Unlocking the genetics of birth abnormalities

Congenital birth defects, including common problems such as cleft palate, heart defects and dislocation of the hips, affect about one in every 30 children born in New Zealand.

Many aspects of their genesis remain a mystery but the landmark findings by University of Otago Chair of Child Health Research, Professor Stephen Robertson, have now implicated filamins, which had until then been considered relatively inert parts of the internal scaffolding of cells, in their causation for the first time.

Working with collaborators at the Cedar Sinai Medical Research Institute in the United States, Professor Robertson and his team discovered that mutations in two particular filamin genes encoding filamin A *(FLNA)* and filamin B *(FLNB)* - underlie eleven separate syndromes involving abnormalities of the skeleton, brain, heart, gut and kidneys in children.

Professor Robertson, a paediatric geneticist, says their research in the 1990s with a large North Island family with a history of one of these syndromes helped them uncover the role of filamins.

"Clearly our work has shown that they have a dynamic role in cellular function during development. They help process and regulate signalling both from outside the cell to within the cell, and also the co-ordination of the responses to those signals within the cell as well."

Their initial focus on *FLNA* soon broadened to *FLNB* when they published a paper in Nature Genetics in 2004 describing how mutations in the gene encoding the related protein filamin B caused birth defects, in much the same way as they had described filamin A the year before.

"*FLNA* related disorders tend to have profound effects on the structure of the kidney, urogenital tract, heart, brain and gut. *FLNB* was found to be responsible for several syndromes associated with malformations of the skeleton and integrity of the joints," Professor Robertson explains.

Studying those syndromes will give them insight into the cause of more common congenital anomalies, such as congenital dislocation of the hips.

Little is known about the consequences of filamin mutations or what Professor Robertson calls the "molecular geography" of the proteins encoded by the *FLNA* and *FLNB* genes and this is the subject of current research.

As one of the few laboratories testing these genes for mutations they get hundreds of samples from all over the world, says Professor Roberston.

"So what we do is take a clinical picture of those patients and their malformations, then correlate that with their molecular pathology so we can draw insight into the function of these genes during development."

They already have a number of clues and can already see there are particular parts of this gene which when mutated, produce particular patterns of malformation.

By understanding more about these processes they will eventually be able to deliver improved diagnostic tools for not only rare filamin-related conditions, but also more common malformations, such as congenital dislocation of the hips and congenital heart defects.

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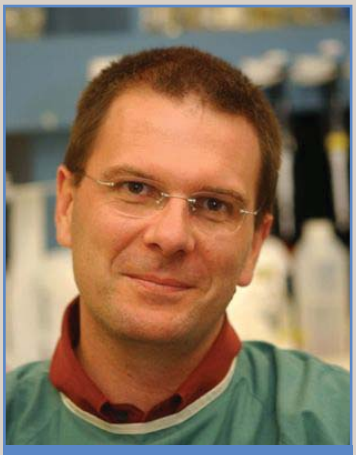

Professor Stephen Robertson

Key facts:

- Filamins form part of the cellular cytoskeleton or internal scaffolding of the cell, which gives it shape and structure
- Mutations in two genes, filamin A *(FLNA)* and filamin B *(FLNB)* are implicated in eleven separate syndromes which cause abnormalities.

Aims of this research:

- To develop a better understanding of the role of *FLNA* and *FLNB* during development
- To identify and understand which mutations are behind the syndromes caused by *FLNA* and *FLNB* mutations
- To increase understanding of more common malformations such as congenital dislocation of the hips and congenital heart defects.

What this research has shown:

- That mutations in both *FLNA* and *FLNB* underlie forms of syndromic congenital birth defects in children
- *FLNA* disorders tend to affect the structure of the kidney, urogenital tract, heart, brain and gut
- *FLNB* mutations are responsible for several syndromes associated with skeletal malformations and joint integrity.

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