

SUMMARY

Chapter I-I describes the current knowledge concerning Osteogenesis Imperfecta (OI). OI is characterized by bone fragility leading to fractures. Because of the clinical and supposed genetic (based on pedigree findings) heterogeneity of OI, a classification in four types was proposed in 1979 by David Sillence. This classification consisted of OI type I (mild, autosomal dominant), type II (perinatal lethal, autosomal recessive), type III (severe deforming, autosomal recessive) and type IV (moderately deforming, autosomal dominant). After the discovery of heterozygous mutations in the *COL1A1/2* genes in all OI types, OI was considered to be an autosomal dominant disease and the Sillence classification was used for clinical/radiological classification only. In 2004 and 2007 the Sillence classification was expanded with OI types V-VIII because of distinct clinical features and/or different causative gene mutations since in 2006 and 2007, recessive causative variants in *CRTAP* and *LEPRE1* had been discovered to cause OI as well. To date, 8 genes are known to cause recessive OI type II-B, III, IV or Bruck syndrome (OI with congenital contractures of the large joints) namely *CRTAP*, *FKBP10*, *LEPRE1*, *PLOD2*, *PPIB*, *SERPINF1*, *SERPINH1*, *SP7*. Only 2 of these 8 genes (*SP7* and *SERPINF1*) appear not to be involved in the collagen type I biosynthesis. The increased knowledge concerning the genetic causes of OI changed in particular the laboratory diagnosis of OI, which has now sequencing of the *COL1A1/2* genes as a starting point. In the past, the diagnostic flow started with collagen electrophoresis. With use of this technique collagen type I production by dermal fibroblasts could be analyzed. In OI type I collagen type I production appeared decreased and in the other OI types production of abnormal collagen type I occurred. Collagen electrophoresis still is important in certain selected cases but it is to be expected that it will be used less frequently. The treatment of OI has not been influenced much by the discovery of genetic heterogeneity in OI and has a multidisciplinary character. Further investigations of therapeutic approaches such as bisphosphonates, growth hormone therapy, gene therapy and stem cell therapy are essential.

Chapter II-1 described for the first time in the literature, deletions of the complete *COL1A1* allele in four families with mild OI and no other phenotypic abnormalities. These findings underline the importance of MLPA analysis of the *COL1A1* gene in cases of suspected OI type I with no detectable mutation.

In **Chapter III-I** five families are described with novel causative variants in *CRTAP* encoding cartilage associated protein (CRTAP). It was concluded that it appeared not possible to discriminate OI caused by recessive variants in *CRTAP* from OI caused by dominant *COL1A1/2* causative variants based on clinical/radiological, histological or biochemical (collagen electrophoresis) characteristics.

Chapter III-2 is the first report in the literature on *PPIB* mutations as a cause of OI type II-B/III as is seen with causative variants in *COL1A1/2*, *CRTAP* and *LEPRE1*. Deficiency of CRTAP or prolyl 3-hydroxylase 1 (P3H1) had been reported in autosomal recessive lethal/severe OI. CRTAP, P3H1 and Cyclophilin B (CyPB) form an intracellular collagen-modifying complex with probably multiple functions.

Chapter III-3 reports a large consanguineous Turkish family in which multiple individuals are affected with autosomal recessive lethal or severe osteogenesis imperfecta (OI) due to a novel homozygous *LEPRE1* mutation. In one affected individual histological studies of bone tissue were performed, which may indicate that the histology of *LEPRE1* associated OI is indistinguishable from *COL1A1/2*, *CRTAP* and *PPIB* related OI.

Chapter III-4 is a report of the first Indonesian patient with the very rare Bruck syndrome, due to a novel homozygous causative *FKBP10* variant .

In **Chapter IV-1** a revised classification of OI is proposed with continued use of the Silience criteria I, II-A, II-B, II-C, III , IV, V and VI for clinical and radiological classification of OI with additional mentioning of the causative mutated gene. Addition of a new type only because it has a different genetic cause (for example OI type VII and VIII) is discouraged.

Chapter IV-2 summarizes the conclusions of the Best Practice meeting in Amsterdam concerning the laboratory diagnosis of OI. Due to the genetic heterogeneity in OI, it was agreed to a new diagnostic flow with DNA analysis (sequencing) of the *COL1A1/2* genes as a starting point as opposed to protein analysis.

Chapter V focuses on the future perspectives in OI research. Approximately 95-96% of genetic causes of OI are discovered and with the next generation sequencing techniques it is to be expected that other rare causes of OI will be discovered. This will shift the challenge in OI research to development of therapy for OI. The combination of osteoblast transplantation (by de- and redifferentiating patient's own fibroblasts) and gene therapy may offer the best therapy for OI. More research into that particular area is needed.