The Role of the AIRE gene in sporadic Autoimmune Addison's Disease

Felix Liu*, Catherine Napier[1], Simon HS Pearce[1].

[1]Institute of Genetic Medicine, Newcastle University, UK. *Presenter; MBBS A100, student number: b2003621, Contact: f.liu4@ncl.ac.uk

Aims

The purpose of this study was to identify novel mutations in exon 8 of the AIRE gene in a cohort of 96 AAD patients.

Background

•Autoimmune Addison's Disease (AAD) is a chronic adrenal insufficiency due to autoimmune destruction of the adrenal glands

•The disease can have two forms: early-onset or sporadic (adult-onset) AAD

•Early-onset AAD is directly caused by a mutation on the Autoimmune Regulator (AIRE) gene

•A specific genetic cause for sporadic AAD has not yet been identified

•80-90% of patients with primary adrenal insufficiency in the developed world have autoimmune Addison's, but patients with the early-onset form only account for up to 15% of these (Arlt and Allolio, 2003)

•If a genetic marker were to be identified, it could be used to screen at risk individuals before the disease becomes clinically apparent, and thus lead to better outcomes

•Recent research has found a small cluster of dominant-negative mutations on the AIRE gene in families with AAD, suggesting it may also play a role in sporadic AAD (Wolff et. al., 2008)

Methods

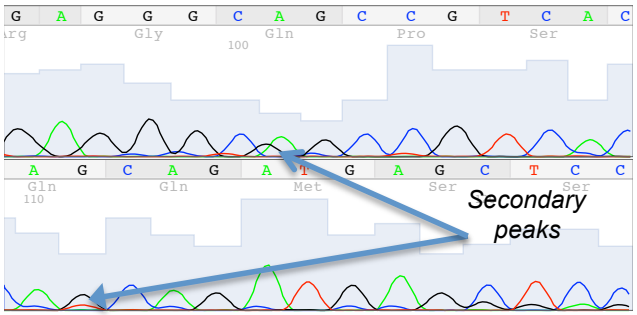
•The cohort included 12 probands with familial AAD, and 84 patients with AAD and either concurrent autoimmune disease, or a strong family history of autoimmune disease

•We PCR amplified DNA samples of these patients, confirmed the method's accuracy using gel electrophoresis, and purified the samples using the QIAquick PCR purification kit. Sent PCR product for Sanger sequencing by GATC biotech.

•Finally, we searched for mutations in the resulting sequence data and chromatograms using computer analysis.

Results

The method yielded chromatograms of good quality, which demonstrated occasional secondary peaks. However, the size of the peaks did not suggest any nucleotide changes representing meaningful mutations.



Nucleotide sequence from exon 8, AIRE of AAD patient with concurring vitiligo and premature ovarian failure

Discussion

Early-onset AAD can be passed on from parent to child because it is caused by a single point mutation on the AIRE gene. This means it can be screened for using genetic testing, helping to identify the disease before symptoms appear. If similar mutations were identified in sporadic AAD, this knowledge could be used to greatly benefit sufferers: genetic screening could be used to identify individuals with the disease, as with the early-onset form of the disease.

We selected our cohort for a strong family history of AAD, or of autoimmune disease in general, suggesting that there is a strong genetic basis for the disease in these individuals. While our results show secondary peaks on chromatograms of exon 8 of the AIRE gene in these patients, these signals were not strong enough to imply mutations had in fact occurred. It follows that exon 8 of the AIRE gene is not involved in causing sporadic AAD.

It has been shown previously, however, that sporadic AAD is, at least in part, influenced by genetic predisposition. In this study, we investigated just one section of one gene in our cohort; it is possible that mutations exist in parts of their genetic codes which we did not examine.

Conclusions

•No new mutations were identified in exon 8 of the AIRE gene in our cohort

•Further research should be undertaken to enhance our understanding of the genetic basis for sporadic AAD

References

Arlt, W. and Allolio, B., 2003. Adrenal insufficiency. Lancet, 361(9372), 1881-1893.

Bøe Wolff, A.S., Oftedal, B., Johansson, S., Bruland, O., Løvås, K., Meager, A., Pedersen, C., Husebye, E.S., Knappskog, P.M.. (2008). AIRE variations in Addison's disease and autoimmune polyendocrine syndromes (APS): partial gene deletions contribute to APS I. Genes and Immunity. 9, p130-136.