Genetics and genomic characterization of Congenital Upper Limb Anomalies

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Primary Objectives: 1. Determine novel pathogenic gene mutations in families with congenital upper limb anomalies by whole genome sequencing;2. Determine the contribution of these genes in embryonic development, including proliferation and cell...

Ethical review	Approved WMO
Status	Pending
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON41954

Source
ToetsingOnline

Brief title
Genetics of CULA

Condition

- Musculoskeletal and connective tissue disorders congenital

Synonym
Congenital hand differences, Hereditary hand disease

Research involving
Human

Sponsors and support

Primary sponsor: Plastische en Reconstuctieve Chirurgie en Handchirurgie
Source(s) of monetary or material Support: Ministerie van OC&W,Esser Stichting (hoofd onderzoeker)

Intervention

Keyword: CULA, Genetics, pheno-/genotype correlation, Whole genome sequencing

Outcome measures

Primary outcome

1. Determine novel pathogenic gene mutations in families with congenital upper limb anomalies by whole genome sequencing;

2. Determine the contribution of these genes in embryonic development, including proliferation and cell death.

Secondary outcome

Secondary Objectives:

1. Evaluate the significance of whole genome sequencing in determining risk genes in syndromal or hereditary congentinal upper limb abnormalities

2. Understand the heredity and the consequences of the new found mutations to ameliorate counselling

Study description

Background summary

Congenital upper limb anomalies (CULA) are rare developmental disorders arising in approximately 1 in 500, CULA associated with a syndrome only arise in 0.5 out of 10.000 live births. There is a broad range of anomalies varying from extra simple extra digits to complex syndromal hand deformities. Since 1976 CULA are described using the classification by Swanson adopted by the IFSSH. Due to numerous genetic studies an increased comprehension of the molecular basis of conditions with primary or secondary limb involvement had been derived. These progressions have reflected in a new classification of limb anomalies in 2009 by Oberg, Manske and Tonkin. This classification better describies the embryonic correlation of these individual anomalies, but also has been revised twice since publication.
Although many genes were identified in the past, the genotype-phenotype

relation is still often poorly understood as illustrated by GLI3 gene mutations. GLI3 gene mutations can cause a variety of hand malformations in a range from isolated polydactyly to Pallister Hall syndrome and Greig*s Cephalopolysyndactyly. Moreover, in many defined syndromes like Greig*s Cephalopolysyndactyly there is a wide variety in both phenotype and underlying genotype. Common hypothesis for these variations are polygenetic alterations hindering strict correlation between phenotype and the molecular or genetic basis. Wider genetic testing and improved phenotypic registration could improve understanding and thereby genetic counseling and patient care.
Researchers have shown that with different genetic research techniques more mutations can be found but research for genetic defects is time and money consuming with the standard techniques. The introduction of Next Generation Sequencing (NGS) supplies us with reliable and quick results. This has previously been shown with the identification of a mutation of the IL11RA gene, causing craniosynostosis, by using NGS and simultaneously using more conventional techniques for validation. Interpretation of the data obtained through NGS requires a database with control samples to quickly filter and eliminate the common, non-pathogenic genetic variations that occur in the normal healthy population. The department of Bioinformatics has a unique database containing more than 180 genomes that can serve as control samples. The use of a transitional research center enables analysis and control capabilities of both genetic and clinical data that scale to millions of patients and hundreds of thousands of whole genome sequences. By collecting detailed clinical data of the 2500 CULA patients of the Sophia*s Children*s hospital and the data from the standard DNA tests performed by the Clinical Genetics department cases fitted for whole genome sequencing can be selected based on syndrome, malformation, location of the malformation, patient history or previously detected genetic anomalies and any combination of the before mentioned. When the first whole genome sequences are included the database can also help identify like-cases fitted for sequencing.
Most centers lack a sufficient amount of patients for genetic research. The Sophia Children*s Hospital is the major hand and upper limb surgery center in the Netherlands and therefore rare congenital upper limb anomalies disorders are centered here. Due to this, a database of over 2500 congenital upper limb anomaly patients is available. Collaborations with the hand and upper limb surgery center in Hamburg possibly extends the amount of includible patients even further.
Drawing upon our database of over 2500 congenital upper limb anomalies malformation patients, a pilot study will be conducted, comparing the costs of conventional testing (about 750 euros per gene, and often not establishing a genetic cause since only previously discovered mutations are tested) to whole genome sequencing. Currently, the cost for a full genome is comparable to the cost of several (five) single-gene tests, and provides the added ability to identify novel causal variants. Futhermore having the knowledge about the whole genome will save costs for insurance companies by the fact that certain future tests or searches for variations will only involve a digital look-up without

any additional laboratory tests.

Study objective

Primary Objectives:
1. Determine novel pathogenic gene mutations in families with congenital upper limb anomalies by whole genome sequencing;
2. Determine the contribution of these genes in embryonic development, including proliferation and cell death.

Secondary Objectives:
1. Evaluate the significance of whole genome sequencing in determining risk genes in syndromal or hereditary congentinal upper limb abnormalities
2. Understand the heredity and the consequences of the new found mutations to ameliorate counselling

Study design

There is no set age for patients with congenital upper limb anomalies to be operated on, while the indication for operation depends on the function deficit experienced by the patient or their parents and the moment of referral to the outpatient clinic.
According to standard protocol, the parents receive a questionnaire prior to their first visit about the pregnancy, family history, growth and development. Standard physical examination includes full body inspection and evaluation of all extremities. Both X-ray and photographic recordings are made of the affected limb(s) and the healthy contralateral limb(s). Patients are referred to the department of Clinical Genetics when a hereditary condition is suspected. Patients will be asked to bring pictures of family members with (upper limb)anomalies to the outpatient clinic of the Clinical Genetics department. The patient and the photos will be analysed for the presence of dysmorphisms. DNA analysis is performed when indicated, blood required in this stage will be drawn during surgery. All data generated by standard protocol will be included in an OpenClinica database compatible with the Translational Research Center. Genomic data will be stored in the Huvariome database.
Patients for the first phase of whole genome sequencing are asked to join this study when there is a suspicion of a hereditary anomaly but no known mutation was found in standard DNA testing. When consent is given, family members with CULA*s will be approached for inclusion in the database as well. The Department of Clinical Genetics is involved for family counseling during the course of this study.
All samples will be will be sent to the United States where whole genome sequencing will be performed by Complete Genomics (Mountain View, CA, USA). DNA profiles will be made. Associations between these profiles and the profiles of 150 normal genomes will be made. A number of risk genes will be evaluated for function and pathogenicity and a final selection will be made by the department

of Bioinformatics of the Erasmus MC. The department of Bioinformatics has a METC approval for conducting whole genome sequence analysis including databasing of the results for re-use(MEC 2011- 253). As control the new found mutation will be tested in affected and unaffected family members by resequencing the gene. By cross-reference with our database incidences of the new mutations can be estimated.
The anonymised genomic data derived from control individuals and patients will be stored and therefore can be used for future analysis of additional CULA patients.

Study burden and risks

The burden and risks are practically none. In phase 1 the blood used for whole genome sequencing has already been collected during surgery for the regular DNA testing. Sometimes more DNA will be necessary or family members will be asked for blood in phase 2. Patients will be asked to complete a questionnaire and a routine elaborate physical examination will be done at the outpatient department.
The whole human genome will be mapped using whole genome sequencing. This will offer lots of information about an individual. In this research project we will focus on disease related genetic alterations. Since knowledge of genetic alterations is expanding rapidly, our data cannot be checked for all new discovered mutations. To prevent incomplete statements no statements will be done about other genetic diseases.
An extensive look at all possible causative genetic alterations causing congenital upper limb anomalies will be made. The patient will probably find out what causes his or her congenital upper limb anomalies and more will be known about its heredity. Counseling will improve for both the parents regarding risks for a future pregnancy and for the patient regarding risk to pass the condition on. Moreover, an enormous amount of knowledge concerning the genetic background, embryology and development of congenital upper limb anomalies will be gained. Future patients will benefit from this enhanced knowledge in improved counseling and in future in personalized medicine. Furthermore, the anonymized genome data will be stored and can be used for future analysis of additional patient data.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Patients will be selected for next generation sequencing when they have a hereditary congenital upper limb anomaly while no known mutation was found in conventional test by the department of Clinical Genetics. Parents will be sequenced as well. Affected family members will be approached and asked to join the study. All patients, parents and family members are included in the 225 subjects.

Exclusion criteria

Non consenting parents or family members
Positive conventional genetic test for know mutation

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2015
Enrollment:	225
Type:	Anticipated

Ethics review

Approved WMO

Date:	10-06-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL50394.078.14