Research Project:

Restoring NKX6-2 function by protein complementation: a proof-of-concept

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Scientific summary

Loss-of-function mutations in the NKX6-2 gene cause spastic ataxia 8 (SPAX8). Many of these mutations, including the Lys41* (c. 121A>T) mutation, lead to truncated, dysfunctional forms of NKX6-2 proteins. In this project, a research team led by Dr. Federico Herrera at the University of Lisboa, Portugal, is studying protein complementation, which could restore the function of truncated proteins like NKX6-2. Protein complementation (PC) involves proteins being split into two or more fragments that are not functional, but that recover their function when they are brought back together.

The researchers believe that PC can be applied to mutations that lead to incomplete NKX6-2 proteins, including K41*, E189*, Q197*, W203* or R66GfsTer122 mutations. They will create fragments of the NKX6-2 protein and combine them with the smallest SPAX8-associated NKX6-2 fragment (K41*) in living cells. They then plan to analyse the reconstituted K41* NKX6-2 to see if it recovers normal function.

By providing information about the structure and function of the NKX6-2 protein, the research team hopes to lay the groundwork for development of curative treatments for SPAX8. Such treatments could be based on gene therapy approaches, as well as the use of these protein fragments as drugs, thereby significantly simplifying their use in patients.

Lay summary

Spastic ataxia 8 (SPAX8) is caused by mutations in a gene called NKX6-2 that result in the formation of incomplete NKX6-2 proteins which are missing fragments. This leads to the NKX6-2 proteins becoming dysfunctional. NKX6-2 proteins are involved in interacting with DNA and controlling production of certain proteins in the central nervous system.

Current evidence suggests that protein function due to mutations of this type can be restored by adding the missing fragments, in a process known as protein complementation. In this project, a research team led by Dr. Federico Herrera at the University of Lisboa, Portugal, propose that protein complementation can be applied to mutations that lead to incomplete NKX6-2 proteins.

In this research project, the team plan to create fragments of the NKX6-2 protein and combine them with the smallest SPAX-8-associated NKX6-2 fragment in human living cell lines. They will observe whether this combination of fragments recovers normal NKX6-2 function.

The researchers hope that by studying the structure and function of the NKX6-2 protein, they can pave the way for the development of possible therapies for SPAX8.

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