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## Recent advances in Dyggve-Melchior-Clausen syndrome

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## Abstract

Dyggve-Melchior-Clausen (DMC) is a rare autosomal-recessive disorder characterized by the association of a progressive spondylo-epi-metaphyseal dysplasia and mental retardation ranging from mild to severe. Electron microscopy studies of both DMC chondrocytes and fibroblasts reveal an enlarged endoplasmic reticulum network and a large number of intracytoplasmic membranous vesicles, suggesting that DMC syndrome may be a storage disorder. Indeed, DMC phenotype is often compared to that of type IV mucopolysaccharidosis (Morquio disease), a lysosomal disorder due to either N-acetylgalactosamine-6-sulfatase or b-galactosidase deficiency. To date however, the lysosomal pathway appears normal in DMC patients and biochemical analyses failed to reveal any enzymatic deficiency or accumulated substrate. Linkage studies using homozygosity mapping have led to the localization of the disease-causing gene on chromosome 18q21.1. The gene was recently identified as a novel transcript (*Dym*) encoding a 669 amino acid product (Dymeclin) with no known domains or function. Sixteen different *Dym* mutations have now been described in 21 unrelated families (3 novel mutations are reported below) with at least 5 founder effects in Morocco, Lebanon and Guam Island. Smith-MacCort syndrome (SMC), a rare variant of DMC syndrome without mental retardation was shown to be allelic of DMC syndrome and to result from mutations in *Dym* that would be less deleterious to the brain. The present review focuses on clinical, radiological and cellular features and evolution of DMC/SMC syndromes and discusses them with regards to identified *Dym* mutations and possible roles of the *Dym* gene product.

## **Introduction and history**

Dyggve-Melchior-Clausen syndrome was first described by H.V. Dyggve, J.C. Melchior and J. Clausen in 1962, as a new form of dwarfism associated with mental retardation [1]. Short trunk, barrel shaped thorax, rhizomelic limb shortening and some other clinical overlap with Morquio disease, a skeletal dysplasia associated with mucopolysaccharidosis, led the authors to speculate that the condition might also result from an inborn error of metabolism. However, clinical and biochemical studies revealed symptoms such as corneal opacity, tooth anomalies, hearing loss and urinary excretion of keratan sulfate as extra-skeletal signs belonging to the common clinical picture specific of Morquio disease [2-5]. Cases described by Dyggve, Melchior and Clausen then appeared clearly different from Morquio disease both because of the absence of these associated symptoms and because of the presence of specific radiological features and mental retardation. The name of “Dyggve-Melchior-Clausen syndrome” (DMC) was finally attributed to this skeletal dysplasia after several additional cases allowed specific clinical and radiological delineation of this novel entity [6-9]. At present, about 70 cases with DMC have been documented. Clinical course and cellular features of this rare condition are now well defined and the genetic cause of this autosomal recessive affection has been recently elucidated.

## **Clinical course and diagnosis of DMCS**

Osteochondrodysplasias are a heterogeneous group of skeletal disorders due to impaired cartilage and/or bone growth. DMC syndrome is an osteochondrodysplasia that belongs to the sub-group of spondylo-epi-metaphyseal dysplasias (SEMDs), which includes a number of conditions all defined by the combination of specific vertebral, epiphyseal and metaphyseal anomalies.

DMC syndrome is clinically characterized by a short trunk dwarfism with a barrel shaped chest, rhizomelic limb shortening, microcephaly with facial dysmorphism, coarse face, and variable mental retardation (Fig. 1). Radiological features include misaligned spine, markedly flattened vertebral bodies (platyspondyly) with a double-humped appearance, metaphyseal irregularities, laterally displaced capital femoral epiphyses, and small pelvis with thickened and lacy iliac crests (Fig. 2). The extremities are generally short and carpal bones are small and irregular in shape (Fig. 3); the proximal bones of phalanges are also more severely affected than the distal ones and accessory ossification centers at the distal ends of the metacarpals are frequently seen [10-13]. In rare cases however, hands were reported to be radiologically normal [7].

DMC is a progressive SEMD, which means that the skeletal phenotype is not obvious at birth (Fig. 1A, 2A and 2B), although several cases where neonatal measurements were available showed small size at birth [9]. The first manifestations of the disorder are usually recognized between one and 18 months of age (Fig. 2C and 2E). The double-humped appearance of the vertebral bodies and the very specific aspect of iliac crests become evident by 3-4 years of age (Fig. 2D and 2F) and persist in adulthood (Fig. 2G). Thoracic deformities and feeding difficulties appear and both microcephaly and statural delay become evident and increase during childhood (Fig. 1B and 1C). Survival into adulthood is not jeopardized but the fully established phenotype

results in a severe dwarfism with strong orthopaedic complications (Fig. 1C). The latter often increase with age and potentially include lumbar lordosis, scoliosis, thoracic kyphosis, subluxation of the hips, deformations of the knees and restricted joint mobility [1, 9, 13-15]. A strong orthopaedic follow-up is therefore recommended for DMC children to manage walking and moving difficulties and to prevent possible spinal cord compression due to atlantoaxial instability [7].

Like the skeletal phenotype, mental retardation is a progressive feature in DMC. Following a series of 16 affected children from 9 families ranging from 3 to 22 years of age, head circumference was found to be normal at birth in the majority of cases (our unpublished data). However, head circumference growth curve progressively decelerated below -3 SD in the first two years of life and developmental delay increased. A 15 year-follow-up of the 3 cases originally reported by Dyggve, Melchior and Clausen in 1962 also mentioned increasing mental retardation and motor disability, further illustrating the evolution of the mental prognosis in DMC [16].

By contrast to the skeletal phenotype, which – when fully installed - is quite clinically homogeneous between patients, mental retardation is a variable feature in DMC. A wide variability was noted at both intrafamilial and interfamilial levels: some children are clearly hyperactive, displaying autistic features and no speech, while some others (even from the same family) are able to speak and have moderate mental retardation. IQ usually varies between 25 and 65. In our series, MRI was performed on 5 children at different ages (but always before age 10) and considered normal in all cases (our unpublished data). However, anomalies of the white matter were found once, in a 15 year-old child. Taking into account the fact that mental retardation is a progressive feature in DMC, MRI should not be performed too early in childhood.

Interestingly, a SEMD with similar bone changes to those of DMC but with normal intelligence was described by Smith and McCort in 1958 and later highlighted by Spranger who

used the term of Smith-McCort dwarfism (SMC) [10, 17]. Bone involvement in SMC and DMC are sufficiently similar that these two conditions have been recognized as clinical variants of the same condition. SMC syndrome illustrates the variability of mental involvement in DMC/SMC dysplasias.

### **Differential Diagnosis of DMC**

Developmental delay during childhood (with strong learning and speech difficulties) and radiological appearance of both the iliac crests (hazy and lacy outlines) and the vertebral bodies (flattened and double-waved) are very pathognomonic features of DMC/SMC, which help to differentiate this rare condition from other SEMD. Despite the clinical arguments that let hypothesize that DMC is a storage disorder, there are, at present, no biochemical investigations allowing diagnostic confirmation of DMC.

### **The storage hypothesis**

From its first description by Dyggve et al, resemblance of the syndrome with Morquio disease led to the hypothesis that DMC may be a mucopolysaccharidosis [1]. The same group reported a few years later that DMC lymphocytes incorporated excessive amounts of leucine and fucose into intracellular macromolecules and that, consistent with a mucopolysaccharidosis, abnormal urinary excretion of acid mucopolysaccharides was detected in DMC patients [18-19]. Like in Morquio disease, in which intralysosomal accumulation of keratan sulfate results from the deficiency of one or the other of two enzymes (the N-acetylgalactosamine-6-sulfatase and the b-D-galactosidase) [20-21], Rastogi et al also suggested the deficiency of a specific sulfatase or

protease involved in proteoglycan processing as a biochemical cause of DMC [22]. Some other studies have also reported biochemical anomalies in DMC, but the differences between findings have made the situation somewhat cloudy: Engfeldt et al reported increased amount of glucosaminoglycans in the cartilage from patients and indicated that the ability of proteoglycan monomers to reaggregate as hyaluronic acid chains was decreased, further supporting the hypothesis of a disturbance of proteoglycan degradation in DMC [23]. On the other hand, Roesel et al pointed out a possible defect in peroxisomal metabolism since plasma and urine of their DMC patient revealed increased amounts of pipercolic, phytanic and very long-chain fatty acids [24]. Conversely, several biochemical studies using cultured fibroblasts of DMC patients and testing their ability to incorporate and degrade sulphated proteoglycans led to the conclusion that these latter are normally metabolized in these cells and that DMC might not be a mucopolysaccharidosis as previously suggested [9, 14, 25, 32]. In an attempt to detect a potential misdegraded metabolite, our team also performed extensive analyses of fibroblasts, urine, and leucocytes of several characterized DMC patients. Peroxisomal and lysosomal contents were examined, lipid, carbohydrate and proteinic work up were checked, and activities of the mitochondrial respiratory chain complexes were assayed. None of these experiments led to any metabolic anomalies detection in DMC takings (our unpublished data). In summary, there are still no specific biochemical tests able to confirm clinical/radiological DMC diagnostic, to date. However, a quite specific phenotype has been described in chondrocytes of DMC patients and may in certain circumstances help diagnosing the disorder.

### **Cellular phenotype of DMC**

Histological analysis of the growth plate of an iliac crest biopsy from a patient with DMC showed that both proliferating and differentiating chondrocytes were not arranged in columns as



expected, but were instead clustered and engaged in a degenerating process in many areas [26]. A fibrous aspect of the hyaline cartilage matrix as well as many cytoplasmic inclusions and vacuoles in resting chondrocytes were noticed. Engfeldt et al described a similar observation in the growth plate from another diagnosed case of DMC [23] and further examined the specimen by electron microscopy. They revealed that chondrocytes contained widened cisternae of rough endoplasmic reticulum and vesicles coated with a smooth single-layered membrane. More recently, the deficient columnar cell organization with chondrocyte clustering and degeneration as well as the dilatation of rough endoplasmic reticulum were confirmed in two children with SMC [27], demonstrating that bone changes in SMC and DMC are identical at both radiological and cellular levels. Thus, the cellular phenotype of DMC/SMC syndrome evokes abnormal storage and/or membrane trafficking, which specifically involve the endoplasmic reticulum network and is therefore clearly different from that of Morquio disease in which ultrastructural anomalies involve lysosomes [28-29]. The cellular phenotype of DMC syndrome is also visible in a variety of cutaneous cell types such as melanocytes, keratinocytes, mastocytes, macrophages, sweat glands [30] and in fibroblasts cultured *ex-vivo* from skin biopsies (Fig. 4). Like chondrocytes, fibroblasts are highly vacuolated and display a very abundant network of rough endoplasmic reticulum membranes. A combination of cellular ultrastructure with specific radiological appearance of iliac crests indisputably argues in favour of DMC phenotype and may refine, when feasible, the differential diagnosis of this condition.

### **Genetics of DMC**

DMC was first delineated in sibs from a consanguineous union in Greenland, suggesting a recessive mode of inheritance of the syndrome [1]. Other cases with healthy consanguineous parents were subsequently reported [9-10, 14, 31] but no genetic study was available until 1979,

probably because of the rarity of the syndrome. Toledo et al reported the first segregation analysis in 23 affected sibs, confirming autosomal recessive inheritance in both DMC and SMC [32]. A recessive X-linked mode of transmission has been considered once, in a large family in which only males were affected [33], but the phenotype studied in this report probably is a spondylo-epiphyseal dysplasia tarda and not a DMC case. Using a homozygosity mapping strategy in 7 consanguineous DMC families, the faulty gene was recently mapped to a 1.8 centimorgan interval on chromosome 18q21.1 [34]. A genome-wide scan of a consanguineous SMC family with 5 affected sibs allowed mapping of SMC to the same chromosomal region, providing evidence that SMC and DMC dysplasias might be allelic disorders [35]. Interestingly, the earlier observation by Spranger et al that DMC and SMC cases never occur in the same family had led the authors to hypothesize that DMC/SMC dwarfism was a genetically heterogeneous condition [10]. However, the study by Ehtesham et al wisely anticipated the fact that SMC and DMC both result from different alterations of a same gene. The disease gene was latter identified in 2003 as a predicted expressed sequence called FLJ20071/FLJ90130 which finally proved to be a novel gene of 17 exons distributed over at least 400kb of genomic DNA and renamed *Dym* [30, 36]. The initiator (AUG) and the terminator (TGA) codons were identified in exon 2 and 17, respectively and a polyadenylation signal (AATAAA) was found 228 bp downstream of the stop codon. The *Dym* gene is predicted to encode Dymeclin, a 669-amino acid protein of unknown function, which is highly conserved through species from human to plants. The sequence of human Dymeclin is very similar to its mouse counterpart (94% amino acid identity) and still well conserved in invertebrates (42% amino acid identity with *D. melanogaster* and 37% with *C. elegans*). However, a function for this protein in these species has not yet been ascribed. In addition, Dymeclin does not share any homology with known protein families and no obvious functional domains could be identified in its amino acid sequence. Comparative searches suggested the presence of three to six transmembrane segments,

a myristoyl site at the amino terminal end and a large number of dileucine motifs all along the protein [30, 36], but these predictions remain to be ascertained at experimental level.

### ***Dym* gene mutations in DMC and SMC**

El Ghouzzi et al identified 7 mutations of the *Dym* gene in 10 unrelated Mediterranean DMC families from Morocco, Tunisia and Lebanon [30]. Cohn et al simultaneously reported 6 other *Dym* mutations in 2 SMC families from Guam Island and 3 DMC families [36]. Including 3 novel mutations reported here, 16 different *Dym* mutations have now been described in 21 unrelated families, which represent 37 affected patients (Table I). Consanguinity was reported in 15/21 families and in 3/6 non-consanguineous families, affected children were compound heterozygotes. The large majority of mutations associated with DMC phenotype are predicted to be deleterious to Dymeclin function since they introduce a premature stop codon through either nucleotide substitutions (within exonic sequence or at splice sites) or nucleotide deletions (inducing frameshifts). In three cases however, the alteration of *Dym* was of another type:

First, the adenosine deletion in the last exon of the gene (1877delA/K626N+frameshift) is predicted to elongate the *Dym* gene product (extension of 49 amino acids), since the legitimate stop codon is no longer in frame.

Second, one Portuguese patient had a homozygous G to C substitution in intron 1, 34 base pairs downstream of the first exon of *Dym*. This mutation has not yet been validated but the clinical features of this patient fitted DMC features at both clinical and cellular levels. Interestingly, this mutation occurs upstream of the initiation codon in exon 2 and could therefore affect the 5' region required for proper *Dym* transcription. Effects on the protein of both the elongating mutation and the intronic substitution have not yet been investigated but Northern

blot analyses using fibroblast RNAs from these patients indicated that the corresponding transcripts are subjected to some degradation [37].

Third, Cohn et al reported a point mutation (1405A>T) in a DMC non-consanguineous patient that predicted a N469Y missense substitution in a region highly conserved across species (Table I). The patient was heterozygous for this substitution and carried a nonsense mutation on the other allele [36]. This is the only missense mutation hitherto identified in DMC phenotype.

No correlation could be established between the type of DMC mutation (truncating, elongating or missense) and the phenotypic severity. This is probably due to the fact that the skeletal phenotype, although progressive throughout childhood, finally reaches a homogeneous bony pattern not really distinguishable between patients. In addition, *Dym* mutations associated with a DMC phenotype are likely to result in the complete absence of Dymeclin since no protein products were detected in HeLa cells after over-expression of either a Q483X- or a N469Y-*Dym* cDNA [38]. As suggested in the clinical section of this review, severity of mental retardation is indeed a variable feature in DMC but again, no phenotype-genotype correlation is possible since this variability also occurs in affected patients from the same family.

Cohn et al reported another missense mutation that was present in a heterozygous state (259G>A, E87K) in two families with SMC phenotype. The E87 residue is also well conserved during evolution although it lies in a quite divergent region of the protein, but the effect of this substitution on the stability of the transcript and/or the protein has not been studied [36]. The other allele bore a splice acceptor mutation 5' of exon 8. The number of SMC cases where a mutation of *Dym* was identified is as yet too low to support any phenotype-genotype correlation between SMC and DMC but it has been proposed that SMC syndrome may result from less deleterious *Dym* mutations than DMC syndrome [38]. Consistent with this hypothesis, Cohn et al indicated that the splice mutation identified in their SMC patients induced leaky exon skipping, suggesting that some normal Dymeclin is nevertheless produced [36]. Such permissive transcription was not observed in a DMC case with a splice acceptor mutation 5' of exon 4

(family 8, see table I), where the whole transcript displayed complete deletion of exon 4 (our unpublished data). By contrast to DMC cases, SMC patients would thus retain some residual Dymeclin function. That a “rescue” mechanism occurs in neurons remains to be tested in order to explain why mental retardation is never observed in SMC.

Five out of the 16 mutations hitherto reported in DMC/SMC syndromes are found in more than one family from a common geographical area (Table I). For example the K626N frameshift mutation was identified in 6 families all originating from Morocco, the splice acceptor mutation 5' of exon 12 was present in 2 Lebanese families and the SMC families from Guam Island both bore the same E87K/splice acceptor mutation genotype. Affected individuals from the families who share the same mutation also have part of the 18q21.1 haplotype in common, indicating that those mutations are ancestral [34]. Ethnical and cultural customs and the relative isolation of those populations may explain the evolutionarily cohabitation of distinct founder effects.

### ***Dym* gene expression**

*Dym* expression based on quantifying ESTs from various tissues indicates that the gene is expressed in a wide range of human tissues including bone marrow, brain, heart, skeletal muscle, pancreas, prostate, lung and kidney. Experimental approaches using RT-PCR, human multiple tissue expression array and *in situ* hybridization suggest that *Dym* is ubiquitously expressed [37]. Northern blot analyses showed *Dym* transcripts as two bands of 3.1 and 5.6 kb, which both appear as specific signals, since they were revealed with two non-overlapping probes [37]. Considering both the size of the coding sequence of *Dym* (2kb between the ATG and the TGA) and the fact that the length of exon 1 is undetermined (as the transcriptional start site has not yet

been defined), the 3.1kb could correspond to the expected size of *Dym* transcripts. On the other hand, Northern blot analysis using fibroblasts RNAs from DMC patients showed that the 5.6 kb band was shifted to 7 kb in the patient with the intronic mutation downstream of exon 1 (family 21, see table I), suggesting that the upper band is specific [37]. These data suggest that the *Dym* gene is alternatively transcribed. If so, a large part of its sequence remains to be established. Alternative transcription of *Dym* may also help to explain how loss-of-function of an ubiquitously expressed gene specifically affects bone growth and brain development. However, the hypothesis that Dymeclin is involved in proteoglycan metabolism could also explain why the phenotype predominantly affects cartilage and brain, since normal proteoglycan biosynthesis is critical for correct elaboration of the extracellular matrix of these tissues [36].

### **Conclusion, future prospects**

Identification of *Dym* as the DMC-causing gene is an important step toward the understanding of this condition. Before then, clinical complications of DMC are serious enough to warrant prenatal diagnosis [13]. Skeletal anomalies are too mild to be detected during intrauterine development but molecular diagnosis by direct sequencing of *Dym* from foetal DNA might be an appropriate approach when the mutation is known.

The finding that SMC and DMC syndromes share identical radiographic features and cartilage histology and are associated with mutations of the same gene support genetic homogeneity of these conditions, unlike the prediction of Spranger et al [10]. However, some patients with typical DMC features harbour a normal *Dym* sequence, although the disease gene was found to be linked to the 18q21.1 region (our personal data). These data along the results of Northern blot experiments suggest that a part of *Dym* coding sequence remains unknown.

The absence of brain involvement in SMC syndrome implies that at least one mutant allele encodes a protein with partial function in SMC patients, as discussed by Cohn et al [36]. This also suggests that a residual expression of *Dym* is sufficient for brain function but not for proper development of the growth plate. On the other hand, overexpression of *Dym* in neuronal cells would have dramatic consequences, as observed in *Drosophila*, where it caused embryo death [39]. Further investigations will shed some light on the importance of *Dym* dosage.

The speculation that Dymeclin deficiency causes a defect in proteoglycan metabolism is indeed the most attractive hypothesis since both the clinical course of the disease and the cellular phenotype suggest a storage disorder that specifically affects tissues where extracellular matrix plays an essential role. However, this would not necessarily imply that *Dym* loss-of-function results in accumulation of a yet unidentified substrate. In view of the numerous membranous vacuoles and the dilated endoplasmic reticulum in cells from DMC patients, the hypothesis of a disturbance of membrane trafficking should be considered. Ongoing studies now aim to decipher the localisation and the function of Dymeclin, especially with regards to intracellular processes of protein maturation.

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Family	Phenotype	Geographical origin	Consanguinity	Affected children	Nucleotide change	Aminoacid change	Mutated exon	Type of mutation	Reference
1	DMC	Dominican Republic	+	1	48C>G	Y16X	2	Nonsense	Cohn et al, 2003
2	DMC	ND	-	1	369T>A 1405A>T	Y132X N469Y	5 13	Nonsense Missense	Cohn et al, 2003
3	DMC	Tunisia	+	2	580C>T	R194X	7	Nonsense	El Ghouzzi et al, 2003
4	DMC	Morocco	+	1	610C>T	R204X	7	Nonsense	El Ghouzzi et al, 2003
5	DMC	Morocco	-	2	656T>G 1877delA	L219X K626N+FSH	8 17	Nonsense Frameshift	El Ghouzzi et al, 2003
6	DMC	Morocco	+	2	1447C>T	Q483X	13	Nonsense	El Ghouzzi et al, 2003
7	DMC	Morocco	+	2	1447C>T	Q483X	13	Nonsense	This review
8	DMC	Lebanon	+	2	IVS 3 194-1G>A	—	5' of exon4	Splice Acceptor	This review
9	DMC	Spain	-	1	IVS 4 288-2A>G IVS 7 621-2A>G	— —	5' of exon5 5' of exon8	Splice Acceptor Splice Acceptor	This review
10	SMC	Guam	+	5	IVS 7 621-2A>G 259G>A	E87K	5' of exon8 4	Splice Acceptor Missense	Cohn et al, 2003
11	SMC	Guam	-	2	IVS 7 621-2A>G 259G>A	E87K	5' of exon8 4	Splice Acceptor Missense	Cohn et al, 2003
12	DMC	Morocco	+	3	IVS 10 1125+1G>T	—	3' of exon10	Splice Donor	El Ghouzzi et al, 2003
13	DMC	Lebanon	+	1	IVS 11 1252-1G>A	—	5' of exon12	Splice Acceptor	El Ghouzzi et al, 2003
14	DMC	Lebanon	+	1	IVS 11 1252-1G>A	—	5' of exon12	Splice Acceptor	El Ghouzzi et al, 2003
15	DMC	Pakistan	+	2	763delA	A254A+FSH	8	Frameshift	Cohn et al, 2003
16	DMC	Morocco	+	3	1877delA	K626N+ FSH	17	Frameshift	El Ghouzzi et al, 2003
17	DMC	Morocco	+	2	1877delA	K626N+ FSH	17	Frameshift	El Ghouzzi et al, 2003
18	DMC	Morocco	+	1	1877delA	K626N+ FSH	17	Frameshift	El Ghouzzi et al, 2003
19	DMC	Morocco	+	1	1877delA	K626N+ FSH	17	Frameshift	This review
20	DMC	Morocco	-	1	1877delA	K626N+ FSH	17	Frameshift	This review
21	DMC	Portugal	-	1	G>C, 34bp 3' of exon1	—	Intron 1	—	This review

**Table I: Mutations in the *Dym* gene in DMC and SMC syndromes**

## Legends to figures

### Figure 1: clinical features and evolution of DMC syndrome

Pictures of a Moroccan patient with the K626N frameshift mutation in *Dym*, at the age of one (A) and 3 (B) and of his brother at the age of 13 (C). DMC features are not recognizable before the first year of life and then appear progressively. Short trunk dwarfism with a barrel shaped chest and proximal limb shortening are evident at 3 years and persist throughout childhood. At 13 years of age, microcephaly is marked as well as broad hands and flexion defects with orthopaedic complications.

### Figure 2: radiological features and evolution of DMC syndrome

Radiographs of Moroccan patients with the K626N frameshift mutation in *Dym* at different ages. The skeletal phenotype is not obvious at birth but vertebrae are flattened (A and B). At 14 months of age, platyspondyly (C) and epiphyseal dysplasia are visible but the iliac wings still have a normal aspect (E). By 3-4 years of age, the double-humped appearance of the vertebral bodies becomes evident (D), the acetabulae are hypoplastic and irregular, the proximal femoral necks are short, with irregular metaphyses and epiphyses (F). The very specific aspect of iliac crests is clearly visible at 4 years of age (F), broadens by age 18 with a demineralised appearance (G) and persists into adulthood.

### **Figure 3: radiological features of hands in DMC**

Radiographs of hands from a DMC patient at the age of 18. Note the short and broad hands with irregular shape of metacarpal bone and phalanges.

### **Figure 4: cellular phenotype in fibroblasts from patients with DMC**

Electron microscopy examination of primary fibroblasts from a control (B) and three DMC patients with the intronic mutation downstream of exon 1 (A), the K626N frameshift mutation (C) and the splice acceptor mutation upstream of exon 4 (D). Unlike the control, DMC fibroblasts show large abnormal cytoplasmic vacuoles that contain osmiophilic bodies (▶), a large number of phagocytosis vacuoles along the cytoplasmic membrane (▶), and abundant granular endoplasmic reticulum (\*). Black bars represent 0.2 $\mu$ m in pictures A, B, D and 0.1 $\mu$ m in picture C.



A



B



C









