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MUTATION DETECTION & CORRECTION EXPERIMENTS

IN EPIDERMOLYSIS BULLOSA SIMPLEX

Stichting Drukkerij C. Regenboog, Groningen

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Contents

Scope of this thesis

This thesis deals with the molecular diagnosis of epidermolysis bullosa simplex (EBS) and the potential gene therapy of this disease. EBS is a blistering skin disease caused by mutations mostly of the keratin genes *KRT5* and *KRT14*. Our first aim was to set up a diagnosis of EBS at the DNA level. Therefore, we developed a genomic mutation detection system. Our second objective was to repair these mutations. Hence, we wanted to investigate gene correction of EBS.

As most of the reported *KRT14* mutations had been identified in exons 1, 4 and 6, we initially developed a genomic mutation analysis system for hotspot mutations of *KRT14* (chapter 2). Subsequently, a genomic mutation detection system for regions outside the *KRT14* hotspots was developed in order to have a comprehensive genomic mutation analysis system for EBS (chapter 4). This *KRT14* genomic mutation detection system, in combination with the previously described mutation detection system for *KRT5*, has been used for screening of EBS patients. For the 18 EBS patients investigated, mutations could be detected in each case (chapters 2, 3 and 4).

With all our knowledge about the causes of EBS, no permanent remedy for EBS patients is available to date. Since EBS is a heritable disease, possible gene therapy might be the definite solution. However, there are some aspects to be taken into consideration. Since the keratin filament network is built up of heterodimers that contain both a K5 and a K14 molecule, disturbance of regulation of these genes should be avoided. Besides, keratin EBS mutations mostly exert a dominant-negative effect. Therefore, an ultimate therapy would be to correct the underlying mutations. Potentially, specific types of oligonucleotides are useful to achieve this. The second part of this thesis (chapters 5 and 6) will focus on this possibility of gene correction.