

# Proposta di studio multicentrico A.I.S.F.

## ***“Genetica della PBC e PSC”***

Coordinatore  
Pietro Invernizzi

# STUDY 1

## Primary biliary cirrhosis

*“Identification of common and uncommon gene variants in PBC”*

IRCCS Istituto Clinico Humanitas, Rozzano, Italy  
Università degli Studi di Milano, Milan, Italy  
San Raffaele Scientific Institute, Milan, Italy  
Gradenigo Hospital, Turin, Italy  
University of Padova, Padova, Italy  
Casa Sollievo della Sofferenza Hospital, San Giovanni  
Rotondo, Italy  
University of Bologna, Bologna, Italy  
Università di Palermo, Palermo, Italy  
Azienda Ospedaliera Universitaria Pisana, Pisa, Italy  
University Sapienza of Rome, Rome, Italy  
University of Florence, Florence, Italy  
Università Politecnica delle Marche, Ancona, Italy  
University of Milan-Bicocca, Monza, Italy  
University of Bari, Bari, Italy  
University of Trieste, Trieste, Italy  
Ospedale Fatebene Fratelli e Oftalmico, Milan, Italy  
Ospedale Niguarda, Milan, Italy  
Santa Croce Carle Hospital, Cuneo, Italy  
University of Udine, Udine, Italy  
University of Genoa, Genoa, Italy  
Azienda Ospedaliero-Universitaria di Parma, Parma, Italy  
Treviglio Hospital, Treviglio, Italy  
Desio Hospital, Desio, Italy  
Magenta Hospital, Magenta, Italy  
Università degli Studi di Napoli "Federico II", Napoli, Italy  
Department of Internal Medicine, AO Lecco, Lecco, Italy  
AO Valduce, Como, Italy  
Ospedale di Negrar, Verona, Italy

**2004**

***“Italian PBC Genetic  
Study Group”***

# HLA polymorphisms in Italian PBC

## *Multicenter Study*

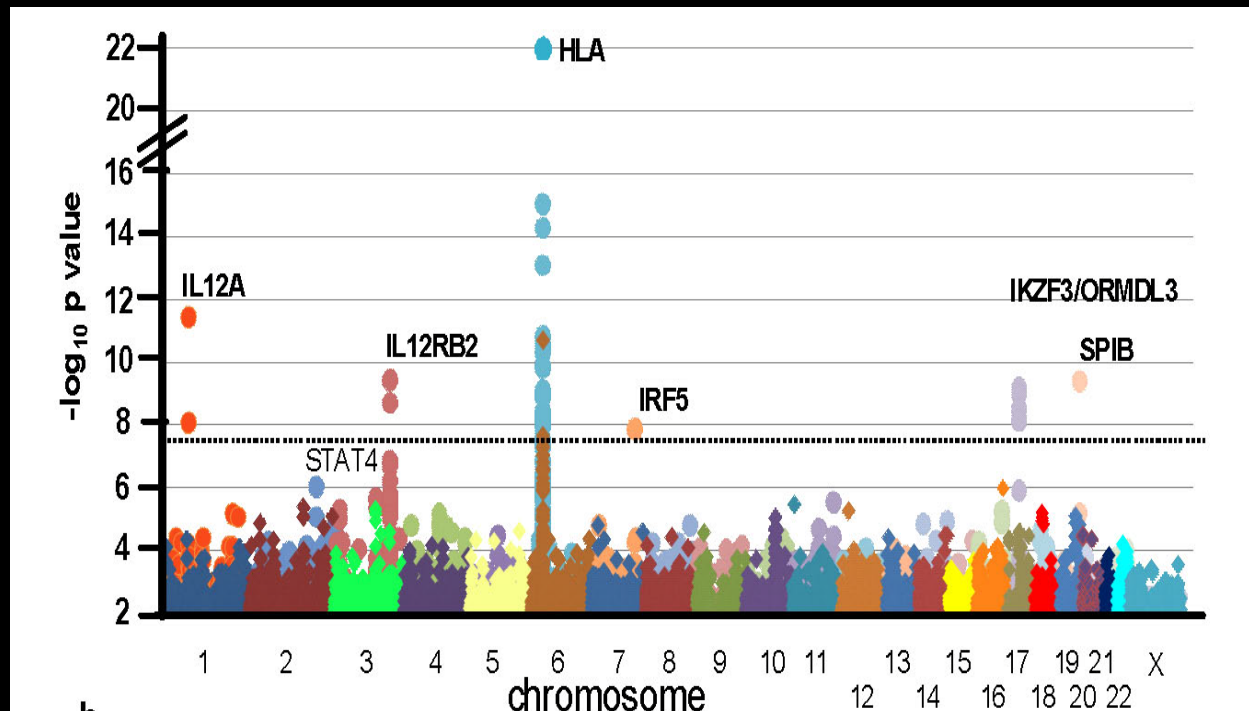
HLA	PBC (n=664) (%)	Controls (n=1992) (%)	<i>P</i> <sub>c</sub>	Odds Ratio	(95% C.I.)
<b>DRB1*08</b>	7.2	2.3	0.000	3.3	2.4-4.5
<b>DRB1*11</b>	13.6	30.0	0.000	0.4	0.3-0.4
<b>DRB1*13</b>	8.6	11.2	0.000	0.7	0.3-0.9

*Invernizzi et al. Hepatology 2008*

# Genome-wide association study in PBC

536 Canadian & US PBC vs. 1536 controls (300K SNPs)

**PLUS 557 Italian PBC vs. 947 controls (1Mb SNPs)**



Risk variants:

**HLA**

**IL12A**

**IL12RB2**

**IRF5**

**IKZF3/ORMDL3**

**SPIB**

*Liu & Invernizzi Nature Genetics 2010*

# N.I.H. grants

## 2007-2012

*“Epidemiology of PBC: a genome-wide association study”* – N.I.H. R01 grant DK056839

## 2011-2016

N.I.H. R01 proposal entitled *“Identification of common and uncommon gene variants in PBC”*

AIMS:

1. To identify sequence variants in the intervals containing novel common variant association peaks in PBC
2. To identify uncommon/rare sequence variants in exonic sequences in PBC
3. To identify differences in gene expression, splicing and/or allelic exclusion due to SNP variation in PBC pathogenesis (CD4+ and CD8+ cells)
4. Validation and Analysis

## **STUDY 2**

# **Primary sclerosing cholangitis**

*“ImmunoChip-project in PSC”*

# “ImmunoChip-project”

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The Wellcome Trust **Sanger Institute**, Hinxton, UK (<http://www.sanger.ac.uk/>) has since the establishing in 1993 participated in several of the major milestones in genetics research.

In 2009, the Sanger Institute initiated the so called “**ImmunoChip-project**”.

The aim of the ImmunoChip project is to characterize genetic similarities and differences between a large number of autoimmune disorders.

More than **210,000 DNA samples** worldwide has been included and will be genotyped for **200,000 single nucleotide polymorphisms (SNPs)** in genes that have previously been shown to confer risk in either one of these diseases. A particular genotyping array (“ImmunoChip” by Illumina<sup>©</sup>) has been developed for the purpose.



# “ImmunoChip-project in PSC”

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Coordinator: Dr Tom Karlsen in Oslo, Norway

## Status January 2011:

**3367 PSC samples** have been or are in the pipeline for ImmunoChip genotyping.

The ultimate goal of an input of **4000 PSC samples** into the project is within reach.

Pietro Invernizzi is coordinating the **Southern Europe** (Italy, Portugal, Spain, Greece) and **Japan** activities.

# MATERIALS and DATA

**Whole blood samples** (two 4-ml aliquots at -20°C)

**Serum samples** (two 500-microliter aliquots at -20°C)

**Demographic, biochemical, serological and clinical data**

(STUDIO multicentrico A.I.S.F.

*“Indagine sulle malattie autoimmuni in Italia”*

M. Lenzi, P. Almasio, A. Floreani, P. Invernizzi,  
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T. Stroffolini)

**FAMILIES with more than one  
PBC or PSC cases (COUSINS)!!!!**

# Studio multicentrico A.I.S.F. “Genetica della PBC e PSC”

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