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# A link among schizophrenia, diabetes, and asthma: Role of Ca<sup>2+</sup>/cAMP signaling

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## Abstract:

Asthma has been associated with an increased risk for developing schizophrenia. In addition, schizophrenia has been associated with an increased risk for developing type 2 diabetes mellitus, resulting in an elevated cardiovascular risk and in a limited life expectancy. It is well discussed that dysregulations related to Ca<sup>2+</sup> signaling could link these diseases, in addition to cAMP signaling pathways. Thus, revealing this interplay among schizophrenia, diabetes, and asthma may provide novel insights into the pathogenesis of these diseases. Publications involving Ca<sup>2+</sup> and cAMP signaling pathways, schizophrenia, diabetes, and asthma (alone or combined) were collected by searching PubMed and EMBASE. Both Ca<sup>2+</sup> and cAMP signaling pathways (Ca<sup>2+</sup>/cAMP signaling) control the release of neurotransmitters and hormones, in addition to airway smooth muscle contractility, then dysregulations of these cellular processes may be involved in these diseases. Taking into consideration, the experience of our group in this field, this narrative review debated the involvement of Ca<sup>2+</sup>/cAMP signaling in this link among schizophrenia, diabetes, and asthma, including its pharmacological implications.

## Keywords:

Asthma, Ca<sup>2+</sup> channel blockers, Ca<sup>2+</sup>/cAMP signaling, diabetes, neurodegeneration, pharmacotherapy, schizophrenia

## Introduction

The concept of a complex clinical link among schizophrenia, diabetes, and asthma has been described in several reports.<sup>[1-4]</sup> The concept that supports a positive link among schizophrenia, diabetes, and asthma rests in the findings that various processes are involved in the pathogenesis of these diseases, for example, a convergent disturbance in the immune-inflammatory system.

Nowadays, it is also well discussed that an increase, and dysregulation, of the intracellular concentration of Ca<sup>2+</sup> ([Ca<sup>2+</sup>]c) is correlated with the pathogenesis

of schizophrenia, diabetes, and asthma.<sup>[5-9]</sup> In accordance with this concept, there are several studies emphasizing that Ca<sup>2+</sup> channel blockers (CCBs) can alleviate symptoms of schizophrenia, diabetes, and asthma.<sup>[10-12]</sup> A debated pharmaceutical principle for these interesting results could result from restoring the dysregulated (Ca<sup>2+</sup>) c, in addition to regulating cAMP signaling pathways (Ca<sup>2+</sup>/cAMP signaling).<sup>[5-9]</sup> Considering the experience of our group in this field,<sup>[5-9,13-18]</sup> this narrative review discussed the contributions of Ca<sup>2+</sup>/cAMP signaling in this link among schizophrenia, asthma, and diabetes. Publications involving Ca<sup>2+</sup> and cAMP signaling pathways, asthma, diabetes and schizophrenia (alone or combined) were collected by searching PubMed and EMBASE, using a search strategy with high sensitivity for studies of etiology, as followed:

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- a. Searches initially used the following strings: Risk (in title or abstract) OR risk (as a Medical Subject Heading [MeSH] term, not exploded) OR cohort studies (as a MeSH term) OR group (as a text word) The results of these searches were combined with sets created with schizophrenia OR diabetes OR asthma
- b. Bibliographies of the articles obtained were also reviewed for possible data sources.

## A Clinical Link Between Schizophrenia and Asthma

Asthma, an established inflammatory disease, has been associated with an increased risk for developing schizophrenia.<sup>[1,2]</sup> Schizophrenia can be considered a chronic mental disorder, affecting approximately 1% of the general population.<sup>[19]</sup> Schizophrenia is associated with deficits in cognitive and psychosocial functioning and also to hallucinations and delusions.<sup>[20]</sup> Disturbances in communication, perception and thought processes are classically related to this disease, as well as abnormalities in behavior.<sup>[21]</sup> Then, social disability and substantial functional impairment are common outcomes of these disturbances.<sup>[22]</sup>

In fact, autoimmune diseases, and infections, have been linked with an increased risk of schizophrenia, and inflammatory mechanisms have been argued to be implicated in this issue.<sup>[1,2]</sup> Then, the report by Pedersen *et al.*<sup>[2]</sup> investigated the link between atopic disorders, with particular emphasis on asthma, and schizophrenia. The authors<sup>[2]</sup> screened two nationwide population-based registers: The Danish Psychiatric Central Register and the National Hospital Register. Pedersen *et al.*<sup>[2]</sup> used two longitudinal designs: A cohort study and a case/sibling study. Rate ratios (RRs) and accompanying 95% confidence intervals (CIs) were obtained. The authors observed that a hospital contact with any atopic disorder increased the RR of schizophrenia by 1.45 (95% CI = 1.31–1.90). The increased risk was mainly driven by asthma: 1.59 (95% CI = 1.31–1.90); this result was confirmed by the authors when cases were compared with siblings, instead of the background population. In fact, hospital contact with atopic disorders (atopic dermatitis, urticaria, and allergic rhinitis) increased the risk of schizophrenia significantly. The report<sup>[2]</sup> indicates the existence of an association between atopic disorders, particular asthma, and the risk of developing schizophrenia. This study<sup>[2]</sup> adds evidence to a growing body of literature suggesting the possible involvement of immune processes in the pathophysiology of schizophrenia.<sup>[2]</sup>

Another report, a retrospective cohort study,<sup>[1]</sup> aimed to investigate the association between asthma, corticosteroid use, and schizophrenia. The report<sup>[1]</sup> compiled longitudinal data (2000–2007) from adults with

asthma ( $n = 50,046$ ) and without asthma ( $n = 50,046$ ), and data were compared on measures of schizophrenia incidence by using Taiwan's National Health Insurance Research Database. Incidence of schizophrenia diagnosis (ICD-9 codes 295.XX) between 2000 and 2007 was compared between groups.<sup>[1]</sup> The authors concluded that asthma was associated with an increased risk for schizophrenia.<sup>[1]</sup> The results suggested that a convergent disturbance in the immune-inflammatory system may contribute to the etiology of asthma and schizophrenia.<sup>[1]</sup>

In addition, dysregulations of the dopamine system are classically associated with schizophrenia, involving dopamine D1/D2 receptors in processing information and cholinergic systems due to a  $Ca^{2+}$  release.<sup>[23–25]</sup> Indeed, the antipsychotic effects of classical medicines are mediated by modulating dopamine D1/D2 receptors.<sup>[23,24]</sup> Furthermore, the cholinergic system has a major impact on cognitive abilities, especially learning and memory.<sup>[23,24]</sup> In addition,  $Ca^{2+}$  dysregulations have also been related to schizophrenia.<sup>[23–25]</sup> In fact,  $Ca^{2+}$  signaling dysregulations may precede dopamine system dysregulations in schizophrenia.<sup>[23–25]</sup> The increased  $Ca^{2+}$  signaling has been recorded in schizophrenia by using a computational mathematical model, called the Boolean network, along with dopamine D1/D2 receptor-generated perturbations.<sup>[24]</sup> The central role of  $Ca^{2+}$  signaling leads with the reception of a signal by hypothalamic nuclei through acetylcholine, and continues with the processing of information into assemblies by dopamine in higher functioning areas, such as the prefrontal cortex, involving mechanisms of  $Ca^{2+}$ -induced calcium release. This central role highlights the unifying effects of  $Ca^{2+}$  signaling in the regulatory mechanisms of schizophrenia.<sup>[23–25]</sup>

Considering a convergent disturbance in the immune-inflammatory system may contribute to the etiology of both asthma and schizophrenia, asthma can be considered a common inflammatory disease of the respiratory tract, characterized by obstruction and hyper-responsiveness of the tracheobronchial system.<sup>[26]</sup> An imbalance of the intracellular  $Ca^{2+}$  homeostasis (e.g. an excess of intracellular  $Ca^{2+}$ ) has been also debated as associated with the pathogenesis of asthma, like in schizophrenia, through a plausible hypercontractility of the airway smooth muscle.<sup>[19,27]</sup> Furthermore, interactions between the immune system and the brain have been also implicated in the cellular mechanisms linking asthma and schizophrenia.<sup>[28]</sup> For instance, several epidemiological reports have reported an increased risk for developing schizophrenia among those patients with autoimmune disorders and/or severe infections.<sup>[29,30]</sup> Indeed, chronic inflammation has been associated with a greater permeability of the blood–brain barrier, facilitating the entry of immune

molecules into the brain,<sup>[31]</sup> then contributing to the pathogenesis of schizophrenia.

## A Clinical Link between Schizophrenia and Diabetes

Schizophrenia has been associated with an increased risk for developing type 2 diabetes mellitus (T2DM), resulting in an elevated cardiovascular risk and a limited life expectancy.<sup>[34]</sup> Diabetes can be classified according to its etiology. For example, type 1 diabetes mellitus (T1DM) is a form of diabetes in which insufficient, or no, insulin is produced by the pancreas, then classified as juvenile diabetes.<sup>[4]</sup> In addition, T2DM is a form of diabetes that is characterized by insulin resistance, then classified as adult-onset diabetes. In fact, the prevalence of T2DM among patients with schizophrenia varies across reports, reaching two-fold higher (compared with the general population).<sup>[3,4]</sup> In fact, in the USA, prevalence estimations of diabetes among patients with schizophrenia reach to ~14.2% in a retrospective cohort study,<sup>[32]</sup> to ~18.7% in a cross-sectional study conducted in 819 patients with schizophrenia,<sup>[33]</sup> and ~23.3% in another cross-sectional with 2,231 patients;<sup>[34]</sup> emphasizing an alarming trend of increase over time (~6.9% in 1997 to ~14.5% in 2004).<sup>[35]</sup> In the European populations, prevalence estimations of diabetes among patients with schizophrenia are evaluated ~15% in the Netherlands,<sup>[36]</sup> ~14.8% in a case-control study conducted in Sweden with 2,058,408 patients,<sup>[37]</sup> ~22% in a cross-sectional study in Finland,<sup>[38]</sup> whereas the prevalence of diabetes among patients with schizophrenia in the UK is estimated to be ~11.3%.<sup>[39]</sup> Similarly, in Asia, the prevalence approaches ~15.3% in a case-control study in India<sup>[40]</sup> and ~15% in Malaysia.<sup>[41]</sup> Finally, the prevalence in Australia<sup>[42]</sup> reaches ~12.1%.

In addition, patients with T2DM are often overweight or obese or have presented an increased percentage of body fat. Obesity is a common comorbidity in schizophrenia.<sup>[43]</sup> For instance, according to a study conducted with 2,548 patients,<sup>[44]</sup> even in the first episode of schizophrenia ~22% of patients were overweight. Another report clearly showed that patients diagnosed with schizophrenia were overweight-obese.<sup>[45]</sup>

Nonetheless, the etiology involving this link between schizophrenia and diabetes is complex and multifactorial. Besides common diabetogenic factors in schizophrenia patients, such as poor diet, obesity, hyperlipidemia, smoking, and hypertension, the link between these diseases is also attributed to unique issues.<sup>[3,4]</sup> Indeed, the adverse effects of antipsychotic drugs and social factors can be considered aggravating issues for the diabetes onset. In addition, schizophrenia (itself) is further suggested as a causal issue for diabetes,<sup>[3,4]</sup> considering an observed higher prevalence of diabetes in young patients,

then newly diagnosed with schizophrenia (unexposed to antipsychotics).<sup>[3,4]</sup> In addition, reports also support a genetic predisposition to diabetes among patients with schizophrenia, suggesting a shared genetic risk. Thus, special attention should be given in preventing diabetes in patients with schizophrenia, then intervening in all possible modifiable risk issues. Finally, an imbalance of the intracellular  $Ca^{2+}$  homeostasis (e.g. an excess of intracellular  $Ca^{2+}$ ) has been also debated as associated with the pathogenesis of diabetes, like in schizophrenia and asthma.<sup>[8,12]</sup> Diabetes has been clearly related to dysregulations of the  $Ca^{2+}$  signaling.<sup>[8,12]</sup> Considering that  $Ca^{2+}$  signaling is essential to regulate the release of both insulin and transmitters release, then both schizophrenia and diabetes are related to abnormal variations of the  $Ca^{2+}$  signals; thus, their dysregulations may affect the secretory homeostasis of both insulin and transmitters.<sup>[7,8,12]</sup> Finally,  $Ca^{2+}$  signaling also affects the contractility of the airway smooth muscle, a process involved in the pathogenesis of asthma, as cited before.<sup>[9,27]</sup>

Complementing current findings, the next topic will discuss the fundamental findings of  $Ca^{2+}$ /cAMP signaling pathways and their relevance for schizophrenia, asthma, and diabetes.

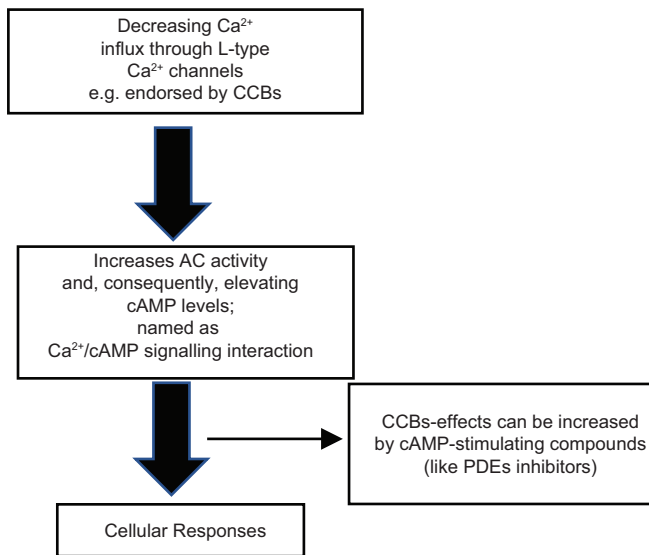
## Schizophrenia, Diabetes, and Asthma role of $Ca^{2+}$ /cAMP Signaling

### Basic mechanisms

Our findings about  $Ca^{2+}$ /cAMP signaling have established the role of these signaling pathways in controlling the neurotransmitter/hormone release, in addition to the smooth muscle contractility.<sup>[5-9,13-18]</sup> Our findings confirmed that by reducing  $Ca^{2+}$  influx through voltage-activated  $Ca^{2+}$  channels, adenylyl cyclases (ACs) are disinhibited (thus elevating cAMP levels, entitled as  $Ca^{2+}$ /cAMP signaling interaction), [Figure 1].

Through this working mechanism, CCBs-effects can be greatly enhanced through their pharmacological combination with cAMP-stimulating compounds (like phosphodiesterases inhibitors). The working mechanisms by which the transmitter/hormone release can be greatly enhanced by modulating  $Ca^{2+}$ /cAMP signaling result from: (1) enhancing the content of transmitters/hormones in the secretory vesicles, (2) increasing the rate of transmitters/hormones release.<sup>[5-9]</sup> In fact,  $Ca^{2+}$  signaling is critical for stimulating the release process: Through increasing cAMP levels, this can enhance the release of  $Ca^{2+}$  from the endoplasmic reticulum (ER), thus stimulating the transmitter/hormones release.

Furthermore, an elevated ( $Ca^{2+}$ )c resulting from profound dysregulations of  $Ca^{2+}$  signaling, such as an increased  $Ca^{2+}$  influx, has been correlated to schizophrenia, asthma,



**Figure 1:** Pharmacological modulation of  $\text{Ca}^{2+}$ /cAMP signalling. Briefly, decreasing  $\text{Ca}^{2+}$  influx through L-type  $\text{Ca}^{2+}$  channels, e.g., endorsed by  $\text{Ca}^{2+}$  channel blockers, increases AC activity (and consequently elevating cAMP levels; named as  $\text{Ca}^{2+}$ /cAMP signalling interaction), then these  $\text{Ca}^{2+}$  channel blockers-effects can be increased by cAMP-stimulating compounds (like PDEs inhibitors)

and diabetes.<sup>[5-9,13-18]</sup> For instance, it was observed that  $\text{Ca}^{2+}$  signaling dysregulations may precede dopamine system dysregulation in schizophrenia.<sup>[23-25]</sup> In addition to schizophrenia, dysregulations associated with  $\text{Ca}^{2+}$  signaling pathways have also been observed in asthma and diabetes.<sup>[8,9]</sup> Then, the pharmacological modulation of these signaling pathways could be a plausible therapeutic strategy for alleviating the symptoms of these diseases.

Opposing  $\text{Ca}^{2+}$  signaling, stimulating cAMP/PKA/CREB pathways can reduce the symptoms of asthma, schizophrenia, and diabetes.<sup>[8,46-51]</sup> In fact, reduced activity of cAMP signaling has been found in platelets of schizophrenic patients.<sup>[46]</sup> The authors highlighted from these findings evidence for an abnormality of cAMP signaling pathway linked to schizophrenia. These findings have been reinforced by other authors.<sup>[47]</sup> Reports from blood platelets, cerebrospinal fluid, or postmortem brains of patients with schizophrenia have also demonstrated abnormalities in cAMP signaling.<sup>[47]</sup> Intriguingly, antipsychotic administration, in animal models, resulted in a restoration of cAMP signaling pathway, outcoming in an effect which alleviates symptoms of schizophrenia.<sup>[47]</sup>

Furthermore, in endocrine cells, along with  $\text{Ca}^{2+}$ , cAMP regulates the release of various hormones, including the insulin from the pancreatic  $\beta$ -cells:<sup>[5,8,49,50]</sup> while elevating cAMP levels by adrenaline may increase the hepatic glucose production, elevating cAMP levels into the pancreatic  $\beta$ -cells can enhance the release of insulin. In fact, the trigger for an exocytosis of insulin granules is due to an increasing of the cytoplasmic  $\text{Ca}^{2+}$  concentration

and is then augmented by cAMP.<sup>[5,8]</sup> In addition to the response of stimulating the insulin synthesis, cAMP is involved in the functions of  $\beta$ -cell by promoting the cell proliferation and differentiation, and by restoring the cells from apoptosis.<sup>[8,51]</sup> Finally, elevating cAMP levels exerts a relaxation of airways smooth muscle, a classical working principle for medicines.<sup>[48]</sup>

Therefore, the pathogenesis of diabetes, asthma, and schizophrenia may also result from a downregulation of cAMP signaling pathways, in addition to a rise of ( $\text{Ca}^{2+}$ ) c, resulting from an imbalance of  $\text{Ca}^{2+}$ /cAMP signaling interaction.<sup>[8,46-51]</sup> Figure 2 summarizes the previous discussion.

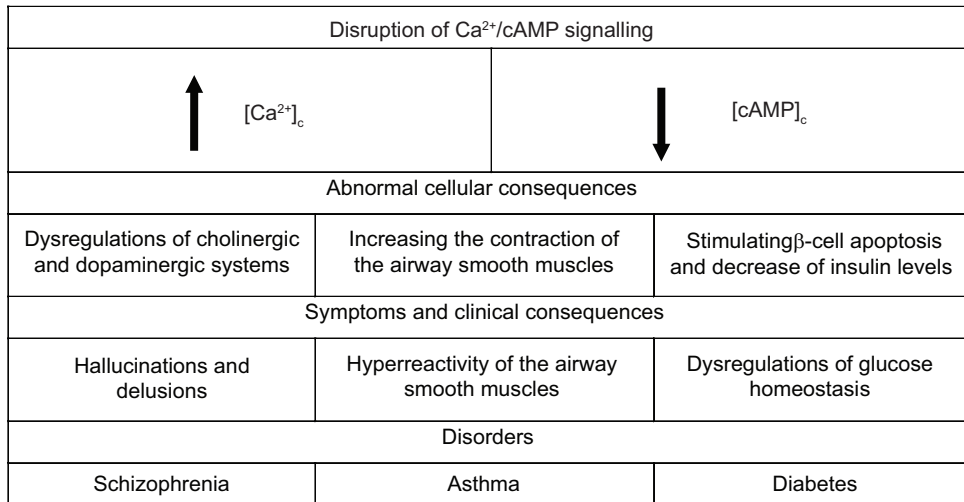
### A clinical link

$\text{Ca}^{2+}$ /cAMP signaling have been currently emphasized as protagonists in the field of schizophrenia, diabetes and asthma.<sup>[5-9,13-18]</sup> Considering the experience of our group in this field,<sup>[5-9,13-18]</sup> our findings clearly demonstrated that a  $\text{Ca}^{2+}$  release from ER can be stimulated by a rise of intracellular concentration of cAMP (cAMP) c. Thus, considering the involvement of these signaling pathways in regulating the neurotransmitter/hormone release and smooth muscle contractility, dysregulations of these signaling pathways can result in disorders such as asthma, schizophrenia, and diabetes.<sup>[5-9,13-18]</sup>

In addition, several findings have been endorsing that CCBs can attenuate the symptoms of schizophrenia, diabetes, and asthma.<sup>[10-12]</sup> Similar effects could be achieved by increasing (cAMP) c.<sup>[46-49]</sup> For instance, CCBs increase the ACs activity, resulting in an increase of (cAMP) c, stimulating a  $\text{Ca}^{2+}$  release from ER, finally stimulating neurotransmitter/hormone release, then reducing diabetes symptoms through increasing insulin levels and reducing  $\beta$ -cell apoptosis, in addition to reducing airway smooth muscle contractility in asthma. Furthermore, the activation of this cellular mechanism may reduce schizophrenia symptoms,<sup>[5-9,13-18]</sup> mainly by restoring cholinergic and dopaminergic systems,<sup>[5-9,13-18]</sup> cellular processes that can be regulated by  $\text{Ca}^{2+}$  and cAMP signaling pathways.<sup>[5-9,13-18]</sup> Then, reestablishing dysregulations related to  $\text{Ca}^{2+}$  signaling is an argued working principle for these CCBs-mentioned effects, achieved due interfering on  $\text{Ca}^{2+}$ /cAMP signaling interaction. Considering a link among schizophrenia, diabetes, and asthma could result from sustained dysregulations of ( $\text{Ca}^{2+}$ )c, the sustained increases of ( $\text{Ca}^{2+}$ )c could also disrupt  $\text{Ca}^{2+}$ /cAMP signaling interaction.<sup>[5-9,13-18]</sup>

### The Pathogenetic Association among Schizophrenia, Diabetes, and Asthma

A study conducted by Liu *et al.*<sup>[52]</sup> is assumed to be the first network and pathway-based systematic analysis



**Figure 2:** The Ca<sup>2+</sup>/cAMP signalling dysregulations and their consequences. Symbols - Up arrow: increasing; Down arrow: decreasing; (Ca<sup>2+</sup>)<sub>c</sub>: Intracellular concentration of Ca<sup>2+</sup>; (cAMP)<sub>c</sub>: Intracellular concentration of cAMP

for schizophrenia and T2DM, which provided the general pathway-based view of the pathogenetic association between these two diseases.<sup>[52]</sup> Moreover, the authors identified a set of candidate genes potentially contributing to the link between schizophrenia and T2DM. This report offered new insights into the potential mechanisms underlying the co-occurrence of both diseases, and then this study highlighted novel hypotheses for the comorbidity of the two diseases. In fact, some etiological factors that may exert pleiotropic effects, shared by significant pathways of both diseases, may have important implications for therapeutic intervention targets.<sup>[52]</sup>

Furthermore, genetic similarities extrapolated from genome-wide association studies may shed some light on the genetic principles underlying the comorbidity link between schizophrenia and T2DM.<sup>[53]</sup> Meanwhile, endophenotypes (e.g., adiponectin level in T2DM and working memory in schizophrenia) may serve as complementary phenotypes that are more directly affected by genes.<sup>[53]</sup> Thus, there are multiple pieces of evidence supporting the role of immune genes in both schizophrenia and T2DM. Future studies aimed to elucidate the relevant pathways could identify novel biomarkers, including therapeutic targets for both diseases.<sup>[53-55]</sup>

Besides schizophrenia and diabetes, over a hundred different genes have been associated with asthma, and the list is still growing.<sup>[56]</sup> However, some genes may be relevant only in a subgroup of asthmatics, for example, in childhood-onset asthma or atopic asthma.<sup>[56]</sup> Moreover, some genes are expressed only in certain environmental situations, for example, in children growing up with a cat. Then, the relevance of gene-environment interaction in asthma causation should not be underestimated.<sup>[56]</sup>

In addition, like schizophrenia, bipolar disorder is a severe mental illness, and also a complex genetic disorder, whose mode of transmission remains to be elucidated.<sup>[57]</sup> In fact, many scientists assume that common genomic variants carry some risk for manifesting the disease, establishing relationships between common single-nucleotide polymorphisms (SNPs) and bipolar disorder.<sup>[57]</sup> Currently, efforts are underway to translate these findings into clinical practice, genetic counseling, and predictive testing. However, common variants explain only a small percentage of the genetic risk, and functional consequences of the discovered SNPs are inconclusive.<sup>[57]</sup> Further studies are clearly needed before establishing genetic testing for common variants in psychiatric disorders.

## Conclusions and Perspectives

Considering asthma, diabetes, and schizophrenia have become critical medical problems around the world, the comprehension of the link among these diseases could improve drug therapy, including the therapeutics with CCBs and medicines which increase (cAMP) c. Finally, there are also multiple pieces of evidence supporting the role of immune genes in schizophrenia, T2DM, and asthma. Future studies aimed to elucidate the relevant pathways could identify novel biomarkers, including therapeutic targets for these diseases.

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## Conflicts of interest

There are no conflicts of interest.

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