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Overexpression of muscarinic receptors in SIDS : genetic data

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Introduction:
Sudden infant death syndrome (SIDS) is unpredictable and poorly understood. It remains the leading cause of death among infants aged between 1 month and 1 year.
Overexpression of muscarinic M_2 Receptors (M_2R) was observed in hearts of newborns deceased from SIDS, and more recently in the blood of infants who experienced idiopathic life apparent threatening event (iALTE), suggesting the involvement of the vagal system overactivity in these pathologies.
We explored a family in which 3 infants out of 6 deceased from SIDS between the ages of 6 weeks and 8 months. To note that the 3 other children and parents are doing well, but they also experienced 2 fetal deaths (figure 1).
Methods:
We first analyzed the blood expression of M_2R as a biological parameter reflecting vagal overactivity in 7 members of this SIDS family: total RNA was blindly extracted from blood samples and reverse transcribed into cDNA. M_2R mRNA expression was measured by PCR.
In terms of genetics, we analyzed the data of the Next Generation Sequencing (NGS) of the exomes of the 8 members of this SIDS family.
Results:
M_2R overexpression was found in the 3 infants deceased from SIDS, in 1 healthy child and in both parents, whereas the expression of M_2R was normal in the 2 other healthy children.
The analysis of exomes identified 3 genes that could be involved in SIDS: *CAV3, CACNA2D2* and *SCUBE2*. However, the scenario and the mode of transmission are difficult to define. The first hypothesis is towards a trigenism, with 2 genes inherited from father, and one gene from mother.
Conclusions:
The exacerbated vagal response, biologically expressed by overexpression of muscarinic M_2R, could be a risk factor for SIDS.
For the first time in this family, the overexpression of M_2R in both parents suggests a genetic transmission of a biological phenotype of vagal overactivity in humans.
The development of the sequencing of human exomes will probably allow the identification of genetic risk factors involved in SIDS. A complementary study of the whole genome may link the M_2R overexpression and the genetics.

Figure 1: Family tree of the « SIDS family » with expression of M_2R and data of NGS