Novel and Recurrent *KIND1* Mutations in Two Patients with Kindler Syndrome and Severe Mucosal Involvement

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Sir,

Kindler syndrome (KS) is a rare genodermatosis characterized by acral skin blistering and photosensitivity, followed by diffuse progressive poikiloderma, and various degrees of mucosal involvement (1). Mutations in the *KIND1* gene (20p12.3) have been disclosed in most patients with clinical signs consistent with KS (2–4). The gene product, kindlin-1, is a 78-kDa phospho-protein expressed in skin in the basal keratinocytes (5). It forms complexes with β1 and β3 integrin subunits and, accordingly, kindlin-1-deficient keratinocytes have adhesion, proliferation, polarization and migration defects (6, 5). This report examines the genetic basis of KS in one Albanian and one Turkish patient with KS with severe involvement of the digestive and genitourinary mucosa, and discusses genotype/phenotype correlations.

CASE REPORTS

Patient 1. A 16-year-old Albanian female, born to non-consanguineous parents, developed acral blistering during infancy, followed by progressive skin atrophy and poikiloderma (Fig. 1A). At 13 years of age, surgical repair of a severe acquired vaginal stenosis had been performed. One year later, she lost all of her teeth due to severe periodontitis and started to suffer from dysphagia. Oesophagoscopy and a barium oesophagogram confirmed oesophageal stenosis and web formation. Her body weight was 29 kg, height 1.58 m and she had profound anaemia. She had proximal webbing of the fingers and toes, pseudo-syndactily, contractures of the fingers, palmoplantar keratoderma, loss of dermatoglyphics, and nail dystrophy (Fig. 1B). There was complete effacement of the external female genitalia; the labia majora, labia minora, clitoris and introitus were absent, and only one 4–5 mm orifice, supposed to be the vestibulum, was present. As she had been menstruating regularly, it is thought that her vagina and urethra terminated at the same orifice. The results of abdominal, urinary system and pelvic ultrasonography were normal. Pelvic magnetic resonance imaging showed normal organs. The configurations of the uterus, cervix and vaginal canal were normal on T2-weighted sagittal images, except for the visible end-point of the vagina, which was located at the level of the symphysis pubis. X-rays of her hands showed diffuse osteoporosis, deformed tips of the phalanges with peri-phalangeal soft tissue not extending to the metacarpal area. Histopathology of a skin specimen from the patient's neck showed epidermal atrophy with diffuse flattening of the rete ridges, telangiectatic vessels, melanophages, and minimal sclerosis of the dermis. Since she had insufficient oral intake, a balanced nutritional oral solution containing protein, lipid, carbohydrates, mineral and vitamins, and 5% dextrose 1000 cc iv infusion per day was started. She has been scheduled to undergo a series of oesophageal dilatation sessions, following temporal parenteral nutrition to improve her general condition.

Patient 2. A 25-year-old Turkish man born to non-consanguineous, but geographically-linked parents. Family history revealed three mildly affected younger patients among his remote cousins. He developed skin blistering 15 days after birth. His skin was atrophic, especially on the dorsal aspects of his hands and feet, and he had progressive poikiloderma (Fig. 1C). There were erosions and scaly crusts on his lips and white membranes on the labial commissures and adjacent, atrophic buccal mucosa. He developed photosensitivity in infancy. He complained of dysphagia and had a history of annual oesophageal dilatation since the age of 15 years. He also had anal and urethral strictures. He had bilateral proximal webbing of the fingers and toes and severe toe-nail dystrophy.

Mutation detection

Genomic DNA extracted from peripheral lymphocytes was used for polymerase chain reaction (PCR) amplification of the

Fig. 1. (A) Poikiloderma on the neck of patient 1. (B) Skin atrophy over the dorsa of the hands, webbed fingers and palmar keratosis in patient 1. (C) Poikiloderma on the trunk of patient 2.

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entire coding region and exon-intron boundaries of *KIND1*, as described previously (3). The PCR products were used for sequencing reactions and then submitted to automated nucleotide sequencing in an ABI 3130XL genetic analyser (ABI, Darmstadt, Germany). DNA sequences were compared with the reference sequence from the NCBI Entrez Nucleotide database (NM_017671) using Mutation Surveyor software (Softgenetics, State College, PA, USA; www.softgenetics.com). Each mutation was confirmed by re-sequencing a PCR product obtained from a second amplification reaction.

In patient 1, the homozygous mutation c.676dupC was identified (Fig. 2A). The duplication of cytosine at position 676 in exon 5 of the kindlin-1 mRNA resulted in frameshift and the formation of a premature termination codon, 16 codons downstream, p.Q226fsX16. In the DNA sample of patient 2, a novel homozygous mutation was disclosed in exon 3 of the *KIND1* gene, c.170C > A (Fig. 2B), leading to a premature termination codon instead of codon 57 for serine, p.S57X. In both cases, the parents were found to be heterozygous carriers of the respective mutations.

DISCUSSION

While the skin phenotype is typical in KS, fragility of mucous membranes seems to vary between cases. The most frequent are the oral mucosal manifestations, which include white patches, atrophy, blistering, gingival bleeding, severe periodontitis, ankyloglossia, restricted mouth opening and malocclusion (7). Development of oesophageal, anal and urethral stenosis, and phimosis are rare findings (7). So far, involvement of the female genitalia has been reported in only two patients, who had vaginal stenosis and vulvar synechia (8, 9).

Both patients described here had severe oesophageal stenosis, necessitating dilatation. Due to poor oral intake, the general condition of patient 1 degraded progressively, leading to severe anaemia and malnutrition, comparable to patients with dystrophic epidermolysis bullosa. She also showed severe vulvo-vaginal synechia, completely effacing the external genital architecture. To the best of our knowledge, this is the third reported case of KS with severe scarring of the female genital tract. It is not clear why the female genitalia are less often reported to be involved in KS compared with males with KS. However, this sex-related difference may not be accurate, for lesions of the vulvo-vaginal area might simply be overlooked.

All 25 *KIND1* mutations described in the literature were nonsense, splice-site or frame-shift mutations, predicted to lead to a premature termination codon and to RNA decay and absence of the full-length protein (10–14). Nevertheless, the associated phenotypes were variable. Several *KIND1* mutations occurred in more than one family, either as ancestral alleles, or as recurrent mutations in diverse ethnic groups (10, 13).

In this report we disclosed one recurrent, c.676dupC, and one novel, c.170C > A, *KIND1* mutation in patients originating from Albania and Turkey, respectively. Both mutations lead to premature termination codons and are predicted to cause absence of the full length kindlin-1 protein. The mutation c.676dupC was previously identified in affected individuals from Pakistani families and was shown to be both a hotspot and a founder mutation (10, 12). Among the patients with KS investigated in our laboratory, patient 1 reported here from Albania-Kosovo, and one previously reported patient originating from Kosovo, were homozygous for this mutation (5). Although they are unrelated, both had the same *KIND1* SNP haplotype, different from the ancestral Pakistani haplotype (10). Thus, our findings confirm c.676dupC, to be both, a hotspot and a founder mutation (10). Including the present case, 13 patients with KS homozygous for the c.676dupC mutation have been published (5, 10, 15). Their skin phenotypes were similar, but mucosal involvement varied: our patient 1 and one 37-year-old patient (15) were similarly severely affected. Genotype-phenotype correlations are difficult in patients of different ages, but it is clear that the same *KIND1* mutation can lead to various degrees of disease severity (2). These data suggest that in KS clinical manifestations are age-dependent and may be influenced by environmental exposure as well as by other currently unknown factors.

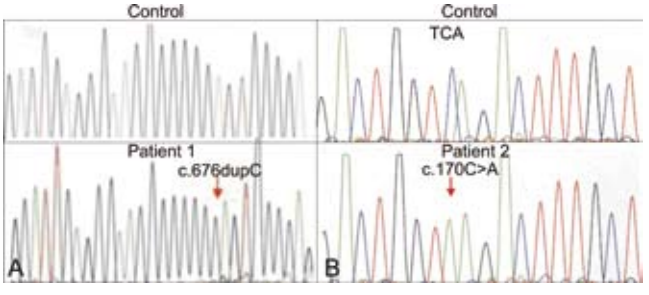

Fig. 2. (A) Partial DNA sequence of exon 5 of the *KIND1* gene. Wild-type sequence (upper panel) and the homozygous mutation c.676dupC (lower panel) in the DNA sample of patient 1. (B) Partial DNA sequence of exon 3 of the *KIND1* gene. Wild-type sequence (upper panel) and the homozygous mutation c.170C > A (lower panel) in the DNA sample of patient 2. Red arrows indicate the mutations.

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ADDENDUM

4th International Workshop for the Study of Itch

Abstract added after printed version of Acta Derm Venereol 2007; 87: 459–480

PSYCHOLOGICAL ASPECTS OF ITCH: QUALITATIVE RESEARCH ON OLDER ADULTS LIVING WITH ATOPIC DERMATITIS SINCE CHILDHOOD *(P30)*

Shelley F. Diamond

Psychological aspects of the itch-scratch cycle were identified in a qualitative study on the development of expertise in self-management of atopy. The purpose of this dissertation research was to identify the knowledge, skills, and abilities needed and the resources used in self-management of atopy. Six adults aged 45–60 with early-onset atopic dermatitis (AD), asthma, allergic rhinitis, and/or anaphylaxis participated in two semi-structured two-hour interviews, using grounded theory and narrative methodologies. Interviewed participants had severe or moderate AD and allergies, and mostly mild asthma. Previously gathered archival data from 225 eczema patients in an Internet listserv peer support group were used to triangulate the interview data. Participants were asked how they learned to manage their conditions, starting in childhood when symptoms first occurred, through adulthood to their current age. Knowledge, skills, and abilities needed to manage itch were inter-related with the management of other symptoms of atopy. Psycho-physiological experiences of stress that contributed to the itch-scratch cycle and its level of severity included: anxiety, frustration, anger, hopelessness, conflicts between competing cognitive-behavioral demands, and pressure to take action in ambiguous circumstances. Habitual behavioral patterns and situationally-derived cues or triggers also increased the likelihood that psycho-physiological sensations would be interpreted as itch. Different knowledge, skills, and abilities were needed to cope with different types of perceived itch, e.g. scratching that triggers more intense itch vs. scratch that relieves itch, emotional triggers of itch, and itch induced by environmental conditions or contact with allergens. Findings suggest new directions for research.

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