Oligonucleotide-Based Splice Correction of the ABCA4 c.5461-10T>C Mutation in Stargardt Disease Type 1

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Introduction

• Stargardt disease type 1 (STGD1) is the most common form of inherited macular dystrophy causing progressive impairment of central vision, with onset typically in childhood or young adulthood.
• STGD1 is an autosomal recessive mode of inheritance associated with ABCA4 mutation in the LFPRD domain, which encodes a transport protein localized in photoreceptor outer segment disk edges.
• ABCA4 mainly functions to remove potentially toxic retinoids, such as N-retinylidene-phosphatidylethanolamine, which originate from the phototransduction process. Failure of this transport, caused by absent or dysfunctional ABCA4, results in accelerated photoreceptor disc loss.
• ABCA4 mainly functions to remove potentially toxic retinoids, such as N-retinylidene-PE, which originate from the phototransduction process. Failure of this transport, caused by absent or dysfunctional ABCA4, results in accelerated photoreceptor disc loss.

Materials & Methods

ABCA4 minigene was generated as described previously. HEK293 cells were transfected with 50 ng pEGFP using Lipofectamine™ 2000. For in vivo experiments, wild-type STGD1 mouse model. Experiments were conducted in accordance with the ARRIVE guidelines and in line with the 3Rs principles.

Results

Acknowledgments

This work was supported by grants from the Netherlands Organization for Scientific Research (NWO), the Netherlands Research School for Genomics (NLRS), and the Dutch Ophthalmic Research Foundation (BOF).

References

4. Garanto A, Gloag C, Widynska A, Wagner N, Livingstone 1, 2, 3, 4. Minigene was generated as described previously. HEK293 cells were transfected with 50 ng pEGFP using Lipofectamine™ 2000. ABCA4 c.5461-10T>C Mutation in Stargardt Disease Type 1.

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Antisense Oligonucleotide Mediated Splice Modulation in Human Retinal Organoids

Generating animal models for splicing defects represents a challenge since human splicing events may not be captured by the splicing machinery of other species. In the absence of animal models, patient iPSC-derived retinal organoids provide an excellent platform to test therapeutic interventions: in addition, they simulate the disease phenotype and provide an appropriate cellular model with the generic mutations in genomic context.

A patient application claiming the invention as disclosed in this patent was filed (PCT/EP2018/095142).

Conclusion

In this study we:

• identified AONs that can correct the ABCA4 c.5461-10T>C mediated splice defect in vitro
• demonstrated in vivo splicing modulating activity of AONs using a surrogate retinal target, Ush2a, in photoreceptors
• observed that AONs have long retinal half-life that might allow monthly or quarterly dosing
• noticed similar splice modulating activity of AON in retinal organoids which represent a promising test system in the absence of an animal model.

Taken together, splice-correcting antisense oligonucleotides represent a promising treatment option for STGD1.

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