes using these technologies have already been published (Wheeler, 2008; Bentley, 2008; Wang, 2008; Ahn, 2009; Lupski, 2010). As an example, the comparison of protein-coding sequences between two individual genomes (Levy, 2007; Wheeler, 2008) and the public reference sequence showed respectively 3,766 and 3,882 non-synonymous single-nucleotide variants, indicating that these two genomes are different from each other by 7,648 protein coding changes. A sampling of 3,898 of the non-synonymous SNPs was tested for their possible functional impact on the protein sequence and 7.3% were classified as 'probably damaging', suggesting that these changes will affect protein function. The remaining SNVs were classified as either 'possibly damaging' (13%) or 'benign' (74%). This was the first comprehensive description of non-

synonymous differences between two diploid genomes (Wheeler, 2008) and the results - still restricted to the coding fraction of the genome - illustrate the challenge we are facing in interpreting rare sequence variations between individuals. More and more sequences from individuals with normal and abnormal phenotypes will become available in years to come: this accumulation of sequence information will help the scientific community to better appreciate the extent of rare genetic variation in human populations and its association with phenotypes.

While extensive efforts have been focused on the genetics of common disease, the precise role of environmental factors to many chronic or ageing conditions is still largely unknown. In contrary to global environmental aspects such as climate change, most environmental factors are typically depending on specific local features, such as geology, industrial activity, agriculture or social habits (Prüss-Üstün, 2006). Our knowledge about the daily local environments surrounding people remains limited. In consequence, it is extremely difficult to differentiate the role of environmental vs. genetic factors and - most importantly - to understand how their combination influences disease risk. There is an urgent need for new approaches to answer the societal demand and develop targeted preventive strategies.

So we propose to implement in the western part of France a new model for translational research, which will integrate projects in epidemiology, anthropology, genetics and environmental sciences (Figure 2). This project, named « GénHi En Santé » (for « Génétique, Histoire, Environnement et Santé »), will set up unprecedented resources to develop basic research based on gene-environment interaction discovery. GénHi En Santé will first be applied to a selection of chronic and ageing pathologies in Bretagne and Pays-de-la-Loire. The methodology and expertise acquired during this first phase will later be extended to other to more common diseases within our region and then disseminated across the entire French country and abroad.

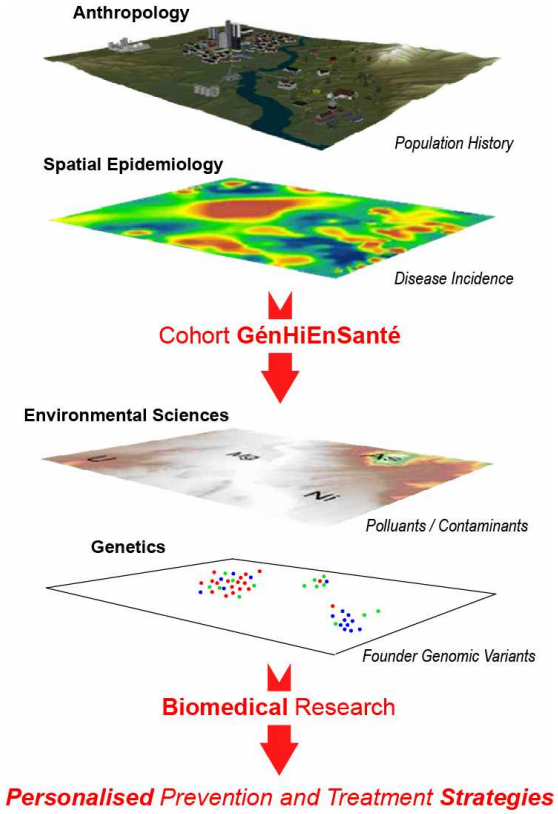


Figure 2: GénHi En Santé, an integrative project of translational research
By gathering experts in anthropology, epidemiology, genetics, environmental sciences and medicine, we aim at setting up unprecedented resources to promote the identification of geographically localised risk factors for chronic and ageing conditions. GénHi En Santé will promote new personalised prevention and care strategies across the French territory.
Adapted from Sloan, 2009

2. DESCRIPTION DU PROJET DE COHORTE / DESCRIPTION OF THE COHORT PROJECT

2.1. DESCRIPTION ET OBJECTIFS / DESCRIPTION AND OBJECTIVES

GénHi En Santé is an integrated survey of genetic and environmental factors influencing chronic conditions during lifetime. It is designed as a multidisciplinary network gathering specialists in anthropology, epidemiology, genetics, environmental sciences and clinical practice. **Our common goal is to promote better adapted prevention and care strategies for chronic and ageing pathologies.** To reach this goal, we propose to work on four complementary objectives: investigate the natural history of chronic conditions; decipher the fine genetic structure of regional populations in France; address the effect of environmental factors on chronic conditions; design new deciding tools for health care strategies in regions. **Integrating such diverse medical and scientific investigations will broaden significantly our knowledge on gene-environment interactions causing both occurrence and worsening of chronic pathologies.**

OBJECTIVE 1: Investigate the natural history of chronic conditions

First we aim to better understand the molecular mechanisms by which chronic conditions occur and worsen with time. To achieve this objective, we will recruit groups of patients born in the same geographical area and affected by the same chronic condition, but at variable disease stages. Selecting patients from the same geographical areas will allow us to apply new genetic screening strategies by considering disease models with founder effects and relatively low environmental variability. Describing disease phenotypes at different stages will enable us to reconstitute the natural history of chronic pathologies and to describe the chronology of events underlying disease worsening. For the first phase of the project, we have selected four chronic conditions, for which clinicians in Nantes, Brest and Rennes have already accumulated knowledge and expertise for several years. For each condition, up to 1,000 patients (and relatives) will be recruited in restricted geographical areas showing high disease frequency. For the second phase of the project, additional chronic pathologies will be selected following the outcomes of the epidemiological investigations performed in parallel. The four pathologies included in phase 1 are introduced below.

Aortic valve stenosis (AVS) is a frequent ageing condition in western countries, it worsen over life (Kuusisto, 2005) and leads to death in severe (advanced) forms if patients are not referred to surgery (Ross, 1968). AVS has been regarded as an atherosclerosis-like process characterized by progressive and extensive leaflet calcifications (Messika-Zeitoun, 2004). However, therapeutic strategies based on this hypothesis have been disappointing so far (Cowell, 2005). Despite the rising prevalence of the disease, epidemiological data on AVS are surprisingly scarce. We have recently reported a highly variable prevalence of AVS in the western part of France, likely linked to genetic factors (Blanc et al, 2005; Probst et al, 2006). However genetic factors have not been identified yet and the influence of environmental factors such as common cardiovascular risk factors remains to be addressed. The natural history of the disease, from early leaflet lesions to severe AVS, is still unknown, most publications ignoring the influence of environmental and cardiovascular risk factors. GénHi en Santé plans to enroll 1,000 patients with early to advanced valves lesions in echocardiography and without short-term life threatening condition other than aortic stenosis. Patients will be recruited from the database of cardiologists working in rural regions around Nantes to focus on sedentary populations with potential common ancestors. At inclusion echocardiography will be carried out by trained nurses according to standardized procedures and stored to allow off-line analysis by cardiologists. The aims of this epidemiological study will be to: (1) precisely define the etiology and characterize the specificities of AVS in western France ; (2) describe the progression of lesions from aortic valve sclerosis to severe stenosis by a 7-year follow-up; (3) detect familial forms of aortic stenosis by questionnaires and clinical screening in patient's relatives, to identify rare genetic variants with strong effect on aortic valve disease ; (4) evaluate the influence of environmental factors, such as traditional cardiovascular risk factors.

Progressive cardiac conduction defect (PCCD) is the main cause for pacemaker implantation. PCCD is characterized by progressive alteration of cardiac conduction over years, leading to syncope or sudden cardiac death (Lenègre, 1964; Lev, 1964). Because PCCD is usually diagnosed at advanced stages - when complications occur - little is known on its natural history. PCCD has long been considered as a purely degenerative process in relation with ageing, in which hereditary and genetics play only a limited role. Recently, we and others have identified two genes responsible for autosomal dominant forms of PCCD: *SCN5A* (Schott, 1999) and *TRPM4* (Kruse, 2009; Liu, 2009). In addition, we have demonstrated progressive worsening of conduction in patients carrying mutations in *SCN5A* as well as strong correlation between *SCN5A* mutation type and conduction defect severity (Meregalli, 2009). We have found that the distribution of patients implanted with a pacemaker for PCCD is highly heterogeneous in western France and genealogical surveys in the area with the highest rate of implants enabled us to recruit new families affected by the disease (unpublished data). So we plan to recruite 1,000 patients with PCCD and follow them up over 7 years. ECG monitoring will be conducted at inclusion and after 7 years: patients with electrocardiographic abnormalities will be followed up between these 2 visits by their practitioners. The aims of this epidemiological study will be to: (1) precisely define the etiology and characterize the specificities of PCCD in western France; (2) describe the natural evolution of the disease over 7 years; (3) detect familial forms of PCCD by questionnaires and clinical screening in patient's relatives, to identify rare genetic variants with strong effect on condition defect; (4) evaluate the influence of environmental factors modifying the natural course of disease.

Haemochromatosis (HMC) is mostly an adult-onset autosomal recessive condition, usually associated with the HFE p.C282Y homozygous genotype (OMIM#235200). In Northern European populations, this genotype is carried by around 1 person in 200. However, some p.C282Y homozygotes develop no clinical feature of HMC or even present without any abnormal parameter justifying venesection therapy. It is now increasingly accepted that the full liver disease develops only in a minority of p.C282Y homozygotes, when these individuals are subjected to modifier factors (Rochette, 2010; Deugnier, 2008). The identification of these modifier factors has been the subject of much research over the past decade, and it must be noted that we have contributed much in the field (Nahon, 2010; Milet, 2010; Island, 2009; Le Gac, 2009; Le Gac, 2008; Milet, 2007; Jacolot, 2004; Le Gac, 2004; Scotet, 2003). However, few factors with a strong effect have been identified. It is still very difficult to predict the development of iron overload and the onset of clinical signs that can be life-threatening. GénHi en Santé plans to recruit 1000 p.C282Y homozygous patients with mild to severe iron burden. Patients will be recruited from the Family Screening Center for Haemochromatosis in Rennes and from health centers of the national blood agency (EFS), where most therapeutical phlebotomies are done. This will allow us to perform coherent and comprehensive recruitments through Bretagne and Pays-de-la-Loire. Patient inclusion will be based on socio-demographic, biological, clinical, therapeutical and environmental criteria. Follow-up visits will be made after 7 years, focusing on the development of clinical symptoms. Our aims are to: (1) define precisely the environmental conditions under which the most impressive phenotypes are observed; (2) isolate sub-groups of patients to identify rare genetic variants with strong effects on the disease; (3) describe evolution of the disease over 7 years; (4) evaluate the influence of environmental and genetic modifiers on the natural course of the disease; (5) elaborate more effective strategies for risk assessment.

Congenital hip dislocation (CHD) is one of the most common congenital skeletal disorders. This disease clusters in families and is particularly frequent in western France: an epidemiological study performed in the 1960s even identified a cluster of cases in a small part of south-western Brittany, called *Pays Bigouden*. CHD is characterised by abnormal seating of the femoral head in the acetabulum, which may be generated by morphological defect of the cavity and/or joint hyperlaxity. Despites newborn screening, CHD remains a public health matter because of its high frequency, the functional disability induced in case of delayed diagnosis, and its natural evolution toward hip osteoarthritis, a major concern for ageing societies worldwide. To date, little is known about the cause and the evolution of this disease. Patients with identical radiographic appearances may evolve very differently. CHD is now considered as a complex disease involving both mechanics

(related to pregnancy and birth) and genetics (suggested by familial aggregation). We began a Britton research program aiming to identify the genetic factors involved in CHD. Recruitment is underway including 8 multiplex families. Given the phenotypic heterogeneity observed in CHD and its unpredictable clinical evolution, it is now essential to initiate a larger prospective cohort focused on CHD cases screened at birth. We plan to recruit 800 newborns over 3 years followed in the University Hospitals of Brest, Rennes and Nantes, as well as in the local Hospital of the Pays Bigouden. Patient inclusion will be based on standardised sonographic and/or radiographic criteria and will include familial history investigation in addition to oral sample collection. Follow-up visits will be made at 7 years of age. The aims of this epidemiological study will be to: (1) precisely define the etiology in western France; (2) describe the natural evolution over 7 years; (3) detect familial forms of CHD by questionnaires as well as clinical screening in patient's relatives, to identify rare genetic variants with strong effect on CHD; (4) evaluate the influence of environmental factors modifying the natural course of the disease.

OBJECTIVE 2: Decipher the fine genetic structure of regional populations in France

In the context of international research projects aiming to define the genetic structure of human populations and with the obvious implications that this has in terms of mapping genes involved in complex traits and diseases, France is a completely unknown genetic landscape. No systematic studies, and even less considering genome-wide variation, have been performed in different French regions. The objective of GénHi En Santé is to start sampling 24,000 individuals from France, covering every region and taking into consideration detailed ethnological and historical data. Samples will then be available for genetic analyses, including whole genome genotyping or sequencing, which is an unbiased approach to define the whole spectrum of allelic variation including low-frequency variants. These downstream genetic analyses will inform us about (i) the occurrence of (fine) genetic structure among the diverse French regions, which has important implication in disease-related research, (ii) the levels of admixture of some populations of France with other populations, (iii) the allelic architecture of the different genes, which will provide important insights into the way the different genes can be involved in disease.

The EFS has the logistics to collect 10,000 donors each day across the country even in the most remote rural municipalities. In addition it holds a database of more than four million donors. This is an important source for the recruitment of healthy volunteers to form a cohort and obtain associated medical information and biological samples. This infrastructure can be harnessed to develop a cohort representative of local populations in France. In GénHi En Santé, as a pilot study, we plan to recruit 4,000 healthy individuals from western France, benefiting from the EFS logistics. To constitute such cohort, we need to cover the regional territories homogenously in order to catch a full picture of the diverse populations living in our regions. However understanding the genome composition of local populations requires knowledge of the population's genetic structure history. So we will put particular emphasis on the recruitment of relevant populations and individuals from an anthropological perspective. We will select geographical areas of particular interest based on the administrative divisions of the Iron Age, which are the oldest known on the French territory. The municipalities located in the heart of this territorial division will be considered in priority. In each municipality, donors will be selected if their four grandparents were from the same area selection and if their surname appeared frequently in the earliest parish records. This cohort, which will be later extended to cover the entire French territory, will help us in improving our knowledge on the genetic structure and stratification of historical French populations and will also serve as a major biological resource in GénHi En Santé as well as in many other future studies in medical, population and evolutionary genetics. Note that this effort will be coordinated with the CoISmmGen Project from Institut Pasteur, who aims to sample a smaller French cohort and establish basic immunological profiles in these individuals.

OBJECTIVE 3: Address the effect of environmental factors on chronic conditions

Environmental factors are diverse and thus complex parameters (including toxicity, geography, psychology, sociology, culture, economy…) that modulate the disease expression and course.

Regional epidemiology is just emerging: one major objective in GenHi En Santé is to characterize the heterogeneous distribution of diseases. We believe that, as for genetics (a somewhat simpler approach), regional epidemiology will create new conditions to get deeper insight into environmental exposures modulating disease expression. During the first phase of GenHi En Santé, we will organize a strategic conference gathering experts in spatial epidemiology and environmental sciences. This conference will guide GéHi En Santé in identifying actors in environmental epidemiology and setting up new research programs in collaboration with them for the second phase of the project. As a pilot investigation during the first phase of GenHi En Santé, we will investigate the effect of air pollutants on asthma and COPD, two highly prevalent chronic diseases with high morbidity. Both diseases are paradigm examples of genes/environment interactions: allergens are predominant risk factors for asthma while tobacco smoke and occupational exposure are associated with COPD. Individuals that have been living stably in farms since their birth suffer significantly less from allergies than the rest of the population. In addition, the generational increase in allergic asthma observed in the past decades did not occur in individuals who were exposed to a farming environment in childhood. The 'protective' farm effect has been associated with livestock farming and thus to microbial exposure. This is consistent with the hygiene hypothesis, which suggests that the increased prevalence of allergic diseases observed over the past decades results from a relative lack of microbial stimuli during infancy and early childhood. However, this protective effect remains controversial. Contrary to common belief, evidence suggests that the prevalence of non-allergic asthma is comparable in rural and urban areas. In addition, current literature suggests that farmers suffer more from COPD than individuals living in urban zones even after accounting for age and this despite the fact that farmers tend not to smoke. Asthma and COPD are complex diseases for which a familial risk has been demonstrated. There is increasing evidence that both pathologies may be aggregations of many conditions, which are clinically similar conditions though caused by various molecular dysfunctions and triggering agents. GénHi En Santé will provide a unique opportunity to identify gene-environment interactions causing asthma and COPD by recruiting groups of individuals in restricted geographical area, where we will be able to apply epidemiological models involving founder effect and restricted environmental variability.

OBJECTIVE 4: Design new deciding tools for health care strategies in regions

Identifying disease causes through geographical mapping is the underlying object of epidemiology. This has been many times exemplified work of John Snow which was able to identify the cause of the cholera epidemics in Soho by "simply" mapping the cases and evidencing the cluster around a water pump in Broad street. Spatial epidemiology is often, rightly, thought of as a tool for analysis of transmissible, infectious, diseases where pathogens are clearly transmitted along a geographical structure (1). But it is also able to evaluate clustering patterns of disease prevalence (2) in an attempt to correlate them with distributions of risk factors such as environmental exposures or genetic variations. GénHi En Santé is based on the increasingly recognized hypothesis that 'common diseases' are rather groups of rare pathologies sharing the same phenotypic characteristics globally, but resulting locally from different combinations of rare genetic variants and local environment factors. A large fraction of rare variants - those of recent origin - are likely to cluster geographically or at least to display clines of frequency in societies with limited migration rates, like rural populations before 20th century (7). Where rare alleles are concentrated locally and increases disease risk with relatively large effects, we'd expect outbreaks of disease prevalence. In this context, we aim at building new integrated strategies in order to identify: (i) spatial disease clusters for pathologies of interest; (ii) new pathologies displaying strong spatial clustering patterns; (iii) new or optimized methods in statistical genetics, according to which patient recruitment can be adjusted. We will then promote new guidelines for population selection, based on observed disease outbreaks and underlying genetic and spatial models. The synergistic input of epidemiologists, statisticians and geographical analysts from regional health agencies and observatories will allow us to deliver precise and locally-tailored disease incidence estimates.

2.2. PERTINENCE DU PROJET ET CARACTERE NOVATEUR / RELEVANCE AND INNOVATIVE FEATURE OF THE PROJECT

Coherent health policies should include prevention against chronic and ageing pathologies – those having a high impact on health and the economy. Most chronic and ageing conditions are diagnosed late during life, when they have already reached an advanced stage at which prevention has become inefficient. Usually, patient therapy is then either long-term medication or surgical repair. The cost of such therapeutic strategies is considerable to our society (see part 5). Here we propose to reevaluate the way we consider those chronic pathologies. Those pathologies occur through active biological processes, which can be influenced by both genetic and environmental modifiers. In order to develop new preventive strategies, we propose to address four major challenges.

Firstly, we aim to better describe the natural history of each disease and to understand the precise biological processes leading to phenotype worsening. Most clinical manifestations are not direct functional consequences of genetic defect or toxic damage. They result rather from tissue remodeling in reaction to initial damage. Assessing patients clinically at earlier disease stages is of extreme importance to identify which lesions are directly associated with the original physiological defect. It can help researchers in generating new functional hypotheses and then test appropriate drugs in clinical trials. To achieve this first objective, GénHi En Santé regroups clinicians from three University Hospitals in western France who are internationally renowned in their specialties (see part 4). The first innovation in GénHi En Santé resides in our clinical approach: our program is neither focused on a common pathology nor on a group of rare disorders. Our aim is to set up new common standards for investigating the etiology and worsening of chronic and ageing pathologies regionally. Our project is based on strong innovative and multidisciplinary strategies that integrate knowledge in medical, population and evolutionary genetics, environmental sciences, and humanities.

Secondly, chronic diseases can be considered as generic phenotypes, each of them resulting from multiple genetic disorders and/or environmental exposures. Identifying genetic and environmental factors influencing the course of those multiple disorders requires the recruitment of homogeneous groups of patients. To optimize patient selection, we will recruit them in restricted geographical area, where there will be higher probability for founder genetic effect and lower environmental variability. This strategy necessitates the involvement of the French health management organizations. The Regional French Agencies for western France have agreed to contribute to GénHi En Santé. Their collaboration with our epidemiologists and biostatisticians will enable the construction of new maps to measure the geographical variability of disease incidence. These new tools will help us not only in defining our recruitment strategies, but also in understanding better how chronic disease affects people in France in relation with their birth and living place(s). To our knowledge, for the first time in France, researchers, clinicians and health managers will collaborate toward the same objective: recognizing the genetic and environmental burdens on chronic conditions across the French territory.

Thirdly, from a genetic perspective, identifying rare variants strongly influencing human disease requires strong knowledge on the fine genetic structure of the local populations living across our territory. We aim to better understand how our genome has been shaped during the past, in response to environmental hazards. Better understanding the fine structure of our genome will facilitate the identification of those rare and recent genetic variants, which are most probably associated with increased risk of disease. Evolutionary genetics and anthropology will be two major topics in GénHi En Santé. In collaboration with genetic epidemiologists and medical geneticists, two leaders in these fields, J Chiaroni and L Quintana-Murci will supervise the recruitment of regional populations representing French diversity, based on the most recent historical data describing human migrations and societies across this part of Europe. Their contribution warrants that GénHi En Santé will eventually deliver a

national population-based cohort, which will become a key biological resource for future studies in genetics, human biology and anthropology in France and abroad.

At last, the medical research community needs to better address the respective roles of genetic and environmental factors on disease. GénHi En Santé aims to integrate genetics, lifestyle and exposure information. Only integrative approaches can efficiently decipher the complex molecular interactions leading from normal to pathological states in humans. Because available data and methodology on this cross-disciplinary field are still scarce, we propose to implement a pilot study in western France, by taking advantage of the operational force set up by the French Blood Agency. The pilot study will aim at designing a comprehensive map of air exposure across western France. This map will be the basis of a translational research program on asthma and COPD, two chronic pathologies with high medical and economical impact. By initiating such integrative translational programs, GénHi En Santé will become a reference model for future studies on the burden of gene-environment interactions on human disease.

We are witnessing a turning point in the evolution of our society. In history, rural societies have long been organized in local population isolates. Until recently, the French populations were still largely rural and fixed in circumscribed geographical areas. However, population migrations have accelerated since the fifeties and this organization is being phased out. The call for proposals *'Investissements d'Avenir: Cohortes'* represents certainly the last opportunity to catch the genetic structure of historical populations in France. The extraordinary rise of new technologies in molecular biology and genetics allows us today to address efficiently the genetic predisposition to disease. With GénHi En santé we will be able to address the evolution and history of our people who for centuries have not been very mobile. So far, very few epidemiological tools enabling detailed analysis of the heterogeneity of our population against the risk of disease have been developed. GénHi En santé is a unique opportunity for researchers in genetic epidemiology and biostatistics to develop new models and methods for identifying disease risks factors by innovative approaches including genealogy and anthropology.

2.3. PROGRAMME DE TRAVAIL : STRUCTURATION DU PROJET & JALONS / WORKING PLAN : PROJECT STRUCTURATION & MILESTONE

GénHi En Santé is organized in 5 Work Packages (WP).
WP1/Patients recruits and follows up patients affected by chronic pathologies. WP1 is first focused on four pathologies for which the clinical groups contributing to the project have already accumulated expertise and experience: aortic valve stenosis (AVS); progressive cardiac conduction defect (PCCD); haemochromatosis (HMC); congenital hip dislocation (CHD). The recruitment will later be extended to other chronic conditions showing a strong medical and economical impact, according to WP4 recommendations. Will be considered in priority: dyslipidemia; asthma and chronic obstructive pulmonary disease (COPD); thrombophilia; stroke in the young.
WP2/Population recruits healthy individuals representing regional populations in France. After an initial 12-month phase to consolidate the inclusion criteria, 4,000 healthy individuals from western France will be recruited in two consecutive steps: (i) 2,000 individuals from Bretagne and Pays-de-la-Loire; (ii) 2,000 individuals from Centre and Poitou-Charentes. Recruitment will then be extended to other French regions, in order to cover the entire national territory.
WP3/Environment investigates the involvement of environmental exposures to chronic disease. WP3 promotes new ideas on the integration of environmental sciences to large-scale studies aiming at deciphering gene-environment interactions associated with disease incidence and/or worsening. As a pilot study, WP3 performs a regional survey of household air pollution, to construct a model of environmental map for respiratory risk across Bretagne and Pays-de-la-Loire.
WP4/Prospective guides GénHi En Santé by identifying geographical areas in western France with particular high incidence of chronic diseases. WP4 also brings strong expertise in genetic and statistical epidemiology to adjust recruitment strategies in WP1 and WP2, both in terms of geographical distribution and sample sizing.
WP5/Bio-Banking pays particular attention to safeguarding the biological resources constructed by GénHi En Santé. WP5 builds on the Biological Resource Centre (CRB) of the University Hospital of Nantes (*see 2.4-Environment*).
WP6/Integration manages the entire project in support to the project coordinator by controlling that every WP delivers on time and collaborates efficiently with other WPs. GénHi En Santé is a multidisciplinary project involving clinicians, researchers and health managers from very diverse fields. Its success resides in efficient connections between those partners working in WP1 to WP4.

WP	Title	Leader	Co-Leader	P1	P2	P3	P4	P5	P6	P7	A8	A9	A10	A11
1	Patients	V Probst	G Le Gac	X	X	X			X	X				
2	Population	J Chiaroni	L Quintana-Murci	X	X	X	X				X			
3	Environment	I Annesi-Maesano	A Magnan	X	X	X	X	X						
4	Prospective	C Dina	V Scotet	X	X							X	X	x
5	Bio-Banking	G Gallot	P Lemarchand	X			X		X	X				
6	Integration	R Redon	C Ferec	X	X									

WP1 / PATIENTS

Objectives
O1.1 Set up tight collaborations between clinicians, geneticists and epidemiologists on complex diseases for which expertise has already been developed in western France: (1) aortic valve stenosis (AVS); (2) progressive cardiac conduction defect (PCCD); (3) haemochromatosis (HC); (4) congenital dislocation of the hip (CDH)
O1.2 Establish large prospective cohorts of patients allowing a better assessment of the natural history of these chronic diseases
O1.3 Share methodological tools and epidemiological expertise to better address the impact of genetic and environmental factor on the phenotypic variance seen within local patient groups
O1.4 Extend objectives **O1.1** to **O1.3** to other chronic pathologies selected in **WP4**

Tasks (Description of work)
T1.1 Define inclusion criteria, considering local population stratification and incidence variability: inclusion criteria will be adjusted for each disease by integrating new epidemiological information generated by **WP4**.
T1.2 Delineate the overall strategy to obtain biological, clinical and therapeutic data: definition of standardized questionnaires associated with blood sample collection, to obtain detailed information on patient lifestyle, disease familial history and environmental factors already known to influence disease incidence and progression.
T1.3 Recruit patients with AVS, PCCD, HMC and CDH based on inter-regional networks of well recognized clinical and healthcare centers:
- signature of an informed consent by the patient
- standardized questionnaire
- clinical test : echocardiography for AVS; electrocardiogram for PCCD; sonography for CDH
- sample collection: saliva for HMC/CDH ; plasma for HMC ; 10-ml blood for AVS and PCCD

T1.4 Patient follow-up (5 to 10 years) to identifying parameters subjected to temporal changes:
- collection of intermediary clinical information from regional networks of practitioners
- standardized questionnaire
- clinical test : echocardiography for AVS; electrocardiogram for PCCD; sonography for CDH

T1.5 Extend tasks **T1.1** to **T1.4** to other chronic pathologies selected in **WP4**

Deliverables (P1, P2, P3, P6, P7)
D1.1 Cohorts of patients with chronic disease from geographical incidence clusters (**month 36**)
D1.2 Deliverable **D1.1** applied to additional chronic pathologies selected with **WP4** (**month 84**)
D1.3 Measurement of disease worsening at 7 years for patients recruited in **D1.1** (**month 120**)

Milestones and expected results
M1.1 More effective strategies for risk assessment and treatment of AVS, HC, CDH and PCCD
M1.2 Identification of new physiological pathways involved in these chronic diseases, through subsequent genetic and environmental studies
M1.3 Extension of the strategies developed by GénHi En Santé to other chronic diseases
M1.4 Dissemination of the strategies developed by GénHi En Santé outside western France

WP2 / POPULATION

Objectives
O2.1 Establish a cohort of 2,000 healthy individuals, representatives of the local populations from 'Bretagne' and 'Pays-de-la-Loire'
O2.2 Extend the cohort constitution to 2,000 additional healthy individuals from two additional regions: 'Poitou-Charentes' and 'Centre'
O2.3 Set up the appropriate conditions for constituting a national cohort, representing local population across the entire French territory.

Tasks (Description of work)
T2.1 Define inclusion criteria, considering both anthropological and clinical perspectives:
- Medical research criteria: comprehensive coverage of regional territories, considering recommendations from **WP4** (statistical genetics)
- Anthropological criteria: focus on particular geographical area (hearts of territorial divisions from the Iron Age); four grandparents from the same area; surname appearing more than 8 times over 100 years in oldest parish records

T2.2 Recruit healthy individual in 'Bretagne' and 'Pays-de-la-Loire' based on the EFS infrastructure:
- Signature of an informed consent by the healthy volunteer
- Standardized questionnaire on lifestyle, familial history and environmental exposure (**WP3**)

- Blood collection: one tube (10 ml) on EDTA for DNA and plasma ; one tube (10 ml) on EDTA for B-lymphoblastoid cell line immortalization
- Distribution of a passive sampler to place in living room and sent back by mail after 5 days

T2.4 Recruit healthy individual in 'Poitou-Charentes and 'Centre' based on the EFS infrastructure:

- Signature of an informed consent by the healthy volunteer
- Standardized questionnaire on lifestyle, familial history and environmental exposure
- Blood collection: one tube (10 ml) on EDTA for DNA and plasma ; one tube (10 ml) on EDTA for B-lymphoblastoid cell line immortalization
- Volunteer contribution to a new environmental survey (optional)

Deliverables (P1, P2, P3, P4, A8)
D2.1 A new organization for recruiting healthy individuals through the EFS infrastructure, with associated collection of biological samples and environmental information (**month 12)**
D2.2 A cohort of 2,000 healthy individuals from 'Bretagne' and 'Pays-de-la-Loire', with associated biological samples and lifestyle information (**month 36**)
D2.3 A cohort of 4,000 healthy individuals from 'Bretagne', 'Pays-de-la-Loire', 'Poitou-Charentes' and 'Centre' with associated biological samples and lifestyle information (**month 60**)

Milestones and expected results
M2.1 A new biological resource for genetic, anthropological and clinical studies in western France
M2.2 Towards a national biological resource representing population diversity in France
M2.3 Transfer of the biological resources from Nantes to the future National Centre for Biological Resources of the EFS

WP3 / ENVIRONMENT

Objectives
O3.1 Design new research programs with experts in environmental epidemiology
O3.2 Produce precise mapping of environmental exposure (EE) across western France
O3.3 Estimate EE effect on asthma and COPD after allowance for confounders of the relationships
03.4 Describe at 5 years the relationship between EE and disease incidence.
03.5 Describe a dynamic mapping of spatiotemporal relationships between EE and asthma/COPD

Tasks (Description of work)
T3.1 Organise an orientation conference with the best specialist in spatial epidemiology and environmental sciences to design new research programs adressing the influence of environmental exposures on chronic diseases
T3.2 Undergo volatile Organic Compounds (VOCs) assessments at homes: passive sampler distributed to the 2,000 healthy individuals recruited in **WP2/T2.3** during recruitment, placed in living room and sent back by mail.
T3.3 For 250 patients with asthma, 250 with COPD and 250 selected volunteers drawn from **WP2/T2.3** (matched on age, gender and geographical location): direct assessment of household air quality (fine particulate, formaldehydes, VOCs, BTEX, endotoxins, molds, allergens by a technician using passive samplers and pumps) + collection of biological samples (including blood products, urine and breath condensate)
T3.4 Follow-up at 5 years: incidence/aggravation of asthma/COPD checked with questionnaires and spirometry, exhaled NO and breath condensate.

Deliverables (brief description and month of delivery)
D3.1 The first Orientation Conference on Environmental and Genetic Epidemiology (**month 18**)
D3.2 A regional population-based cohort characterized for EE, providing an estimation of the range of exposure according to geographical and socio-economic characteristics (**month 36**)
D3.3 Characterization of household EE in patients with asthma/COPD and controls (**month 60**)

D3.4 Evolution at 5 years: incident cases of asthma/COPD and decline of respiratory function according to EE (**month 120**)

Milestones and expected results
M3.1 New research programs on environmental epidemiology in western France
M3.2 Measurement of Environmental Exposure (EE) in a population-based cohort
M3.3 Precise EE measurements associated with biocollections for 250+250 patients with asthma and COPD and 250 matched controls

WP4 / PROSPECTIVE

Objectives
O4.1 Establish protocols to construct maps of incidence for diseases of interest in western France
O4.2 Identify new chronic pathologies of interest based on maps of incidence and clinical expertise available in western France
O4.3 Guide the recruitment of patients affected by the pathologies of interest using genetic and epidemiological models

Tasks (Description of work)
T4.1 Geographical mapping of disease incidence using data from the ARS: retrieve anonymized data on Long-Term Medical conditions ('ALD', which includes more than 30 severe and thus potentially costly diseases), with associated birth and living place; retrieve anonymized data from hospitalization lists, with associated pathologies as well as birth and living places
T4.2 Geographical mapping of disease burden using data from the ORS: retrieve information from the CépiDC mortality database, which maps causes of death at very fine spatial scale
T4.3 Generate and evaluate maps of disease prevalence: integration of incidence and burden data; capture/recapture studies to compare data and assess the effectiveness of each individual source
T4.5 Generate genetic and environmental model through simulations and assess impact on geographical correlation of disease and genotype: use (i) forward-simulation in an island model in order to mimic the scenario of several small inhabitation units with limited migration and (ii) backward (coalescent) simulation under the same conditions. (iii) Association methods will then be applied in the simulated datasets in order to identify the best selection strategies.

Deliverables (P1, P2, A9, A10, A11)
D4.1 Precise guidelines to complete the recruitment of patients affected by chronic pathologies defined in WP1, phase I (**month 18**)
D4.2 Precise guidelines to recruit patients with newly selected chronic pathologies (**month 36**)

Milestones and expected results
M4.1 New recommendations to set up maps of disease incidence in relation to people birth and living place using ARS healthcare data
M4.2 New statistical methods for investigations in clinical genetics, based on the biological resources generated by GénHi en santé (**WP1** & **WP2**)
M4.3 New information about population genetics of diseased individuals (relationship between fitness and disease risk)

WP5 / BIO-BANKING

Objectives
05.1 Prepare, preserve and distribute the bio-collections created by GénHi En Santé
05.2 Establish a computer database containing clinical and personal information from patients recruited in GénHi En Santé

05.3 Enable WP1/WP2 participants to enter clinical and/or personal data to the database and access them over secure connections

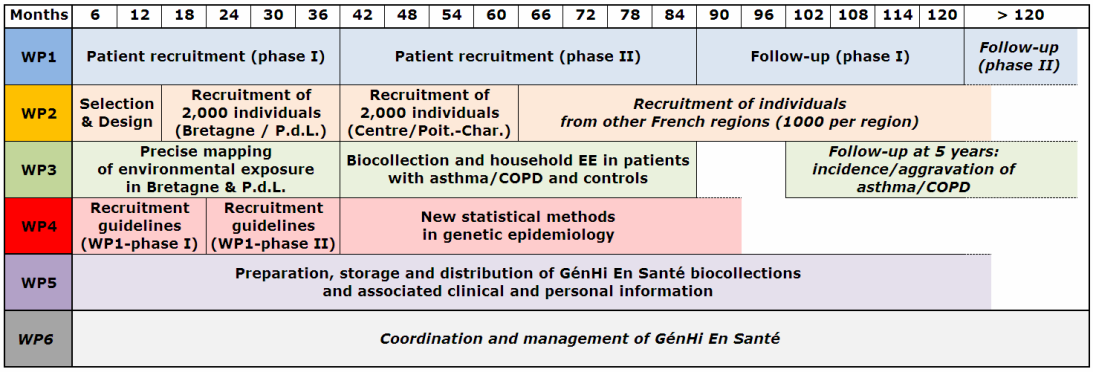
Tasks (Description of work)
T5.1 Biological sample preparation for patients recruited in WP1: for each patient with AVS/PCCD, one 10-ml tube of blood on EDTA will be transferred to the CRB where DNA and plasma will be prepared using standardized procedures. For each patient with CDH/HMC, DNA will be either prepared from saliva at delivery of the collection kit, or DNA will be stored at delivery. For each patient with HMC, plasma will also be transferred from EFS centres to the CRB 4 times a year.
T5.2 Biological sample preparation from blood collected in WP2: twice a week, for 10 healthy individuals, two 10-ml tubes of blood on EDTA will be transferred to the CRB. One tube will be used for DNA and plasma preparation, the other for B-EBV cell line immortalization. Tubes collected on Monday/Tuesday will be stored at room temperature and delivered on Wednesday morning; tubes collected on Wednesday/Thursday will be stored at room temperature and be delivered on Friday morning. Sample preparation will be performed on the same day as delivery.
T5.3 Secure storage and distribution of clinical and personal data collected in WP1 and WP2: individual reports will all be centralized and managed at the CIC of Nantes. Data entry will be performed by clinical research technicians into databases managed by the software 'Integralis'. A thesaurus defining the values allowed and/or the ranges for each variable will prevent the entry of incorrect data and outliers. Quality controls will be performed to eliminate potential duplicates, complete missing values and check inconsistent data. In addition, double entries of questionnaire data will be organised to estimate clinical/personal data reproducibility. Databases will be installed on computers dedicated to the management of those studies. Computer servers will be located in locked offices and accessible only by personal passwords. Computer files will be reported to the National Commission for Informatics and Liberties (CNIL). Data will be anonymized before distribution to partners and external users.

Deliverables (P1, P2)
D5.1 A biocollection of 2,000 healthy individuals from Bretagne and Pays-de-la-Loire with associated familial and lifestyle data (**month 36**)
D5.2 Biocollections of patients with AVS, PCCD, HMC and CHD with associated clinical, familial and lifestyle data (**month 36**)
D5.3 A biocollection of 2,000 healthy individuals from Centre and Poitou-Charentes with associated familial and lifestyle data (**month 60**)
D5.4 Biocollections of patients with four additional chronic pathologies with associated clinical, familial and lifestyle data (**month 84**)

Milestones and expected results
M5.1 A cohort of 4,000 individuals representing regional populations in western France
M5.2 Cohorts of patients to investigate locally both genetic susceptibility and environmental risk associated with the occurrence and progression of chronic pathologies across western France
M5.3 A national cohort representing the diversity of French regional populations

WP6 / INTEGRATION

WP6 is responsible for the management and coordination of GénHi En Santé, by keeping efforts focused on the long-term goals and managing contingency in case of problems and/or conflicts. Its role is to ensure that WP1-5 deliver on time and with appropriate quality standards, as described in the research program below.



Objectives
O6.1 Contractual, legal, intellectual property and financial management
O6.2 Coordination of Boards, Task Forces and meetings
O6.3 Management of knowledge and communication
O6.4 Day-to-day management
O6.5 Overview of ethical and dissemination issues

Tasks (Description of work)
T6.1 Contractual, legal and intellectual property management, to establish: (1) a network of legal/financial/IP/communication representatives of each partner during the negotiation phase; (2) a section in the management guide dealing with contractual/ legal/IP issues during the first quarter of the project; (3) good operating practices to ensure that all requirements are fulfilled on time
T6.2 Financial management, in order to: (1) establish a dedicated section relative to financial issues in the management guide; (2) provide partners with detailed budgets to ensure that all budgetary actions are performed correctly and within the rules and regulations established by the FNRA and the consortium agreement; (3) update this budget, at least every 18 months
T6.3 Coordination of Boards, Task Forces and meetings, in close connection with the Scientific Coordinator, to ensure the preparation, organization, administration, minutes and follow-up of Boards, Task Forces and Executive Committee meetings. The Project Manager will develop the template management toolbox necessary to ensure that meetings are fully productive
T6.4 Day-to-day management to ensure: (1) centralized communication between the FNRA and consortium partners; (2) collection of progress reports for WP deliverables; (3) monitoring work progression with WP Leaders; (4) setting up communication tools for information sharing; (5) organization of partners' meetings, including those with FNRA reviewer(s); (6) financial transactions; (7) mediation between partners; (8) dissemination of results; (9) coordination of interdependencies between WPs; (10) edition of the management guide

Deliverables (month of delivery - P1, P2)
D6.1 Update/amendment of the grant of consortium agreements (**months 1-120**)
D6.2 Original/updated versions of the management guide and toolbox (**months 1-120**)
D6.3 Original/updated versions of the detailed budget to partners (**months 1-120**)
D6.4 Launching of the quarterly E-Newsletter (**months 3-120**)
D6.5 Launching of the intranet website (**month 6**)
D6.6 Proposition for a communication plan updated each year (**months 6-120**)
D6.7 Organization and minutes of Boards, Task Forces and Committee Meetings

Milestones and expected results
M6.1 Signature by all partners of the grant (**month 1**) and consortium (**month 6**) agreements
M6.2 Kick-off meeting (**months 1-3**)
M6.3 Active involvement of partners (**months 1-120**)

2.4. ENVIRONNEMENT/ ENVIRONMENT

The 'institut du thorax' (IDT) is an institute established in April 2004 at the University-Hospital of Nantes and focused on cardiovascular and respiratory diseases. It assembles healthcare, teaching and research under unified management. The IDT has developed routine and innovative patient care modalities to meet the needs and expectations of a community of 1,200,000 inhabitants. The IDT comprises 360 beds: more than 12,000 patients are hospitalized each year, for a total of 90,000 hospitalization days, and 26,000 outpatients are seen in clinical consultations. To fulfill its mission, the IDT employs 32 full-time senior MDs, 22 residents from different specialties and more than 600 nurses and other personnel. In the same service, patients of the IDT can find renowned clinicians in many specialties such as cardiology, pulmonology, thoracic and vascular surgery, endocrinology and hemodynamics.

Clinical research is conducted according to good medical practice in a Clinical Investigation Center (CIC4), which is also sponsored by Inserm. The role of the CIC is to provide clinicians and scientists with every technical tool needed to perform translational research. Among the 82 ongoing clinical studies in the IDT, 55% are sponsored by an academic promoter and 33% are translational research directly linked to research programs from UMR915. Since 2006, 17 new IDT programs have been sponsored by the French Ministry of Health. The IDT is also promoting 'contracts of translational research', facilitating the integration of researchers within clinical teams and the integration of clinicians within research teams. Six researchers and four clinicians from the IDT have obtained such contracts, organized between Inserm and University-Hospitals.

Basic research at the IDT is conducted in a large INSERM Unit (UMR915, headed by Pierre Pacaud), which employs 150 persons including 12 faculty members and 18 full-time tenured researchers. The UMR915 is an active member of the biomedical research community in Nantes (700 employees federated by the IFR26). Through this organization, the IDT has access to state-of-the-art technologies, but also provides platforms and shares high-cost equipment. Two IDT platforms in particular have been recognized as national infrastructures since 2009 (IbiSa) and have become major technological strengths.

1) The Platform for Integrative Genomics (director: R Houlgatte) offers methodological services, such as sequencing, genotyping, epigenetic and expression analyses, large-scale signature validation. The Platform also develops and maintains its own bioinformatics tools for microarray data interpretation (http://www.madtools.org/). It is part of BioGenOuest, an interdisciplinary organization regrouping technological platforms from Britanny and Pays-de-La-Loire. Five BiogenOuest genomics platforms collaborate within a network created in June 2010 and coordinated by P Vandenkoornhuyse (Rennes) and R Redon (UMR915), which objective is to offer cutting-edge services in genotyping and next-generation sequencing. Within this network, (i) one Roche GS-FLX machine is available at the university of Rennes; (ii) funding is granted for one Illumina HiSeq2000 sequencer at the Hospital of Rennes; (iii) funding has been requested for a third NGS machine to be installed at the IDT in 2011; (iv) one Affymetrix GeneTitan machine - for high-throughput genome-wide genotyping - is currently set up in UMR915 and will be transferred to the Platform by the end of 2011. The BioGenOuest Genomic Network aims at becoming an efficient technological structure promoting large-scale genetic investigations in western France.
2) Cardiex (director: P Pacaud) is a platform for functional exploration of the small animal certified by IBISA (http://www.cardiex.univ-nantes.fr). Cardiex services allow the generation of new animal models of human diseases (or mutations) by somatic trans-genesis. These models are explored from gene functional analysis, in vitro molecular and cellular assays to in vivo phenotype characterization. Access to equipments includes technical support and personal training. Services are structured into 8 modules: animal model generation, metabolic functions, vascular functions, cardiac functions, pulmonary functions, motor functions, digestive/neuro-digestive functions, tumors and carcinogenesis. In addition, R&D projects can be carried out by

Cardiex or as collaborative projects for the development of new animal models by innovative strategies of for the validation of therapeutic targets of interest.

Many bio-collections dedicated to cardiac, vascular and pulmonary diseases are managed at the IDT. They will be progressively transferred to a new specialized structure at the University-Hospital, the Centre for Biological Resources (CRB), which opens its doors in June 2011. Indeed, in support to strong and dynamic biomedical research activity in Nantes, the hospital has approved plans to build a shared CRB on a single site, which will be a centralized platform for preparation, preservation and provision of high quality biological resources to the entire scientific community. One building is currently refurbished to create a new centre (650 m2) including two laboratories for sample preparation, one storage area (RT, +4°C, -20°C, -80°C and liquid nitrogen) and offices for meetings, administration and archives. The CRB, partly funded by the regional council of Pays-de-la-Loire, has gained recognition IBISA in October 2008 by merging the five largest bio-collections in Nantes, including those from the 'institut du thorax'. It is also a member of the national network of bio-banks operated by the Inserm, which is candidate as 'infrastructure of excellence'. The direction of Nantes University Hospital has appointed a team project for the development of this structure, which includes one scientific coordinator, one project manager and future manager of the CRB, one quality engineer at the Institute of the thorax, one computer scientist, one lawyer, one purchasing manager, one clinical researcher, one assistant engineer and one laboratory technician. To ensure quality service, the CRB is currently establishing a system of quality management based on the establishment of adequate resources and appropriate security measure: compliance with the standard NF S 96-900 ; validated techniques for preparation of biological resources (including automated DNA extraction, RNA extraction, cell culture, immortalization of B-EBV cell lines, PBMC preparation, isolation of serum and plasma); secure rooms and equipments; qualified personnel ; implementation of control and security systems ; traceability of biological samples; ethical and legal aspects.
To facilitate technological transfer, the IDT has actively participated in creating the 'Atlanpole Biotherapies' competitiveness cluster, which associates regional biotech companies and academic research laboratories. 'Atlanpole Biotherapies' has the ambition to become a European reference for the development of therapeutic and diagnostic strategies and new products in the field of Biotherapies. *- ici mettre un mot sur notre participation au projet IHU (reprendre celui que Pierre est en train d'écrire pour le projet d'unité)*
The IDT has been for years a key player in translational research against cardiac arrhythmias. It has developed a specific clinical platform in tight connection with basic research, which was the basis for the Center of Reference for Rare Diseases created by the French Ministry of Health in 2004. This Center of Reference organizes care and follow-up of patients affected by hereditary rhythmic diseases and elaborates recommendations for diagnosis and treatment of these pathologies. In cooperation with the major European and International teams of the field, it has contributed to the change in the prognosis of hereditary diseases. As an example, the risk of sudden death in Long QT syndrome was 15%, it is now close to 0. Biomedical research investigations have since been extended to other hereditary cardiovascular diseases. The numerous articles produced in collaboration with other European and US groups illustrate the international dimension of its research. The leading team of the GénHi en Santé project has been involved in several Leducq Foundation Transatlantic Networks of Excellence ("Alliance against Sudden Cardiac Death", "Mitral Valve Disease: from Genetic Mechanisms to Improved Repair", "Leducq European-North American Atrial Fibrillation Research Alliance") and a EU-FP7 project ("EuTrigTreat").
Integrating clinical research, genetics, genome and cell biology, physiology and functional exploration in animal models inside a single structure led to the success of translational research at the IDT. We will extend our research model through GénHI En Santé, by merging our expertise and knowledge with those of epidemiologists, anthropologists, population geneticists, biostatisticians as well as other key players in biomedical research. GénHi en Santé will become the leading project of the IDT and its partners. We propose to build a new Laboratory of Excellence aiming to optimize biomedical research based on the exceptional biological resources provided by this cohort program.

3. STRATEGIE DE VALORISATION DES RESULTATS/ DISSEMINATION AND EXPLOITATION OF RESULTS

4. MANAGEMENT DU PROJET, GOUVERNANCE/ PROJECT MANAGEMENT

4.1. ASPECTS ORGANISATIONNELS / MANAGEMENT

4.1.1 QUALIFICATION DU COORDINATEUR DE PROJET /RELEVANT EXPERIENCE OF THE PROJECT COORDINATOR

(1 page maximum)

Fournir les éléments permettant de juger la capacité du coordinateur à coordonner le projet.

Génhi En Santé is a large ambitious integrated project that needs the active cooperation of several institutions and people originating from different fields. Hervé Le Marec MD PhD, the project coordinator, is professor of cardiology and expert in cardiac arrhythmias. He is the co-founder of the "institut du thorax" with Denis Escande. The "institut du thorax" is a large academic structure (800 people) which gathers physicians and scientists to a common objective: develop biomedical knowledge in the fields of cardiovascular, pulmonary and metabolic diseases and transfer it as quickly as possible to patient care. This objective needs the coordination of research, medical care and education, the three pillars of the "institut du thorax". Hervé Le Marec has been the director of the "institut du thorax" since 2007.

Since the early nineties, he has created and developed a research group dedicated to genetics of cardiac arrhythmias. In 2004 the French ministry of health lunched its first campaign for the certification of centers of reference for rare diseases. The group of cardiac arrhythmias in Nantes was one of the 30 centers that obtained the certification. Hervé Le Marec was the coordinator of the center. This center coordinates the activity of most of the French centers of competence dedicated to hereditary cardiac arrhythmias. It has been positively evaluated in 2009.

In 1997 Hervé Le Marec was nominated coordinator of clinical research of Nantes University Hospital and plays a major role in the development of this structure and the creation of the clinical research center recognized by INSERM and DHOS (CIC 04). In 2002 and 2006 he coordinated the second and the third five-year medical programs of Nantes University Hospital (2003-2007 and 2008-2012). In 2003 he was elected chairman of the medical board ("commission médicale d'établissement") of the University Hospital and conducted the medical strategy during six years.

To improve the coordination of clinical research in France and cooperation between hospitals, the French ministry of health decided to create interregional coordination (DIRC). The six university hospitals members of HUGO (Hopitaux Universitaires du Grand Ouest) decided to appoint Hervé Le Marec coordinator of this new structure. He created the structure and convinced all the members to create several networks that gathered expertise from the different hospitals. One of these networks was dedicated to epidemiology and genetics. Claude Férec was designated coordinator of this original network. After four years of coordination, DIRC Hugo is considered as a real success. Since its creation the number of national grants (PHRC) has doubled, placing HUGO as the second most successful structure after the region "Ile de France" (Paris).

Hervé Le Marec has an exceptional experience in coordinating programs and people coming from multiple areas of expertise. He has just completed his four-year delegate function for DIRC HUGO and renounced to his position as chairman of the medical board of Nantes University Hospital. His

aim is now to strengthen the "institut du thorax" and to anticipate the development of personalized medicine with innovative and integrated research projects such as GénHi En Santé.

4.1.2 MODALITES DE COORDINATION ET DE GESTION / COORDINATION MODALITIES AND MANAGEMENT

4.2. ORGANISATION DU (DES) PARTENARIAT(S) ENGAGE(S) OU POTENTIEL(S)/ PRESENT AND FUTUR PARTNERSHIPS ORGANIZATION

4.2.1 DESCRIPTION, ADEQUATION ET COMPLEMENTARITE DES PARTENAIRES / PARTNERS' DESCRIPTION, RELEVANCE AND COMPLEMENTARITY

Partner 1: UMR915 (Inserm / University of Nantes)

Created in April 2004, the institut du thorax (IDT) brings together care, teaching and research in the field of cardiovascular and pulmonary diseases at the Nantes University Hospital. The Inserm UMR915 hosts the basic research conducted within the IDT. For many years, the IDT has been a key player in the field of inherited cardiac arrhythmias. Researchers and clinicians at IDT discovered important new concepts by elucidating the mechanisms responsible for these pathologies. This is due not only to the efficiency of its molecular and clinical genetics group (H Le Marec, V Probst and JJ Schott) but also because of the synergistic studies conducted in parallel on the mechanisms of cardiac arrhythmias, based on molecular and cellular physiology, cell biology and transgenic animals. The IDT is one of the very few places worldwide where all these abilities are gathered in the same laboratory. New research programs have been initiated on the genetics and physiopathology of cardiac valvulopathies and have already resulted in the discovery of the first gene responsible for mitral valve disease. Note that the IDT has recently recruited a clinician renowned as specialist in heart valve physiopathology, T Le Tourneau, to strengthen its expertise on those chronic conditions.
Cardiovascular risk factors are major contributors to cardiovascular morbidity and mortality. At the IDT, vascular research programs aim at elucidating the physiopathological mechanisms underlying major vascular diseases and to develop new therapeutic strategies. Team leaders P Pacaud and G Loirand are key players in the elucidation of the role signaling pathways in arterial smooth muscle cells and contribute to the discovery of new therapeutic targets in hypertension. They have developed translational projects, based on its close interaction with interventional cardiologists. This team has recently developed remarkable research capacities at the frontier of clinical science (B. Cariou) and basic research (P. Costet) on dyslipidemia. For years, they have conducted kinetic studies in patients using stable isotopes and mass spectrometry analysis. Using specific population, they have contributed to discover a major gene involved in familial hypercholesterolemia.
The third team of our unit conducts research projects in the field of genomics, cell and gene therapy. The aim is to produce new diagnostic and therapeutic tools for cardiovascular diseases. Two new Avenir teams have been recently created in the Unit. The first one, "respiratory diseases" (A Magnan), was created in 2008 and drives translational research projects on the role of CD8+ lymphocyte in asthma and on pulmonary transplantation. The second one, "genetic variations and sudden death" (R Redon), was created in 2010 and aims at identifying new genetic risk factors for sudden death by new genomic approaches.

Partner 2: Inserm UMR 613

The first research structure in Brest opened in 1996: it was an Inserm Research Contract ('CRI') dedicated to human molecular genetics, a then emerging research specialty,. Originally, research

was mostly devoted to the study of CFTR gene mutations causing cystic fibrosis, a disease particularly common in Brittany. In the late nineties, at the time when many genes involved in disease were discovered, we initiated new genetic investigations on pathologies such as chronic pancreatitis and haemochromatosis. The joint team UMR 613 was then created, associating the Inserm, the 'Université de Bretagne Occidentale' and the French Blood Agency (EFS). This new organization enabled the recruitment of additional researchers and engineers and the emergence of new research topics. We also started to collect genetic material from large groups of patients, an initiative from which we have since developed ambitious research programs in genetic epidemiology. Our projects are now moving from discovering gene defects to better characterizing gene function. We aim to improve our understanding of genotype-phenotype relationships as well as fine regulation of gene function.
The research team - Inserm UMR 613 "molecular genetics-genetic epidemiology" - comprises 25 permanent clinicians and researchers. It includes five research groups working on: functional genetics; yeast as a model for gene dysfunction; alternative splicing and applied cancerology; gene and cell therapy; channelopathies and calcium signaling. By integrating molecular genetics, epidemiology, functional genomics and meta-analysis, our objective is to generate new insights into the origin and functional consequences of disease-causing mutations. Our translational research program is now evolving toward complex diseases, such as hip dislocation, with the aim to decipher the complex relationships between genetic and environmental factors influencing disease risk.

Partner 3: CHU de Nantes

The University Hospital of Nantes (CHU de Nantes) has been supporting biomedical research for twenty years. In partnership with the Inserm and the University of Nantes, it has played a major role for the early emergence of translational research in Nantes. The common structure dedicated to the management of clinical research (DRC) was markedly reinforced in the late nineties and the Department of Cardiology of the Hospital was one of the three founders of a multi-thematic centre for clinical research (CIC), which was recognized by INSERM and DHOS in 20O1. In 2004, the Hospital played also a key role in the creation of the "Institut du Thorax" (IDT), a large structure that is now gathering 5 clinical departments, a clinical structure for cardio-thoracic explorations, a clinical research platform (CIC 04 DHOS/INSERM), 3 centers of reference for rare diseases and the UMR 915. The IDT became in 2006 one of the five French Thematic Centers for Research and Care (CTRS) created by a joined call from the French Ministries of Research and of Health. The cardio-thoracic branch of the CIC is part of the IDT. It includes 14 nurses or technicians dedicated to clinical research. The salaries of most of them are provided by private or public contracts. They are able to conduct large-scale studies, in conformity with good clinical practice. This structure has conducted preliminary works on aortic stenosis, mitral valve prolapse and cardiac conduction diseases. It will constitute a strong and effective infrastructure supporting "GenHi En Santé".
The Hospital has also been instrumental in the coordination of clinical research in Western part of France: Hervé Le Marec, the director of the IDT, was the first coordinator of clinical research activities in western France (HUGO, for 'Hôpitaux Universitaires du Grand Ouest') and played a major role in the creation of the HUGO network in genetic epidemiology. In response to the needs of structures such as the IDT and to support the creation of large cohorts of patients, the Hospital has decided the creation of a centre for biological resources (CRB). The IDT was an active partner at every step of this development: creation of the CRB, recruitment of dedicated staff, procedure validation and development of every tool required for cohort bio-banking (preparation, storage and databasing). Brand new facilities will be open in summer 2011 and will be ready to manage the bio-collections generated by GénHi En santé. During the last 6 years, the clinical genetics group has developed a specific database, Integralis, which is accessible through a web interface and has been approved by the CNIL. Integralis can manage thousands of individuals and includes a specific package for the management of genealogical information, enabling the creation of very large genealogic trees. Note that Integralis and the CRB database are fully compatible.

In summary, the University-Hospital of Nantes - and particularly the "Institut du Thorax" - has set-up every condition needed for the successful management of large cohorts such as "GénHi En Santé".

Partner 4: UMR 6578 (EFS / CNRS / Université de la Méditerranée)

Created in 2000, the French Blood Agency (EFS) is the only organization responsible for blood transfusion in France. Under the management of the French health ministry, its main task is to ensure national autonomy in blood products, under optimal security and quality conditions. The EFS is organized in 17 regional institutes, including 3 in overseas territories. At the EFS, 9700 collaborators run 154 fixed collection sites and organize 40,000 mobile blood collections per year. Each year, this unique organization collects 3 million donations from 1.7 million donors (including 420,000 new volunteers) to treat one million diseased people. The EFS is driven by strong ethical values and strengthened by cutting-edge technologies to ensure efficient and secure collection, qualification, preparation and distribution of blood products.
As a public health organization, the EFS is mandated to promote research in immunology, genetics, microbiology in relation to human and social sciences. Indeed, better understanding human societies across a territory with their own genetic and behavioral characteristics can help in deciphering specific factors influencing the decision to donate blood. In particular, previous surveys indicate that social factors can influence the risk of virus infection as much as biological ones.
The research unit UMR 6578, strongly supported by the EFS, is focused on Human Evolution and Diversity. Our research team, "Genetic Anthropology and Viral Biodiversity", aims at studying the genetic diversity of humans and viruses transmitted by blood. Two research themes are developed within the team. The group "Geographical Immuno-Hematology", relying on the expertise of EFS in erythroid and platelet markers, studies human genetic diversity among those markers in order to optimize therapeutic strategies using human body products and to learn more about human historical migrations by multidisciplinary approaches. The group "Viral emergence and co-evolution: virus genomics and human behavior" is focused on C-hepatitis and other viruses transmitted by emerging arthropods or susceptible to become transfusion hazards, in parallel with pathogen detection in ancient biological samples.

Partner 5: Inserm/UPMC UMR 707

The Epidemiology of Allergic and Respiratory diseases (EPAR) department at UMR-S 707, directed by Dr Isabella Annesi-Maesano, is one of the France's leading centres for epidemiological research on allergic and respiratory diseases, with particular emphasis on effects related to air pollution. EPAR has conducted several population-based surveys in order to investigate risk factors for allergic and respiratory diseases. Risk factors taken into account have been: genetic, individual, environmental, socio-economic, and demographic. Studies implemented by EPAR include among others the 6 Cities Study the French contribution to the International Study of Asthma and Allergies in Childhood (ISAAC) which brought original results on the association between indoor and outdoor air-pollution at home proximity, in classrooms and home and childhood asthma and allergies, the LARES (Large analysis and review of European housing and health status) project in the frame of the WHO Housing on health effects of indoor air pollution. Ongoing studies of EPAR department deal with the the effects of early life environment on the development of immunity, asthma and allergy in newborns (EDEN Birth Cohort Study), the effects of rural environment and pollution on asthma and allergy (FERMA Study), the gene environment interaction in asthma and allergies (EGEA Study), and. Since 2009, the EPAR department is leading the DG-Sanco funded project GERIE study on health effects of air quality in elderly living in nursing homes and contributes to the DG-Sanco funded HESE (Health Effects of School Environment) study and the related intervention study HESEINT. Pollutants of interest have been numerous including airborne particulate matter (both mass and number) and emerging VOCs and polycyclic aromatic hydrocarbons and various environments including micro-environments like dwellings and classrooms have been considered.

In all the projects, the epidemiological investigation has been interfaced with metrological studies through modelisation. Recent works in EPAR have focused on the quantification of human exposure to air pollutants and health impacts of indoor and outdoor air pollution by assessing the validity of biomarkers to estimate exposure and on gene-environment interactions taking into account transcriptomics. The EPAR department has contributed to international debate on climate change and allergic/respiratory health with position papers. EPAR is also collaborating in WHO ARIA and GARD initiatives conducting epidemiological studies on the prevalence, severity and environmental determinants of allergic and respiratory diseases in Africa and very recently in DG-Sanco funded SINPHONIE and FP7 funded MedAll on air quality in schools and related effects and environmental determinants of allergy respectively. Biobanks have been or are being constituted for each study. The department hosts various researchers (biostatisticians, environmental epidemiologists, metrologists), distinguished clinicians and doctoral students for a total of 22 personnels. The department is situated in Medical School St-Antoine and has satellites cells in 3 Parisian hospitals (St-Antoine, Tenon, Trousseau).

Partner 6: University hospital of Brest (CHRU)

At the university hospital of Brest, the Laboratory of Molecular genetics and Histocompatibility is specialized in molecular diagnosis for disorders, which are highly prevalent in Brittany (e.g. cystic fibrosis, haemochromatosis) or particular topics of medical collaborators (e.g. chronic pancreatitis, deafness, polycystic kidney disease). In 2001, our laboratory was recognised by the French Ministry of Health as a national reference centre for molecular diagnosis of cystic fibrosis. Such a distinction has since also been obtained for haemochromatosis, chronic pancreatitis and deafness and the laboratory is now member of several clinical research networks in Europe.
The development of new genetic tests and their transfer to routine diagnosis has always been a major focus for the laboratory. We have progressively developed an expertise for innovative tools such as DGGE, DHPLC, HRM, QFM-PCR and CGH. Accuracy of our strategies is exemplified by cystic fibrosis, where we have proved our capacity to detect up to 99% of the mutated alleles (more than 25% of the known mutations in the CFTR genes have been identified in the laboratory). Another topic of interest has been designing effective procedures for risk assessment, prevention, treatment and genetic counseling. We have been pioneers in the development of epidemiological studies, as exemplified by reports on the incidence and special distribution of CTFR mutations in our geographic area. This has practical incidences, such as optimization of diagnostic kits.
After 20 years of an intensive work in the field of genetics, we have elaborated a translational research program that integrates molecular genomics, epidemiology and functional genomics. This has been facilitated by the creation of an Inserm U613 team in 2001 and the recruitment of young and senior scientists.

Partner 7: CHU de Rennes A COMPLETER/EDITER

In the field of cardiovascular diseases, the University Hospital of Rennes is particularly involved in the management of cardiac arrhythmia and valvular diseases. The department of cardiovascular surgery, as a regional referent center, follows, through a prospective database including pre- and post-operative data, a large cohort of patients requiring valvular surgery, either for aortic valve stenosis or mitral regurgitation, for more than 30 years. This database was already used to conduct cooperative projects to characterize populations on phenotypic and genotypic aspects. The clinical research program of the department of cardiology is oriented to the management of cardiac rhythm disorders and heart failure especially in the fields of implantable cardiac devices and genetic arrhythmic diseases. Theses activities are conducted in close collaboration with the laboratory of signal and image processing at the University of Rennes I (Inserm 642 unit) for developing and evaluating new concepts and new products. The group is accredited by the French ministry for Health (DGOS) and Inserm as a CIC-IT (clinical evaluation center for technologic innovations) to initiate and conduct projects in collaboration with industry and start-up companies,

driving large multicentre trials, pilot studies and exploratory projects supported by ANR (Tecsan program). As a "competence center", the group works for many years in collaboration with the group of Pr Le Marec at the University Hospital of Nantes ("Reference center") for the management of genetic disorders. The group is involved in national and international projects as associated or promoting center.

Associate 8: Lluis Quintana-Murci, CNRS/Institut Pasteur

Lluis Quintana-Murci is research director and head of a mixed CNRS research unit at the Institut Pasteur of Paris. He received his PhD in Human and Population Genetics at Pavia University, then trained at the University of Oxford and the University of Arizona. LQM's laboratory covers two highly inter-related areas of research: the study of human genetic diversity at the population level, from which one can infer human origins and population structure, and the study of diversity in genomic regions involved in immune response or host-pathogen interaction, with which one can unmask the footprints of natural selection. Inferences on the action of natural selection in the human genome provide a powerful tool for predicting genomic segments potentially associated with disease. As infectious diseases have exerted, and exert, strong selection pressures, the identification of selected loci or variants of immunity-related genes may provide insight into immunological defence mechanisms and highlight host pathways playing an important role in pathogen resistance. The studies carried out in LQM's laboratory, based on a multi-locus approach and considering the different forces shaping the patterns of human genome variability, are helping to understand better the complex demographic history of our species as well as deepen our understanding of the extent to which pathogens have exerted selective pressures on the variability of the human genome. For this, this laboratory combines molecular and population genetics approaches, with computational modelling and development of new statistical frameworks. In the context of this proposal, LQM will provide with the expertise of his laboratory in study-design of population genetic cohorts, statistics, knowledge of population history and all the background needed to cover as much as possible the genetic diversity of the different French populations. LQM is author of more than 80 peer-reviewed publications in high impact factor journals, such as Nature Genetics, Nature Immunology, Nature Reviews Genetics, Science, The Lancet and the American Journal of Human Genetics, and 6 book chapters. Among the numerous awards, he has received the "Marie Curie Fellowship" from the European Union, the European Prize for "Impact of Genetics on Science and Society", the CNRS Ivory Medal, prizes from the French Academy of Sciences, and the Debiopharm- EPFL Life Sciences Award (Switzerland).

Associate 9 : Emmanuelle Génin, Inserm UMR 946 A DEVELOPPER

Emmanuelle Génin, research director at Inserm UMR946, has strong expertise in statistical genetics and genetic epidemiology. EG and her colleagues have contributed to many projects aiming to discover genes causing monogenic diseases - in particular rare recessive diseases by homozygosity mapping. They have developed an original method to estimate inbreeding coefficients and identify regions of homozygosity by descent using the genomic information from individuals. They are currently evaluating and extending this method to find rare recessive variants involved in complex diseases by comparing regions of identity by descent in cases and controls. EG is also expert in the study of isolated populations and the statistical methods that can be used in this particular context.

Associates 10 and 11: Agences Régionales / Observatoires Régionaux de Santé (ARS/ORS)

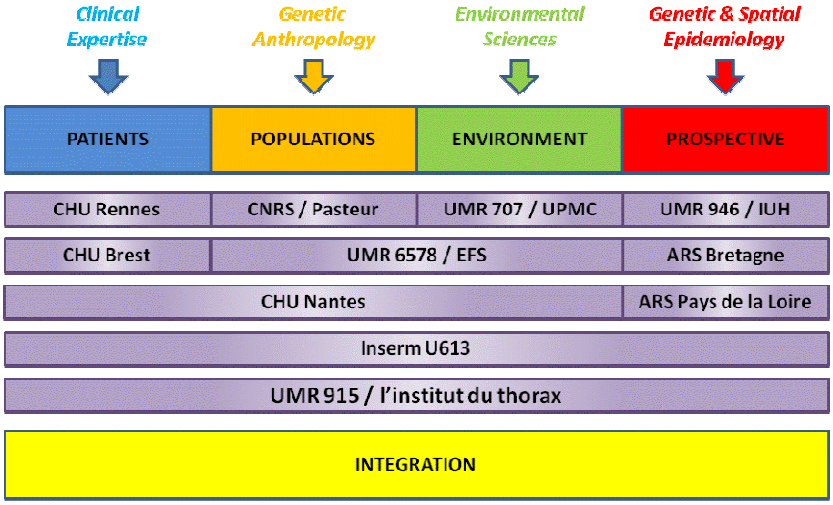
Created by the French Ministry of Health in April 2010, the Regional Health Agencies (ARS) are responsible for implementing regional public health policies, taking into account the specificities of each region and its territories. Their actions are aimed at improving the health of the population and optimizing health system efficiency. They are the keystones of the new organization set up under the Act "Hospital Patient Health Territories" of July 21, 2009 (Article 118). The ARS Pays de

la Loire is headed by Marie-Sophie Desaulles who is assisted by dedicated teams involved in the following areas: Prevention and Health Promotion, Support and Care, Quality and Efficiency and the Regional Health Plan. The ARS Bretagne is headed by Alain Gautron who relies on four specialized and two support management teams: Strategy, Performance and Evaluation; Healthcare and Support; Public Health; Health Democracy and Partnerships; Resources; Finance. In each region, the ARS organization ensures transparency and cooperation to adapt to health issues by applying health policies and consulting with other public bodies as well as user representatives.
Regional Health Observatories (ORS) are non-profit organizations, aiming to produce and disseminate regional health intelligence in order to inform health policies and medical practice. There are 26 ORS in French, four of which are in overseas territories, which are all coordinated by a National Federation (FNORS in French). As a whole, ORS have published more than 2000 reports since their creation in the early eighties. The ORS of Bretagne and Pays-de-la-Loire have a longstanding experience of public health and institutional databases, such as information gathering bodies and registries. In Pays-de-la-Loire and Bretagne, each ORS, headed by Dr Anne Tallec and Dr Isabelle Tron respectively, employs 10 persons, of which 7 are dedicated to analytical studies. Those multi-disciplinary teams comprising statisticians, geographical analysts, sociologists and economists are responsible for specific surveys on health matters, monitoring reports, epidemiological studies and assessment of health policies. By their organization, ORS are key partners in processes aiming to: (i) identify geographical areas showing high prevalence for pre-defined diseases; (ii) select additional diseases displaying particular demographical and geographical patterns. At last, the FNORS is perfectly adapted to the extension of GénHi En Santé to the entire French territory.

Complementarities between partners and participants

GénHi En Santé involves seven institutional partners, which will work in close collaboration to construct the biological resources described in this proposal. The Inserm UMR 915, in tight connection with the Inserm UMR 613, will coordinate the overall project and drive the general management. Both research units are currently constructing a new laboratory of excellence (Labex), which will build his new research programs based on the biological resource constituted by GénHi en santé by gathering many basic and clinical researchers located in Bretagne and Pays-de-la-Loire. The CHU of Nantes, Rennes and Brest will be responsible for the recruitment and follow-up of patients with chronic pathologies. These three hospitals have already initiated many clinical investigations in collaboration and have set up strong connections with regional networks of practitioners. These connections will be instrumental to keep contact with the patients recruited in GénHi En Santé and to collect clinical information on disease evolution between first patient inclusion and follow-up. The CHU of Nantes, through its CRB, will be responsible for the preparation, storage and management of every biological sample collected during the program. The CRB of Nantes will also manage the bio-collection from healthy individuals recruited in parallel by the EFS, which has accepted to open its infrastructure to GénHi En Santé. The involvement of the EFS is a warrant of the effective construction of a large national cohort of healthy individuals representing the regional French population. Following our pilot study in western France, EFS aims at building a new national centre for biological resources. This future CRB will progressively take full responsibility for the management of the national cohort of healthy individuals initiated by GénHi En Santé. To start investigating the relative effect of the environment on chronic disease, the UMR 707 will manage a pilot study on the role of air pollution on respiratory disease, in collaboration with the CHU of Nantes. This study is a first step towards better integrating genetic and environmental investigations in biomedical research.
Four associated participants will share their expertise and external resources to optimize the design and efficiency of the project. Lluis Quintana-Murci and Emmanuelle Génin are international specialists in population genetics and genetic epidemiology. By sharing their expertise, they will help in optimizing the design of our recruitment. The ARS/ORS of Bretagne and Pays-de-la-Loire

will open their healthcare databases and enable us to construct new tools in spatial epidemiology. This will be critical in identifying new clusters of chronic diseases in western France.
In summary the involvement of experts in anthropology, population genetics, epidemiology, medical genetics, environmental sciences and clinics warrant the GénHi en santé will optimize the recruitment of patients with chronic disease as well as healthy individuals in western France. The biological resource developed by GénHi en santé will be available to the scientific community for future investigations in basic and clinical research. The pilot study in western France will set up a new model for biomedical research, model to be extended to the entire French territory.



4.2.2 QUALIFICATION, RÔLE ET IMPLICATION DES PARTENAIRES / QUALIFICATION, ROLE AND INVOLVEMENT OF INDIVIDUAL PARTNERS

Qualification des personnes : préciser leurs activités principales et leurs compétences propres. Pour chaque partenaire remplir le tableau ci-dessous

Partenaire/Partner	Nom/Surname	Prénom/First name	Poste/Position	Discipline/Domain	Organisme de rattachement ou entreprise/Organization or company	Rôle dans le projet (4 lignes max.) / project' involvement (max 4 lines)
Exemple	LATIFI	Fatima	Professeur		CNRS	

5. IMPACT MEDICO-ECONOMIQUE ET SOCIO-ECONOMIQUE DU PROJET / MEDICO-ECONOMIC AND SOCIO-ECONOMIC IMPACT OF THE PROJECT

In its design, GénHi En Santé includes approaches in spatial epidemiology, genetics of chronic diseases with high medical and economic impact, population genetics and analysis of the environmental impact on disease expression. The project starts with pilot projects for which the project partners have recognized expertises. The long term goal is broader. GénHi En Santé is designed to better understand individual risks, drive biomedical research toward broader directions to identify new biomarkers and therapeutic targets in chronic diseases with high-impact health. It also aims to clarify the relationship between genetic predisposition and environment and open up to social and humanities sciences. This includes the history of our population but also the societal impacts of disease risk identification in regional populations. These objectives require different skills from many scientific fields. Some of them are not yet incorporated in the project. One objective of the project coordinators and the governing board will be, with the advices of the SAB, to ensure the openness of GénHi En Santé to new actors from the scientific community who wish to participate in the project, bringing new skills, to develop new programs and use data already collected.

In monogenic genetic diseases, translational research from bedside to bench led to the identification of genetic variants then to understanding the molecular mechanisms involved and the development of effective strategies for prevention and treatment. This is true, not only for inherited cardiac arrhythmia, but also for diseases such as Marfan syndrome for which the scientific community did not imagined, still a few years ago, the possibility of developing preventive therapy.

Chronic diseases are obviously more complex. They are likely results of progressive remodelling mechanisms leading to final phenotypes characterizing pathologies. The mechanisms involved in the development of most diseases are still very incompletely known. It is necessary to identify new strategies for biomedical research. The ambitious scientific challenge of the teams involved in the project GénHi En Santé is that the identification of the rare variants involved in the development of chronic diseases will lead, through a modern translational research, to the identification of the mechanisms involved in the molecular, cellular and tissue remodelling. This research, from an initial genetic defect, to a final phenotype should lead to the identification of new biomarkers as well as new therapeutic targets and preventive strategies.

Disease epidemiology, better understanding their natural history and characterizing risk factors will undoubtedly have a major impact on strategies for improving health and medical practices. Chronic diseases are a major public health issue. Among them, cardiovascular diseases represent the second leading cause of death in France and a significant economical burden. Almost 35 billion euros are devoted to the treatment of patients affected by cardiovascular disease - regardless of their classification as chronic disease (ALD) by the French National Health System (Sécurité Sociale, managed by the CNAM). The cost even reaches 46 billion Euros when including patients with cardiovascular complications of diabetes. Overall, between 2005 and 2008, chronic diseases have accounted for 80% of the spending growth, with high predominance of cardiovascular diseases. Considering dyslipidemia as a major risk factor for cardiovascular disease, it is also important to note that lipid-lowering drugs alone represented an expenditure of 1 billion Euros in France in 2008.

The directions of the ARS of Bretagne and Pays-de-la-Loire are very favourable to the project and will be associated with the program whenever necessary. They will provide Génhi En Santé with precious healthcare information, since a national agreement has been signed with the CNAM in terms of long-term diseases (ALD) surveyed by health plans or patient care. GénHi En Santé aims

at identifying local environmental risk and genetic predisposition to chronic pathologies. It will provide decision makers with new tools that will influence their choice when implementing health polices, in particular primary and secondary prevention strategies. Génhi en Santé will also lead to more targeted - or even personalised - therapeutic protocols.

6. EVALUATION FINANCIERE DU PROJET/ FINANCIAL ASSESSMENT

Justification scientifique et financière du coût complet du projet (fonctionnement dont personnel, et équipement) / adaptation des coûts de coordination

(Se référer au Règlement relatif aux modalités d'attribution des aides au titre de l'appel à projets Cohortes, ainsi qu'au texte de l'appel à projets Cohortes).

Ces éléments sont nécessaires pour la préparation du document de soumission A.

Chaque partenaire justifiera les moyens qu'il mettra en œuvre, en distinguant les différents postes de dépenses.

ANNEXES / APPENDICES

6.1. REFERENCES BIBLIOGRAPHIQUES DE L'ETAT DE L'ART/STATE OF ART REFERENCES

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Partner 7: CHU de Rennes

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Associate 8: Lluis Quintana-Murci, CNRS/Institut Pasteur

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6.3. DEVIS / ESTIMATE

Insérer la copie des différents devis nécessaires à la justification financière (équipements, prestation de service…).