One Gene, Two Functions, Many Possibilities

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SCA6 is caused by a mutation in the CACNA1A gene, which encodes for a calcium channel and a transcription factor, α1ACT. α1ACT is involved in neurite growth in Purkinje cells, and when expanded causes SCA6.

What if you couldn't walk or couldn't control your movements? What if your eyes were unable to focus, inhibiting your ability to see properly? Some people may not be the most coordinated, but what if it got to the point where you needed to be in a wheel chair? Would you want someone to try and do everything possible in order to help you? Spinocerebellar ataxia is a disease in which a person loses control over their movements, and it will eventually progress to a point where a person can no longer walk (Kordasiewicz & Gomez, 2007).

Spinocerebellar ataxias (SCAs) are a wide class of neurodegenerative disorders that are caused by mutations in various genes. However, most SCAs are autosomal dominant characterized by a CAG repeat in the gene, although some are caused by coding mutations or gene deletions (Sailer & Houlden, 2012). For most SCAs there is an inverse correlation between the length of the repeat and the age of onset (Manto, 2005).

In Spinocerebellar ataxia type 6 (SCA6) specifically, there is a CAG repeat in the CACNA1A gene which leads to a mutated α1A dependent calcium channel (Cav2.1) (Ishiguro et al., 2010). In SCA6, a healthy number of repeats is between 4-20 and an unhealthy number is between 20-28, which is a smaller number of diseased repeats than in other polyQ diseases (Ishiguro et al., 2010). These repeats then lead to disease progression with neurodegeneration in the cerebellum, leaving patients wheelchair bound due to loss of balance and coordination (Kordasiewicz & Gomez, 2007).

It is known that α1A calcium channel function is essential for normal and healthy Purkinje cell function in the cerebellum, and any mutation will lead to ataxia, specifically SCA6 (Zuchenko et al., 1997). However, there seems to be another player in the SCA 6 field. The CACNA1A gene also seems to encode for a transcription factor, α1ACT (Ishiguro et al., 2010). However, the mechanism for this is unknown.

There are many different mechanisms that mRNAs can use in order to override the expression of protein synthesis; however, further understanding for most of them is still needed (Spriggs, Bushell, & Willis, 2010). One possible mechanism is an Internal Ribosomal Entry Site (IRES), which has been defined as a highly structured RNA sequence found within the 5' of the untranslated region of cellular mRNAs that functions to recruit ribosomes for the initiation of translation (Brodel et al., 2013). This cap-independent mechanism of translation is unique, as most cellular mRNAs use a cap-dependent mechanism of initiation (Fitzgerald & Semler, 2009).

The origin and function of α1ACT is not known, but Xiaofei and colleagues (2013) hypothesized that α1ACT fragment may possibly be controlled by an internal ribosomal entry site (IRES) that dictates the production of α1ACT and α1A in addition to the fact that α1ACT controls neural cell development.

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In their findings Xiaofei and colleagues (2013) report that α1ACT is indeed controlled by an IRES, which is what allows the CACNA1A gene to encode for α1ACT and the calcium channel. The IRES could be detected by inserting DNA segments of different lengths from the 5' region to the α1ACT start site in-between R-Luc and F-Luc. Since R-Luc contains a stop-codon, the increase in F-Luc activity indicated the presence of an IRES as it enabled the rebinding of the ribosomes.

In addition, it was found that α1ACT is needed for healthy Purkinje cell growth, and when mutated as in SCA6 there is lack of neurite growth. When healthy α1ACT cells were injected with nerve growth factor there was enhanced neurite outgrowth. In contrast, when cells expressing mutated α1ACT were injected with nerve growth factor there was significantly lower percentage of cells with neurites.

The researchers also discovered that mutated α1ACT mediates ataxia in transgenic mice. When the researchers generated knockout mice that did not have the α1A channels nor α1ACT, there was severe neurological impairment. However, if the mouse lacked the α1A channel but had α1ACT, there was some improved behavioral phenotype. This then led to the conclusion that α1ACT enhances neurite outgrowth and allows for healthy behavior.

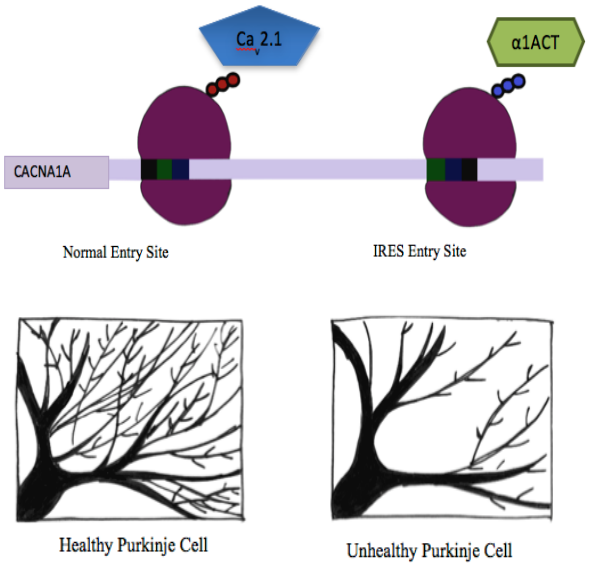

Figure 1. The CACNA1A genes encodes for the transcription factor α1ACT and a calcium channel. This is done by the presence of RNA that forms an IRES. α1ACT is implicated in SCA6 as when it is mutated, Purkinje cells are no longer able to grow or develop causing degeneration of the cerebellum.

The presence of mutated protein in SCA6 causes the Purkinje cells to have reduced growth in comparison to the non-mutated protein, and the Purkinje cells are therefore unable to function properly. In SCA6 when α1ACT is mutated, the neurite outgrowth is affected, which is what then causes the symptoms seen in the disease.

The authors of this article were able to find that healthy α1ACT is essential for the normal function of Purkinje cells and that this protein is formed due to the IRES within the CACNA1A gene. In addition, this study gives further support to the notion

that SCA6 is due to the polyQ repeat rather than the disturbed function of the calcium channel, as was hinted to in other studies analyzing the calcium channel in knock in mice (Watase et al., 2008)

This discovery allows for further research to be done in order to target some potential therapeutic strategies. For instance, the IRES that leads to the formation of mutated α1ACT in a person with SCA6 could be blocked, which would inhibit the degeneration of Purkinje cells. Blocking the pathway would inhibit formation of the mutated protein, which would help prevent many patients from slowly losing their ability to function. While this article looked at many facets of the transcription factor α1ACT, they could further study the IRES, as there may be other implications associated with the IRES beyond its initiation of α1ACT. In addition, further studies on how the calcium channel and transcription factor work together in SCA6 should be done. While the authors looked into past research on the implications of the calcium channel in SCA6, they should continue to see if the two work together in the disease.

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