



ITALIAN PRIMARY IMMUNODEFICIENCIES STRATEGIC SCIENTIFIC COMMITTEE

**AUTOSOMAL – RECESSIVE
AGAMMAGLOBULINAEMIA**

Addendum to the Recommendations for XLA

Update: April 2004

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INTRODUCTION

Between 10 and 15% of male patients with hypo/agammaglobulinaemia and fewer than 2% circulating B cells associated with a negative family history do not present mutations in the Btk gene, thereby ruling out X-linked agammaglobulinaemia. In addition, the finding of a similar immunological phenotype in female patients suggested the existence of autosomal recessive forms of agammaglobulinaemia. Cytofluorimetric analysis of markers differentiating B cells in the spinal cord blood of these patients demonstrated a block in the differentiation of pro-B from pre-B lymphocytes similar to that observed in X-linked agammaglobulinaemia. These findings and the new insights into the effect of expression of some gene products on the early differentiation of B cells, and the demonstration that knock-out mice for certain genes present an immunological phenotype compatible with autosomal recessive agammaglobulinaemia, led to the identification of possible genes responsible for the autosomal recessive forms of agammaglobulinaemia. Sequence analysis of these candidate genes showed that autosomal recessive forms of agammaglobulinaemia are caused by mutations in the genes coding for the μ chain, the $\lambda 5$ chain of the pre-B cell receptor, the $Ig\alpha$ chain of the B cell receptor and the cytoplasmic protein BLNK. In particular, mutations in the μ chain genes are the commonest cause of autosomal recessive agammaglobulinaemia (9/40 patients without mutations in the Btk gene). Individual cases have been described with mutations in the gene coding for the $\lambda 5$ chain, the $Ig\alpha$ chain, or BLNK. This implies that the gene responsible has yet to be identified in more than half the patients with autosomal recessive agammaglobulinaemia. Sequence analysis of these genes in agammaglobulinaemia patients without mutations in the Btk gene offers the possibility of grouping autosomal recessive forms of agammaglobulinaemia into groups with a uniform molecular defect and studying the natural history of the individual forms to better define the prognostic factors and devise appropriate therapeutic protocols. In addition, identifying the genetic defect is important for the purposes of genetic counselling and prenatal diagnosis.

DIAGNOSTIC PROTOCOL

Inclusion criteria

The addendum for autosomal recessive agammaglobulinaemia will include:

- Patients enrolled under the recommendations for XLA who proved negative on analysis of the Btk gene mutation. The AIEOP Coordinating centre will automatically shift these patients from the recommendations for XLA to those for autosomal recessive agammaglobulinaemia alerted by the person responsible for XLA recommendations.
- Female patients with an immunological phenotype similar to that of XLA (hypo/agammaglobulinaemia with <2% circulating B cells.).

A registration form and diagnosis form and thereafter the annual follow-up forms will be filled in directly in internet in the specific database for patients fulfilling these inclusion criteria.

Sending samples

On request of a Centre in the network, the Coordinating Centre will analyse the mutation of genes coding for the μ chain, the $\lambda 5$ chain, the Ig α chain and the cytoplasmic protein BLNK.

No blood samples need be sent for patients enrolled under the recommendations for XLA who proved negative on analysis of the Btk gene mutation because the DNA already available will be used for mutation analysis.

The following must be sent for female patients:

- 1 test tube containing **5 ml blood in EDTA**.

The samples must be sent at room temperature to one of the following address:

Prof. Alessandro Plebani
Laboratorio di Clinica Pediatrica
Spedali Civili
P.le Sedali Civili n°. 1
25123 Brescia.

- Samples must also be accompanied by **Form A/Autosomal recessive agammaglobulinaemia** duly compiled and sent via TRACO 10 service which guarantees delivery of samples by 10 a.m. on the following day.

- Samples must be accompanied by **n° 1 National Health Service request form** duly filled in (date of sampling, patient details with place and date of birth, place of residence, health card number, tax code number, reason: molecular screening for autosomal recessive agammaglobulinaemia).
- Samples must be sent from **Monday to Thursday** each week after calling Dr. Maurilia Fiorini: tel. 030 3996282).
- The outcome of mutation analysis will be notified within 2 months.

TREATMENT RECOMMENDATIONS

Treatment recommendations are the same as those proposed for X-linked agammaglobulinaemia.

Form A/Autosomal recessive agammaglobulinaemia

Patient's Surname _____ Name _____

Date of birth |_|_|_|_|_|_|_|
day month year

Referring physician :
Institution.....
Address
post code..... City.....
Tel..... Fax.....
e-mail.....

Requests:

Mutation analysis of the genes coding for the μ chain, the $\lambda 5$ chain, the Ig α chain and the cytoplasmic protein BLNK.

Blood sample dispatched on |_|_|_|_|_|_|_|
day month year

Send to: Prof. Alessandro Plebani
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Clinica Pediatrica
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