ge of skeletal dysplasias and deciphering their molecular bases has contributed to the understanding of this complex process. Here, we report a homozygous mutation in the mitochondria-associated granulocyte macrophage colony stimulating factor-signaling gene (*MAGMAS*) in a novel and severe spondylodysplastic dysplasia. MAGMAS, also referred to as PAM16 (presequence translocase-associated motor 16), is a mitochondria-associated protein involved in preprotein translocation into the matrix. We show that *MAGMAS* is specifically expressed in trabecular bone and cartilage at early developmental stages and that the mutation leads to an instability of the protein. We further demonstrate that the mutation described here confers to yeast strains a temperature-sensitive phenotype, impairs the import of mitochondrial matrix pre-proteins and induces cell death. The finding of deleterious *MAGMAS* mutations in an early lethal skeletal dysplasia supports a key role for this mitochondrial protein in the ossification process.

P04.64-M
A novel missense mutation in ST14 in a patient with ichthyosis, follicular atrophoderma and hypotrichosis

S. Baldassari[1], *G. Tortora*[1], *R. Balestri*[2], *I. Neri*[2], *M. Seri*[1];
[1]U.O. Genetica Medica, Dipartimento Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy, [2]U.O. Dermatologia, Policlinico Sant'Orsola-Malpighi, Università di Bologna, Bologna, Italy.

Congenital ichthyoses are a clinically and genetically heterogeneous group of genodermatoses characterized by disorders of cornification. Mutations in *ST14* are causative of two syndromes: Ichthyosis, Follicular Atrophoderma and Hypotrichosis (IFAH, OMIM 602400) and Autosomal Recessive Ichthyosis and Hypotrichosis (ARIH, OMIM 610765). These two syndromes are caused by different types of mutations in the gene: loss of function mutations (splice site or deletion) have been found in 2 IFAH families, while missense mutations have been found in 2 ARIH probands. We report on the identification of a new homozygous disease-causing mutation in *ST14* in a girl with diffuse ichthyosiform scaling of the trunk and arms, follicular atrophoderma of both forearms and sparse hair. The screening of *ST14* by Sanger sequencing revealed a homozygous missense mutation, p.Glu519Gln, inherited by healthy parents, both carriers of the variation described. The mutation is not present in 1000Genomes nor in ESP databases, involves a highly conserved aminoacid and is predicted to be pathogenic by Polyphen2 and SIFT. *ST14* encodes the matriptase, a type II transmembrane serine protease, expressed predominantly in the epithelial cells of the surface-lining epithelium. Our result supports the role of matriptase alterations in IFAH, but the finding of a missense mutation points out the need of other experiments to better define the functional role of different mutations in the pathogenesis of IFAH and ARIH.

P04.65-S
De Novo Mutation of the Latency-Associated Peptide Domain of TGFB3 in a Patient with Clinical Features of Loeys-Dietz Syndrome

G. Matyas[1], *P. Naef*[1], **K. Oexle**[2];
[1]Zentrum fuer Kardiovaskuläre Genetik und Gendiagnostik, Schlieren-Zürich, Switzerland, [2]Institut für Humangenetik, Technische Universität München, München, Germany.

We report the first case of a patient with a disease-causing mutation in the LAP domain of TGFB3 [c.899G>A, p.Arg300Gln; no mutation detected in FBN1, TGFBR1, TGFBR2, TGFB2, and SMAD3]. Previously, TGFB mutation has been described in one patient only (Rienhoff et al. 2013, Am J Med Genet A 161A:2040-6). That mutation was hypomorphic while we cannot exclude that mutations of the LAP domain result in constitutive activation of TGFB3 as in case of LAP mutations of TGFB1 [Saito et al., 2001, J Biol Chem 276:11469-72]. There were phenotypic similarities between our patient and the patient reported by Rienhoff et al. (2013) such as low muscle mass, hypertelorism, cleft soft palate, pectus excavatum, and arachnodactyly, but also considerable differences such as overgrowth and generalized hyperextensibility of joints instead of growth retardation and digital contractures, respectively. Both the previous case and our present case emphasize the inclusion of TGFB3 in the comprehensive genetic testing of (Marfanoid) patients with LDS clinical features, such as bifid uvula and hypertelorism. Further studies are needed to clarify the phenotypic spectrum of TGFB3 mutations including the risk for vascular disease.

P04.66-M
Modelling Poikiloderma with Neutropenia in zebrafish: a start point to elucidate disease pathogenesis

E. A. Colombo, *S. Carra, L. Fontana, E. Bresciani, F. Cotelli, L. Larizza;*
Università degli Studi di Milano, Milano, Italy.

Poikiloderma with Neutropenia (PN; OMIM#604173) is a rare autosomal recessive genodermatosis characterized by early onset poikiloderma, hyperkeratosis, pachyonychia, bone alterations, craniofacial dysmorphisms and non-cyclic neutropenia, which accounts for recurrent infections in infancy and susceptibility to myelodysplastic syndrome and solid tumours.
C16orf57, disclosed in 2010 as the causative gene of PN, has been recently renamed USB1 (U six biogenesis 1) as its protein is a RNA exonuclease involved in the 3' end processing and stability of U6 snRNA, a core component of the active spliceosome. However, no evidence for splicing defects could be achieved in PN patients cells unlike in Usb1 defective yeast. As no multicellular organism has been modeled for PN, we enrolled zebrafish, a vertebrate model increasingly important for the study of human genetic diseases and haematological malignancies, to gain insights into the consequences of USB1 disruption during early embryogenesis.
The zebrafish genome harbours only one copy of the USB1 orthologue (NM_001003460.1) ubiquitously expressed and with a high degree of conservation in genomic structure and aminoacid sequence (73% similarity and 46% identity).
Loss-of-function experiments, performed injecting three different specific antisense, morpholinos in embryos at one cell stage, allowed to obtain embryos with an overall phenotype that recapitulates the major traits of PN.
Usb1 depletion causes the development of embryos with decreased skin pigmentation, small head with defects in early cartilages of pharyngeal arches, oedema in the pericardial area, defects in blood circulation with a reduction of myeloid and erythroid cells as highlighted by in-situ hybridization and real-time experiments.

P04.67-S
Whole-exome sequencing identifies polymorphic variants in a large Arab family with split-hand/foot malformation with long-bone deficiency

U. Radhakrishna[1], *U. Ratnamala*[1], *M. Naveed*[2], *M. T. Al-Ali*[2], *S. K. Nath*[3];
[1]Green Cross Pathology & Molecular Laboratory, Paldi, Ahmedabad, India, Ahmedabad, India, [2]Center for Arab Genomic Studies (CAGS), Dubai, United Arab Emirates, [3]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, United States.

Split-hand/foot malformation with long-bone deficiency (SHFLD) is a rare, severe limb deformity**.** This is characterized by tibia aplasia with or without split-hand/split-foot deformity. Using DNA microarray analysis and employing various statistical methods, we have mapped the SHFLD1 and SHFLD2 phenotypes to chromosomes 1q42.2-q43 and 6q14.1 regions respectively. Additionally, we have identified six suggestive loci with evidence of linkage on chromosomes 1p36.13, 1q31.1, 1q42.3, 4q34.3, and 6q14.1 and 17p13.1 regions in a large multigenerational Arab family (Am. J. Hum. Genet.2007; 80:105-111). Subsequently, we have reported microduplications on chromosome 17p13.3, suggesting the association of BHLHA9 gene within the duplication in the pathogenesis of SHFLD development (J Med Genet.2012 Feb;49:119-25). Our recently performed exome sequencing using the SOLiD™ system at x200 coverage followed by prioritized mutation search within the linkage region between SNP markers rs1124110/rs535043, and rs623155/rs1547251 in selected SHFLD subjects showed polymorphic variants within the coding regions of *FILIP1* gene on 6q14.1 regions. A heterozygous nucleotide substitution G>A (c.3476G>A) resulting in a change from arginine and histidine Arg1159His (R/H) was observed in heterozygous condition in selected affecteds. However the data on chromosome 1q31.1 region is yet to be analyzed. Our present analysis provides the understanding the pathophysiology of the SHFLD disease and also provides ultimate genetic diagnosis of the condition. Additionally, the data can also help us in developing non-invasive methods of screening for the disorder in at-risk family members, in order to reassure those are not carrying the mutation and to plan prophylactic measures for those who are/will be affected.

P04.68-M
Biomarkers and early stage drug development in ectodermal dysplasias

K. M. Huttner[1], *O. F. Gaide*[2], *S. Chang*[1], *P. Schneider*[3];
[1]Edimer Pharmaceuticals, Inc., Cambridge, MA, United States, [2]Service de Dermatologie, CHUV, Lausanne, Switzerland, [3]Dept of Biochemistry, University of Lausanne, Lausanne, Switzerland.

EDI200 is a recombinant ectodysplasin currently in clinical trials for the correction of abnormal ectoderm development in neonates affected by X-linked hypohidrotic ectodermal dysplasia (XLHED). For early drug trials, there is a premium placed on identifying molecular markers of drug response likely to predict long-term clinical benefit, especially when endpoints in XLHED such as teeth, hair and sweat function may take months to years to ascertain. The ectodysplasin-deficient Tabby mouse model for XLHED demonstrates a consistent and sustained phenotype response to EDI200. Through a combined approach of qPCR and RNA-seq we have begun to map the Tabby ectodysplasin-responsive biological pathways. EDI200 at 2 mg/kg (or vehicle alone)