**Description, prevalence, diagnosis, and treatment of isolated congenital asplenia (ICA)**

ICA ([OMIM](https://www.omim.org/entry/271400)# 271400) is characterized by the absence of a spleen at birth without any detectable associated developmental abnormalities. In particular, cardiac malformations, as described in Ivemark syndrome (also known as “asplenia syndrome”) and related disorders are absent. ICA renders otherwise healthy children and adults susceptible to life-threating invasive infections with encapsulated bacteria, most commonly *Streptococcus pneumoniae*, and occasionally *Neisseria meningitidis* and *Haemophilus influenzae b*.

ICA is the only known developmental defect in humans solely affecting a lymphoid organ. It is a rare primary immunodeficiency (PID) (also known as “inborn errors of immunity”) that affects at least **1/300,000** live births. It can be lethal without warning signs during the first episode of invasive bacterial disease, and is therefore both under-diagnosed and under-reported. Increasing awareness of ICA is important, as a diagnosis is crucial for both improving the survival of patients with ICA and the diagnosis of asymptomatic relatives.

The absence of a spleen can be detected by ultrasound (US) or computed tomography (CT) scan of the abdomen. The associated defective phagocytic function of the spleen is confirmed by the identification of Howell-Jolly bodies of erythrocytes on a blood smear. Diagnosing ICA enables efficient prevention of invasive pyogenic disease, by initiating penicillin prophylaxis and repeated vaccinations against pyogenic bacteria, and by default their efficient treatment, by prompt and aggressive antibiotic treatment of high fevers.

**The genetic basis of ICA: knowns and unknowns**

The Casanova Lab at the Rockefeller University in NYC is presently the only research laboratory worldwide studying ICA. Prior to the initiation of their in-depth study of this condition, only 73 patients with ICA from 48 kindreds had been reported worldwide in the literature. None of these reports explored the genetic etiology of ICA. What was known was that ICA is often inherited, with familial cases often following an autosomal dominant mode of inheritance (transmitted from one generation to the next).

The Casanova Lab enrolled 33 additional patients with ICA from 23 kindreds by 2013. This recruitment allowed them to discover the first gene underlying this condition. In 2013, they found, by whole-exome sequencing (WES), that germline coding mutations in the *RPSA* gene, encoding ribosomal protein SA, caused ICA in 18 patients from 8 kindreds ([1](http://science.sciencemag.org/content/340/6135/976)). The mutations were heterozygous, underling an autosomal dominant (AD) ICA phenotype by haplo-insufficiency and with full penetrance, i.e. all subjects carrying a coding *RPSA* mutation had ICA.

They have since enrolled 33 additional kindreds and identified 11 new ICA-causing RPSA protein-coding mutations, as well as the first two ICA-causing non-coding mutations (in the 5**′**-UTR of this gene). A few individuals carrying one of the new *RPSA* mutations had a spleen, indicating that mutations in *RPSA* can cause ICA with incomplete penetrance ([2](https://www.pnas.org/content/115/34/E8007/tab-article-info)). Collectively, they found that 40% of their patients have mutation in *RPSA.*

They are actively recruiting patients with ICA to diagnose more families with *RPSA* mutations and try to understand the molecular basis of incomplete penetrance (why do some individuals mutated in RPSA have a normal spleen). They also search for causes of ICA other than RPSA in families not mutated in this gene. Overall, they strive to define the genetic architecture of ICA, as a comprehensive understanding of its genetic basis will improve ways to diagnose and manage this condition.

Contact : [casanova@rockefeller.edu](mailto:casanova@rockefeller.edu)

**For additional reading:**

1 - Bolze A, Mahlaoui N, Byun M, Turner B, Trede N, Ellis SR, Abhyankar A, Itan Y, Patin E, Brebner S, Sackstein P, Puel A, Picard C, Abel L, Quintana-Murci L, Faust SN, Williams AP, Baretto R, Duddridge M, Kini U, Pollard AJ, Gaud C, Frange P, Orbach D, Emile JF, Stephan JL, Sorensen R, Plebani A, Hammarstrom L, Conley ME, Selleri L, Casanova JL. [Ribosomal protein SA haploinsufficiency in humans with isolated congenital asplenia.](https://www.ncbi.nlm.nih.gov/pubmed/23579497) **Science.** 2013 May 24;340(6135):976-8.

2 - Bolze A, Boisson B, Bosch B, Antipenko A, Bouaziz M, Sackstein P, Chaker-Margot M, Barlogis V, Briggs T, Colino E, Elmore AC, Fischer A, Genel F, Hewlett A, Jedidi M, Kelecic J, Krüger R, Ku CL, Kumararatne D, Lefevre-Utile A, Loughlin S, Mahlaoui N, Markus S, Garcia JM, Nizon M, Oleastro M, Pac M, Picard C, Pollard AJ, Rodriguez-Gallego C, Thomas C, Von Bernuth H, Worth A, Meyts I, Risolino M, Selleri L, Puel A, Klinge S, Abel L, Casanova JL. [Incomplete penetrance for isolated congenital asplenia in humans with mutations in translated and untranslated *RPSA* exons.](https://www.ncbi.nlm.nih.gov/pubmed/30072435) **Proceeding of the National Academy of Science USA.** 2018 Aug 21;115(34):E8007-E8016.