Molecular Genetics Service Profile
Osteogenesis Imperfecta (OI)

Introduction

◊ OI is a genetic disorder generally recognised in children by the presence of brittle bones and osteopenia. It is divided in four major types: Type I (MIM 166200) is the mildest form, with normal stature, little deformity and blue sclerae; Type II (MIM 166210) is lethal in the perinatal period; Type III (MIM 259420) and IV (MIM 166220) are moderately severe with very short stature, hearing loss, dentinogenesis imperfecta and variable scleral hue. Recently some additional types of OI have been described.

◊ Most cases of OI are inherited as autosomal dominant traits and are associated with mutations in the genes for type I collagen (*COL1A1, COL1A2)*. A few families have been reported with an autosomal recessive transmission which are often difficult to distinguish from sporadic dominant mutations or somatic mosaicism.

◊ For the mildest form (type I), a reduced type I collagen is the predominant cause of the disease whereas for the 3 more severe forms, in most of the cases a structurally abnormal type I collagen is observed at the biochemical level.

Contact details for the laboratory carrying out the genetic test for OI
Center for Medical Genetics Ghent (CMGG) Ghent University Hospital Medical Research Building (MRB), 2nd floor De Pintelaan 185, B-9000 Ghent, Belgium. http://medgen.ugent.be
Prof Paul Coucke. Tel: +32 9 332 3634. Fax: +32 9 332 6549. Email: paul.coucke@UGent.be

Reasons for referral

◊ For confirmation of a clinically suspected diagnosis of OI. (or a suspicion of child abuse)

◊ Evaluation of at-risk relatives for management reasons and genetic counselling. In this case the mutation in the index case must be known.

◊ Prenatal diagnosis (preferentially offered after genetic counselling). The mutation in the parent must be known.

Samples

◊ To perform the protein (and gene) studies, a skin biopsy from the proband is required. The biopsy must be taken under sterile conditions and kept either in tissue culture medium or in any other sterile solution. If tissue culture facilities are not available, the skin biopsy can be sent directly to us, either in tissue culture or in sterile solution. It is essential that the biopsy reaches the laboratory within 48 hours. It should be sent by special courier. If a tissue culture facility is available in your institute, we prefer you to grown the skin fibroblasts and store a frozen part of the fibroblast culture in case a problem arises with the transport. The remaining material can be sent to us. Ideally, we need two tissue culture flasks (T25 or T80), containing a confluent fibroblast culture. The flasks have to be filled completely with medium to avoid drying out of the cells. If antibiotics other than streptomycine/penicillin are used for the culture, it should be mentioned explicitly.

Technical

◊ Each patient is investigated at the **biochemical level** by analysis of radioactively labelled type I (pro)collagen molecules by SDS-PAGE. Based on the biochemical results and if the knowledge of the mutation is necessary (for future prenatal diagnosis), **molecular analysis** is performed (this is NOT a routine diagnostic procedure):

- Patients with evidence for the presence of a structurally abnormal collagen are subjected to a cDNA mutation screening of COL1A1 and COL1A2.
- In the patients presenting reduced collagen, screening for the presence of a COL1A1 null-allele is the first step in the molecular investigations. If a null allele is present, a genomic mutation screening is performed. In patients with two transcripts, a mutation screening on cDNA is started.
- In patients with a normal collagen profile the clinical history is used to direct further molecular work i.e. in patients with clinically mild OI, the possibility of a COL1A1 null-allele is investigated prior to genomic DNA mutation screening while in patients with a more severe clinical phenotype, a cDNA based mutation analysis is an option.

Target turn-round time

◊ Biochemical analysis: – 6 months. Mutation scanning of *COL1A1* and *COL1A2* – 6 months. Routine, single mutation test - 4 weeks. Urgent, single known mutation test - 2 weeks. Prenatal diagnosis – 2 weeks. Turn-round times are from the receipt of all required samples and information, including appropriate clinical information and radiographs.

Cost

◊ Biochemical analysis – €500. Mutation screening COL1A1 and COL1A2 - +€1000.

References

◊ Osteogenesis Imperfecta P. Byers and W. Cole Chapter 8 (p385) in Connective tissue and its heritable disorders. Sec. Edition P. Royce and B. Steinmann.

ESDN Administrator contact details

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

Please photocopy and distribute this sheet as required