ABSTRACT

Common variable immunodeficiency (CVID) 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 (CVID) is classified as a predominantly antibody deficiency (table I). It comprises a heterogeneous group of alterations all characterized by deficient antibody synthesis (CVID). In the past it was known as late-onset hypogammaglobulinemia, and earlier still was referred to as Giedion-Scheidigger deficiency or dysglobulinemia – due to the multiple combinations of immunoglobulin levels involved. CVID is related to selective IgA deficiency, and both abnormalities may often coincide in one same family. CVID can manifest at any age as recurrent bacterial infections, and is characterized by the presence of hypogammaglobulinemia with failure in the production of antibodies in response to different antigens. The number of B and T lymphocytes tends to be normal or almost normal, though important reductions in cell count are sometimes observed. The incidence of CVID ranges from 1/25,000 to 1/66,000 inhabitants, though the more milder cases probably go undetected. Although selective IgA deficiency is much more common, it is also frequently asymptomatic.
CD19 deficiency

+ HLA-DR

BAFF receptor deficiency

CD27

ICOS deficiency

+ +

Th1 predominance has been demonstrated

TACI deficiency

Common variable immunodeficiency disorders (CVID)

+ lympho-IgD–) is as-

the HLA-III system, e.g., C2 and C4 factors, or TNF.

some of these families present mutations in genes of

tensities and at different times – even in adults. Thus,

some instances and CVID in others, with different in-

mentation genes, develop isolated IgA deficiency in

deficiency. It is believed that the carriers of certain mu-

same individual, of cases of CVID and of selective IgA

deficiency. AID deficiency and UNG deficiency

subclasses and IgA deficiency)

specific antibody deficiency with normal Ig concentrations and

number of B cells (Four variants are accepted with different IgG

infections recently described in CVID17)

2. Severe reduction in at least 2 serum Ig isotypes with normal

or/and numbers of B cell

a. Common variable immunodeficiency disorders (CVID)

b. ICOS deficiency
c. CD19 deficiency
da. TACI deficiency
e. BAFF receptor deficiency

3. Severe reduction in serum IgG and IgA with increased IgM

and normal numbers of B cells (Two variants are accepted: AID deficiency and UNG 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)

sequently, CVID is considered to be the most frequent

ease does not rule out CVID, and the

definitive diagnosis requires confirmation of the

lack of specific antibody response following protein

and/or polysaccharide antigen challenge9,10.

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 forms11, and such populational anom-
amies may increase with patient age12. The most rele-
vant observation has been the detection of anomalies in

the memory B cells, which serves to classify the

different forms of CVID and to predict the course of

the disorder in each patient13-18 (table II). The reduc-
tion in memory B cells (CD19 + CD27 + IgD–) is as-

associated in both children and in adults to severe

forms, with bronchiectasis and/or splenomegalia11,

though not so the immunoglobulin levels, which lack

prognostic value18. In contrast to what was expect-
ed, the situation in terms of the memory B lympho-
cytes was not seen to correlate to the genetic muta-
tions recently described in CVID17.

The T cells are seen to be normal in some pa-

patients, though other affected individuals present

anomalies in proliferation or cytokine synthesis in

response to different stimuli. T-B lymphocyte co-

operation is particularly affected1. 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+)19. High counts of large

granular lymphocytes (LGL) have also been report-
ed20.

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 monocyte origin21,22. In some cases

the defect is accompanied by variable alterations in

the production of IL-1221,24, which causes secondary

anomalies in T cell activation, though no significant

Th2 > Th1 predominance has been demonstrated21.

A defect in IL-7 synthesis has also recently been

published that appears to be relevant, since it oc-

curred in a subgroup of patients with CVID compli-
cated by splenomegalia, autoimmune disorders and

Table I

Immunodeficiencies of antibody synthesis with special attention to CVID

(From the Primary Immunodeficiency Diseases Classification Committee of IUIS. Budapest 2005)

1. Severe reduction in all 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

or/and numbers of B cell

a. Common variable immunodeficiency disorders (CVID)

b. ICOS deficiency
c. CD19 deficiency
da. TACI deficiency
e. BAFF receptor deficiency

3. Severe reduction in serum IgG and IgA with increased IgM

and normal numbers of B cells (Two variants are accepted: AID deficiency and UNG 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)

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-

ation. 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.

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an increase in circulating CD8+ lymphocytes. 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.

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. 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. 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. 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. The most frequently isolated pathogens are *Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis* and different staphylococci. It is also possible to find *Pneumocystis jiroveci* (previously *carinii*), Mycoplasma pneumoniae and certain mycobacteria and fungi.

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. The risk of lung damage is associated to a deficient production of antibodies against bacterial polysaccharides, and to a decrease in memory B lymphocytes. 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.

Granulomatosis

The etiology underlying granulomatosis is not clear, though it has been associated with a chronic infection due to human herpes virus 8 (HHV8). 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. Granulomatosis is an unfavorable finding, due to the treatment difficulties involved and its frequent association to autoimmune and lymphoproliferative processes.

<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 been 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.
**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. Lympophoid hyperplasia, symptoms 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 *Heliocobacter 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 arthritides, scleroderma, dermatomyositis, lupus erythematosus, and particularly Sjögren’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 any atypical thrombopenia, and CVID has been associated to insulin-dependent diabetes in children and adolescents. A celiac patient with the typical DQ2 A1 0501 haplotype has been documented.

**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 characterized negatively for Epstein Barr virus. Gastric lymphomas have been associated with *Heliocobacter 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 splenomegaly, 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 CD8 + 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).
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. Posterily, 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.

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...
the switch to IgG and IgA in mice previously subjected to CD40+ lymphocyte depletion – thus demonstrating its independence of the CD40-CD40L lymphocyte route\(^\text{71-73}\) (fig. 2).

**BAFF factor**

The BAFF molecule (also known as BLYS or zTNF4) is encoded for by a 6-exon gene located in 13q34\(^\text{74}\). It is synthesized by antigen-presenting cells (APCs), dendritic cells and monocyctic cells, and also by neutrophils. IL-10, IFN-γ and IFN-α are potent stimulators of BAFF expression\(^\text{75}\). Its principal function 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 participation 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 possibly also acts upon mature plasmocytes, though action upon the particular population of peritoneal B1 lymphocytes has been discarded\(^\text{76}\). In sum, BAFF supplies the body with a numerous B cell population. The selectivity of this action, targeted to partially mature subpopulations, is fundamental – since an increased survival of marrow B cells (more immature and difficult to control) would increase the risk of autoimmune phenomena and tumors\(^\text{75}\). BAFF also activates non-immune cells, and an excess in its synthesis induces autoimmunity in transgenic mice\(^\text{77}\). High serum BAFF levels have been reported in humans with autoimmune or inflammatory diseases such as systemic lupus, rheumatoid arthritis, myasthenia gravis, and particularly Sjögren’s disease\(^\text{76,78}\). 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 receptors, their functions are not the same. APRIL factor does not intervene in B cell survival\(^\text{80}\), though an influence upon T lymphocytes is not ruled out. Its principal function is oncogenic, not immune – with expression in different tumor lines, particularly glioblastoma\(^\text{81}\). In addition, it has been speculated that blockade of APRIL factor could be of therapeutic utility\(^\text{76}\).

**Receptors**

The BAFF and APRIL factors bind to three different 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 maturation 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 intracytoplasmic portion of the TACI molecule activates the nuclear factor of the activated T cells (NF-AT) following a long metabolic route involving the participation of JNK (c-Jun NH2-terminal kinase) and nuclear factor NFκB. The B subpopulation located in the marginal zone and the CD27 + memory cells are those that express TACI most intensely.

**Deficiencies in mice**

The activator molecules partially share their receptors, which explains the fact that the consequences of the elimination of a molecule or receptor in a transgenic mouse are different.

In mice lacking BAFF factor, a serious block of B lymphocyte maturation is observed, and these cells moreover have a much shortened half-life. Antibody synthesis is strongly deficient for both the thymus-dependent and thymus-independent systems. The lack of BAFF receptor (BR3) induces a similar though less intense phenotype, with a normal production of IgA antibodies – thus suggesting that synthesis of the latter is mainly dependent upon the TACI receptor, which compensates the defect.

Mice lacking APRIL present B cells with normal counts and survival. However, the switch to IgA is seen to fail, and there is no IgA antibody response following oral challenge. In contrast, a lack of BCMA does not appear to alter either antibody synthesis or the switch to IgA.

The transgenic mice without TACI, some experiments have revealed the presence of adenopathies and splenomegaly, with a notorious increase in B lymphocytes, since it seems that the TACI molecule normally emits apoptotic signals of relevance for homeostasis of the B cell population. These deficient mice present a deficient thymus-independent humoral response; of particular severity is their inability to produce antibodies against bacterial polysaccharides, and upon aging, over 15% of the animals develop autoantibodies, lupus, glomerulonephritis and lymphoproliferative alterations.

**Deficiencies in humans**

The function of these molecules in humans remains 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 humans, possibly due to the transgenic model itself, or because humans have acquired alternative functional routes. The TACI molecule belongs to the TNF receptor superfamily (TNFRSF), and in humans several inflammatory or immune diseases are known, attributable to alterations in this group of molecules. Thus, TNFRSF1A mutations cause TNF receptor associated periodic fever syndrome (TRAPS), which exhibits a dominant autosomal hereditary pattern. Mutations affecting TNFRSF5, commonly referred to as CD40, are responsible for the type 3 (recessive autosomal) presentation of hyper-IgM syndrome. Mutations affecting TNFRSF6, also called FAS, induce autoimmune lymphoproliferative syndrome (ALPS) – a special type of immune deficiency with lymphoproliferation.

**CVID with TACI defect**

In the year 2005, a group in Europe and another in Boston, respectively directed by Grimbacher and Geha, simultaneously published several cases of CVID and of IgA deficiency with mutations of the TNFRSF13B gene, which encodes for the TACI molecule. The findings of both groups were similar, and the mutations identified coincided (S144X, C104R, A181E, S194X and R202H) and appeared in both sporadic and in familial presentations – though never in normal controls. The B lymphocytes of the ill patients expressed TACI, but were unable to synthesize either IgG or IgA in response to the corresponding ligand (APRIL) (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 findings in knock-out transgenic mice, though it also produced asymptomatic hypogammaglobulinemia and never an increase in the B cell population, as in mice (table IV).

In several families, the same mutation caused selective IgA deficiency in some individuals and CVID in the rest. The variable penetrance of the deficiencies means that in addition to the actual mutation, other environmental or genetic factors influence the
immune and clinical alterations[22,23], 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 splenomegalia or tonsillar hypertrophy, and which were only a little more frequent than in the normal population of the

Table IV

<table>
<thead>
<tr>
<th>Genetic defect</th>
<th>TACI</th>
<th>ICOS</th>
<th>CD19</th>
<th>BAFF-R</th>
</tr>
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<tr>
<td>Chromosome</td>
<td>17p11.2</td>
<td>2q33</td>
<td>16p11.2</td>
<td>22q13.2</td>
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<td>Autosomal-recessive</td>
<td>Autosomal-recessive</td>
<td>Autosomal-recessive</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Early or late CVID</td>
<td>Early or late CVID</td>
<td>Early or late CVID</td>
<td>Early or late CVID</td>
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<tr>
<td>% of CVID</td>
<td>5-10%</td>
<td>2%</td>
<td>&lt;1%</td>
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<td>B-cell number</td>
<td>normal</td>
<td>normal/low</td>
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<td>Ig decreased</td>
<td>IgG and IgA, IgM may be normal</td>
<td>IgG and IgA, IgM may be normal</td>
<td>IgG and IgA, IgM may be normal</td>
<td>IgG and IgA, IgM may be normal</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Recurrent bacterial infections and lymphoproliferative/autoimmune disorders</td>
<td>Recurrent bacterial infections</td>
<td>Recurrent bacterial infections</td>
<td>Recurrent bacterial infections</td>
</tr>
</tbody>
</table>

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.
same age\(^{12}\). 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 presentations\(^ {12}\), because in all these patients the IgM values were found to be normal – this situation not being common in other cases of CVID\(^ {11}\).

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-5 and IL-6. Both mice and humans with mutations of the ICOS gene show humoral immune failure compatible with CVID, with anomalous germinal centers\(^ {13,26,37}\). However, the frequency of the ICOS mutation in CVID patients is very low (a little over 1 %)\(^ {14,15}\).

CD19

CD19 regulates the development, activation and proliferation of B lymphocytes\(^ {16}\). Although no defects in the so-called co-receptor molecules (CD19, CD21, CD81 and CD225) had been detected in immune deficient patients\(^ {10}\), a recent report describes a homozygous mutation of the CD19 gene in four families with CVID presenting hypogammaglobulinemia and diminished memory B cell and CD25 + B cell counts\(^ {7,10}\). 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\(^ {11}\) 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 low\(^ {10}\). Moreover, and in contrast to the TACI gene, the BAFF gene is highly preserved and shows scant variability\(^ {12}\). 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 susceptibility\(^ {12}\).

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 role\(^ {13,14}\).

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