Potential genetic link in sudden infant death syndrome identified

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Credit: Medical Research Council

Rare genetic mutations associated with impairment of the breathing muscles are more common in children who have died from sudden infant death syndrome (SIDS) than in healthy controls, according to new research co-authored by Medical Research Council scientists.

The findings, published in *The Lancet*, suggest a possible genetic element of the disorder (also known as 'cot death'). The research was co-funded by the MRC.

Typically, these mutations are either not found in controls or are very

rare, and found in fewer than five people in every 100,000. However, the study found mutations of this kind in four of the 278 children who had died of sudden infant death syndrome, compared to none of the 729 healthy controls.

Prof Michael Hanna, of the MRC Centre for Neuromuscular Diseases and the UCL Institute of Neurology, said: "Our study is the first to link a genetic cause of weaker breathing muscles with sudden infant death syndrome, and suggests that genes controlling breathing muscle function could be important in this condition."

Prof Hanna said: "While there are drug treatments for children and adults with genetic neuromuscular disorders caused by SCN4A gene mutations, it is unclear whether these treatments would reduce the risk of sudden infant death syndrome, and further research is essential before these findings can become relevant to treatment."

Study co-author Dr. Michael Ackerman, of the Mayo Clinic, said: "This international collaborative UK-USA study provides interesting new evidence for a possible link between respiratory muscle sodium channel dysfunction and SIDS; further research is needed to confirm these findings and to evaluate any potential clinical relevance."

The research team includes scientists from UCL, St George's University of London, the Mayo Clinic, King's College, University of Bristol, University of Edinburgh and Copenhagen University Hospital, among other institutions.

The authors stress that more research will be needed to understand the link identified, and whether drug treatments might be suitable. They also highlight that this is not the sole cause of sudden infant death syndrome, and other elements also play a part.

Sudden infant death syndrome is the unexpected death of a seemingly healthy child. It is the leading cause of post-neonatal death in high income countries, but deaths are rare, and an individual baby's risk is low. Typically, it affects children aged between two to four months, and accounts for 2,400 deaths each year in the USA, and around 300 in the UK.

The cause of the disorder is unknown, but babies being unable to regulate their breathing is thought to be an important component. It is more common in male babies and those born prematurely. Putting babies to sleep on their back, and not sleeping in the same bed as a parent is known to reduce the risk.

The study looked at the prevalence of mutations in the SCN4A gene, which codes for an important cell surface receptor (a skeletal muscle sodium ion channel protein). The expression of this cell receptor in breathing muscles is low at birth and increases over the first two years of life.

Mutations in this gene are associated with a range of genetic neuromuscular disorders, such as myotonia, periodic paralysis, myopathy, and myasthenic syndrome, and with life-threatening pauses in breathing, and spasms of the vocal cords that make breathing or speaking temporarily difficult.

The study included two cohorts of children of Caucasian European ancestry who had died from sudden infant death syndrome in the UK and USA, including 278 children overall (84 from the UK and 194 from the USA). All deaths were unexplained after thorough post-mortem investigations. These were matched with 729 adults who had no history of cardiovascular, respiratory or neurological disease.

Tissue from each group was used and their genes were analysed to

identify whether they had a mutation in the SCN4A gene, and to confirm whether the mutations affected the cell surface receptor that the gene codes for.

While the study found general mutations in the SCN4A gene in six of the 284 infants who died, and in nine of the 729 controls, mutations that disrupted the cell surface receptor were only found in four of the children who had died of sudden infant death syndrome, and none of the controls.

The authors conclude that the disruptive variants are over-represented in this group, and could indicate a genetic element of sudden infant death syndrome.

The authors suggest that this may increase susceptibility to sudden infant death syndrome in some cases as the cell receptor becomes more commonly used. During this period, the mutation could potentially leave these children with weaker breathing muscles, and, if an external stressor impacts their breathing (such as tobacco smoke, getting tangled in bedding, a minor illness or a breathing obstruction), they may be less able to correct their breathing, cough or catch their breath in response.

They stress that the gene mutation is probably not the sole cause of death, however, and safe sleeping measures for babies are still essential to ensure safety.

In addition, since SCN4A variants are found in some adults with neuromuscular disease, it is evident that SCN4A mutations are not always lethal.

The authors note some limitations, including that the study only included white people of European ancestry, and the results will need confirmation in other ethnicities. In addition, as the information from

children who died from sudden infant death syndrome was anonymised there was limited other clinical data and other family members could not be tested. Prospective studies will be needed to confirm the link between the mutation and sudden infant death syndrome.

Provided by Medical Research Council