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REVIEW

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# Genetic predisposition to nephropathy and associated cardiovascular disease in people with type 1 diabetes: role of the angiotensinl-converting enzyme (ACE), and beyond; a narrative review

Kamel Mohammedi<sup>1,5\*</sup>, Michel Marre<sup>2,3</sup> and François Alhenc-Gelas<sup>4</sup>

## Abstract

Hypertension, cardiovascular disease and kidney failure are associated with persistent hyperglycaemia and the subsequent development of nephropathy in people with diabetes. Diabetic nephropathy is associated with widespread vascular disease affecting both the kidney and the heart from an early stage. However, the risk of diabetic nephropathy in people with type 1 diabetes is strongly genetically determined, as documented in familial transmission studies. The search for the underlying genes has been extensive, using specific hypotheses, sibling linkage studies and genome-wide association studies (GWAS). The role of the angiotensinl-converting enzyme/kininase II (*ACE*) gene and genetic variability in *ACE* levels as a susceptibility and prognostic factor for diabetic nephropathy has been well documented in people with type 1 diabetes. The *ACE* gene insertion/deletion polymorphism, which is associated with plasma and tissue *ACE* levels, has been the most studied genomic variant in diabetic nephropathy. Recently, this polymorphism has also been associated with longevity in people with type 1 diabetes. The *ACE I/D* polymorphism has also been associated with vascular, extra-renal complications including myocardial infarction and lower-limb amputation in this population. Other genes and loci have been identified in linkage studies and GWAS, such as the *COL4A3* gene or a region on chromosome 3q with the *adiponectin* gene. Replication was not always attempted and was rarely achieved, even for GWAS. Overall, effect sizes remain modest and no major gene has been identified, despite the strength of the genetic effect in transmission studies. We searched bibliographic databases for studies reporting genomic variants associated with diabetic nephropathy and meta-analyses of such studies. We selected important relevant studies for further discussion in this narrative review. This brief review attempts to summarise the current knowledge on the genetics of diabetic nephropathy and associated cardiovascular disease in people with type 1 diabetes, and discusses some conceptual and methodological issues relevant to the interpretation of past studies and the design of future ones.

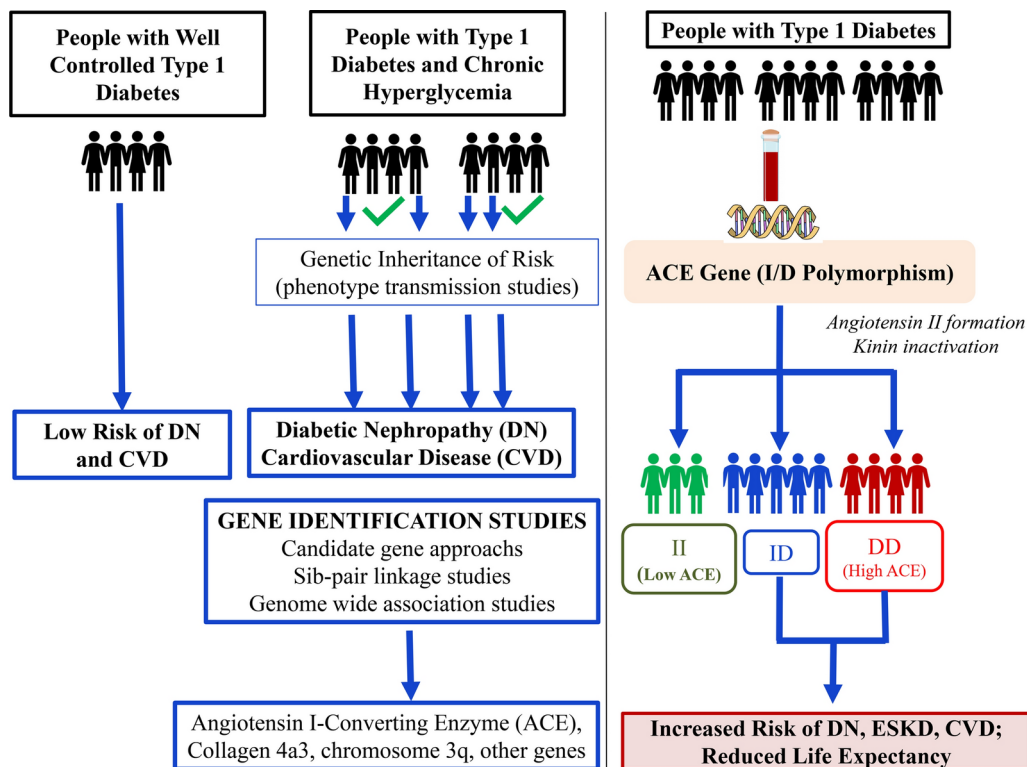
\*Correspondence:  
Kamel Mohammedi  
km.mmohammedi@gmail.com

Full list of author information is available at the end of the article



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**Graphical abstract**



Genetic determinism of diabetic nephropathy and associated cardiovascular disease in people with type 1 diabetes. Close-up on the Angiotensin I-Converting Enzyme gene. ACE, Angiotensin I-converting enzyme; I/D, ACE gene Insertion/Deletion Polymorphism; DN, diabetic nephropathy; CVD cardiovascular disease; ESKD, End-Stage Kidney Disease. ✓ Genetically protected individuals

**Background**

The prevalence of hypertension is increased in patients with type 1 diabetes [1]. Hypertension is associated with persistent hyperglycemia and the occurrence of diabetic nephropathy (DN). It is causally linked to nephropathy, even incipient, albeit other factors such as age, body-mass, familial history of hypertension are also involved [2]. High blood pressure, in turn, accelerates the progression of DN [3].

Diabetic nephropathy is also associated, as early as its incipient stage that is marked by elevated urinary albumin excretion, to increased incidence of major cardiovascular events, especially myocardial infarction [4, 5]. Diabetic nephropathy occurs in the setting of a widespread vascular disease [6]. The risk of coronary heart disease and myocardial infarction is influenced by genetic factors in people with type 1 diabetes and it can be postulated that at least some of these factors are operating through DN [7].

Diabetic nephropathy is primarily caused by chronic hyperglycemia in poorly controlled patients with type

1 and type 2 diabetes, but the risk for these patients of developing nephropathy is genetically determined [8–10]. The genetic predisposition to nephropathy was originally identified in people with type 1 diabetes, which is already evident in the microalbuminuric stage. Roughly half of the patients with long-standing hyperglycemia remain protected from the occurrence of DN, and this is explained by heritable factors [8, 10]. Heritability has also been documented for diabetic retinopathy, but appears to be weaker than for DN and only observed in advanced stages of retinopathy [11, 12].

Diabetic nephropathy is a polygenic condition. However, given the strength of the genetic effect observed in familial transmission studies, it is reasonable to speculate that major gene effects are involved in nephropathy in people with type 1 diabetes [13]. Both candidate gene studies and linkage studies in sib-pairs or overall patient populations through whole genome scanning (genome wide association studies, GWAS) have been used to identify DN susceptibility genes. New pathophysiological hypotheses for chronic kidney disease, hypertension and

coronary heart disease are expected to emerge from this research, and eventually new treatments will be developed. Results rarely overlap between studies, including GWAS. However, the first and perhaps the best clinically characterised susceptibility and prognostic gene for DN in type 1 diabetes to date is the angiotensin I-converting enzyme/kininase II gene (peptidyl-dipeptidase A, *ACE*), as summarised below. The identification of other genes through specific hypotheses, sib-pair linkage studies and GWAS is then discussed, taking into account the pathophysiological and clinical relevance of the findings and the limitations of the studies. Studies, including meta-analyses, were identified through Medline searches and review of article bibliographies and selected for discussion on the basis of relevance and methodology.

### **Genetic variation in *ACE/kininase II* and diabetic nephropathy**

*ACE* was a plausible candidate for DN because of its physiological role in promoting local vasoconstriction through angiotensin II formation and kinin inactivation [14]. Plasma or tissue levels of *ACE* have been shown to be genetically determined and genomic markers for this trait have been identified [15–18]. The most clinically studied genomic marker is the *ACE* gene insertion/deletion (*I/D*) polymorphism in intron 16, which is strongly associated with plasma and tissue *ACE* levels, albeit through incompletely understood molecular mechanisms [18]. The prerequisite for a genetic risk factor of a strong genetic component in inter-individual phenotypic variability was thus fulfilled. Moreover, genetic association with DN could be addressed at both the genomic and phenotypic levels.

Initial observations were made in case–control studies in Europe and the US [19–21]. The topic was then extended to cohort studies. Many dedicated studies have been conducted over the years in European, American and Asian populations, or cohorts of patients with diabetes. Overall, these studies and their meta-analyses have confirmed the association of the *ACE* gene, and the genetically determined plasma *ACE* levels, with the risk of developing DN in type 1 diabetes (despite some early exceptions in low-powered case–control studies) [22, 23]. Large and well-phenotyped cohorts that have allowed the role of the *ACE* gene in DN to be established include the Génétique de la Néphropathie Diabétique (GENEDIAB) study, the Pittsburgh Epidemiology of Diabetes Complications Study, the landmark Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC) study in the US, and the European consortium for the genetics of diabetic nephropathy (EURAGEDIC) [24–27]. Most of these studies were conducted before patients with elevated urinary albumin excretion were systematically prescribed *ACE*

inhibitors or angiotensin II-AT1 receptor blockers. This has allowed the role of *ACE* in both the development and progression of DN to be documented. Some studies have also been conducted in patients treated with renin-angiotensin system blockers. These studies claimed a residual effect of the *ACE* gene on the prognosis of patients with DN under treatment, suggesting that the underlying constitutive *ACE*-related pathogenic mechanisms were not fully controlled by treatment [28, 29].

Overall, the studies suggest that having genetically high *ACE* levels and/or carrying the *D* allele of the *ACE* gene, which is associated with higher plasma and tissue *ACE* levels, increases the risk of developing nephropathy in uncontrolled type 1 diabetes, and worsens its prognosis. The frequency of this allele varies in different populations worldwide, being lower in Asian than in European or African populations. However, an association with the risk of DN was observed in all populations studied, with effects of similar magnitude [22, 23].

Clinical studies can only document an association, but for *ACE*, the underlying causality has been established in genetically modified mice that carry a specific number (1 to 3) of the *ACE* gene and display all together an *ACE* level range in the same magnitude as humans. When rendered diabetic, mice with three copies of the *ACE* gene and moderately elevated *ACE* levels show accelerated DN and develop hypertension [30].

Finally, and importantly, genetic variation in *ACE* has recently been reported to be associated with end-stage kidney disease and all-cause death in patients with long-standing type 1 diabetes who were poorly controlled at baseline and followed for a median of 14 years (inter-quartile range 13 years) [31]. Carriers of the *D* allele and patients with high levels of *ACE* were more likely to experience these fatal adverse events [31]. The *ACE* gene is the first gene to have an association with mortality and long-term survival in people with type 1 diabetes.

The role of the *ACE* gene in DN has been extended to people with type 2 diabetes, a more heterogeneous condition in terms of cardiovascular risk factors, cardiovascular disease and chronic kidney disease. Accordingly, an association between the *I/D* polymorphism and urinary albumin excretion has been observed in most, but not all, studies of people with type 2 diabetes. Of note, the role of the *ACE* gene in DN susceptibility has been documented particularly in Asian populations of type 2 diabetes [32].

### **Genetic variation in *ACE/kininase II* and cardiovascular disease**

To our knowledge, no study has been specifically designed to investigate the role of the *ACE* gene in cardiovascular disease risk in people with type 1 diabetes. However, an association has been observed in DN studies that included coronary heart disease and myocardial

infarction as secondary analyses [21, 33]. In the general population the *ACE* gene *I/D* polymorphism has been studied in relation to cardiovascular disease but with contrasting results [34–36]. An observational study has reported that the *DD* genotype, which is associated with higher levels of circulating and tissue-bound ACE than the *ID* and *II* genotypes, was significantly more frequent in individuals who have had a myocardial infarction compared to controls without this condition [34]. Other studies reported only a marginal or no significant association between the *ACE* gene *I/D* polymorphism and myocardial infarction, ischaemic heart disease or ischaemic cerebrovascular disease [35, 36]. These studies in the general population did not specifically analyse people with diabetes. Further studies are needed that focus on people with diabetes and cardiovascular disease.

### **Genetic variation in ACE/kininase II and other diabetes vascular complications**

The genetic variation in *ACE* levels was also associated with extra-renal hyperglycaemic vascular complications, as might be expected from the association of these complications with DN. This is particularly the case for lower-limb amputation, a consequence of both macrovascular and microvascular diabetes complications, the incidence of which was higher in *D* allele carriers [37]. For retinopathy, several case-control studies have examined the association with the *ACE* gene in people with type 1 diabetes, with variable but mostly negative results. These studies were often underpowered [22, 38]. In addition, clinical trials did not support a major role for the renin-angiotensin system in the progression of retinopathy, unlike DN [39].

### **Pathophysiological role of the ACE gene in diabetes**

The cellular and molecular mechanisms behind the deleterious renal and cardiovascular effects of the *ACE* gene in the setting of chronic hyperglycaemia have previously been reviewed [40]. It is worth noting that the clinical observations in DN concerning ACE have triggered a series of studies aimed at reappraising the physiology of the renin-angiotensin and kallikrein-kinin systems in the kidney, emphasizing the critical role of ACE levels besides that of renin. Both theoretical and experimental considerations suggest that genetic variation in ACE levels influences the bioavailability of kinins to a much larger extent than for angiotensin II [41, 42]. Kinins exert protective effects in the diabetic or ischemic kidney. Mice deficient in kallikrein (the enzyme that releases kinins) or kinin receptor display, like mice with a duplicated *ACE* gene, aggravated nephropathy when rendered diabetic [43, 44]. Thus, ACE-mediated kinin inactivation in the kidney, together with local angiotensin II production, is thought to play an important role in the development of

DN. This dual pathophysiological hypothesis has been experimentally documented in the ischaemic heart [40]. Observations made in DN and coronary heart disease emphasizing the deleterious effect of high constitutive ACE levels in these conditions have susciated studies unraveling the heterogeneous pattern of distribution of ACE, an endothelial ectoenzyme also secreted in plasma, along the human vascular tree. These studies have highlighted the physiological importance of the reduced ACE content in the heart and kidney vasculature compared to other vascular beds, protecting these organs against excess vasoconstriction and maintaining local blood flow [40, 45]. ACE is also present in plasma and circulating ACE, with its strong genetic component, is believed to exert deleterious effects in the kidney circulation in the setting of hyperglycemia.

Therapeutic inhibition of ACE or its product angiotensin II, which also leads to kinin potentiation, is already available and commonly used in incipient DN [46]. New therapeutic approaches targeting the renin-angiotensin system or kinins are currently under development and may eventually benefit the treatment of DN [47, 48]. It should be emphasised that achieving normoglycaemia is the most direct approach to preventing DN, but other therapeutic approaches may be helpful for secondary prevention and to avoid kidney failure or cardiovascular disease. Current approaches have limited effectiveness and new treatments are needed [49].

### **Other genes involved in diabetic nephropathy identified through candidate gene studies, sib-pair linkage studies and GWAS**

Many candidate genes for susceptibility to DN in people with type 1 diabetes or for DN prognosis have been proposed based on hypotheses concerning their putative pathophysiological role in the disease. These genes are involved in vascular physiology, redox metabolism, inflammation, extracellular matrix formation and kidney function, especially at the level of the glomerulus, Bowman's capsule and proximal tubule. These are kidney structures directly involved in the early pathophysiological events of DN, hyperfiltration and impaired renal albumin metabolism.

A non-exhaustive list of candidate genes associated with DN in clinical studies of type 1 diabetes includes *ACE*, *Adiponectin*, *APOE*, *carnosinase*, *T-cadherin*, *Coll4A1*, *GLUT1*, *IL1*, *eNOS*, *renin*, *SOD2*, *Sox2* [50–67]. A number of other candidate genes have also been tested [68, 69]. Some studies included both discovery and replication cohorts but replication has not always been performed, or reported, in subsequent independent studies in people with type 1 diabetes. *Endothelial nitric oxide synthase*, *carnosinase*, *GLuT1*, and *ApoE* have been investigated in several studies of individuals with type 1 or

type 2 diabetes, but with contrasting findings [70–73]. The role of the *adiponectin* gene in DN, initially suggested by a combination of linkage and candidate gene studies, was not confirmed in two other studies, although serum adiponectin was recognised as a biomarker of DN progression in type 1 diabetes [64, 74, 75]. Other biomarkers have been reported as putative markers of diabetes complications, such as adrenomedullin and copeptin [76–78]. The *adrenomedullin* gene has been linked to plasma adrenomedullin levels and DN prognosis in people with type 2 diabetes, but there have been no reports of an association in the type 1 diabetes population [79].

Negative studies may have suffered from power issues while, conversely, spurious associations may be detected in a setting of multiple testing. The appropriate selection of patients at risk of DN is a critical issue. These methodological issues are discussed below.

Causality is inferred from the known physiological role of the genes assessed and their role in experimental DN in mice, where this role has been studied [80]. The effect of the identified genomic variants on the primary protein phenotype can be difficult to assess and has rarely been documented. In some cases, causality and mechanisms have been addressed by overexpressing in cellular systems the putative causal variants identified in clinical studies [63].

Genomic regions and genes involved in DN susceptibility in people with type 1 diabetes have also been identified by linkage studies in sib-pairs or GWAS in overall patient populations. Sib-pairs studies have identified a region on chromosome 3q that includes the *glucose transporter 2*, *kininogen* (protein precursor of the peptides kinins, discussed above) and *adiponectin* genes [64, 81].

GWAS have identified putative DN loci on at least eleven different chromosomes, but the results do not consistently overlap among studies [82–85]. Moreover, loci corresponding to DN genes well documented by other approaches did not appear in GWAS. Thus, the *ACE* gene is located on chromosome 17q23, but this chromosomal region did not reach the GWAS significance level in the meta-analyses. Likewise, the chromosomal 3q region and the *adiponectin* gene identified through sib-pair linkage analysis did not show up in these GWAS. This is discussed further below. Nevertheless, GWAS and their meta-analyses have revealed some new candidate genes, such as the *AFF3* (a transcription factor) and *ERBB4* (a tyrosine kinase) genes, raising new pathophysiological hypotheses [83]. However, in another GWAS meta-analysis that extended the previous one, these two genes were attenuated, becoming nonsignificant by today's stringent criteria, and new associated variants were identified. The *COL4A3* gene, on chromosome 2, gave a strong signal; and a missense mutation (rs55703767) in this gene has

**Table 1** Methodological factors relevant to detection/exclusion of DN susceptibility genes

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Number of included patients, based on prespecified association hypotheses
Phenotypic relevance to risk of diabetic nephropathy: chronic exposure to hyperglycemia, advanced retinopathy
Study of both genomic variants and associated protein phenotype variability, when feasible
Appropriate stringency of statistical analysis in settings of multiple testing
Documentation of causality in genetically modified animals (gene titration or mutation studies)
Long term follow-up studies required to examine clinical relevance

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been suggested to protect against the development of DN [82]. Type IV collagen is a major constituent of the glomerular membrane and its genes have been implicated in several kidney diseases [86]. Alteration in collagen metabolism is believed to play a widespread role in microvascular complications of diabetes [87, 88].

### Synthesis and perspective: outstanding questions and methodological issues in DN genetic research

Overall, there is a discrepancy between the observation of a major gene effect for DN in people with type 1 diabetes in phenotype transmission studies and the results of genomic studies, including GWAS, where no major gene effect has been clearly identified. There are also discrepancies between studies, which can be illustrated by comparing two subsequent large GWAS meta-analyses [82, 83]. The same problems of lack of heritability and poor reproducibility arise in the study of other multigenic conditions with strong genetic determinism, such as essential hypertension [89, 90]. One gene, the *ACE* gene, has been well established in DN through extensive replication in large cohorts, but the magnitude of the effect, although variable between studies, remains modest and does not appear to be consistent with a major gene effect [21, 24].

Several conceptual or methodological issues can be considered in the interpretation of genetic studies of DN in individuals with type 1 diabetes, and future developments can be discussed, including the generation of polygenic risk scores [91, 92] (Table 1):

- The risk of false-negative findings due to lack of power or spurious association findings in the setting of multiple testing are common to all clinical genetic association studies. GWAS require large groups of patients to ensure power, which raises the issues of inclusion criteria and population homogeneity, as discussed below. The use of a stringent sensitivity threshold (such as  $p < 5 \times 10^{-8}$ ) to document an association is now considered mandatory, but less stringent criteria were used in some early studies.

- Inclusion of patients truly at risk of DN is a critical point for the genetic studies. Patients should not only have had long standing diabetes, but also have been

exposed to chronic hyperglycemia. This can be a logistical problem for studies in the type 1 diabetes population, where patients are treated with insulin and are often well controlled. Proliferative retinopathy reflects long-term exposure to hyperglycaemia, which was one of the inclusion criteria in some trials, but glycaemic exposure and retinopathy severity were not always well controlled in the trials [21]. Patients with insufficient exposure to hyperglycaemia will not develop DN, even if they carry susceptibility genes. Including such patients in analyses reduces the power to detect DN genes or minimises the effect size, even in GWAS. Patient sample size and phenotypic relevance/homogeneity need to be balanced. A concern with adjusting for retinopathy is that advanced retinopathy is also genetically influenced, but the genes may be different from those associated with DN [93]. A related issue is the possible confounding effect of genes involved in glucose metabolism on the severity of hyperglycaemia and thus the development of complications. However, this is probably more relevant for people with type 2 diabetes.

Discrepancies between studies should lead to an expansion of research rather than a pause. GWAS do not require further pathophysiological knowledge, but are limited by issues of enrolment of large groups of narrowly relevant patients and may miss genes with small effect sizes. The pathophysiology of DN is still incompletely understood. Advances in the field may lead to new genetic hypotheses and candidate genes that should be studied in well-defined populations of patients at risk.

## Conclusions

In summary, DN is associated with chronic hyperglycaemia but is strongly genetically determined, as evidenced by familial transmission studies in people with type 1 diabetes. The investigation of the underlying genes has been extensively pursued by candidate gene studies, sibling-pair linkage studies and GWAS. The role of genetic variation in ACE/kininase II levels in DN susceptibility and prognosis has been well documented and recently extended to long-term patient survival. Causality and mechanism have been documented in genetic animal models. Other genes and loci have been identified in adequately powered studies, especially linkage studies and GWAS, such as the *Coll4A3* gene or a region on chromosome 3q with the *adiponectin* gene. Causality is supported by the known physiological role of these genes. However, replication has not always been attempted and is rarely achieved, even in GWAS. There is still no practical clinical application of genetic findings in DN risk identification. Diabetic nephropathy in type 1 diabetes is an interesting model of multigenic disease because of its frequency and phenotypic homogeneity. The search for DN genes should be continued to clarify controversial

issues and eventually validate polygenic risk scores of clinical relevance.

## Abbreviations

ACE	Angiotensin-converting enzyme
AT1	Angiotensin II receptor type 1
CVD	Cardiovascular disease
DCCT-EDIC	Diabetes control and complications trial/Epidemiology of diabetes interventions and complications
DN	Diabetic nephropathy
EURAGEDIC	European consortium for the genetics of diabetic nephropathy
GENEDIAB	<i>Génétique de la néphropathie diabétique</i>
GWAS	Genome wide association study
I/D	Insertion/deletion polymorphism

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## Author contributions

K.M. M.M., and F.A.G. conducted bibliographic research. F.A.G. drafted the first version of the manuscript. K.M. and M.M. contributed to discussion and reviewed/edited the manuscript. All authors approved the current version of the manuscript. All authors are the guarantors of this work.

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### Competing interest

The authors declare no competing interests.

### Author details

<sup>1</sup>INSERM U1034, Biology of Cardiovascular Diseases, Bordeaux University Hospital, 33000 Bordeaux, France

<sup>2</sup>Clinique Ambroise Paré. Diabétologie-Endocrinologie, 92200 Neuilly-Sur-Seine, France

<sup>3</sup>Immunity and Metabolism in Diabetes, Institut Necker Enfants Malades, INSERM U1151, CNRS UMR 8253, Paris, France

<sup>4</sup>INSERM U1138-Centre de Recherche Des Cordeliers, Paris Cite University, Sorbonne University, 75006 Paris, France

<sup>5</sup>Department of Endocrinology, Diabetes, and Nutrition, Hôpital Haut-Lévêque, Avenue de Magellan, 33604 Pessac Cedex, France

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