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Understanding the Pathophysiology of Intracranial Aneurysm: The ICAN Project

Romain Bourcier, Stéphanie Chatel, Emmanuelle Bourcereau, Solène Jouan, Hervé Le Marec, Benjamin Daumas-Duport, Mathieu Sevin-Allouet, Benoit Guillon, Vincent Roualdes, Tanguy Riem, et al.

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Neurosurgery

Understanding the pathophysiology of intracranial aneurysm: The ICAN Project --Manuscript Draft--

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| Abstract: | <p>Background: Understanding the pathophysiologic mechanism of intracranial aneurysm (IA) formation is a prerequisite to assess the potential risk of rupture. Nowadays, there are neither reliable biomarkers nor diagnostic tools to predict the formation or the evolution of IA. Increasing evidence suggests a genetic component of IA but genetics studies have failed to identify genetic variation causally related to IA.</p> <p>Objective: To develop diagnostic and predictive tools for the risk of IA formation and rupture.</p> <p>Methods: The French ICAN project is a non-interventional nationwide and multi-centric research program. Each typical IA of bifurcation will be included. For familial forms, further IA screening will be applied among first-degree relatives. By accurate phenotype description with high-throughput genetic screening, we aim to identify new genes involved in IA. These potential genetic markers will be tested in large groups of patients. Any relevant pathway identified will be further explored in a large cohort of sporadic carriers of IA, which will be well documented with clinical, biological and imaging data.</p> <p>Expected outcomes: Discovering genetic risk factors, better understanding the pathophysiology and identifying molecular mechanisms responsible for IA formation</p> |

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| | <p>will be essential bases for the development of biomarkers and identification of therapeutic targets.</p> <p>Discussion: Our protocol has many assets. A nationwide recruitment allow for the inclusion of large pedigrees with familial forms of IA. It will combine accurate phenotyping and comprehensive imaging with high-throughput genetic screening. Last, it will enable exploiting meta-data to explore new pathophysiological pathways of interest by crossing clinical, genetic, biological and imaging information.</p> |
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| Question | Response |
| <p>Significance of the Work:</p> <p>Please include a brief statement summarizing the significance of the work and in particular how it differs from and advances existing literature.</p> | <p>We launch an ambitious multicenter project (I CAN) addressing the pathophysiology of IA. To date, no transmitted variation related to familial forms of IA has been published. Our protocol has many assets. First, our nationwide recruitment allow for the inclusion of large pedigrees with familial forms of IA. Second, it will combine accurate phenotyping and comprehensive imaging with high-throughput genetic screening. Last, it will enable exploiting meta-data to explore new pathophysiological pathways of interest by crossing clinical, genetic, biological and imaging information. This should lead us to identify the biological pathways involved in the formation of IA. Currently no blood test has been established to help in diagnosing IA, and there is still no way to predict the natural history of an IA. Discovering relevant biomarkers would undoubtedly facilitate early detection, risk assessment and therapeutic monitoring of IA.</p> |
| <p>Compliance with Research Reporting Guidelines: <i>Neurosurgery</i> endorses several reporting guidelines and requires authors to submit their research articles in accordance with the appropriate guideline statement(s) and checklist(s). Completed applicable checklists and flow diagrams must be included with submissions.</p> <p>Research articles that must be submitted according to the appropriate reporting</p> | <p>Yes - Submission Adheres to Appropriate Reporting Guideline(s) and Applicable Checklists/Materials Are Included</p> |

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| <p>guideline(s) include, but are not limited to: randomized trials, systematic reviews, meta-analyses of interventions, meta-analyses of observational studies, diagnostic accuracy studies, and observational epidemiological studies (eg, case series, cohort, case-control, and cross-sectional studies). Consult the EQUATOR Network, which maintains a useful, up-to-date list of guidelines as they are published, with links to articles and checklists: http://www.equator-network.org.</p> <p>Please confirm below that information is reported according to the relevant reporting guideline(s) and any required materials are included with the submission:</p> | |
| <p>Please indicate which reporting guideline(s) the study adheres to (eg, STROBE, PRISMA, CONSORT). as follow-up to "Compliance with Research Reporting Guidelines: <i>Neurosurgery</i> endorses several reporting guidelines and requires authors to submit their research articles in accordance with the appropriate guideline statement(s) and checklist(s). Completed applicable checklists and flow diagrams must be included with submissions.</p> <p>Research articles that must be submitted according to the appropriate reporting guideline(s) include, but are not limited to: randomized trials, systematic reviews, meta-analyses of interventions, meta-analyses of observational studies, diagnostic accuracy studies, and observational epidemiological studies (eg, case series, cohort, case-control, and cross-sectional studies). Consult the EQUATOR Network, which maintains a useful, up-to-date list of guidelines as they are published, with links to articles and checklists: http://www.equator-network.org.</p> <p>Please confirm below that information is reported according to the relevant reporting guideline(s) and any required materials are included with the submission:"</p> | <p>STROBE</p> |
| <p>Statistical Analysis:</p> <p>For manuscripts that report statistics, the Editor requires that the authors provide evidence of statistical consultation or expertise.</p> <p>If your article includes statistics, has the</p> | <p>Not Applicable - Article does not report statistics.</p> |

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| <p>information reported been evaluated by an expert?</p> | |
| <p>IRB/Ethics Approval:</p> <p>Please indicate if your study has received institutional review board/ethics approval. If yes, these materials are readily available should the Editor request them.</p> | <p>Yes</p> |
| <p>Funding:</p> <p>Study Protocols must have received grant funding from a major extramural funding body at the time of submission. Please provide the name of the sponsor/funding agency below.</p> | <p>This study was supported by a grant from the French Ministry of Health (ANR-DGOS 2015), the INSERM (UMR 1087) and the GENAVIE foundation</p> |
| <p>Trial Registration:</p> <p>Please provide the trial registration information for the study below. Include the trial registry, along with the unique identifying number.</p> | <p>The ICAN project is a non-interventional clinical research, approved by the Institutional Review Boards and Ethics Committees of Nantes. Informed written consent has been obtained from all patients. The ICAN study group is constituted in France of one coordinating center (University Hospital of Nantes), one genotyping center (Inserm UMR 1087) and 23 clinical centers of recruitment. This study has been registered in Clinical Trial under the reference RC15_0304.</p> |

Dear Mr Nelson M.Oyesiku,

In hopes of being published in your journal, we are pleased to offer you a proposal of our work, entitled "**Understanding the pathophysiology of intracranial aneurysm: The ICAN project**"

To this day, despite enormous progress in sequencing, the field of genetics has not been able to elucidate any signaling pathway involved in intracranial aneurysm formation.

We have developed a nationwide collaborative project gathering neuroradiologists, neurosurgeons, neurologists ,geneticists, cardiologists, ophthalmologists, vascular specialists and biologists with the aim of discovering genes and pathways involved in this major health problem.

Our project addresses the urgent and obvious need to develop diagnostic and predictive tools of risk of IA formation and rupture. Discovering genetic risk factors, better understanding the pathophysiology and identifying molecular mechanisms responsible for IA formation will be essential bases for the development of biomarkers and identification oftherapeutic targets

Our study raises important questions and encourages novel reflection on the issue of physiopathology of intracranial aneurysms.

Others works stemming from this project are to be published, particularly with the first results of genetic analysis of the most informative families.

All authors have seen and approved the content and have contributed significantly to the work. No author has any related conflict of interest to disclose regarding this work.

Our study should be frequently cited and could represent a significant contribution to the journal. Finally, this manuscript has not been submitted elsewhere.

We hope you find our manuscript suitable for publication.

Sincerely,

RomainBourcier

Understanding the Pathophysiology of Intracranial Aneurysm: The ICAN Project

Romain Bourcier, MD, MSC¹⁻², Stéphanie Chatel, PhD², Emmanuelle Bourcereau, BSC², Solène Jouan, BSC¹, Hervé Le Marec, MD, PhD²⁻³, Benjamin Daumas-Duport, MD, MSC¹, Mathieu Sevin-Allouet, MD, PhD⁴, Benoit Guillon, MD⁴, Vincent Roualdes, MD, MSC⁵, Tanguy Riem, MD⁵, Bertrand Isidor, MD, MSC⁶, Pierre Lebranchu, MD, PhD⁷, Jérôme Connault, MD, MSC⁸, Thierry Le Tourneau, MD, PhD²⁻³, Alban Gaignard, PhD², Gervaise Loirand, PhD², Richard Redon, PhD², Hubert Desal, MD, PhD¹⁻², and the ICAN Investigators

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ABSTRACT

Background: Understanding the pathophysiologic mechanism of intracranial aneurysm (IA) formation is a prerequisite to assess the potential risk of rupture. Nowadays, there are neither reliable biomarkers nor diagnostic tools to predict the formation or the evolution of IA.

Increasing evidence suggests a genetic component of IA but genetics studies have failed to identify genetic variation causally related to IA.

Objective: To develop diagnostic and predictive tools for the risk of IA formation and rupture.

Methods: The French ICAN project is a non-interventional nationwide and multi-centric research program. Each typical IA of bifurcation will be included. For familial forms, further IA screening will be applied among first-degree relatives. By accurate phenotype description with high-throughput genetic screening, we aim to identify new genes involved in IA. These potential genetic markers will be tested in large groups of patients. Any relevant pathway identified will be further explored in a large cohort of sporadic carriers of IA, which will be well documented with clinical, biological, and imaging data.

Expected Outcomes: Discovering genetic risk factors, better understanding the pathophysiology and identifying molecular mechanisms responsible for IA formation will be essential bases for the development of biomarkers and identification of therapeutic targets.

Discussion: Our protocol has many assets. A nationwide recruitment allows for the inclusion of large pedigrees with familial forms of IA. It will combine accurate phenotyping and comprehensive imaging with high-throughput genetic screening. Last, it will enable exploiting meta-data to explore new pathophysiological pathways of interest by crossing clinical, genetic, biological, and imaging information.

Keywords: Aneurysm, Familial, Genetics, Pathophysiology

Short Title: The ICAN Project

GENERAL INFORMATION

Title: Understanding the pathophysiology of intracranial aneurysm: The ICAN project

Study Dates: May 2016 to May 2019; this study is ongoing.

Funding Agencies: This study was supported by a grant from the National Research Agency and the French Ministry of Health (ANR-DGOS 2015), Agence Nationale de la Recherche, 50, avenue Daumesnil, 75012 PARIS, 01.78.09.80.00 – DGOS 14 Avenue Duquesne, 75007 Paris, France, 01 40 56 60 00, The French Regional Council of Pays de la Loire (RFI VaCaRMe), Hôtel de la région 1, rue de la Loire 44966 Nantes Cedex 9, 02 28 20 50 00, and The Fondation GENAVIE 8 Quai Moncoussu, 44000 Nantes, France, 02 28 08 01 13.

Registry: (Clinical Trial) RC15_0304

Investigators: The project Management is ensured by Dr. Romain Bourcier MD and Pr. Hubert Desal MD Ph D from the Department of Neuroradiology of the Centre Hospitalier Universitaire of Nantes, 8 Quai Moncoussu, 44000 Nantes, France.

L'institut du thorax, INSERM Unit 1087, CNRS, Centre Hospitalier Universitaire of Nantes, 8 Quai Moncoussu, 44000 Nantes, France, 02 28 08 01 13, particularly the director Richard Redon PhD, ensures the genetic analysis. The co-director of the unit, Gervaise Loirand PhD is responsible of the functional analysis for candidate genes.

The ICAN study group is constituted in France of 1 coordinating centre (Centre Hospitalier Universitaire of Nantes), 1 genotyping centre (L'institut du thorax, INSERM Unit 1087, CNRS, Centre Hospitalier Universitaire of Nantes) and 22 clinical centers of recruitment.

RATIONALE AND BACKGROUND INFORMATION

Intracranial aneurysms (IA) are acquired cerebrovascular abnormalities affecting 3% of the general population (mean age 50 years).¹ They are characterized by a localized dilation and wall thinning in typical locations in intracranial arteries². The most notorious and deleterious complication of an IA is the rupture, resulting in subarachnoid hemorrhage that can lead to severe disability and death³. Unfortunately, there are neither reliable biomarkers nor diagnostic tools to predict the formation and/or the evolution of an IA in any given individual. Current treatments are more or less invasive (microsurgical or endovascular treatment) with a risk of procedural morbidity/mortality⁴.

Although the pathogenesis of IA has been the subject of several studies for many years, the mechanisms underlying their formation, growth and eventual rupture are largely unknown⁵. IA are mostly acquired lesions resulting from a defective vascular wall response to local hemodynamic stress⁶. The structural deterioration of the arterial wall involves inflammation and tissue degeneration with degradation of the extracellular matrix and smooth muscle cell apoptosis⁷. Risk factors such as hypertension, female sex, increasing age, cigarette smoking, excessive alcohol consumption, and familial history of aneurysm, predispose to IA formation and rupture⁸. Furthermore, increasing evidence suggest a genetic component of IA formation⁹. Genome wide association studies and subsequent replication case-control studies identified variants on chromosomes 4q31-23, 8q11 and 9p21.3 that were strongly associated with IA formation¹⁰. However, these loci explain only 5% of the familial inheritance cases¹¹.

STUDY GOALS AND OBJECTIVES

Our project addresses the urgent and obvious need to develop diagnostic and predictive tools of risk of IA formation and rupture. Discovering genetic risk factors, better understanding the pathophysiology and identifying molecular mechanisms responsible for IA formation will be essential bases for the development of biomarkers and identification of therapeutic targets.

STUDY DESIGN

For this global project including observational and basic science research, we have developed a

nationwide collaborative project gathering neuroradiologists, neurologists, neurosurgeons, geneticists, cardiologists, ophthalmologists, vascular specialists, and biologists.

IA Phenotype Definition

A typical IA is defined as a saccular arterial dilatation occurring at a bifurcation of the intracranial vasculature. Neuroradiological phenotyping is performed in each center by experienced interventional neuroradiologists, neurologists, and neurosurgeons, in order to exclude other IA types and to recruit only the typical saccular bifurcation IA.

IA are recorded as follows for all the cases included in the study:

“Certain”

if an imaging exam demonstrates a **typical IA of bifurcation whatever the measurement,**

or

if medical records document the presence of a **typical IA of bifurcation** on cerebral angiogram, operative report or autopsy.

“Uncertain”

if an imaging exam demonstrates **an ectasia measuring < 2 mm,**

or

if medical records document the presence of a **subarachnoid hemorrhage without traumatism** on cerebral angiogram, operative report or autopsy.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Familial cases of IA: Subject carrying a certain IA and at least 1 first-degree relative with a certain IA (no age limit).

- Healthy first-degree relatives: Subject of 20 years or more and having at least 2 first-degree relatives with a certain IA. For these, an MRI screening will be proposed.
- Sporadic cases of IA: Subject aged 20 years or more with a certain IA.

Exclusion Criteria

- A mycotic, fusiform-shaped, or dissecting IA, an IA in relation with an arteriovenous malformation.
- A family history of polycystic kidney disease, Ehlers Danlos Syndrome, Marfan's syndrom, fibromuscular dysplasia, or Moya-Moya disease.
- A failure to obtain informed consent.

METHODOLOGY

Recruitment Process

Recruitment of Familial Cases and Relatives

Once a potential family is identified, the proband is asked to complete a family history questionnaire; study information sheets and recruitment letters are provided for later distribution to additional family members. Each relative expressing his/her interest to the proband is then contacted by phone.

If he/she meets the inclusion criteria, MRI screening and blood sampling are proposed. In order to optimize the recruitment of large families, only clinical centers with extensive experience in clinical management and IA imaging were selected as recruitment sites.

For each family selected for primary genetic investigations (ie, exome sequencing), the IA phenotype will be further assessed. First, a medical genetics consultant will check whether IA occurrence may result from any syndromic disease (such as Marfan disease or vascular forms of Ehlers Danlos). Then eye fundus, transthoracic echocardiography, non-invasive analysis of

endothelial dysfunction, and echography Doppler analysis of peripheral arteries (sub clavians, radials, femorals, renals, digestives, etc) will be carried out in order to test any other vascular malformation or variation potentially linked to the presence of IA, thus constituting a syndrome yet unknown.

Recruitment of Sporadic Cases

A patient with a **certain and typical IA of bifurcation** seen in consultation will be included, regardless of a history of rupture or treatment.

Data recorded

Clinical Data

Data related to environmental risk factors are collected for each included patient. Smoking history is recorded as:

- never smoked
- stopped smoking for more than 3 years
- stopped smoking for less than 3 years or current smoker

If the patient was a current or former cigarette smoker, the number of pack-years prior to diagnosis of IA is evaluated.

Parameters as high blood pressure defined as a past history of hypertension prior to the diagnosis of IA, diabetes mellitus, hypercholesterolemia, alcohol consumption, body mass index, history of migraine (according to the International Headache Society) or of cryptogenic cephalalgia, medical treatment by statins, antiplatelet agents, vitamin K antagonists, long term intake of anti-inflammatory drugs and hormone replacement therapy are recorded.

History of ruptured IA, stroke, carotid stenosis, ischemic heart disease, lower limbs occlusive arterial disease, cancer, hematologic disorder is also recorded.

Biological Data

The bio collection will consist of blood sampling taken from each included patient; 2 tubes for DNA analysis and 2 tubes for serum extraction.

Imaging Data

IA imaging in first-degree relatives is assured by MRI/MRA with the following protocol: MR angiography Time of Flight, FLAIR, Gradient Echo T2-weighted imaging. The sensitivity of MRI in detecting IA ranges from 81 to 95 %^{12–20}. The inter-observer consistency, particularly for IA > 3 mm is good to excellent (kappa 0.59–0.82)^{13,15–17,19,21}.

Angiographic imaging will allow recording all parameters regarding the aneurysm form (height, width, neck size, the presence of lobulation, or wall irregularities) and the parent artery diameter.

Any cervical loop of the carotid artery, hypoplastic first segment of the anterior cerebral artery, basilar or vertebral fenestration, and foetal type of posterior cerebral artery will also be registered.

On the FLAIR imaging sequences, the presence of vascular white matter disease (graded according to the Fazekas classification²²), territorial ischemic sequelae, inflammatory white matter disease, atypical white matter disease evocative of Col4a1 mutation or Fabry disease will be noted.

On Gradient Echo T2-weighted imaging, we will quantify the presence of microbleeds in the deep or superficial brain parenchyma.

Some patients, particularly the sporadic cases of IA, that had independently undergone MRI, computed tomography angiography or digital subtraction angiography for their standard clinical care will be reviewed in a blinded manner by neuroradiologists from the coordinating center. Imaging files will be uploaded on a global server for each included patient (SHANOIR).

DISCUSSION

National Recruitments in France

Because populations living in rural areas of western France have been sedentary for centuries, this geographical area is a preferred location to detect and recruit large families with hereditary diseases. By a systematic research of familial history of IA, we have already recruited more than 100 families. We have then selected 4 large families with 4 or more relatives harboring IA for primary genetic investigations based on whole exome sequencing (Figure 1). In relation with our network, we will also ensure the recruitment of sporadic IA (without familial screening) to constitute a collection of clinical, biological, genetic, but also imaging data of patients with IA.

Whole Exome Sequencing

Whole exome sequencing allows systematic detection of genetic variation across the whole coding portion of the human genome. By this method, one can list the rare genetic variants that are shared between several related individuals affected by IA. The coding portion of the genome is captured then sequenced. After read alignment and variant calling, a series of filters are applied.

Further Testing of Candidate Genes

In a second step, any candidate genes selected through whole exome sequencing on familial cases are further tested on an extended group of unrelated familial IA carrier, which is currently under construction through our clinical network. In order to test the presence of rare variants associated to IA in this cohort, rare-variants association studies will be performed

In addition, the most promising candidates are subjected to preliminary functional investigations, to check whether their biological activity is relevant to the pathophysiology of IA.

Exploiting Diverse and Massive Datasets

Discovering or validating novel risk factors in IA relies in the setup of a data infrastructure capable of jointly exploiting diverse and possibly massive datasets (whole exome sequencing, multi-modality imaging, and clinical data). Based on such a linked data infrastructure, we can imagine in silico validation scenarios, ie, algorithms, querying and combining diverse clinical features (age, hypertension, and smoking habits) with circulating or quantitative imaging biomarkers. Following the FAIR (Findable, Accessible, Interoperable, and Reusable) data principle and technically adopting a Linked Data approach (structured metadata, reference controlled vocabularies or ontologies) will allow: (i) to query, filter, and join these

heterogeneous datasets from multiple viewpoints, and (ii) to open data reuse perspectives, beyond the project timeframe and beyond its initial objectives.

Conclusion

We launch an ambitious multicenter project (ICAN) addressing the pathophysiology of IA. To date, no transmitted variation related to familial forms of IA has been published. Our protocol has many assets. First, our nationwide recruitment allows for the inclusion of large pedigrees with familial forms of IA. Second, it will combine accurate phenotyping and comprehensive imaging with high-throughput genetic screening. Last, it will enable exploiting meta-data to explore new pathophysiological pathways of interest by crossing clinical, genetic, biological, and imaging information. This should lead us to identify the biological pathways involved in the formation of IA. Currently no blood test has been established to help in diagnosing IA, and there is still no way to predict the natural history of an IA. Discovering relevant biomarkers would undoubtedly facilitate early detection, risk assessment, and therapeutic monitoring of IA.

TRIAL STATUS

This is an ongoing study

SAFETY CONSIDERATIONS

No adverse event is expected in this non-interventional study.

FOLLOW-UP

We are building a biocollection but in the close follow-up and depending on the grants obtained, this project will probably become a cohort study with a follow-up corresponding to the recommendation for IA management.

EXPECTED OUTCOMES OF THE STUDY

Discovering biomarkers correlated with the presence of IA should allow better detection and prevention of IA rupture. In the longer term, our systematic nationwide collection of each typical IA of bifurcation together with the registration of clinical, biological, genetic, and morphological data will allow deciphering the pathophysiology of this orphan, frequent, and serious cerebrovascular disease.

DURATION OF THE PROJECT

We have initially scheduled a recruitment period of 3 years (May 2016 to May 2019) but according to the evolution of the project we can move towards a cohort study making the project more sustainable.

PROJECT MANAGEMENT

The project Management is ensured by Dr. Romain Bourcier MD and Pr. Hubert Desal MD Ph D from the Department of Neuroradiology of the Centre Hospitalier Universitaire of Nantes, 8 Quai Moncoussu, 44000 Nantes, France.

L'institut du thorax, INSERM Unit 1087, CNRS, Centre Hospitalier Universitaire of Nantes, 8 Quai Moncoussu, 44000 Nantes, France, 02 28 08 01 13, particularly the director Richard Redon PhD, ensures the genetic analysis. The co-director of the unit, Gervaise Loirand PhD is responsible of the functional analysis for candidate genes.

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ETHICS

The ICAN project is a non-interventional clinical research, approved by the Institutional Review Boards (« Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé », « Commission Nationale de l'Informatique et des Libertés ») and Ethics

Committees of Nantes. Informed written consent has been obtained from all patients and the biobank called « Génétique et biomarqueurs des pathologies cardiovasculaires, respiratoires et leur facteur de risques » is approved by the French Ministry of Research (n° DC-2011-1399) and by the « Comité de Protection des Personnes ».

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FIGURE LEGEND

Figure 1: Pedigree of a 3 generation family with 6 patients affected by IA. Arrows indicate probands. Asterisks indicate exome-sequenced individuals.

