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Letter to Editor

Cathepsin C involvement in the aetiology of Papillon–Lefevre syndrome

We read with interest the report by Drs Patel and Davidson [1] concerning Papillon–Lefevre syndrome (PLS). Since the writing of their paper, the cause of the aggressive periodontitis observed in PLS has become more evident. Although defective neutrophil chemotaxis has sometimes been suggested to account for the aggressive periodontitis of PLS [2,3], and associations with certain HLA haplotypes (i.e. HLA DRB1*0406, DRB1*08032, DQB1*0302 and DQB1*06011 [4]) or herpes virus infection have been described [5], the probable cause of the aggressive periodontal destruction is a defect of cathepsin C (CTSC).

The definite gene of PLS has been mapped to chromosome 11q14-q21 [6–8], particularly in the interval between D11S4082 and D11S931, where the gene (CTSC) encoding the lysosomal protease cathepsin C (or dipeptidyl aminopeptidase I) lies [9–11]. Patients with PLS have a defect of cathepsin C expression, principally because of a mutation in the CTSC gene. To date, more than 40 such mutations have been identified world-wide in PLS and related conditions [12], most of which result in a loss of enzymic function [13–14].

Heterozygous carriers of CTSC mutations do not have the palmoplantar hyperkeratosis nor aggressive periodontitis, and thus, the presence of one wild-type CTSC gene is sufficient to prevent such disease [15–16]. Clinical disease arises only when CTSC activity is virtually absent, thus making it unlikely that weak CTSC mutations are a cause of more common types of early-onset periodontal disease – as confirmed by analysis of patients with aggressive periodontitis but without the features of PLS [16].

Cathepsin C is involved in a wide variety of immune and inflammatory responses. It plays an essential role in activating serine proteinases expressed in the granules of bone-marrow-derived cells from both the myeloid and lymphoid series. These serine proteinases are implicated in a variety of inflammatory and immune processes, including phagocytic destruction of bacteria [7], and the activation of phagocytic cells and T-lymphocytes [12]. Therefore, deficiency of cathepsin C function will result in a loss of immunological responses, leading to a liability to infection [12]. A defect that principally interferes in phagocytic function (as with cathepsin C deficiency) is likely to give rise to aggressive periodontitis of PLS since nearly identical features occur in other defects of phagocytic function [16].

Cathepsin C may be functionally important in the development and maintenance of integrity of the skin [15]. It is interesting to note that, once the teeth are exfoliated and the junctional epithelium is consequently eliminated, the severe gingival inflammation of PLS resolves. Since the sulcular and junctional epithelium represents the first line of defence against pathogens, their aberrant differentiation could potentially alter the mechanical barrier to periodontal pathogens [12,15].

Since 1985, there have been reports of patients presenting with atypical PLS, in particular late-onset periodontitis with early-onset palmoplantar keratoderma [17]. This phenomenon can be explained on the basis of the genetic heterogeneity of cathepsin C [17]. It has also been suggested that Haim–Munk syndrome (PPK, severe periodontal destruction, pes planus, recurrent pyogenic skin infections, possible arachnodactyly) may be an allelic variant of PLS [15].

The rapid identification of the site of the genetic defect of PLS and the consequent realization of the causative enzymic defect demonstrates how important it is for clinicians to recognize genetically determined disease patterns (often presenting in childhood) and to collaborate with scientists in finding the cause. Only through such focused collaboration

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will the treatment (and prevention) of unusual orofacial diseases in children be ultimately improved.

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