Genetics of Dupuytren's disease

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DD is a nodular palmar fibromatosis of unknown cause, commonly affecting the hands. DD is often a familial condition that has been reported in twins and is extremely common in individuals of North European extraction. Genetic studies have yet to identify the genes involved in DD formation. It was Dupuytren's assistant Goyrand in 1834 who first noted the link between DD and its familial predisposition. Since then, several reports have suggested the presence of familial tendency in DD. Average figures for family incidence have been reported to vary from 10 to 30 %, however, studies with specific enquiries and clinical examination of relatives of DD cases have shown the presence of a family history in patients with rates as high as 44 % to 68 %. Ling in 1963 interviewed 50 DD cases and reported a 16 % positive family history but after examination of the hands of 832 relatives of those 50 DD cases he showed that the incidence of family history had risen to 68 %. Several case reports have indicated the presence of DD in twins. Observations in twin studies and family studies suggest genetic heredity for DD. Early case reports documented four pairs of monozygotic twins both presenting the disease. Familial prevalence in DD has been documented and individuals with a strong family history of DD may develop more severe forms of the disease at a younger age. We determined a sibling recurrence-risk ratio of 2.9 in north-western England population. Studies characterising racial population prevalence and DD phenotype also suggested a geographic variation that may be consistent with genetic predisposition. DD inheritance mode has been shown to be autosomal dominant mode with variable penetrance; however, it is currently unclear if DD is a complex oligogenic or a simple monogenic mendelian disorder. Hu et al. have established a 6cM region on chromosome 16q (between marker D16S419 and D16S3032) in a five-generation Swedish family, with a maximal two-point logarithm of odds score of 3.18 at D16S415. In addition, a possible role for transforming growth factor (TGF)-β in DD has been suggested. Case-control

studies have been carried out to assess the association between DD susceptibility and single nucleotide polymorphisms (SNP) in the TGF-β pathway. These studies have focused on TGF-β1, TGF-β2, TGF-β receptor one (TGF-βRI), TGF-βRII, and TGF-βRIII. Although there is a lack of association between DD and these SNPs, it is possible that other un-investigated regions of the genes may still contain DD causative polymorphisms or mutations. Increased activation or expression of TGF-β1 can be induced by Zf9 transcription factors or mitochondrial alterations (partial mitochondrial depletion or treatment with mitochondrial inhibitor). Positive association has been determined between DD susceptibility and the presence of a G allele versus an A allele SNP at position 1140 of Zf9 transcription factor. In addition, we reported a positive association between DD susceptibility and a heteroplasmic mutation located within the mitochondrial 16s rRNA region. Previous cytogenetic studies have shown acquired structural and numerical chromosomal abnormalities in cells grown from DD tissue samples compared to normal palmar fascia. These studies demonstrated a variable number of abnormalities in affected tissue, compared to normal palmar fascia. All studies showed cells grown from DD tissue to be trisomic for chromosome 8 with a few being trisomic for 7 and Y chromosome abnormalities. However, the transverse fascial tissue used as control showed similar chromosomal aberrations as the DD nodular tissue. Evidence for chromosome trisomy 8 is also found in other benign tumours. However, another study looking at 40 DD tissue samples from 36 DD cases did not reveal any consistent chromosomal structural changes. The HLA-antigen status of Dupuytren's patients has been recorded and at least one possible pattern of association has emerged. There is a gradation in expression of certain genes in DD tissue phenotypes (cords and nodules) compared to external control fascia. Transcriptome (mRNA transcripts present in a cell at a given time) profiling is not only predictive of disease but of disease phenotype. These results indicate a number of significant candidate genes associated with DD formation. Genetic studies may provide clues for molecular mechanisms involved in DD pathogenesis and may help further development of strategies for diagnosis, therapy and prophylaxis of DD.