In this thesis the natural development and growth of osteochondromas is addressed to increase the understanding of the disease Hereditary Multiple Osteochondroma (HMO). The subjects described are origin and development, structure and clinical visualisation of osteochondromas.

**Origin and Development:** In the past different hypotheses regarding the formation of osteochondromas have been postulated. Studies presented in this thesis support the hypothesis of the epiphysis as the origin of osteochondromas, because of two reasons; firstly because of the histological comparison between osteochondroma cartilage and epiphyseal cartilage and secondly because growth patterns of osteochondromas equal growth patterns of the epiphysis in individual patients. Development of osteochondromas seems to be directed by growth hormones. Since HMO is a genetic disorder, the systemic influence of the genetic abnormality may be responsible for many HMO-related clinical features, for example the general influence of HMO-associated gene mutations on the maturation of the growth plates. Genetic mutations in the exostosin genes lead to abnormal chondrocyte differentiation and proliferation, due to aberrant expression and function of growth factors and other signaling molecules. Families of these signaling molecules play crucial regulatory roles in epiphyseal skeletal development. This may result in decreased stature and growth deformities that are typically associated with HMO. Data presented in this thesis show that the skeletal age in young children with HMO is lower than their calendar age, while for adolescent boys it is higher. This general influence on growth is of direct clinical relevance in the planning of epiphysiodesis in leg length discrepancy and hemi-epiphysiodesis in axial deformities, which are common features in HMO patients. Until now there is no algorithm available to predict the growth in these patients, therefore individual monitoring of patients’ bone age and the development of growth deformities is advised.

**Structure:** The microstructure of osteochondromas is addressed in a pilot study. It shows that osteochondromas have thicker and wider spaced trabeculae. This is combined with a relatively normal trabecular number and a normal bone volume fraction, compared to normal trabecular bone of children in the same age range.
These observations may provide an explanation why osteochondromas have an osteoporotic-like appearance and why they can spontaneously fracture. In future a better understanding of the microstructure might potentially lead to early interventions to influence the growth of the osteochondromas.

**Clinical visualisation:** Conventional radiographs clearly show the bony part of osteochondromas but fail to visualize the cartilaginous cap. Because osteochondromas grow, they can compress surrounding tissues. As the cartilaginous cap is a substantial part of the osteochondroma, especially in children, there is a need to increase the visibility of the cartilaginous part of osteochondromas as well. A study using Whole body MR (Wb MRI) with proton density SPIR setting showed accurate detectability of osteochondromas based on the clear visualisation of the cartilaginous cap. The use of MR imaging reduces the exposure to ionising radiation and it may lead to early detection of osteochondromas compared to conventional radiography. Another way to improve the visibility of the growth of osteochondromas over time could be the use of time-lapse technique. This technique enhances the visibility of slow changes over time. It is suitable to monitor growth of wrists in HMO patients, but showed no direct relationship between growth of wrists and osteochondromas. It did show however osteochondromas disappearing, demonstrating that not all osteochondromas remain.

Future studies are directed towards the use of the HR-pQCT (XtremeCT) for imaging the osteochondromas in vivo. Furthermore the missing link between the affected gene loci and the underlying pathways could be uncovered through a better understanding of the role of heparan sulphate chains in sequestering of signaling proteins.

Progress in these fields is expected to increase understanding of osteochondroma growth patterns and may help in the search for early diagnosis and early treatment.