RaDiCo-ACOEIL - National cohort on congenital defects of the eye: natural history, genetic determinisms and improved ocular and extra-ocular outcome prediction for better patient management

Head :Chassaing Nicolas , Inserm U 1056
Calvas Patrick

Last update : 12/03/2024 | Version : 2 | ID : 73377

General

Identification

Detailed name	National cohort on congenital defects of the eye: natural history, genetic determinisms and improved ocular and extra-ocular outcome prediction for better patient management
Sign or acronym	RaDiCo-ACOEIL
CNIL registration number, number and date of CPP agreement, AFSSAPS (French Health Products Safety Agency) authorisation	CCTIRS n° 16.051 / CNIL decision DR-2016-349

General Aspects

Medical area	Disability/handicap Neurology Ophthalmology Pediatrics Rare diseases
Study in connection with Covid-19	No
Pathology (details)	microphthalmia, anophthalmia, aniridia, other anterior segment dysgenesis: These ocular defects include a large spectrum of malformations mainly involving cornea or iris. They includethe classical Peters, Rieger and Axenfeld anomalies8, 9. Peters' anomaly corresponds to total or central clouding of the cornea associated with irido-corneal synechia. This malformation frequently leads to glaucoma or cataract. Peters anomaly can be isolated or frequently associated with a wide variety of extra-ocular features as with intellectual disability10. One syndromic form, Peters-plus syndrome is well defined and encompasses Peters anomaly, growth retardation, brachydactyly, intellectual disability, and various other malformations11. Axenfeld-Rieger

	anomaly corresponds to iris involvement (posterior embryotoxon, iris hypoplasia, corectopia, polycoria) and synechia between iris and trabecular meshwork. Once again, this ocular developmental defect may be isolated or associated with extra-ocular features and intellectual deficiency12, 13. One syndromic form, Rieger syndrome, consists of Axenfeld-Rieger anomaly together with hypodontia, peg-shaped teeth, facial dysmorphism, and redundant periumbilical skin.
Health determinants	Genetic Healthcare system and access to health care services Medicine Social and psychosocial factors
Keywords	Ophthalmic diseases, Rare diseases, Quality of life

Scientific investigator(s) (Contact)	
Name of the director	Chassaing
Surname	Nicolas
Address	Service de génétique médicale - Pavillon Charles Lefebvre Hôpital Purpan ? CHU de Toulouse 31 059 Toulouse Cedex FRANCE
Phone	+ 33 (0)5 61 77 90 55
Email	chassaing.n@chu-toulouse.fr
Unit	Inserm U 1056
Organization	French National Institute for Health and Medical Research (Inserm)
Name of the director	Calvas
Surname	Patrick
Address	Service de génétique médicale - Pavillon Charles Lefebvre Hôpital Purpan ? CHU de Toulouse 31 059 Toulouse Cedex
Email	calvas.p@chu-toulouse
Organization	French National Institute for Health and Medical

	Research (Inserm)
Collaborations	
Participation in projects, networks and consortia	Yes
Details	Healthcare Networks for Rare Diseases (National Rare Diseases Healthcare Networks): SENSGENE and ANDDIRARE
Others	Patient Associations: Microphtalmie France, Gêneris, Retina France
Funding	
Funding status	Public
Details	RaDiCo received financial support from the State managed by the National Research Agency (ANR) under the Investments for the Future Program (PIA) with the reference "ANR" 10-COHO-0003.
Governance of the database	
Sponsor(s) or organisation(s) responsible	French National Institute for Health and Medical Research (Inserm)
Organisation status	Public
Presence of scientific or steering committees	Yes
Labelling and database evaluation	Security audit certification of the database / Continuous Data Management and Quality Control.
Additional contact	
Main features	
Type of database	
Type of database	Morbidity registers
Study databases (details)	Cohort study
Database recruitment is carried out by an intermediary	A selection of health institutions and services
Database recruitment is is made on the basis of:	Another treatment or procedure

Database recruitment is carried out as part of an interventional study	No
Additional information regarding sample selection.	Patients from 0 to 7 years old We aim to include most patients born with a developmental ocular defect. Even if most ocular defects are diagnosed during the first months of age, patients could be included in the cohort until 7 years old (age at the first neuropsychological evaluation). Given the estimated incidence of microphthalmia and anophthalmia (~1/10.000), aniridia (~1/60.000), and other anterior segment dysgenesis (~1/30.000), 80 new patients should be born each year in France (800.000 births/year) with AM, 14 with aniridia, and 27 with other anterior segment dysgenesis. We planned to enrol at least half of these patients each year (50 patients: 25 with microphthalmia or anophthalmia, 10 with aniridia, and 15 with anterior segment dysgenesis). This estimation is based on our diagnostic activity during the past three years. Indeed, within this period, we recruited each year for diagnostic purpose, 43 unrelated patients (including 33 children) with microphthalmia/anophthalmia, 29 unrelated patients (including 14 children) with aniridia, and 25 unrelated patients (including 19 children) with anterior segment dysgenesis. Patients over 8 years old Affected adults and children over 8 years old will not be included in the follow-up subgroup. However their phenotype (ocular defect, extra-ocular malformations, and visual and neurological outcome) will be retrieved in the database as retrospective cases to increase collected data about outcome of patients affected by these ocular defects. We retrieved historic patients (150 patients or families with microphthalmia/anophthalmia, 100 with aniridia and 80 with anterior segment dysgenesis) in our clinical database (CNIL authorisation 1458306V0 du 09-10-2010) through our diagnostics laboratory. These patients will be contacted again by their geneticist or ophthalmologist to participate to the standard evaluation procedure. In addition to these already known patients, we are still collecting each year about 30 ?novel? adult patients through this diagnostics activity. Combining the known cases, and the newly identified adult (or children over 8 years) cases, we could expect to enrol at least 30 patients each year in this subgroup.

	Study duration - Up to ten year follow-up of patients under 7 years old at time of inclusion (incident subgroup): two evaluations after inclusion (at 6-7 years old and 9-11 years old) - Unique evaluation of patients over 8 years old (? prevalent subgroup?) at time of inclusion.
Database objective	
Main objective	Main objective The principal objective of this study is to delineate the long term outcomes of the patients with ocular developmental defects, focusing on visual and neuro-developmental issues. Secondary objectives I) Identification of prognostic factors (such as ocular defects, unilateral or bilateral involvement, extra-ocular malformations) that would be associated with unfavourable visual and/or neurologic outcome. These data will be essential for the formulation of recommendations to enhance diagnosis and patient management. II) Repercussions of the ocular developmental defects on patients and families quality of life. Exploratory objectives Searching for potential genotype/phenotype correlations to unravel - the frequency of implication of each gene in these ocular developmental defects; - the phenotypic spectrum associated with mutations in these genes; - the identification of novel genes involved in these ocular developmental defects. Given genotyping will not be mandatory to participate to the cohort; this objective will involve only the patients who accepted it.
Inclusion criteria	Patients from 0 to 7 years old - Newborns and/or children from birth to 7 years old, affected with the following ocular defects: ? anophthalmia, ? microphthalmia ? aniridia ? anterior segment dysgnesis whose parents will have properly evaluated risks (those related to the actual standard of care for these pathologies) and benefits (improvement of knowledge and standard of care) of the study, and will be given an informed consent to participate the protocol.

- Patients affiliated to the "Régime National d'Assurance Maladie"
- Inclusion of foreign patients will be possible through the French inclusion centers when they agreed to be charged for all medical fees.

Patients over 8 years old

- Children from 8 years old, affected with the following ocular defects :
? anophthalmia,
? microphthalmia
? aniridia
? anterior segment dysgenesis

whose parents will have properly evaluated risks and benefits of the study, and will be given an informed consent form to participate to the protocol.
- Patients affiliated to the "Régime National d'Assurance Maladie"
- Inclusion of foreign patients will be possible through the French inclusion centres when they agreed to be charged for all medical fees.

Adult Patients

- Adults affected with the following ocular defects :
? anophthalmia,
? microphthalmia
? aniridia
? anterior segment dysgenesis
- Adult patients under guardianship whose guardians will have properly evaluated risks (those related to the actual standard of care for these pathologies) and benefits (improvement of knowledge and standard of care) of the study, and will be given an informed consent to participate the protocol. Indeed, intellectual disability may be associated with the ocular defects and we will need to include these patients in order to evaluate incidence of this event.
- Adult patients able to properly evaluate risks (those related to the actual standard of care for these pathologies) and benefits (improvement of knowledge and standard of care) of the study and to give their informed consent to participate to the protocol.
- Adult parents of an affected child participating to the study and willing to participate to the inheritance study (results of DNA analysis).
- Patients affiliated to the "Régime National d'Assurance Maladie".
- Inclusion of foreign patients will be possible through the French inclusion centres when they agreed to be charged for all medical fees.
- Pregnant women can be included in the study (as examination proposed have no interference or

	adverse effect during pregnancies). Non-inclusion Criteria - Patients with ocular developmental defects other than the ones listed above. - Patient or patients' parents/tutor not able to approve or declining participation to the protocol. - French patients not affiliated to the "Régime National d'Assurance Maladie" or foreign patients not willing to pay charges of medical services.
Population type	
Age	Newborns (birth to 28 days) Infant (28 days to 2 years) Early childhood (2 to 5 years) Childhood (6 to 13 years) Adolescence (13 to 18 years) Adulthood (19 to 24 years) Adulthood (25 to 44 years) Adulthood (45 to 64 years) Elderly (65 to 79 years) Great age (80 years and more)
Population covered	Sick population
Pathology	Q11 - Anophthalmos, microphthalmos and macrophthalmos
Gender	Male Woman
Geography area	National
Detail of the geography area	All French territory via rare disease reference and competence centers
Data collection	
Dates	
Date of first collection (YYYY or MM/YYYY)	2016
Date of last collection (YYYY or MM/YYYY)	up to 2036
Size of the database	
Size of the database (number of individuals)	[500-1000[individuals
Details of the number of	800

individuals	
Data	
Database activity	Current data collection
Type of data collected	Clinical data Declarative data Paraclinical data Biological data Administrative data
Clinical data (detail)	Direct physical measures Medical registration
Details of collected clinical data	clinical data, as well as biological, uniform molecular and comparative data of patients suffering from ocular congenital malformations. The retrieved data are dedicated to:- Implement the family history including the pregnancy and delivery follow-up; - The description of patient's phenotype (either ocular and extra-ocular); - The collection of paraclinic investigations data; - The description of visual and neurologic status;; - The evaluation of sociological state and quality of life
Declarative data (detail)	Paper self-questionnaire Internet self-questionnaire Face to face interview
Details of collected declarative data	SF-36 (adults) / SF-10 (children)
Biological data (detail)	For patients agreeing to have such analysis, molecular screening for diagnosis purposes will be performed by the genetic diagnosis laboratory led by the two principal investigators at the CHU (University Hospital) Toulouse. These analyses include the high-throughput sequencing of, to date, 25 genes known to be involved in these pathologies (ALDH1A3, B3GALTL, BCOR, C12ORF57, CYP1B1, FOXC1, FOXE3, MAB21L2, MFRP, OTX2, PAX2, PAX6, PITX2, PITX3, PRSS56, PXDN, RARB, RAX, RCN1, SIX6, SMOC1, SOX2, STRA6, TENM3, VSX2), and possibly more once new genes will be identified. These analyses are performed by Sanger, targeted sequencing (NGS).; Further molecular analysis for research purposes that may be required for identification of new or modulator genes, will be performed by the EA-4555 research laboratory (research laboratory of the two principal investigators). These analyses will be performed by whole exome and whole genome sequencing.

Presence of a biobank	No
Health parameters studied	Health event/morbidity Health event/mortality Quality of life/health perception Others
Quality of life/perceived health (detail)	SF-36 (adults) / SF-10 (children)
Procedures	
Data collection method	Electronic Case Report Form (eCRF) using REDCap EDC; Cloud-based platform, accessible via the web, secure by design. Certified Health Data Hosting resource (HADS).
Classifications used	HPO, ICD10, Snomed CT, Orpha Codes and ORDO, Drug dictionary (DCIs)
Quality procedure(s) used	Continuous data management; Data Management Plan and Data Validation Plan. Native controls and Query system
Participant monitoring	Yes
Monitoring procedures	Monitoring by convocation of the participant Monitoring by contact with the referring doctor
Followed pathology	Q11 - Anophthalmos, microphthalmos and macrophthalmos
Links to administrative sources	No
Promotion and access	
Promotion	
Access	
Presence of document that lists variables and coding procedures	Yes
Terms of data access (charter for data provision, format of data, availability delay)	Access requests to RaDiCo -AC OEIL data (rough / structured), or to analytic reports will be examined by the scientific committee following submission of a Specific Research Project (SRP) synopsis, as defined in the Resource Access Charter. Must be sent to ac-oeil@radico.fr
Access to aggregated data	Access on specific project only

Access to individual data

Access on specific project only