

Protein clue to sudden cardiac death

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A team led by Oxford University researchers was looking at how a protein, iASPP, might be involved in the growth of tumours. However, serendipitously they found that mice lacking this gene died prematurely of sudden cardiac death. More detailed investigations showed that these mice had an irregular conductance in the right side of the heart, a condition known as arrhythmogenic right ventricular cardiomyopathy (ARVC).

The researchers discovered that iASPP had a previously unknown role in controlling desmosomes – one of the main structures that 'glue' individual [heart muscle cells](#) (cardiomyocytes) together. The genetic

defect was shown to weaken desmosome function at the junctions of [heart muscle](#) cells: this affected the structural integrity of the heart, making mice lacking iASPP prone to ARVC.

Further studies of heart tissue from human patients who had died from ARVC showed that some of them have similar defects in desmosomes as in the mice suggesting that the faulty iASPP gene could also be responsible for ARVC deaths in humans. This finding also explains why a previously reported cattle herd with spontaneous iASPP gene deletion died of sudden [cardiac death](#).

A report of the research is published this week in the *Proceedings of the National Academy of Sciences*.

'We set out to investigate how this protein might cause cancer and found by chance that it could play a key role in this rare genetic heart condition,' said Professor Xin Lu, Director of the Ludwig Institute for Cancer Research at Oxford University, the lead investigator of the report. 'It took my DPhil student Mario Notari, the lead author of the study, over two years of further detective work, in collaboration with our colleagues in Oxford and London, to show how a single faulty gene can affect the function of desmosomes, one of the main structures that 'glue' heart [muscle cells](#) together. Our studies suggest that these changes can threaten the structural integrity of the heart and predispose humans and animals to AVRC.'

ARVC is uncommon in humans, affecting around 1 in 2000 people in the UK [1], and is a leading cause of sudden cardiac death, which is estimated to kill around 100,000 people a year in the UK [2]. Whilst approximately 50% of human ARVC cases are related to known genetic defects in desmosomes, the cause of the other 50% of cases still remains unknown. The new study suggests that mutations in the gene encoding the iASPP protein may contribute to the development of ARVC in these

previously-unexplained cases.

Professor Lu said: 'Our hearts are pumping every second of our lives so the heart is an organ that is under constant mechanical strain. If you think of these desmosomes as 'gluey' joints that hold heart cells together any weaknesses or 'cracks' that you introduce into these structures weaken the whole organ. Mice with the faulty gene controlling the protein, or that do not have sufficient amount of the protein to maintain the full function of desmosomes, develop weaknesses in the right ventricle of their hearts at early stages such as embryos. With time, the 'cracks' get bigger and when they reach a certain level it leads to premature death in adults – and these are strikingly similar to the weaknesses we see in the tissues of human ARVC patients.'

The team says that further research is needed into iASPP to establish exactly how it controls desmosomal structure and function to maintain heart tissue integrity for proper mechanical and electrical activity. Follow-up research will look into families with a history of ARVC to see if the gene controlling iASPP could be used to diagnose those at risk of developing the condition. If a reliable biomarker could be developed it could help clinicians to advise people to make lifestyle changes that would put them at less risk of [sudden cardiac death](#) and enable them to live longer.

One of the long-term side effects of cancer therapy is cardiotoxicity, a condition caused by a weakening of the heart function after cancer therapy. It could be that the same genes being targeted to treat cancer may also regulate desmosomes in the [heart](#). So this discovery may also have implications for research into cancer drug discovery programs in order to find ways to minimise cardiotoxicity.

A report of the research, entitled 'iASPP, a previously unidentified regulator of desmosomes, prevents arrhythmogenic right ventricular

cardiomyopathy (ARVC)-induced sudden death', is published in *PNAS*.

More information: iASPP, a previously unidentified regulator of desmosomes, prevents arrhythmogenic right ventricular cardiomyopathy (ARVC)-induced sudden death, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1408111112

Provided by Oxford University

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