During the past 5 years we have witnessed a furious race for the discovery of genes causing primary immunodeficiencies. With whole-exome sequencing a reality, a novel genetic etiology is seemingly being published every month. To date, the online Resource on Asian Primary Immunodeficiencies (RAPID at rapid.rcai.riken.jp) lists 269 primary immunodeficiency diseases, with 248 responsible genes identified. Professor Casanova has predicted the number to rise to at least a thousand by 2020.

The list includes, for 2009: DOCK8, STIM1, CARD9, ITK, G6PC3; in 2010: NLRP3; in 2011: STAT1, MAGT1, GATA2; in 2012: TRAC, RHOH, STK4 (MST1), LCK, UNC119, WIPF1, PLCG2, PIK3R1, CD21, LRBA, PLDN, CD27, ISG15, NKX2-5, TRIF, TBK1, MCM4, ADAM17, IL36RN; and in 2013: CARD11, VPS45, PRKCD, COR1A.

In 2009, one of the biggest news in the field was the identification of DOCK8 deficiency by two groups. Large genomic deletions and other mutations in this sub-telomeric gene in chromosome 9 account for most cases of the so-called autosomal-recessive Hyper-IgE syndrome, currently classified as a combined immunodeficiency. DOCK8 is a small GTP-ase interacting with Cdc42 and WASP, and as such, it has important roles in lymphocyte activation and signaling. Affected patients have increased susceptibility to viruses, bacteria, and fungi. Prominent clinical features include eczema, food allergies, viral cutaneous infections, sino-pulmonary and gastrointestinal bacterial
infections, extensive abdominal vasculitis and chronic liver disease. The prognosis is complicated by the development of aneurysms in the central nervous system and thoracoabdominal territories, as well as epidermoid carcinomas following chronic HPV infection. HSCT is the treatment of choice.

That same year mutations in G6PC3 were reported to cause Dursun syndrome or a syndromic severe congenital neutropenia that includes: very low absolute neutrophil counts, transient thrombocytopenia and variable lymphopenia, prominent veins in the limbs and torso, atrial defect with primary pulmonary hypertension, and genitourinary malformations, which stem from a defect in the regulation of apoptosis. The neutropenia usually responds well to filgastrim. Lately, mutations in G6PC3 have also been identified in cases of non-syndromic and even cyclic neutropenia.

Picard et al. described STIM1 (Stromal interaction molecule 1) deficiency in a family with autosomal recessive combined immunodeficiency that included hepatosplenomegaly, autoimmune hemolytic anemia, thrombocytopenia, muscular hypotonia, and defective enamel dentition. This defect completes the phenotype of calcium influx deficiencies, previously identified as caused by ORAI1 mutations. T-cell counts and repertoires are normal, but their proliferation and function are severely impaired, which result in recurrent viral and fungal infections as well as congenital myopathy and ectodermal dysplasia.

CARD9 was the first of a series of genes identified to cause susceptibility to fungal disease or chronic mucocutaneous candidiasis (CMC), also in 2009.
Several genetic etiologies have been identified for autoinflammatory diseases in the past five years. Of note, NLRP3 mutations have been ascribed to a number of phenotypes that include the Cryopyrin-associated periodic syndrome, Schnitzler syndrome, Behcet syndrome, and Muckle-Wells syndrome.

In 2011, a group led by Steven Holland described GATA2 deficiency, an autosomal dominant and sporadic defect formerly known as MonoMAC for the combined findings of monocytopenia and susceptibility to environmental mycobacteria. These patients usually present at a late age with B-cell depletion, low NK cells and mycobacterial, viral and fungal infections, with an increased incidence of malignancies that include myeloid leukemias.

Autosomal dominant STAT1 mutations were identified via next-generation sequencing in 2011 as responsible for familial CMC. Of note, STAT1 defects will cause autoimmunity (to the point of resembling IPEX) when there is overexpression (gain-of-function mutations), and immunodeficiency with susceptibility to viruses, mycobacteria and fungi. Heterozygous loss-of-function STAT1 mutations were known to cause MSMD since 2001.

In 2012, CD21, CD27 and LRBA were added to the list of genes that cause a small portion (10%) of CVID or CVID-like disease; PLDN mutations and autosomal recessive Pallidin deficiency was found to cause Hermansky-Pudlak syndrome type 1 with partial albinism and dysregulation; TRIF, down the cascade of TLR3 signaling with autosomal recessive heritability, was added to the list of genes that cause a small portion (10%) of Herpes Simplex Encephalitis; while autosomal recessive mutations in ADAM17 and IL36RN were identified in patients with autoinflammatory skin and bowel disease.
In 2013, PRKCD was identified in Vienna as the cause of Mendelian Systemic Lupus Erythematosus, in patients suffering from severe autoimmunity and B-cell deficiency; CARD11 was reported as the cause of yet another autosomal recessive SCID in an infant with *Pneumocystis jirovecii* pneumonia; homozygous mutations in VPS45 were identified as the cause of yet another congenital neutrophil defect syndrome; and COR1A as the cause of yet another functional T-cell defect with developmental delay in a female patient with oral thrush, respiratory infections, vaccine-associated diarrhea, chronic diarrhea, failure to thrive and severe T-lymphopenia caused by Coronin-1a deficiency.

An increasing number of patients with yet unidentified congenital immune defects await to be diagnosed. The “gene hunters” are out in the field with next-generation shotguns, so we can expect the list to grow in the following months.