Molecular Genetics Service Profile
Spondylo-Costal Dysostosis (SCD) type 1, 2 and 3

Introduction

◊ SCDs are part of a clinically and genetically heterogeneous group of disorders affecting vertebral and rib segmentation. Autosomal recessive SCDs are characterized by short trunk dwarfism, usually evident at birth, with usually no respiratory insufficiency and no neurological signs of spinal cord compression. Associated anomalies in other organs are rare: inguinal hernias are probably due to raised abdominal pressure and congenital heart disease has been observed in rare cases. Affected individuals usually reach adulthood without major invalidity, but need physical and pharmacological therapy against back pain. Three types of SCD have been charactrised molecularly: SCD1 (OMIM No.277300), SCD2 (OMIM No.608681) and SCD3 (OMIM No.609813).

◊ Radiological features vary slightly between the three type: **SCD1**: longitudinal and lateral fragmentation of vertebral bodies; irregular "subvertebral" elements reminiscent of a "pebble beach" because of their number and their rounded contours; involvement of the costal elements consisting in reduction in number and/or fusion of adjacent ribs, mainly in their posterior parts; **SCD2**: trunkal shortening and short neck, lumbar vertebrae more angular and irregular than in SCD1; **SCD3**: severe foreshortening of the spine, vertebral anomalies also present in the cervical and lumbar spine.

◊ SCD1 is caused by mutations in the *DLL3* gene, SCD2 by mutations in the *MESP2* gene, SCD3 by mutations in the *LFNG* gene. All three proteins are involved in the Notch signalling pathway, which is required for propagation and maintenance of the "segmentation clock" in the presomitic mesoderm. DLL3 is a membrane-bound protein, which interacts with the Notch receptor. MESP2 activates the Ps1-independent Notch signaling cascade to suppress DLL1 expression, DLL1 being another membrane-bound ligand of Notch; LFNG is a Notch glycosilation enzyme, expressed in a cyclic manner, which exerts a negative feedback on Notch expression.

Contact details for the laboratory carrying out the genetic test for SCD1, 2 and 3
Division of Molecular Pediatrics, Centre Hospitalier Universitaire Vaudois, Clinique Infantile 02-35 Av. Pierre Decker 2, CH-1011 Lausanne, Switzerland.
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Reasons for referral

◊ Mutation analysis in patients with a diagnostic suspicion of SCD on clinical or radiographic grounds.

◊ Carrier testing of relatives of an index case with previously identified mutations.

◊ Prenatal diagnosis may be an option. We recommend that this be offered only within the context of appropriate genetic counselling. Moreover, prenatal testing is possible only in families where the mutations in the index case have been confirmed in advance. Screening for unknown mutations in a prenatal sample is not feasible.

Samples

◊ Minimum 100μg of DNA from peripheral lymphocytes or fibroblasts from your local laboratory. Blood samples (minimum of 10 ml in EDTA) can also be sent to our laboratory by express mail (FedEx / UPS) at room temperature. Prenatal samples must be sent with parental samples. Please contact our laboratory (as above) for further details, including the minimal amount of DNA required for babies and small children.

Technical

◊ Mutation analysis by PCR amplification and bi-directional fluorescent sequencing.

Target turn-round time

◊ Mutation analysis of each of the 3 genes (*DLL3, MESP2, LFNG*) by sequencing: 6-12 months. Prenatal diagnosis - only in families with known mutations: 1 - 2 weeks.

◊ Turn-round times are from the receipt of all required samples and information, including appropriate clinical information and radiographs. Relevant clinical-radiographic expertise is currently offered at no cost through the use of the secure online submission system (the **ESDN Case Manager**). Testing is only performed after clinical and radiographic evidence has been reviewed using the **ESDN Case Manager**. To obtain a username and password for the **ESDN Case Manager** please email info@esdn.org.

Cost per gene

◊ Mutation analysis in an index case and parents: CHF 800 (€500) if the specimen is extracted DNA. Additional cost: CHF 50 (€30) if the specimen is a blood sample.

◊ Prenatal diagnosis: CHF 800 (€500). ADVANCE NOTICE IS MANDATORY.

◊ Carrier testing: CHF 100 (€60) if the specimen is extracted DNA. Additional cost: CHF 50 (€30) if the specimen is a blood sample.

References

◊ Bulman M.P. *et al.* (2000) Nature Genet **24**:438-441.

◊ Bonafé L. *et al.* (2003) Clin Genet in press.

ESDN Administrator contact details

◊ Email: info@esdn.org Website: www.esdn.org

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