REVIEW ARTICLE

The *p63* gene in EEC and other syndromes

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Several autosomal dominantly inherited human syndromes have recently been shown to result from mutations in the *p63* gene. These syndromes have various combinations of limb malformations fitting the split hand-split foot spectrum, orofacial clefting, and ectodermal dysplasia. The *p63* syndrome family includes the EEC syndrome, AEC syndrome, ADULT syndrome, limb-mammary syndrome, and non-syndromic split hand/foot malformation. The pattern of heterozygous mutations is distinct for each of these syndromes. The functional effects on the p63 proteins also vary between syndromes. In all of these syndromes, the mutation appears to have both dominant negative and gain of function effects rather than causing a simple loss of function.

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EEC SYNDROME

The EEC syndrome (MIM 129900) is characterised by the triad of ectrodactyly, ectodermal dysplasia, and facial clefting. A number of associated anomalies are frequently found, among which are lacrimal tract anomalies, urogenital anomalies, and conductive hearing loss.[1–3] The EEC syndrome is relatively common with over 200 cases published. It is well known for having both variable expressivity and reduced penetrance. A comparison of interfamilial and intrafamilial variability in expressivity found significantly larger interfamilial variability, suggesting that more than one gene or allele might be involved.[3]

p63 gene mutations in EEC syndrome

p63 gene mutations account for most and possibly all cases of classical EEC syndrome (fig 1). An extended analysis of EEC syndrome patients showed heterozygous mutations in 40 of 43 unrelated families. This indicates that *p63* is the major if not the only gene mutated in EEC syndrome.[4] All but one of these mutations give rise to amino acid substitutions in the DNA binding domain common to all known *p63* isoforms. The arginine codons 204, 227, 279, 280, and 304 are most frequently mutated. Mutations involving just these five amino acids account for 75% of all EEC syndrome cases. A single frameshift mutation was detected in exon 13 in a patient with EEC syndrome characterised by cleft lip and palate, ectodermal dysplasia, split hand-split foot malformation, and mammary gland aplasia.[5] Although the phenotype of this patient most closely resembles EEC syndrome, the mammary gland aplasia would also be consistent with a diagnosis

of limb-mammary syndrome (LMS).[6] Interestingly, two typical limb-mammary syndrome patients have also been found to have frameshift mutations affecting the C-terminal region of the gene.

Different factors may contribute to this highly specific distribution of *p63* mutations in EEC syndrome. It is possible that the mutations involve nucleotides that are highly mutable. The fact that mutations commonly affect CpG sites is consistent with this notion. However, it is more likely that the restricted mutation spectrum in EEC syndrome reflects a specific pathogenetic mechanism. This possibility is supported by the finding that for each of the frequently mutated amino acids a number of different missense mutations occurred, such as R204W/Q, R279C/H/Q, R280C/H/S, and R304W/Q. All of these mutations were associated with EEC syndrome, whereas mutations affecting other domains of the p63 protein yield phenotypically distinguishable syndromes, such as AEC or LMS. This suggests that, although mutations can occur at many different sites along the *p63* gene, only those affecting specific amino acids in the DNA binding domain of the molecule will yield an EEC phenotype.

The EEC syndrome community

Several syndromes have been described which share features with EEC (table 1). Some of these are now known to result from mutations of the *P63* gene and are thereby allelic to classical EEC syndrome in 3q27. In others, allelism has been excluded, and for yet others this is unknown.

A large kindred has been reported in which a syndrome segregated that combines ectrodactyly with cleft palate, without cleft lip or the ectodermal features that occur with the EEC syndrome.[7] The term ectrodactyly-cleft palate syndrome was suggested (MIM 129830).

The AEC syndrome (MIM 106260) of ankyloblepharon, ectodermal dysplasia, and clefting was originally described by Hay and Wells.[8] It shares the ectodermal dysplasia and clefting with EEC syndrome. However, the ectodermal involvement is much more severe in AEC syndrome. Severe scalp dermatitis is common. In addition, the clefting when present in EEC syndrome is

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Abbreviations: EEC, ectrodactyly, ectodermal dysplasia, facial clefting; LADD, lacrimo-auriculo-dento-digital syndrome; ADULT, acro-dermato-ungual-lacrimal-tooth syndrome; SHFM, split hand/foot malformation; AEC, ankyloblepharon, ectodermal dysplasia, and clefting; SAM, sterile alpha motif; LMS, limb-mammary syndrome; CHANDS, curly hair, ankyloblepharon, and nail dysplasia syndrome; CLPED1, cleft lip/palate, ectodermal dysplasia syndrome; AER, apical ectodermal ridge
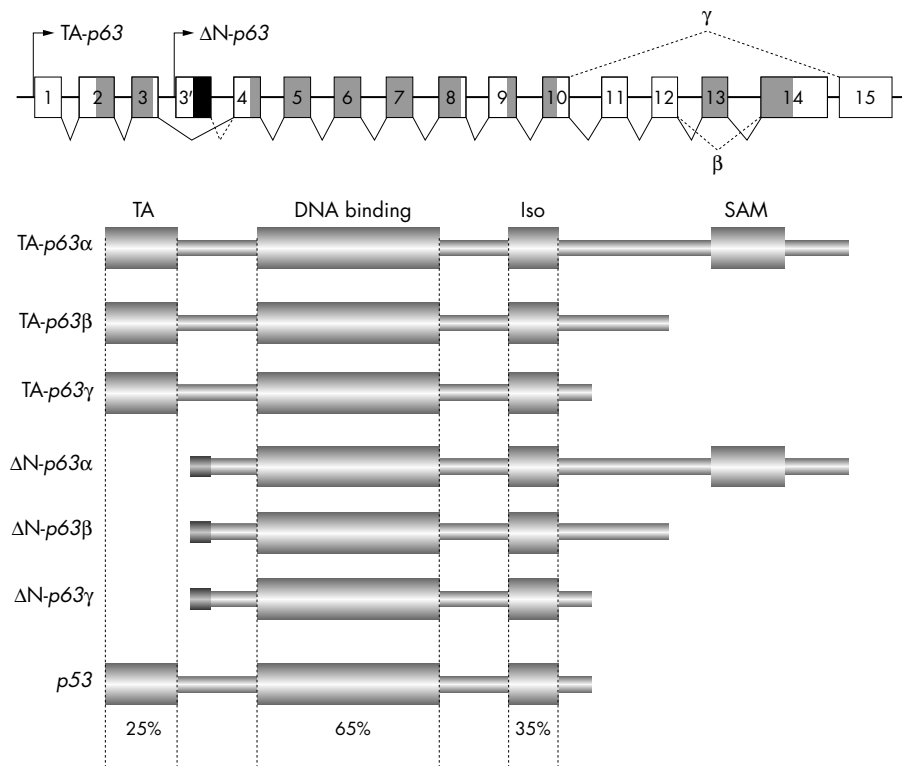
Figure 1 *p63* gene structure and transcripts. The top panel is a diagram of the intron-exon structure, showing the two transcription initiation sites and alternative splicing routes, yielding at least six different *p63* isotypes. The structure of the TAp63γ isotypes is most similar to *p53*, both containing a transactivation domain (TA), DNA binding domain, and tetramerisation domain (ISO). The α isotypes contain an additional C-terminal SAM domain.

always cleft lip (with or without cleft palate), whereas it can be cleft palate only in AEC. Limb involvement in AEC syndrome is minimal or absent.

Popliteal pterygium syndrome (MIM 119500) may resemble AEC syndrome since it has ankyloblepharon filiforme, filiform bands between the jaws, lip pits, and cleft palate with or without cleft lip.[9] Many patients have syndactyly. The characteristic popliteal pterygium is not present in all cases. A pathognomonic sign is a typical, triangular overgrowth of skin over the nail of the big toe.[2] Popliteal pterygium syndrome may be allelic to van der Woude syndrome in 1q32.[10]

The limb-mammary syndrome (MIM 603543) was originally described in a large Dutch kindred with split hand-split

foot malformation (ectrodactyly) and aplasia or hypoplasia of the mammary gland and nipple. Some patients had complete absence of breast tissue (amastia).[6] Although a number of features were shared with the EEC syndrome, the frequent mammary gland abnormalities and the fact that ectodermal involvement occurred in only a small minority of patients clearly indicated a separate syndrome. In addition, clefting occurred, but unlike EEC syndrome it was cleft palate and not cleft lip.

Another EEC-like condition (MIM 103285) was described in a single large German kindred.[11] Features included ectrodactyly, syndactyly, fingernail and toenail dysplasia, hypoplastic breasts and nipples, intense freckling, lacrimal

Table 1 Dominantly inherited syndromes that share similarities with EEC syndrome

	EEC	SHFM	LMS	ADULT	AEC	ECP	Rapp-Hodgkin	Popliteal pterygium	LADD
SHFM	+	+	+	+	−	+	−	Syndactyly	Syndactyly
CLP	+	−	−	−	−	−	+	+	−
CP	−	−	+	−	+	+	−	+	−
Hair	+	−	−	−	+	−	+	−	−
Skin	+	−	−	+	++	−	+	−	−
Teeth	+	−	+/−	+	+	−	+	−	+
Nail	+	−	−	+	+	−	+	−	−
Mammary gland	+/−	−	++	+	−	−	−	−	−
Lacrimal	+	−	+/−	+	+	−	+	−	+
Ankyloblepharon	−	−	−	−	+	−	−	+	−
Lip pits	−	−	−	−	−	−	−	+	−
Pterygium	−	−	−	−	−	−	−	+	−
Radial ray abnormality	−	−	−	−	−	−	−	−	−
Abnormal ear	−	−	−	−	−	−	−	−	+
Freckling	−	−	−	++	−	−	−	−	−
p63 mutation	+	+	+	+	+				

duct atresia, frontal alopecia, primary hypodontia, and loss of permanent teeth. The absence of clefting in this multigenerational family, and the intense freckling were thought to set it apart from the EEC syndrome. The authors suggested the acronym ADULT syndrome for this condition to reflect acro-dermato-ungual-lacrimal-tooth involvement.

The combination of ectodermal dysplasia and clefting occurs in several other syndromes. One of these is the autosomal dominant Rapp-Hodgkin syndrome of wiry hair (pili torti or pili canaliculi), anhidrotic ectodermal dysplasia, and cleft lip and palate[12] (MIM 129400). Because of overlapping features of EEC and Rapp-Hodgkin syndromes in a mother and child, it has been suggested that these are fundamentally the same disorder.[13] This would seem to be supported by the findings of Rodini and Richieri-Costa,[14] who reported on a Brazilian family with 11 affected patients over four generations. Clinical findings in different patients ranged from isolated trichodysplasia (sparse, brittle, and dry hair) to ectodermal dysplasia, cleft palate, tear duct anomaly, and minor limb anomalies.[14] It has been suggested that AEC syndrome and Rapp-Hodgkin syndrome could represent the same entity.[15] These authors described a child affected by ectodermal dysplasia associated with clefting, ankyloblepharon, severe scalp dermatitis, and the characteristic Rapp-Hodgkin facies.

Another dominantly inherited syndrome which shares features with EEC is the lacrimo-auriculo-dento-digital (LADD) syndrome (MIM 149730). LADD syndrome has aplasia or hypoplasia of the puncta with obstruction of the nasal lacrimal ducts, cup shaped pinnae with mixed hearing deficit, small and peg shaped lateral maxillary incisors, and mild enamel dysplasia. The digital features include fifth finger clinodactyly, radial ray abnormalities, and syndactyly.[16] Clinical differentiation between LADD and EEC syndromes was difficult in a family in which the mother had a split hand/split foot deformity and the daughter a condition consistent with a diagnosis of LADD syndrome.[17]

Some recessively inherited syndromes share similarities with EEC syndrome, notably the Bowen-Armstrong syndrome of recessively inherited ectodermal dysplasia, and cleft lip and/or cleft palate. Some patients have congenital adhesions between the eyelids, cicatricial atrophy of the scalp, abnormal EEG, partial anodontia, genital hypoplasia, syndactyly, and delayed skeletal growth and maturation.[18] This condition could be a separate syndrome or it could be the same as the CHANDS syndrome of curly hair, ankyloblepharon and nail dysplasia, which may further include alveolar synechiae (MIM 214350).[19 20]

Another recessively inherited syndrome consists of syndactyly, ectodermal dysplasia, and cleft lip/palate. This condition has been termed the cleft lip/palate, ectodermal dysplasia syndrome (CLPED1, MIM 225000) or Zlotogora-Ogur syndrome. The patients have sparse eyebrows and eyelashes, sparse, short and dry scalp hair, and hypodontia. Cleft lip/palate, syndactyly of fingers and toes, and onychodysplasia are often present. Some patients have mental retardation. CLPED1 was recently shown to result from mutations in the *PVRL1* gene, encoding nectin-1, an immunoglobulin related transmembrane cell-cell adhesion molecule that is part of the NAP cell adhesion system.[21]

Specific patterns of mutation of the *p63* gene in other syndromes

Mutations of the *p63* gene have been found in five human malformation conditions to date (fig 2). In addition to EEC, these are the AEC or Hay-Wells syndrome,[8 22] limb-mammary syndrome,[4 6] ADULT syndrome,[11 23 24] and non-syndromic split hand-split foot malformation[25] (SHFM, MIM 183600). These syndromes are characterised by limb abnormalities that fit the split hand-split foot spectrum, ectodermal dysplasias affecting the hair, teeth, nails, and sweat glands, absence of the mammary glands, and a range of other malformations of the facial skeleton, the urogenital system, and the eyes. The various malformations can be largely explained by assuming that the effect of the mutation is to disrupt normal ectoderm formation or function. This is probably also true for the limb malformations which are thought to reflect interference with normal formation of the apical ectodermal ridge (AER), which is the distal most part of the growing limb during embryogenesis. Combined *p63* mutation data for these syndromes indicate extensive genotype-phenotype correlations, with each of these syndromes having a distinct pattern and type of mutations.[4] This suggests that each of these mutations causes
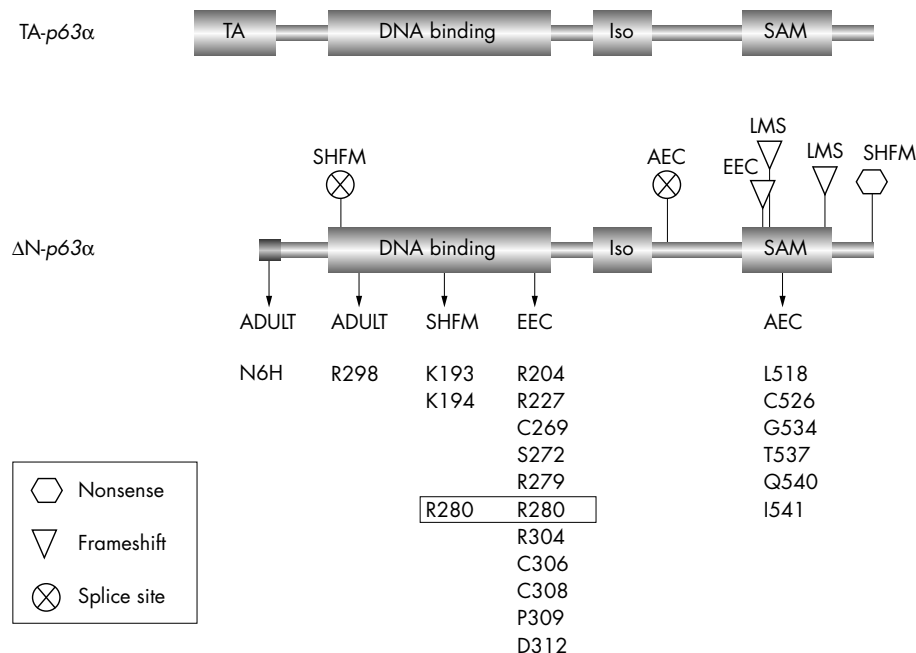

Figure 2 Pattern of *p63* mutations in human syndromes. The *p63* mutations identified in five different human disorders are indicated. Note the clustering of mutations in the DNA binding domain for EEC syndrome and in the SAM domain for AEC syndrome.

a specific perturbation of normal *p63* gene function. Functional data are consistent with dominant negative as well as dominant gain or change of function defects (P Duijf, unpublished data).[5] The *p63* gene encodes at least six different protein isotypes through the use of alternative transcription start sites and alternative splicing at the 3' end of the gene.[26]

p63 gene mutations in Hay-Wells or AEC syndrome were initially detected in eight families.[22] All were missense mutations in the SAM (sterile alpha motif) domain. These mutations are predicted to disrupt protein-protein interactions of the p63 protein with as yet unknown partners. A single family with AEC syndrome has been shown to have a mutation that results in a splicing defect that removes exon 11 and affects the C-terminus of both the alpha and beta isotypes of p63 (J Murray, personal communication). In vitro analysis of the functional effects of the mutations in the AEC patients indicated that such mutations have complex gain of function as well as loss and change of function effects.[22]

Initially, no *p63* mutations were detected in the large Dutch LMS family that first linked this class of diseases to the *p63* locus.[6] However, two isolated, unrelated patients with an LMS phenotype were found to have frameshift mutations in exon 13 that resulted in truncations of the p63 protein.[4] The location of these mutations may be significant, as LMS differs from EEC syndrome in at least three respects. The first is that mammary gland and nipple hypoplasia is a consistent feature of LMS and is only occasionally seen in EEC syndrome. The second is that LMS patients do not have hair and skin defects. The third is that whereas LMS patients have cleft palate or bifid uvula, those with EEC syndrome more often have cleft lip. Very recently the mutation in the original LMS kindred[6] was found to reside in the N-terminal part of the gene, in exon 4 (P Duijf *et al*, unpublished data). This mutation differs from that in the two other LMS kindreds, but is also clearly different from the mutations seen in EEC syndrome.

ADULT (acro-dermato-ungual-lacrimal-tooth) syndrome differs from EEC syndrome by the absence of facial clefting. Instead, these patients show neurodermal signs, including exfoliative dermatitis of the digits and excessive freckling.[11] Linkage studies in this large German family indicated allelism with EEC syndrome in 3q27.[27] A *p63* gene mutation was found in a small French kindred with ADULT syndrome by Amiel *et al*.[23] This mutation is clearly different from the *p63* gene mutations in EEC. The mutation is localised in exon 3', which is included only in the TA isotypes of p63 and causes an amino acid substitution (N6H) outside the DNA binding domain.[23] Another ADULT syndrome mutation involving arginine 298 has now been found in the German kindred originally described by Propping and Zerres.[24] Transactivation studies indicate that this latter mutation confers significant transactivation capacity to ΔN-p63gamma, which is otherwise inert in these assays.[24] This unusual result raises that possibility that the ADULT syndrome mutation confers a novel gain of function to *p63*, although the precise molecular mechanism is still under investigation.

p63 gene mutations associated with non-syndromic split hand and foot malformation were first identified in two South African kindreds.[25] Subsequent analysis of a larger group of 45 unrelated SHFM patients indicated that four out of 45 had a *p63* mutation, suggesting that *p63* mutations probably account for no more than 10% of non-syndromic SHFM.[4] Four of the six *p63* mutations detected in SHFM patients are not found in other syndromes: missense mutations K193E and K194E, splice site mutation IVS4-2A>C, and nonsense mutation Q634X. Two other mutations, R280C and R280H, both involving codon 280, have been found in SHFM as well as in EEC syndrome. Thus, there is partial overlap between the EEC and SHFM mutational spectra. This might perhaps have been expected from the considerable phenotypic variability that can be seen within and between EEC syndrome families. If this were the explanation, then some of the affected subjects in these kindreds should have shown mild EEC features. This does not seem to be the case. The two large South African SHFM families described by Ianakiev *et al*[25] were carefully examined for signs of ectodermal dysplasia and none was found. Since these families are quite large, the fact that all family members with the R280H mutation had only SHFM and none of the other signs of EEC syndrome suggests specific modifier effects, possibly through interacting genes.

The power of genotype-phenotype correlations

The finding that *p63* mutations cause at least five different malformation conditions with a strong genotype-phenotype correlation suggests a number of topics for future research. First, these results validate the concept that human malformation syndromes can be grouped into syndrome families based on clinical similarities. This concept was first articulated for the skeletal dysplasias.[28] Spranger's classification was based on the realisation that different skeletal dysplasias could be grouped on the basis of radiological similarities. The grouping together of achondroplasia, hypochondroplasia, and thanatophoric dysplasia has been fully vindicated by molecular studies. The same is true for diastrophic dysplasia and achondrogenesis 1b. Yet other examples are the type II collagenopathies that range from achondrogenesis II, via hypochondrogenesis, spondyloepiphyseal dysplasia congenita, and Kniest dysplasia, to Stickler arthro-ophthalmopathy and mild dominant spondyloarthropathy.[29]

This concept may be applicable in a more general sense. For syndromes that are clinically similar, we should assume a shared or at least related pathogenesis. As a case in point, one might consider the Stickler and Marshall syndromes. For many years their status as independent syndromes was debated.[30 31] Molecular studies have since shown that both involve genes encoding component chains of type XI collagen protein. However, there is preferential involvement of the *COL2A1* gene in Stickler syndrome and of the *COL11A1* gene in Marshall syndrome.[32] This not only illustrates that functionally related genes are involved in clinically similar syndromes, it also shows that even relatively small phenotypic differences may point to important differences at the molecular level. Our finding that many phenotypes are associated with *p63* gene mutations would seem to support this notion.

Although superficially similar to EEC, the presence of pigmentary disturbances and the absence of clefting set the ADULT syndrome apart,[11] and this is now confirmed by our recent demonstration of a specific gain of function mechanism.[24] Our recent finding that the ADULT syndrome mutations in these families uncover a putative second transactivation domain underlines how pertinent clinical observations may help show aspects of a protein's function that would otherwise have been more difficult to detect.

Finally, the contrasting phenotypes associated with different classes of *p63* mutations shows promise for our understanding of embryonic development in general. It is significant in this respect that EEC mutations but not AEC mutations cause limb involvement. Also, limb-mammary syndrome mutations cause mammary gland aplasia, whereas EEC and SHFM rarely or never do. Taking these clinical differences as leads, we can now start to assess which downstream targets of *p63* are specifically perturbed by each of these classes of mutations. In doing so, we may be able to pinpoint some of the developmental pathways that are specifically involved in shaping the limbs, skin, and mammary gland during development. Clearly, molecular genetics will provide the answers, but only if the power of clinical genetics is exploited to pose the right questions.

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REFERENCES

1 **Rudiger RA**, Haase W, Passarge E. Association of ectrodactyly, ectodermal dysplasia, and cleft lip/palate. *Am J Dis Child* 1970;**120**:160-3.
2 **Gorlin RJ**, Cohen MM, Levin LS. *Syndromes of the head and neck*. 3d ed. New York: Oxford University Press, 1990.
3 **Roelfsema NM**, Cobben JM. The EEC syndrome: a literature study. *Clin Dysmorphol* 1996;**5**:115-27.
4 **Van Bokhoven H**, Hamel BCJ, Bamshad M, Sangiorgi E, Gurrieri F, Duijf PHG, Vanmolkot KRJ, van Beusekom E, van Beersum SEC, Celli J, Merkx GFM, Tenconi R, Fryns JP, Verloes A, Newbury-Ecob RA, Raas-Rothschild A, Majewski F, Beemer FA, Janecke A, Chitayat D, Crisponi G, Kayserili H, Yates JRW, Neri G, Brunner HG. p63 gene mutations in EEC syndrome, limb-mammary syndrome, and isolated split hand split foot malformation suggest a genotype-phenotype correlation. *Am J Hum Genet* 2001;**69**:481-92.
5 **Celli J**, Duif P, Hamel BCJ, Bamshad M, Kramer B, Smits APT, Newbury-Ecob R, Hennekam RC, Van Buggenhout G, van Haeringen A, Woods CG, van Essen AJ, de Waal R, Vriend G, Haber DA, Yang A, McKeon F, Brunner HG, van Bokhoven H. Heterozygous germline mutations in the p53 homolog p63 are the cause of EEC syndrome. *Cell* 1999;**99**:143-53.
6 **van Bokhoven H**, Jung M, Smits APT, van Beersum S, Ruschendorf F, van Steensel M, Veenstra M, Tuerlings JHAM, Mariman ECM, Brunner HG, Wienker TF, Reis A, Ropers HH, Hamel BCJ. Limb mammary syndrome: a new genetic disorder with mammary hypoplasia, ectrodactyly, and other hand/foot anomalies maps to human chromosome 3q27. *Am J Hum Genet* 1999;**64**:538-46.
7 **Opitz JM**, Frias JL Cohen MM Jr. The ECP syndrome, another autosomal dominant cause of monodactylous ectrodactyly. *Eur J Pediatr* 1980;**133**:217-20.
8 **Hay RJ**, Wells RS. The syndrome of ankyloblepharon, ectodermal defects and cleft lip and palate: an autosomal dominant condition. *Br J Dermatol* 1976;**94**:277-89.
9 **Froster-Iskenius UG**. Popliteal pterygium syndrome. *J Med Genet* 1990;**27**:320-6.
10 **Lees MM**, Winter RM, Malcolm S, Saal HM, Chitty L. Popliteal pterygium syndrome: a clinical study of three families and report of linkage to the Van der Woude syndrome locus on 1q32. *J Med Genet* 1999;**36**:888-92.
11 **Propping P**, Zerres K. ADULT-syndrome: an autosomal-dominant disorder with pigment anomalies, ectrodactyly, nail dysplasia, and hypodontia. *Am J Med Genet* 1993;**45**:642-8.
12 **Rapp RS**, Hodgkin WE. Anhidrotic ectodermal dysplasia: autosomal dominant inheritance with palate and lip anomalies. *J Med Genet* 1968;**5**:269-72.
13 **Moerman P**, Fryns JP. Ectodermal dysplasia, Rapp-Hodgkin type in a mother and severe ectrodactyly-ectodermal dysplasia-clefting syndrome (EEC) in her child. *Am J Med Genet* 1996;**63**:479-81.
14 **Rodini ESO**, Richieri-Costa A. EEC syndrome: report on 20 new patients, clinical and genetic considerations. *Am J Med Genet* 1990;**37**:42-53.
15 **Cambiaghi S**, Tadini G, Barbareschi M, Menni S, Caputo R. Rapp-Hodgkin syndrome and AEC syndrome: are they the same entity? *Br J Dermatol* 1994;**130**:97-101.
16 **Hollister DW**, Klein SH, Dejager HJ, Lachman RS, Rimoin DL. The lacrimo-auriculo-dento-digital syndrome. *J Pediatr* 1973;**83**:438-44.
17 **Lacombe D**, Serville F, Marchand D, Battin J. Split hand/split foot deformity and LADD syndrome in a family: overlap between the EEC and LADD syndromes. *J Med Genet* 1993;**30**:700-3.
18 **Bowen P**, Armstrong HB. Ectodermal dysplasia, mental retardation, cleft lip-palate and other anomalies in three sibs. *Clin Genet* 1976;**9**:35-42.
19 **Toriello HV**, Lindstrom JA, Waterman DF, Baughman FA. Re-evaluation of CHANDS. *J Med Genet* 1979;**16**:316-17.
20 **Toriello HV**. Alveolar synechia-ankyloblepharon-ectodermal defects likely CHANDS. *Am J Med Genet* 1994;**49**:348.
21 **Suzuki K**, Hu D, Bustos T, Zlotogora J, Richieri-Costa A, Helms JA, Spritz RA. Mutations of PVRL1, encoding a cell-cell adhesion molecule/herpesvirus receptor, in cleft lip/palate-ectodermal dysplasia. *Nat Genet* 2000;**25**:427-30.
22 **McGrath JA**, Duijf PHG, Doetsch V, Irvine AD, de Waal R, Vanmolkot K, Wessagowit V, Kelly A, Atherton DJ, Griffiths AD, Orlow SJ, Van Haeringen A, Ausems M, Yang A, McKeon F, Bamshad MA, Brunner HG, Hamel BCJ, van Bokhoven H. Hay-Wells syndrome is caused by heterozygous missense mutations in the SAM domain of p63. *Hum Mol Genet* 2001;**10**:221-9.
23 **Amiel J**, Bougeard G, Francannet C, Raclin V, Munnich A, Lyonnet S, Frebourg T. TP63 gene mutation in ADULT syndrome. *Eur J Hum Genet* 2001;**9**:642-5.
24 **Duijf PHG**, Vanmolkot KRJ, Propping P, Friedl W, Krieger E, McKeon F, Dötsch V, Brunner HG, van Bokhoven H. Gain-of-function mutation in ADULT syndrome reveals the presence of a second transactivation domain in p63. *Hum Mol Genet* 2002;**11**:799–804.
25 **Ianakiev P**, Kilpatrick MW, Toudjarska I, Basel D, Beighton P, Tsipouras P. Split-hand/split-foot malformation is caused by mutations in the *p63* gene on 3q27. *Am J Hum Genet* 2000;**67**:59-66.
26 **Yang A**, Kaghad M, Wang Y, Gillett E, Fleming MD, Dotsch V, Andrews NC, Caput D, McKeon F. *p63*, a *p53* homolog at 3q27-29, encodes multiple products with transactivating, death-inducing, and dominant-negative activities. *Mol Cell* 1998;**2**:305-16.
27 **Propping P**, Friedl W, Wienker T F, Uhlhaas S, Zerres K. ADULT syndrome allelic to limb mammary syndrome (LMS)? *Am J Med Genet* 2000;**90**:179-82.
28 **Spranger J**. Pattern recognition in bone dysplasias. In: Bartsocas C, ed. *Endocrine genetics and genetics of growth*. New York: Alan R Liss, 1985:315-42.
29 **Spranger J**, Winterpacht A, Zabel B. The type-II collagenopathies - a spectrum of chondrodysplasias. *Eur J Pediatr* 1994;**153**:56-65.
30 **Temple IK**. Stickler's syndrome. *J Med Genet* 1989;**26**:119-26.
31 **Liberfarb RM**, Hirose T. The Wagner-Stickler syndrome. *Birth Defects* 1982;**18**:525-38.
32 **Annunen S**, Korkko J, Czarny M, Warman ML, Brunner HG, Kaariainen H, Mulliken JB, Tranebjaerg L, Brooks DG, Cox GF, Cruysberg JR, Curtis MA, Davenport SLH, Friedrich CA, Kaitil I, Krawczynski MR, Latos-Bielenska A, Mukai S, Olsen BR, Shinno N, Somer M, Vikkula M, Zlotogora J, Prockop DJ, Ala-Kokko L. Splicing mutations of 54 bp exons in the COL11A1 gene cause Marshall syndrome but other mutations cause overlapping Marshall/Stickler phenotypes. *Am J Hum Genet* 1999;**65**:974-83.