Universität Basel

Research Project

Massively parallel Sequencing for gene discovery in lethal fetal disorders

Third-party funded project

Project title Massively parallel Sequencing for gene discovery in lethal fetal disorders
Principal Investigator(s) Filges, Isabel ;
Project Members Kalantari, Silvia ;
Organisation / Research unit
Bereich Kinder- und Jugendheilkunde (Klinik) / Medizinische Genetik (Miny)
Department
Project start 01.09.2015
Probable end 31.08.2019
Status Completed

The announcement of a serious or even lethal condition during pregnancy or at birth is a devastating experience for the parents and the health professionals involved. The demand for the determination of the cause is high, not only for psychological reasons, but also for determining pregnancy and perinatal management, recurrence risks as well as counseling for subsequent pregnancies. Malformations and genetic disorders are the leading cause of infant mortality in the developed countries accounting for more than one third of cases; more than 70% present with organ malformations. Today, major, also potentially lethal, malformations are often already detected prenatally during ultrasound examination. The prevalence of malformations during fetal development is even higher, because a proportion of these pregnancies will not survive until birth. In about 10-15% the genetic origin is due to chromosome anomalies including submicroscopic anomalies detected by chromosomal microarrays. In the remaining patients genetic testing for mutations in single genes can only be offered if a clinical diagnosis of a specific disorder is suspected. Novel high-throughput next generation sequencing technologies have now enabled the discovery of many novel genes in children with developmental impairments. However, only little attention has been paid to using these sequencing strategies for gene identification in human malformation syndromes that are lethal in utero or at birth despite their frequency and their importance in pregnancy and newborn health care. Aim: In this project we will use massively parallel genomic sequencing for gene identification in deceased fetuses and newborns with multiple malformations of unknown cause after normal chromosomal array analysis. The general goal of this project is to identify disease genes where mutations lead to autosomal recessive forms of these lethal conditions. Hypotheses: We test the hypotheses that (1) massively parallel sequencing of all protein-coding regions in the genome (exome sequencing) can identify novel genes by detecting the mutations that cause malformations in fetuses and newborns in whom such etiological factors exist, that (2) autosomal recessive mutations are an important cause of early human lethality and 3) the comparison of human and animal morphology - cross-species phenotyping - is an important means to validate novel potentially causal genes. Methods: We select families in which at least two children (and at least one girl) died during pregnancy or after birth because of their malformations. The malformation pattern can be correlated to a particular developmental pathway in embryogenesis. Genes with homozygous or compound heterozygous mutations will be considered candidate genes. In order to investigate the causality of mutations, the expected inheritance of these recessive candidate mutations will be confirmed in the family, and the absence of these variants in normal populations will be confirmed by analysis of the publicly available genome sequences of unaffected individuals. A critical aspect of this project is genotype-phenotype correlations of candidate genes in which we will include developmental pathway analysis and cross-species phenotyping using animal models. Relevance: Malformations and genetic disorders are the leading cause of prenatal and

newborn mortality in the developed countries. Knowledge of the impact of genetic diseases on mortality is important for the integration of preventive measures and health care strategies to care appropriately for patients and their families. Our approach will provide a means of obtaining the genetic cause for fatal malformation syndromes for whom this is not currently available. We expect to discover previously unknown autosomal recessive genes, to discover novel mutations in known genes which have not been yet associated with fetal or perinatal human death and to describe novel prenatally observed syndromes which have not been recognized before. The comparison of human and animal morphology allows validating genes involved in those unrecognized and so far neglected conditions. Complementary to the current large scale international efforts to characterize lethal malformations and causal genes in mice we will focus on increasing our knowledge about normal and abnormal human development. The genes identified may also serve as candidate genes for the cause of similar non-lethal conditions through different mutational mechanisms which would not have been recognized otherwise. Ultimately, families and health care professionals will benefit from novel care and treatment approaches based on the research into these biological mechanisms.

Keywords genotype-phenotype correlation; Medical Genetics; children/families; exome sequencing; gene identification; Malformations; fetal disorders
Financed by
Swiss National Science Foundation (SNSF)

Add publication

Add documents

Specify cooperation partners