

**Focus on Dyggve-Melchior-Clausen and Smith-McCort dysplasias:
Six years after the identification of the responsible gene, recent data suggest a
perturbation of intracellular trafficking**

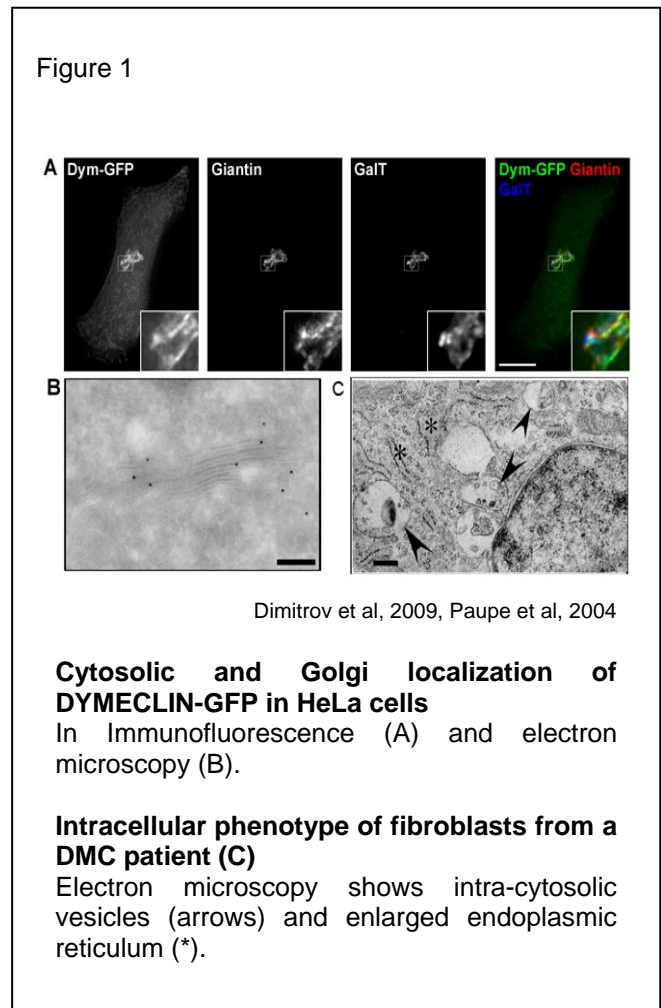
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Dyggve-Melchior-Clausen (DMC, MIM#223800) and Smith-McCort dysplasias (SMC, MIM#607326) are autosomal recessive skeletal dysplasias which belong to the group of spondyloepimetaphyseal dysplasias. DMC and SMC diseases share similar skeletal features (a progressive short-trunk dwarfism, a barrel shaped thorax, and proximal limb shortening) but differ by mental retardation, present in DMC disease only. Although variable in severity, mental retardation is constantly observed in DMC and children are often described as hyperactive, displaying autistic features and do not speak. Skeletal features are progressive and the phenotype often leads to strong orthopedic complications (El Ghouzzi et al 2003a, Paupe et al 2004). DMC/SMC dysplasias also share clinical and radiological similarities with type IV mucopolysaccharidosis (Morquio disease), a lysosomal disorder due to either N-acetylgalactosamine-6-sulfatase or β -galactosidase deficiency. This may hinder the diagnosis during the onset of the condition (Rodríguez Rodríguez CM et al 2007), although some distinctive radiological features such as the lacy aspect of iliac crests and a double-humped appearance of the vertebral bodies are typical of DMC/SMC dysplasias (Thauvin-Robinet et al 2002). A common gene has been identified as responsible for both entities in 2003 (El Ghouzzi et al 2003b, Cohn et al 2003) and named *DYM* (El Ghouzzi et al 2003b). Most of the mutations identified in *DYM* predict the generation of a truncating product; however, a few frameshift mutations in the last exon predicting an elongated protein, two complex genomic duplications resulting in exon repetition, and two missense mutations have also been reported (El Ghouzzi et al 2003b, Cohn et al, 2003, Kinning et al, 2005). *DYM* encodes DYMECLIN, a novel protein of unknown expression, localization and function which could not be ascribed to any family of proteins, despite a high conservation across species. Fibroblasts and chondrocytes from patients display major structural abnormalities, including an abundant and swollen endoplasmic reticulum and accretion of intracytosolic membranous vesicles (Engfeldt 1983, Nakamura 1997, El Ghouzzi 2003b, Paupe 2004). Due to this cellular phenotype and because clinical features resemble Morquio disease, it has been hypothesized that the condition could be a storage disease. Although we can not rule this possibility, no enzymatic deficiency or specific accumulated compound in DMC cells which

would have been consistent with a specific storage of a putative mis-degraded metabolite has been found. More recently, we have shown that the *DYM* gene is ubiquitously expressed and, in an attempt to understand the cellular consequences of DYMECLIN mutations we have analyzed the biochemical properties of DYMECLIN, the protein product of *DYM*. Using cell biology techniques and immuno-electron microscopy, we have found that DYMECLIN is a myristoylated protein which associates with the Golgi apparatus and with transitional vesicles of the reticulum-Golgi interface (see figure 1).

Moreover, time lapse confocal microscopy experiments on living cells have demonstrated that the protein is highly dynamic as it can shuttle very rapidly between a cytosolic pool and a Golgi apparatus pool (Dimitrov et al, 2009). Interestingly, these features are shared by other Golgi proteins such as GRASP65 or ARF1. Like DYMECLIN, these two proteins are localized to the Golgi apparatus, they are myristoylated and they shuttle rapidly between a cytosolic pool and a Golgi pool. DYMECLIN could therefore be involved in a GRASP like function and have a role in the structure and/or the function of the Golgi apparatus. This would be consistent with the findings of Dr Osipovich who has recently described a *Dym* knock-out mouse that mimics the human phenotype and has observed less-compact and fragmented Golgi stacks in *Dym*-deficient cells from mouse (Osipovich et al, 2008).



Although it is not yet clear whether the structure of the Golgi is affected in *Dym*-deficient cells of human origin, we have found that *DYM* mutations associated with DMC result in mis-localization and subsequent degradation of Dymeclin thus inducing a loss of DYMECLIN function. Interestingly, the only SMC mutation identified so far (E87K) did not result in mis-localization or degradation in our system (Dimitrov et al, 2009). Although the precise role of DYMECLIN remains to be uncovered, these findings suggest a role of DYMECLIN in intracellular trafficking.

Because DMC and SMC are rare conditions, only a few groups throughout the world are trying to understand these diseases and to provide appropriate therapies to the patients. We must say that big pharmaceutical companies are only interested in “market-associated” targets such as osteoporosis or osteoarthritis and degenerative joint diseases. We hope to find the financial support to carry on studying DMC/SMC with the aim to understand why DYMECLIN deficiency results in cartilage and neuronal abnormalities. With the goal to go deeper in the pathophysiology of DMC/SMC dysplasias, our team is going to start working on the *Dym* knock-out mouse, kindly provided by Dr Osipovich. Studies combining *ex vivo* cellular models and *in vivo* studies of this mouse will undoubtedly help us to decipher the role of DYMECLIN and determine whether it is possible to block the progressiveness of the disease.

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