Common variable immunodeficiency is a heterogeneous entity characterized by an impaired ability to produce antibodies. The failure is localized in partially mature B lymphocytes, though T lymphocyte abnormalities are occasionally present. This deficiency affects antibody synthesis and class switch from IgD and IgM, to IgG and IgA. CVID is related to selective IgA deficiency, and both abnormalities may coincide in one same family, and evolve from one to another in the same patient. The symptoms generally manifest in adults, but can occur at any age, even in infancy. Recurrent bacterial infections or pneumonias are frequent, and may be complicated by gastrointestinal problems, granulomas, autoimmune disorders or malignancies. A defect in memory B cells seems to condition the clinical severity. Recently, several mutations in genes encoding for molecules (CD19, TACI, ICOS) involved in B cell survival and isotype switch have been identified in patients with CVID. Nevertheless, genetic abnormalities have been found in less than 25% of cases with CVID; the underlying mechanism thus remains unknown in the majority of CVID patients, and research in this field must continue. 

Key words: Antibody class switch. Autoimmunity. Common variable immunodeficiency. B cells. CD19. ICOS. TACI.
Common variable immunodeficiency disorders (CVID) IgD) is as-
CD27+ TACI deficiency (table II). The reduc-
CD19 deficiency HLA-DR lympho-
Th1 predominance has been demonstrated +
the HLA-III system, e.g., C2 and C4 factors, or TNF.

some of these families present mutations in genes of
tensions and at different times – even in adults. Thus,
mentary genes, develop isolated IgA deficiency in
tations, depending on exogenous factors or comple-
– though this appears to constitute a secondary alter-
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with primary B cell deficiency. IL-2, IL-4, IL-5 and IFN-γ deficiency may be associated, and in
somes a CD40 ligand (CD40L) defect is observed – though this appears to constitute a secondary alter-
etation. Genetic and molecular studies have shown the coincidence in one same family, and even within one
same individual, of cases of CVID and of selective IgA deficiency. It is believed that the carriers of certain mu-
tuations, depending on exogenous factors or comple-
mentary genes, develop isolated IgA deficiency in
instances and CVID in others, with different in-
tensities and at different times – even in adults. Thus,
some of these families present mutations in genes of
the HLA-III system, e.g., C2 and C4 factors, or TNF.

Table I

<table>
<thead>
<tr>
<th>Immunodeficiencies of antibody synthesis with special attention to CVID (From the Primary Immunodeficiency Diseases Classification Committee of IUIS, Budapest 2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Severe reduction in serum Ig isotypes with absent B cells</td>
</tr>
<tr>
<td>2. Severe reduction in at least 2 serum Ig isotypes with normal</td>
</tr>
<tr>
<td>3. Severe reduction in serum IgG and IgA with increased IgM</td>
</tr>
<tr>
<td>4. Isotypes or light chain deficiencies with normal numbers</td>
</tr>
<tr>
<td>5. Specific antibody deficiency with normal Ig concentrations and</td>
</tr>
<tr>
<td>6. Transient hypogammaglobulinemia of infancy (Serum IgG and</td>
</tr>
</tbody>
</table>

Immunodeficiencies of antibody synthesis with special attention to CVID (From the Primary Immunodeficiency Diseases Classification Committee of IUIS, Budapest 2005)

1. Severe reduction in serum Ig isotypes with absent B cells (Six variants are accepted. The prototype is the X-linked agammaglobulinemia).

2. Severe reduction in at least 2 serum Ig isotypes with normal (CD27+ TACI deficiency).

3. Severe reduction in serum IgG and IgA with increased IgM (CD19 deficiency).

4. Isotypes or light chain deficiencies with normal numbers of B cells (Four variants are accepted with different IgG subclasses and IgA deficiency).

5. Specific antibody deficiency with normal Ig concentrations and number of B cells (Variable inheritance and unknown genetics).

6. Transient hypogammaglobulinemia of infancy (Serum IgG and IgA decreased. Variable inheritance and unknown genetics).

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PATHOGENESIS

The defect underlying CVID is located in the termi-
nal maturation phase of the B lymphocytes, affecting
the production of antibody-generating plasma cells or
the immunoglobulin class switch from IgM to IgG. The
effect is generally intrinsic to the B cell population,
though in some cases regulatory T cell function fails,
with or without primary B cell deficiency. IL-2, IL-4,
IL-5 and IFN-γ deficiency may be associated, and in
some cases a CD40 ligand (CD40L) defect is observed – though this appears to constitute a secondary alter-
atation. Genetic and molecular studies have shown the coincidence in one same family, and even within one
same individual, of cases of CVID and of selective IgA deficiency. It is believed that the carriers of certain mu-
tations, depending on exogenous factors or comple-
mentary genes, develop isolated IgA deficiency in
some instances and CVID in others, with different in-
tensities and at different times – even in adults. Thus,
some of these families present mutations in genes of
the HLA-III system, e.g., C2 and C4 factors, or TNF.

Patients with CVID usually present hypogamma-
globulinemia, and IgG and IgA are more affected
than IgM, though there are multiple possible levels
and combinations. It should be pointed out that im-
munoglobulin normality does not rule out CVID, and
the definitive diagnosis requires confirmation of the
lack of specific antibody response following protein
and/or polysaccharide antigen challenge.

The B lymphocyte count is usually normal or al-
most normal, with a mature B phenotype, though in
contrast the plasma cells of the lymphoid tissues are
diminished in number. Nevertheless, imbalances in
some B cell subpopulations have been found, such as
the immature forms, with bronchiectasis and/or splenomegaly, though not so the immunoglobulin levels, which lack prognostic value.
In contrast to what was expected, the situation in terms of the memory B lympho-
cytes was not seen to correlate to the genetic muta-
tions recently described in CVID.

The T cells are seen to be normal in some pa-
ients, though other affected individuals present
anomalies in proliferation or cytokine synthesis in
response to different stimuli. T-B lymphocyte co-
operation is particularly affected. Patients with se-
rious complications tend to present a low CD4/CD8
ratio due to an increase in activated CD8+ lympho-
cytes (CD8+ HLA-DR+). High counts of large
granular lymphocytes (LGL) have also been report-
ed.

Recently new anomalies have been described in
CVID, though their relationship to the pathogenesis
and clinical severity of the disease remains the sub-
ject of research, since they appear to manifest in
some but not in all patients. These anomalies in-
clude innate immune defects, particularly in relation
to the activation, development and function of the
dendritic cells of monocyctic origin. In some cases
the defect is accompanied by variable alterations in
the production of IL-12 and IL-10, which causes secondary
anomalies in T cell activation, though no significant
Th2 > Th1 predominance has been demonstrated.
A defect in IL-7 synthesis has also recently been
published that appears to be relevant, since it oc-
urred in a subgroup of patients with CVID compli-
cated by splenomegaly, autoimmune disorders and
an increase in circulating CD8+ lymphocytes\(^2\). Another recently identified failure in native immunity involves the TLR9 (toll-like receptor 9), which recognizes the CpG motifs present in viruses and bacteria – a situation that could have defensive consequences\(^2\).

**CLINICAL MANIFESTATIONS**

Although CVID is attributable to a genetic defect with immune failures that are present from birth, the clinical manifestations of the disease often only appear in adulthood – though there have been reports of complications in patients aged 2 to 66 years\(^2\). Of note is the variety of symptoms and their severity, which can be seen in members of one same family presenting the same mutation. The clinical manifestations generally begin in the form of bacterial respiratory infections, complicated years later by lymphoid hyperplasia, autoimmune processes, lymphomas or granulomas\(^2\). Since the infections may not appear or may be of scant intensity, it is not unusual for the diagnosis of CVID to be delayed for years, until the complications appear.

**Infections**

Although the infections tend to manifest in adults, children may also be affected, with two peaks in frequency: one in the 1-5 years age range, and the other in the 16-20 years age interval\(^2\). The most common clinical presentation consists of recurrent sinus-bronchial infections. At the time of diagnosis of the disease, most patients have already suffered some episode of bacterial pneumonia\(^9\). The most frequently isolated pathogens are *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and different staphylococci. It is also possible to find *Pneumocystis jiroveci* (previously *carinii*), *Mycoplasma pneumoniae* and certain mycobacteria and fungi\(^6\).

**Late complications**

Some patients, either before or after the recurrent respiratory infections, develop gastrointestinal problems, granulomas, autoimmune manifestations, lymphomas, or cancer. These complications are inherent to adults, but occasionally may also be found in children.

**Chronic lung disease**

Chronic lung pathology is very common, and many adults ultimately develop bronchiectasis despite adequate management from childhood\(^2\). The risk of lung damage is associated to a deficient production of antibodies against bacterial polysaccharides\(^3\), and to a decrease in memory B lymphocytes\(^16\). Another common cause of chronic lung disease in adults with CVID is lymphocytic interstitial granulomatosis, which associates progressive dyspnea and is an indicator of poor prognosis, since it is usually accompanied by lymphoproliferative processes\(^33,34\).

**Granulomatosis**

The etiology underlying granulomatosis is not clear, though it has been associated with a chronic infection due to human herpes virus B (VHHB)\(^33\). Although the lungs are the most commonly affected region, granulomas may also appear in the skin, intestine or liver. Alternatively, generalized multisystemic presentations simulating sarcoidosis can be seen\(^22,25\). Granulomatosis is an unfavorable finding, due to the treatment difficulties involved and its frequent association to autoimmune and lymphoproliferative processes\(^33,34\).

**Table II**

Characteristics of memory B-cells

<table>
<thead>
<tr>
<th>Name</th>
<th>Phenotype</th>
<th>Cell</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM0</td>
<td>CD19+ CD27- IgD+</td>
<td>Naive B-cell</td>
<td>No modification after antigen-stimulated</td>
</tr>
<tr>
<td>BM1</td>
<td>CD19+ CD27+ IgD+</td>
<td>Memory B-cells without switch</td>
<td>Immunologic memory without switch from IgD to IgM and later to IgG or IgA</td>
</tr>
<tr>
<td>BM2</td>
<td>CD19+ CD27+ IgD-</td>
<td>Memory B-cells with switch</td>
<td>Normal memory B-cells</td>
</tr>
</tbody>
</table>

BM: B memory.

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\(^{29}\) Table downloaded from http://www.elsevier.es, day 28/04/2017. This copy is for personal use. Any transmission of this document by any media or format is strictly prohibited.
Gastrointestinal manifestations

Some patients with CVID develop inflammatory bowel disease, Crohn's disease or ulcerative colitis in early or later stages. Although the clinical picture and histological findings may be typical, it is more common to observe atypical forms of inflammation with malabsorption, diarrhea and weight loss. Other possible clinical conditions are chronic malabsorption with steatorrhea and vitamin B12 deficiency; protein-losing enteropathy; lactose intolerance; and villous atrophy more often related to Giardia lamblia parasitosis than to gluten. Some cases of colitis have been associated to viral infection, the recommendation being to search for herpes virus or cytomegalovirus in CVID patients with colitis. Lymphoid hyperplasia, symptomatic or otherwise, is often identified if radiological explorations are carried out.

The risk of gastrointestinal infections is high in some patients with CVID – the main causal agents being Salmonella, Shigella and Campylobacter. It has been reported that Helicobacter pylori infection occurs in 80% of patients with CVID who suffer dyspepsia. Systematic evaluation of such infection is recommended, with eradication in view of the high risk of gastric cancer involved.

Rheumatological and autoimmune diseases

Approximately 20-25% of all adults with CVID ultimately develop some autoimmune disorder, or a combination of several such disorders. These complications generally comprise rheumatological problems such as chronic arthritis, scleroderma, dermatomyositis, lupus erythematosus, and particularly Sjogren's syndrome. Other common problems include autoimmune cytopenias (hemolytic anemia, thrombopenia, neutropenia), and disorders such as hepatitis, biliary cirrhosis, Guillain-Barré syndrome, parotiditis, pernicious anemia, growth hormone deficiency, etc. Globally, these disorders are all more frequent in CVID than in selective IgA deficiency or in IgG subclass deficiency. In children, thrombopenic purpura is possibly the most common autoimmune disorder, and it should be pointed out that the hematological diagnosis often precedes that of CVID. Consequently, an immune evaluation is essential in the event of atypical thrombopenia, disappearing after triple antibiotic. It is recommended to vaccinate against pneumococcus and tetanus.

Cancer and lymphomas

Elderly adults with CVID have a high cancer risk: lymphomas and intestinal lymphoreticular processes being the most common disorders. Patients diagnosed with non-Hodgkin lymphoma may possibly present occult CVID. Extranodal marginal zone B lymphomas, previously known as MALT (Mucosa-Associated Lymphoid Tissue) lymphomas, are the most typical presentations. In contrast to the lymphomas of other immune deficiencies, these tend to be well differentiated, secreting immunoglobulins, and are characteristically negative for Epstein Barr virus. Gastric lymphomas have been associated with Helicobacter pylori, disappearing after triple antibiotic treatment. As a result, some authors recommend such treatment in all CVID patients with dyspepsia, even if the infection has not been demonstrated. The diagnosis of lymphoma is a particularly delicate matter, since the patients usually present lymphoid hypertrophy and benign adenopathies for many preceding years. Lymphoproliferative infiltration is frequent, causing lymphoid hyperplasia in the form of adenopathies and splenomegalia, though infiltration of other organs is also observed, such as the liver or kidneys – resulting in functional failure. The alterations are polyclonal, though malignization may occur. Their relation to B lymphomas, and the lymphoid lineage involved, is not clear. Recently, in a case of CVID with TACI mutation, the lymphocytes of the infiltration were identified as corresponding to T CDB + cells.

DIAGNOSIS OF CVID

In view of the clinical variability of the disease and the limited usefulness of the genetic studies, the diagnosis of CVID is based on the immune findings. However, due to the heterogeneity of the disorder, no single protocol has been established, and adaptations to each individual case are required. Hypogammaglobulinemia is the most suggestive finding, though normal immunoglobulin levels do not rule out the diagnosis. Consequently, in suspect cases, evaluation is required of antibodies targeted to thymus-independent polysaccharide antigens or thymus-dependent protein antigens, e.g., vaccinating against pneumococcus and tetanus. Isohemagglutinins tend to be absent or present at low levels. Other studies of B and T cell population and subpopulation function or number are useful for defining the prognosis and risk of complications (table III).

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Differential diagnosis

The diagnosis of CVID is largely based on the exclusion of other immune deficiencies, though this is not always easy, since the disease shares many characteristics with other disorders. Some patients diagnosed with CVID afterwards have been shown to present Btk gene mutations – the disorder actually corresponding to mild forms of sex-linked agammaglobulinemia. Differentiation from hyper-IgM syndrome based only on immune studies is a delicate matter, since IgM is not always increased, and because some cases of CVID show poor expression of the CD40L molecule despite no mutation of its encoding gene. The differential diagnosis with respect to chronic granulomatosis may prove difficult in some concrete cases, though a clue is provided by the older age of patients with CVID. The greatest differential diagnostic difficulty refers to selective deficiency of IgA, since its genetic and pathogenic relationship to CVID has been demonstrated, and a given patient may evolve from one disorder to the other.

The differential diagnosis will become easier once more genetic information on CVID becomes available. For the time being, high IgM levels or a B lymphocyte population < 2 % are immune data against a diagnosis of CVID.

TREATMENT

Years ago, cimetidine was evaluated in patients with CVID, though the results were disappointing. Posteriory, pegylated IL-2 was administered. At present, IgG is considered the treatment of choice, and drastically reduces the incidence of respiratory infections. In the past, the treatment was started when the infections appeared, though IgG is known to prevent the pulmonary complications; consequently, it should be administered to all CVID patients with hypogammaglobulinemia, until serum IgG stabilizes at between 500-700 mg/dl. This requires the infusion of individualized doses of between 270-500 mg/kg/month. The administration of subcutaneous IgG on a rapid (20 ml/h) and domiciliary basis is increasingly popular in children and adults, because it is well tolerated, avoids hospital dependency and improves patient quality of life – ensuring protection against infections similar to that afforded by administration via the intravenous route.

The rheumatic manifestations (Sjögren’s syndrome and rheumatoid arthritis) improve by adding IgG to conventional therapy, though not so the cutaneous granulomas. Indeed, it is better not to treat the latter as long as they remain asymptomatic, because they tend to recur after surgical removal. Recently, remissions have been reported with anti-TNF (etanercept, infliximab) – thus opening up new therapeutic perspectives for granulomatosis.

Management of the autoimmune cytopenias involves the usual treatment protocol. Good experience has been gained in relation to thrombopenias treated by splenectomy – though logically the antiinfectious coverage must be extremely rigorous. Antibiotic treatment should adhere to the cautions of choice, duration and rotation recommended for chronic infections. Some authors recommend the use of macrolides, because they offer a certain antiinflammatory capacity in addition to antibacterial action.

GENETIC AND MOLECULAR FINDINGS IN CVID

The mechanism underlying CVID remains unclear, and is certainly not the same for all forms of the dis-
ease. The theory – popular during the eighties – that CVID is an acquired disorder secondary to viral infection has been abandoned. Paradoxically, however, the correction of immune anomalies has been reported in CVID patients following infection with the human immunodeficiency virus. At present, CVID is considered to be a primary genetic alteration with a molecular mechanism that directly or indirectly affects B cell maturation and immunoglobulin synthesis (fig. 1).

Maturation of B lymphocytes immunoglobulin isotype switch

Two simultaneous processes are involved in the maturation of B lymphocytes: maturation of the cells to form plasma cells, and a switch in the immunoglobulin isotype synthesized, from IgD to IgM, and then to IgG or IgA – without changing the specificity of the antibody. A detailed review of lymphocyte development has recently been published.

This switch, or more specifically CSR (class-switch recombination) takes place through DNA recombination and excision, and depends on expression of the AID (activation-induced deaminase) gene. This complex genetic process has drawn special attention. Its initiation requires two signals. The first signal comprises a release of cytokines involved in B cell maturation and in the synthesis of antibodies. Thus, TGFβ activates the IgA heavy chain promoter, while IL-4 and IL-13 do the same for IgG and IgE. The second signal comprises intimate contact with other cells. For years cooperation with T lymphocytes has been known through the CD40 molecule of B lymphocytes and the CD40 ligand (CD40L) of the T lymphocytes, which activate the AID promoter in the same way as TLR9 (toll-like receptor 9).

BAFF/APRIL system

Posteriorly, a new cell cooperation system independent of the lymphocytes was discovered. This system is based on two membrane molecules of the TNF family (BAFF: B cell activating factor and APRIL: proliferation-inducing ligand). This mechanism allows

Figure 1.—B-cell differentiation from a progenitor stem cell to a pro-B, to a pre-B, and finally to a mature B-lymphocyte (some steps are not shown). The arrows indicate the B cell stages affected by genetic mutations causing immunodeficiency. Within the frame is represented the B cell receptor complex, with the two presently reported mutations, which are located in CD19 and the α chain. ADA affects very immature cells, producing relevant deficiencies; in contrast, CD19 or BCR defects occur in mature B cells. ADA: adenosine deaminase; RAG: recombinant-activating gene; BTK: Bruton’s tyrosine kinase; BLNK: mutated B cell-linked protein.
the switch to IgG and IgA in mice previously subject-
ed to CD40 + lymphocyte depletion – thus demon-
strating its independence of the CD40-CD40L lym-
phocyte route 71-73 (fig. 2).

BAFF factor

The BAFF molecule (also known as BLyS or
zTNF4) is encoded for by a 6-exon gene located in
13q34 74. It is synthesized by antigen-presenting cells
(APCs), dendritic cells and monocytic cells, and also
by neutrophils. IL-10, IFN-γ and IFN-α are potent
stimulators of BAFF expression 75. Its principal func-
tion is to prolong B lymphocyte life, thus increasing
the available B cell population. To this effect, BAFF
factor acts upon the cell cycle molecules with partic-
ipation in cancer processes, such as Bcl-2, Pim or
p53. Curiously, the BAFF and p53 genes are very
close to each other (a mere 200 kb).

The increase in cell survival is only exerted upon
certain partially mature B lymphocytes that have
emerged from the bone marrow and are located in
the spleen and lymphoid follicles. The factor possi-
bly also acts upon mature plasmocytes, though ac-
tion upon the particular population of peritoneal
B1 lymphocytes has been discarded 75. In sum, BAFF
supplies the body with a numerous B cell population.
The selectivity of this action, targeted to partially ma-
ture subpopulations, is fundamental – since an in-
creased survival of marrow B cells (more immature
and difficult to control) would increase the risk of au-
toimmune phenomena and tumors 70.

BAFF also activates non-immune cells, and an ex-
cess in its synthesis induces autoimmunity in trans-
genic mice 76. High serum BAFF levels have been re-
ported in humans with autoimmune or inflammatory
diseases such as systemic lupus, rheumatoid arthri-
tis, myasthenia gravis, and particularly Sjögren’s dis-
ease 76-78. This finding opens up new pathogenic and
therapeutic perspectives for these illnesses.

APRIL factor

Although APRIL factor and BAFF factor have
50 % protein homology, and moreover share recep-
tors, their functions are not the same. APRIL factor
does not intervene in B cell survival 80, though an in-
fluence upon T lymphocytes is not ruled out. Its
principal function is oncogenic, not immune – with
expression in different tumor lines, particularly glo-
blastoma 81. In addition, it has been speculated that
blockade of APRIL factor could be of therapeutic
utility 76.

Receptors

The BAFF and APRIL factors bind to three differ-
ent receptors (BR3, TACI and BCMA) belonging to
the TNF receptor superfamily (TNFRSF), and which
are found on the surface of B lymphocytes — though TACI is also weakly expressed by other cells, such as activated T lymphocytes. Binding to these receptors induces different actions related to the matura-
tion and survival of B lymphocytes.

The TACI receptor is a molecule encoded for by a 5-exon gene located in 17p11.2, containing two cysteine-rich domains where the TNF-type molecules bind, and moreover facilitating the interbonding of several TACI molecules — their prior trimerization or oligomerization being necessary in order to behave as a receptor and activate the cell. The intracytoplas-
mic portion of the TACI molecule activates the nu-
clear factor of the activated T cells (NF-AT) following the synthesis of the TACI molecule, some experiments have revealed the presence of adenopathies and splenomegaly, with a notorious increase in B lymphocytes, since it seems that the TACI mole-
cule normally emits apoptotic signals of relevance for homeostasis of the B cell population. These deficient mice present a deficient thymus-independent hyper-IgM syndrome and appear in both sporadic forms and in familial presentations — though never in normal controls. The B lymphocytes of the ill patients expressed TACI, but were unable to syn-
thesize either IgG or IgA in response to the corre-
sponding ligand (APRIL) (72) (fig. 3).

An observation of note is the fact that there were cases in homo- and heterozygosis, and although some of the former presentations exhibited a more serious phenotype, this was not always the case. The S144X mutation was associated to the cases that were more serious and more similar to the find-
ings in knock-out transgenic mice, though it also pro-
duced asymptomatic hypogammaglobulinemia and never an increase in the B cell population, as in mice (table IV).

In several families, the same mutation caused se-
lective lgA deficiency in some individuals and CVID in the rest. The variable penetrance of the deficien-
cies means that in addition to the actual mutation, other environmental or genetic factors influence the

Deficiencies in humans

The function of these molecules in humans re-
 mains unclear, and the findings moreover coincide only partially with those obtained in mice — being more akin to those recorded in certain monkeys. The murine anomalies are more intense than in hu-
 mans, possibly due to the transgenic model itself, or because humans have acquired alternative functional routes. The TACI molecule belongs to the TNF re-
ceptor superfamily (TNFRSF), and in humans several inflammatory or immune diseases are known, attrib-
utable to alterations in this group of molecules. Thus, TNFRSF1A mutations cause TNF receptor associat-
ed periodic fever syndrome (TRAPS), which exhibits a dominant autosomal hereditary pattern. Mut-
tations affecting TNFRSF5, commonly referred to as CD40, are responsible for the type 3 (recessive auto-
somal) presentation of hyper-IgM syndrome. Mut-
tations affecting TNFRSF6, also called FAS, induce autoimmune lymphoproliferative syndrome (ALPS) — a special type of immune deficiency with lympho-
proliferation and splenomegaly, with a notorious increase in B lymphocytes — though never in normal controls. The B lymphocytes of the ill patients expressed TACI, but were unable to syn-
thesize either IgG or IgA in response to the corre-
sponding ligand (APRIL) (72) (fig. 3).

An observation of note is the fact that there were cases in homo- and heterozygosis, and although some of the former presentations exhibited a more serious phenotype, this was not always the case. The S144X mutation was associated to the cases that were more serious and more similar to the find-
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In several families, the same mutation caused se-
lective IgA deficiency in some individuals and CVID in the rest. The variable penetrance of the deficien-
cies means that in addition to the actual mutation, other environmental or genetic factors influence the
immune and clinical alterations\(^{23,25}\), and that the activation system in which the TACI molecule participates is highly redundant in humans\(^{14}\). The majority of cases of CVID with TACI defect reported to date correspond to adults in the 30-70 years age range, with a similar sex distribution. Infectivity was little or slightly increased, and very limited to encapsulated bacteria. The most constant defect was a selective absence of response to polysaccharide vaccination (Pneumovax-23)\(^{22}\). A little over 30% showed generally mild autoimmune alterations, or lymphoproliferative processes, usually limited to splenomegaly or tonsillar hypertrophy, and which were only a little more frequent than in the normal population of the

\[\text{ICOS: “Inducible co-stimulator” of activated T-cells; TACI: Transmembrane activator and calcium-modulator and cyclophilin ligand interactor; CVID: Common variable immunodeficiency; BAFF-R: Receptor of B-cell activating factor of the TNF family; TNFRSF: TNF receptor super-family.}\]

**Table IV**

<table>
<thead>
<tr>
<th>Genetic defects reported in CVID</th>
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</thead>
<tbody>
<tr>
<td><strong>Genetic defect</strong></td>
</tr>
<tr>
<td>Chromosome</td>
</tr>
<tr>
<td>Inheritance</td>
</tr>
<tr>
<td>Immunodeficiency</td>
</tr>
<tr>
<td>% of CVID</td>
</tr>
<tr>
<td>B-cell number</td>
</tr>
<tr>
<td>Ig decreased</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
</tbody>
</table>

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![Figure 3.—Structure of the TACI receptor. The two ligands are bound by the cysteine-rich domain-2 (CRD-2). Molecular oligomerization occurs when the receptor is activated. Six mutations have been described in the TACI gene, located in 17p11.2, two of them affect CRD-2.](image-url)
same age10. Such moderation was unexpected, considering the intensity of the findings in transgenic mice.

It has been proposed that cases of CVID with TACI defect should be regarded as an entity independent of the rest of CVID presentations12, because in all these patients the IgM values were found to be normal – this situation not being common in other cases of CVID11.

Other mutations in CVID

ICOS (inducible costimulatory receptor)

This is a T cell costimulatory factor that facilitates intense IL-10 production and also participates in the synthesis of IL-4, IL-6 and IL-7. Both mice and humans with mutations of the ICOS gene show humoral immune failure compatible with CVID, with anomalous germinal centers13,36,43. However, the frequency of the ICOS mutation in CVID patients is very low (a little over 1 %)73,101.

CD19

CD19 regulates the development, activation and proliferation of B lymphocytes14. Although to date no defects in the so-called co-receptor molecules (CD19, CD21, CD81 and CD225) had been detected in immune deficient patients102, a recent report describes a homozgyous mutation of the CD19 gene in four families with CVID presenting hypogammaglobulinemia and diminished memory B cell and CD25 + B cell counts73,101. In future, defects of other molecules of this type may appear.

BAFF

On confirming the importance of the BAFF molecule (BLyS) in the development and maturation of B lymphocytes, its encoding gene was considered a candidate for CVID, and has recently been investigated. Losi et al.14 sought mutations in the 6 exons of the gene, though without success. Although mutations of the BAFF gene in CVID have not been ruled out, their frequency would be very low10,10. Moreover, in contrast to the TACI gene, the BAFF gene is highly preserved and shows scant variability10,43. To date, BAFF mutations have only been found in patients with systemic lupus erythematosus or rheumatoid arthritis, though with a frequency insufficient to associate them with an increase in susceptibility13,36.

BR3 or BAFF-R

The BAFF receptor is important for the development and survival of B lymphocytes. A mutation of the BAFF-R gene was detected in a patient with CVID, though it also appeared in a healthy relative – thus raising doubts as to its potential role13,36.

REFERENCES


