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Co-shared genetics and possible risk gene pathway partially explain the comorbidity of schizophrenia, major depressive disorder, type 2 diabetes, and metabolic syndrome

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Abstract

Schizophrenia (SCZ) and major depressive disorder (MDD) in treatment-naive patients are associated with increased risk for type 2 diabetes (T2D) and metabolic syndrome (MetS). SCZ, MDD, T2D, and MetS are often comorbid and their comorbidity increases cardiovascular risk: Some risk genes are likely co-shared by them. For instance, transcription factor 7-like 2 (*TCF7L2*) and proteasome 26S subunit, non-ATPase 9 (*PSMD9*) are two genes independently reported as contributing to T2D and SCZ, and *PSMD9* to MDD as well. However, there are scarce data on the shared genetic risk among SCZ, MDD, T2D, and/or MetS. Here, we briefly describe T2D, MetS, SCZ, and MDD and their genetic architecture. Next, we report separately about the comorbidity of SCZ and MDD with T2D and MetS, and their respective genetic overlap. We propose a novel hypothesis that genes of the prolactin (PRL)-pathway may be implicated in the comorbidity of these disorders. The inherited predisposition of patients with SCZ and MDD to psychoneuroendocrine dysfunction may confer increased risk of T2D and MetS. We illustrate a strategy to identify risk variants in each disorder and in their comorbid psychoneuroendocrine and mental-metabolic dysfunctions, advocating for studies of genetically homogeneous and

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CONFLICT OF INTEREST

None to declare.

phenotype-rich families. The results will guide future studies of the shared predisposition and molecular genetics of new homogeneous endophenotypes of SCZ, MDD, and metabolic impairment.

Keywords

Schizophrenia; Major Depressive Disorder; Type 2 Diabetes; Metabolic Syndrome; Prolactin; Oxytocin Gene Pathway

1. | INTRODUCTION

For a long time, researchers have noted that individuals with psychiatric diseases have a high comorbidity of heart disease and type 2 diabetes (T2D). However, they have only started to explore the possible connection between the diseases in recent years. Emerging findings indicate that the connection may be at least partially genetic. This outcome may have important implications for how these diseases are understood and managed.

Genetic predisposition and loci are known to be shared among polygenic complex disorders, including psychiatric diseases, type 2 diabetes (T2D), and metabolic syndrome (MetS; Andreassen et al., 2013; Liu et al., 2013; Zhang et al., 2013). T2D is a polygenic complex disorder (Sun, Yu, & Hu, 2014) with an accompanying high prevalence of polygenic psychiatric disorders, particularly major depressive disorder (MDD; Demakakos, Pierce, & Hardy, 2010; Rustad, Musselman, & Nemeroff, 2011), and schizophrenia (SCZ; Wandell, Ljunggren, Wahlstrom, & Carlsson, 2014). MDD confers a 60% increased T2D risk (Mezuk, Eaton, Albrecht, & Golden, 2008), independently from antidepressant therapy (Pan et al., 2010). SCZ also increases T2D risk, unrelated to antipsychotic therapy, and SCZ patients have higher rates of prediabetes, T2D, MetS, and obesity than control subjects (Q. Li et al., 2016; Subashini, Deepa, Padmavati, Thara, & Mohan, 2011) and share common risk variants with MetS traits (Andreassen et al., 2013). Several studies have demonstrated that drug-naive SCZ patients have impaired fasting glucose (IFG), impaired insulin action, and increased T2D risk (Dasgupta, Singh, Rout, Saha, & Mandal, 2010; Fernandez-Egea et al., 2009; Ryan, Collins, & Thakore, 2003; van Nimwegen et al., 2008); and SCZ/nonaffective psychosis (NAP) are significantly associated with increased odds of parental T2D and first-degree relatives' impaired-glucose tolerance (IGT) (Fernandez-Egea, Miller, Bernardo, Donner, & Kirkpatrick, 2008; Miller et al., 2016; Spelman, Walsh, Sharifi, Collins, & Thakore, 2007). Furthermore, distinct SCZ phenotypes differentially associate with varying glucose levels (Kirkpatrick, Fernandez-Egea, Garcia-Rizo, & Bernardo, 2009).

Several genetic pathways have been reported to contribute to the comorbidity of SCZ and MDD with T2D and MetS (Andreassen et al., 2013; Liu et al., 2013; Wolkowitz, Reus, & Mellon, 2011; Zhang, Hui, et al., 2013). We advocate that the comorbidity of SCZ and MDD with T2D and MetS is due at least in part to genetic variants shared by both groups of disorders and that altered pathways in SCZ and MDD may impair metabolism leading to T2D and MetS. For example, specific gene and/or gene variants may contribute to the comorbidity of SCZ or MDD with T2D and/or MetS, some only to SCZ or MDD, and others only to T2D and/or MetS. We consider that, under a polygenic-oligogenic model, genome-

wide variants (including common, low and very low-frequency variants, rare coding and copy number variants [CNVs]), potentially contribute to SCZ, MDD, T2D, and MetS, and any metabolic-psychological-associated trait.

However, identifying causal loci for psychiatric disorders has proven difficult (Hek et al., 2013; Levinson et al., 2014; Major Depressive Disorder Working Group of the Psychiatric et al., 2013), requiring the recruitment of thousands of clinically well-characterized individuals. Recently, meta-analyses of genome-wide association studies (GWAS), refining the genetic architecture of SCZ and MDD (Pardinas et al., 2018; Wray et al., 2018) supported the existence of genetic and biological processes common to SCZ and MDD, and likely to other psychiatric disorders.

The fact that SCZ and T2D loci overlap has raised interest in the possibility of co-shared SCZ-T2D genetic risk (Gough & O'Donovan,2005). A recent study reported an association of the SCZ dopamine D2 receptor (*DRD2*) risk variants with significant increases in glucose levels, after various adjustments (e.g., BMI, age, dose, and/or type of antipsychotics) (Lawford et al., 2016). A European study found that the strongest worldwide T2D risk gene, transcription factor 7-like 2 (*TCF7L2*), significantly contributes to SCZ (Hansen et al., 2011) and is also a risk gene for the comorbidity of mood disorders and cardio- metabolic traits (Amare, Schubert, Klingler-Hoffmann, Cohen Woods, & Baune, 2017). Future studies are needed to risk stratify patients based on genetically defined phenotypes contributing to the clinical association of SCZ and MDD with T2D and MetS.

Some loci have shown linkage in different populations to T2D (Mahtani et al., 1996), MDD, SCZ, bipolar disorder (Cassidy et al., 2007; Christiansen, Tan, Kruse, McGue, & Christensen, 2009; Holmans et al., 2009), anxiety (Hodgson et al., 2016), cardiovascular phenotypes such as coronary artery disease [CAD], myocardial infarction, stroke (Erdmann et al., 2009; Sherva et al., 2008), dyslipidemia (Aberg et al., 2008), early microvascular retinopathy (Ikram et al., 2010), hypertension, obesity, visceral obesity, and body mass index (BMI) joint to C-reactive protein (Wilson et al., 2006; Wu et al., 2009). For instance, within the 12q24 locus, we have identified proteasome 26S subunit, non-ATPase 9 (*PSMD9*) as a strong T2D risk gene reporting a strongly significant linkage (Gragnoli, 2010a) as well as conferring risk for depression (Gragnoli, 2012c), while independent research groups have reported *PSMD9* as one of the top genes contributing to MDD (Wong, Dong, Andreev, Arcos-Burgos, & Licinio, 2012; Wong, Dong, Maestre-Mesa, & Licinio, 2008) and SCZ (Lee, Kim, & Song, 2013).

In what follows, we first briefly define T2D, MetS, SCZ, and MDD, and what is known about their disease-related genetic architecture. Second, we illustrate what is known about the comorbidity of SCZ and the metabolic disorders and of MDD and the metabolic disorders. Third, we respectively report about the genetic overlap of the above-mentioned diseases' comorbidity. To identify the genetic overlap, we have searched PubMed using the keywords "Type 2 Diabetes" (separately "T2D") and "Metabolic Syndrome" (separately "MetS") as independent phenotypes joint to 'major depressive disorder' (separately "depression", and "MDD") in one search and joint to "schizophrenia" (separately "SCZ") in another search, with the additional keywords "gene". We have included findings of genes

significantly contributing to the metabolic and mental comorbidity. Our goal was not to be exhaustive in our search but to highlight the conceptual framework of the metabolic and mental comorbidities and the genetic findings supporting the theory.

In our novel hypothesis, we propose a genetic basis for the comorbidity of the above-mentioned disorders, and describe what is known about the aforementioned mental and metabolic comorbidities in regards to the prolactin (PRL)-pathway, and describe how the PRL-related genes may at least in part underlie the mental traits and metabolic disorders comorbidity. Finally, we describe the research expectations, research needs, and a strategy for identification of risk variants in each disorder and in their comorbid common psychoneuroendocrine and mental-metabolic traits.

2 | METABOLIC DISEASES, MENTAL DISEASES, AND THEIR COMORBIDITY

2.1 | T2D and MetS

T2D (8% prevalence) mostly appears after age 40, but lately at younger ages too. T2D is defined by fasting glucose level ≥ 126 mg/dL on at least two occasions, or random glucose level of ≥200 mg/dL associated with symptoms, or glycated hemoglobin of ≥6.5%.

MetS (42% prevalence after age 60; Ford, Giles, & Dietz, 2002) is strongly comorbid with T2D (Tan, Wong, Ng, Joseph, & Hejar, 2014). MetS is defined as ≥3 of the following: waist circumference in men >102 cm and in women >88 cm (or BMI ≥ 30), triglycerides levels ≥150 mg/dL, high-density lipoprotein (HDL) <40 mg/dL in men, and < 50 mg/dL in women, blood pressure ≥ 130/85 mmHg and/or antihypertensive medication use, and fasting glucose ≥110 mg/dL and/or antidiabetic medication use.

2.2 | T2D- and MetS-genetic contribution

T2D and MetS are complex heterogeneous disorders whose genetic architecture may be both polygenic and oligogenic. Genetic studies have focused on families and/or case-controls studies mostly with T2D, and with the most common associated traits of MetS. Also, the studies have been often performed in admixed populations. GWAS have identified ≥88 common variants for T2D (and 83 for one or more associated traits) or ≥97 loci contributing to glycemic traits (Wheeler, Marenne, & Barroso, 2017), which do not always overlap and do not explain the total disease inheritance. The identified risk genes are mainly involved in insulin secretion and processing, insulin action, protein function, and regulatory processes in the adipose tissue, skeletal muscle, liver, and brain (Gaulton, 2017). Of note, the strongest T2D risk *TCF7L2* gene variant is inversely correlated with health and longevity (Garagnani et al., 2013). Trans-ancestry studies have identified new T2D loci successfully combining data from diverse populations. Next-generation sequencing (NGS) allowed discovering new low-frequency loci for T2D and/or glycemic traits (Mohlke & Boehnke,2015). GWAS studies have identified variants conferring risk for MetS traits, with most variants showing risk for one MetS trait (e.g., over 100 variants for BMI), and some gene variants showing risk for more than two MetS traits (e.g., fat mass and obesity-associated protein [*FTO*] and transmembrane protein 18 [*TMEM18*] for higher triglycerides, lower HDL, increased fasting

insulin, increased blood pressure, and CAD, or adiponectin, C1Q and collagen domain containing (*ADI-POQ*) for T2D, hypertension, and dyslipidemias; Abou Ziki & Mani, 2016).

The analysis of other ethnic groups with different demographic characteristics will allow the discovery of new variants associated with psychiatric and metabolic traits.

2.3 | SCZ

SCZ is a severe and chronic psychiatric disorder with 1% prevalence. SCZ develops with positive (e.g., hallucinatory-mostly auditory, delusions-mostly persecutory, and bizarre behavior) or negative (e.g., anhedonia, flat affect, and lack of purposeful action) symptoms lasting ≥1 month, concurrent to ≥6 months of disturbance signs, and continuous social impairment (APA, 2000).

2.4 | SCZ-genetic contribution

SCZ has a genetic contribution up to 80%. The inheritance is complex and mostly polygenic, as a large number of genes seem to contribute to SCZ (International Schizophrenia Consortium et al., 2009), which has been confirmed in previous work (Ott, Liu, & Shen, 2012; Ott & Sun, 2012). However, there must be genes that play a larger role than others (oligogenic disease model; Gershon, 2000), and this is likely in at least a subset of families. Many genetic studies have been performed, however, often in admixed populations. Genetic variants have been identified via GWAS, and most recently via NGS. Several genetic micro-duplications and deletions are recognized SCZ risk factors. CNVs and their linkage to single nucleotide polymorphisms (SNPs) play a role as well. Various clinical phenotypes and multivariate analyses would better elucidate the disease pathogenesis (Giegling et al., 2017; Schmitt et al., 2016). The major histocompatibility complex (MHC) locus is also robustly implicated in SCZ, as associations have repeatedly been found between SCZ and genetic variants across the extended MHC chromosome 6 locus (25–34 Mb), implicating the locus as the strongest of the >100 loci of genome-wide significance (Henriksen, Nordgaard, & Jansson, 2017; Mokhtari & Lachman, 2016); of note, maternal immune activation due to infectious agents is a risk factor for SCZ, implicating the relevance of environmental factors in the disease etiology as well. However, different pathways are implicated in SCZ such as dopaminergic, serotonergic, glutamatergic, cholinergic, and gabaergic; Dean, 2001; Javitt, 2007).

A recent large-scale GWAS study (Pardinas et al., 2018), and meta-analysis of data of the Working Group of the Psychiatric Genomics Consortium (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), identified 50 novel SCZ-loci and 145 SCZ-associated loci (Pardinas et al., 2018). By integrating genomic fine-mapping with brain expression and chromosome conformation data, the study identified 31 loci with candidate causal genes. SCZ-SNPs are enriched in regions under strong background selection with mutation-intolerant genes, which account for 30% of the SNP-based SCZ heritability. Six sets of independent SCZ-genes stand out: target genes of Fragile-X mental retardation protein (FMRP), abnormal behavior-related genes, 5-hydroxytryptamine 2C (5-HT_{2C}) receptor complex genes, neuro-electrophysiology genes, voltage-gated calcium-channel

complexes genes, and long-term potentiation genes (Pardinas et al., 2018). An SCZ-risk SNP is in the manganese and zinc transporter gene (*SLC39A8),* with nonsynonymous variants leading to *SLC39A8* deficiency and being associated with severe neurodevelopmental disorders, via manganese transport and glycosylation damages of Park et al. (2015).

2.5 | MDD

MDD has a 9% adult prevalence (Centers for Disease Control and Prevention, 2010) and presents with at least one episode (seldom) or recurrent episodes (more common) of 2 weeks of low mood or hopelessness and/or marked diminished interest or pleasure in almost all activities and in addition at least four of the following features occurring during the same period of time: Weight loss or gain unrelated to diet changes, insomnia or hypersomnia, motor retardation or restlessness, fatigue or loss of energy, worthlessness or inappropriate guilt, inability to think or concentrate or indecisiveness, and recurrent thoughts of death. These symptoms must cause significant distress or impairment in important areas of functioning.

2.6 | MDD-genetic contribution

MDD is a complex heterogeneous disorder with a polygenic architecture. Genetic factors contribute to 31–42% of MDD (Sullivan, Neale, & Kendler, 2000), and genetic and environmental interactions are thought to be highly relevant. In particular, environmental stress and stress responses are implicated in the pathogenesis (Smoller, 2016). Several candidate genes and GWAS studies have been performed to identify risk genes, but often these studies used admixed populations. At least 97 candidate genes have been reported showing risk variants for MDD, but replication efforts have not consistently been successful, perhaps due to the role of environmental factors; they have been more successful in selected subsamples, highlighting the necessity to better ascertain the phenotype and study homogenous family datasets (Luo et al., 2016). Recently, a low-coverage whole-genome sequencing in a case–control study of Han Chinese women with recurrent MDD identified two genome-wide significant loci, one near sirtuin 1 (*SIRT1*), and the other in the phospholysine phosphohistidine inorganic pyrophosphate phosphatase (*LHPP*) gene; both loci were replicated in an independent Chinese sample, and highly significant in the discovery and replication joint analysis (consortium, 2015). Wray et al. refined the genetic architecture of MDD by a large-scale GWAS study (135,458 cases and 344,901 control subjects), identifying 44 independent statistically significant loci (Wray et al., 2018), of which 30 were new, and 14 were significant in a prior study of MDD or depressive symptoms. MDD risk was also associated with SCZ. Gene-wise analyses identified 153 significant genes, of which 45 are associated with the MHC region, a novel finding (Wray et al., 2018).

3 | MENTAL AND METABOLIC COMORBIDITY

As previously mentioned, SCZ, MDD, T2D, and MetS are heterogeneous polygenic complex disorders.

3.1 | SCZ, T2D, and Mets

SCZ increases T2D risk in drug-naive patients (Dasgupta et al., 2010 ; Fernandez-Egea et al., 2009; Kirkpatrick et al., 2009; Ryan et al., 2003; van Nimwegen et al., 2008), independently from antipsychotics potentially impairing metabolism. SCZ patients have higher prevalence of prediabetes, T2D, MetS, and obesity than control subjects (Subashini et al., 2011). Specific SCZ phenotypes are associated with differences in glycemia: Nondeficit SCZ patients (positive symptoms) have higher glycemia 2-hr postoral glucose tolerance test (OGTT) than deficit SCZ patients (negative symptoms); the latter have higher glycemia than control subjects. Thus, each SCZ phenotype may entail a distinct glucose impairment etiology, independent from other factors (Kirkpatrick et al., 2009).

The prevalence of T2D in SCZ is 11.3% compared with 6.3% of the hospitalized controls (Schoepf et al., 2012) and the prevalence of MetS in untreated SCZ patients is 10.8% (Reddy, Goudie, & Agius, 2013).

A recent Chinese study found that obesity is more prevalent in SCZ than in the general population (Q. Li et al., 2016). Our theory regarding the comorbidity of SCZ and T2D stems from the evidence that subjects with NAP are at increased T2D risk in early adulthood and prior to antipsychotic use. Recently, three independent meta-analysis studies have each independently reported that firstencounter antipsychoticnaive SCZ and/or psychosis patients have significantly increased levels of fasting glucose, fasting insulin, and insulin resistance, glucose levels post OGTT, and subsequently develop IGT after an OGTT or antipsychotics, and that the number of IGT patients were significantly increased in subjects with the firstepisode of SCZ and/or psychosis compared with healthy subjects (Greenhalgh et al., 2017; Perry, McIntosh, Weich, Singh, & Rees, 2016; Pillinger et al., 2017). Thus, glucose metabolism is impaired since at least SCZ first-onset, signifying that SCZ subjects carry a greater T2D risk (Greenhalgh et al., 2017; Perry et al., 2016; Pillinger et al., 2017; Figure 1).

The comorbidity of SCZ and T2D is of paramount importance for the increased morbidity and mortality risk of the affected patients (Ward & Druss, 2015). SCZ and T2D are contributed by an interaction of environmental and genetic risk factors. Prenatal famine is a common environmental factor associated with T2D and SCZ risk (Wang & Zhang, 2016; N. Wang et al., 2017). Furthermore, several possible SCZ-pathways (Dean, 2001; Javitt, 2007) may contribute to T2D and MetS.

3.2 | MDD, T2D, and Mets

MDD confers a 60% increased T2D risk (Mezuk et al., 2008), and increases risk for MetS and cardiovascular disease as well. The association of MDD–T2D cannot be attributed to antidepressant therapy (Pan et al., 2010). On the contrary, the relative risk for incident MDD associated with T2D is only 15% (Mezuk et al., 2008). A recent study reported in the Bangladeshi population that people with T2D have seven times more coexisting MDD in comparison to subjects without T2D (Chowdhury et al., 2017). Das et al. (2013) reported the rate of MDD to be 46.15% in T2D patients. In a population sample of 972 subjects (mean age 25.81), MDD patients had a 35.1%, prevalence of MetS compared to the 22.1% of the population sample (Moreira et al., 2017). Several pathways are implicated in MDD, and, if

impaired, may contribute to T2D and/or MetS (Figure 1). Both the serotonergic and hypothalamic–pituitary-axis systems are implicated in MDD (Lanfumey, Mongeau, Cohen-Salmon, & Hamon, 2008) and both may play a role in T2D and MetS (Price et al., 2002; Silic, Karlovic, & Serretti, 2012; Vogelzangs et al., 2007). For example, as we reported, MDD and T2D are both associated with hypothalamic-pituitary-adrenal axis dysfunction leading to hypercortisolemia, weight gain, and insulin resistance (Gragnoli, 2012a, 2014a). Impaired circadian rhythms also may contribute to increased insulin resistance and T2D, and often insomnia is associated with MDD (Nechita, Pirlog, & ChiriTa, 2015). Chronic inflammation, cytokines, and inflammatory markers are increased in MDD and could contribute to T2D risk (Hajebrahimi, Kiamanesh, Asgharnejad Farid, & Asadikaram, 2016). Also, environmental factors and interactions between the gut microbiota and the diet play a significant pathogenic role in MDD, obesity, and T2D; gut dysbiosis and leaky gut may modulate pathways, such as the immune activation and inflammatory response, which are involved in the pathobiology of depression and metabolic disorders (Slyepchenko et al., 2017).

Recently, it has been reported that when T2D and MDD are present simultaneously they drastically worsen quality of life and become associated with significant morbidity and mortality; in fact, their comorbidity leads to reduced compliance, higher complications rates, inB194adequate metabolic outcome, and greater disability, productivity loss, and death rates. Hence, it is necessary to perform studies focused on the association between the two disorders (Reus et al., 2017).

3.3 | Mental and metabolic-genetic overlap

Of interest, MDD is comorbid and genetically overlaps with SCZ, psychosis, and/or bipolar disorder (Bozkurt, Duzman Mutluer, Kose, & Zoroglu, 2015; Lim et al., 2015). In a recent large-scale GWAS study, MDD and SCZ partly share biological etiology (Wray et al., 2018); the comparison of the MDD-loci with 108 SCZ-loci (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) identified 6 shared MDD- and SCZ-loci, among which strong associations are in the MHC region and transcription factor 4 gene (*TCF4*), key in brain development (Wray et al., 2018).

There is also genetic overlap for T2D, SCZ, and MDD (Kavanagh, Tansey, O'Donovan, & Owen, 2015; Lin & Shuldiner, 2010; Figure 1). For instance, the 12q24 locus is linked to MDD, bipolar disorder, SCZ (Cassidy et al., 2007; Christiansen et al., 2009; Holmans et al., 2009), and anxiety (Hodgson et al., 2016), as well as T2D (Mahtani et al., 1996) and the associated cardiovascular phenotypes of CAD, myocardial infarction, stroke (Erdmann et al., 2009; Sherva et al.,2008), dyslipidemia (Aberg et al., 2008), early microvascular retinopathy (Ikram et al., 2010) hypertension, obesity, visceral obesity, and BMI joint to C-reactive protein (Wilson et al., 2006; Wu et al., 2009). Thus, at least one or a few genes and/or gene variants across this locus are expected to explain the pleiotropic or comorbid possibly unitarian linkage of the above-mentioned phenotypes. One of these genes may be the *PSMD9* gene as previously reported by us to be in linkage with several of the 12q24 linked phenotypes (T2D, depression, anxiety, hypertension, microvascular disease, retinopathy, hypercholesterolemia, overweight condition, and macrovascular disease) (Gragnoli, 2010a,

2011a, 2011b, 2011c, 2012b, 2011d, 2012c, 2013, 2014b; Gragnoli & Cronsell, 2007; Hao, Haas, Wu, & Gragnoli, 2015), and insomnia. Of note, *PSMD9* has been reported by other groups as one of the top risk genes for MDD (Wong et al., 2008, 2012) and SCZ (Lee et al., 2013).

3.4 | SCZ and metabolic-genetic overlap

In recent years, the interest of the possible SCZ-T2D risk co-sharing and the evidence of overlapping SCZ-T2D loci has increased (Gough & O'Donovan, 2005). Recently, a "pleiotropic enriched" GWAS study found shared common risk variants of SCZ and cardiovascular risk factors and MetS traits (dyslipidemia, waist-to-hip ratio, systolic blood pressure, and increased BMI) (Andreassen et al., 2013). A recent GWAS study detected shared loci of sleep disturbance traits with SCZ and the adiposity traits BMI and waist circumference (Lane et al., 2017). In a systematic review of genetic variants associated with MetS in SCZ patients, several genes showed strong evidence for association, including the genes leptin (LEP), leptin receptor (*LEPR*), 5-hydroxytriptamine receptor 2C (*HTR2C*), *FTO*, and *MTHFR* (Malan-Muller et al., 2016), with the latter two being also MDD-risk genes (Amare et al., 2017).

Despite many studies showing that drug-naive SCZ patients have increased metabolic-T2D risks (Dasgupta et al., 2010; Fernandez-Egea et al., 2009; Kirkpatrick et al., 2009; Ryan et al., 2003; van Nimwegen et al., 2008) and that SCZ and/or NAP are significantly associated with familial metabolic risk (Fernandez-Egea et al., 2008; Miller et al., 2016; Spelman et al., 2007), only a few studies have aimed to detect gene risk variants co-shared by SCZ and T2D. These studies focused only on known SCZ or T2D risk genes, but reported significant associations of the SCZ-risk *DRD2* SNP with regulatory function with glycemia in SCZ (Lawford et al., 2016; Luykx, Broersen, & de Leeuw, 2017), and of the T2D-risk genes insulin-like growth-factor-2 mRNA-binding protein-2 (*IGF2BP2*) and the strongest T2D-risk gene *TCF7L2* with SCZ (Hansen et al., 2011; Zhang, Hui, et al., 2013), the latter identified in a Danish and European study (Hansen et al., 2011). Of note, a SCZ family-based GWAS study in homogeneous Arab-Israeli SCZ families reported by chance—status postsignificant 10q24.26 linkage identification under a dominant model (Alkelai et al., 2011)—*TCF7L2* significant association with SCZ (Alkelai et al., 2012). These findings support the shared genetics SCZ and T2D; the importance of integrating in family-studies parametric linkage and association in regions of interest (Alkelai et al., 2012); and strongly emphasize family-studies substantial advantages, as they allow testing for both linkage and association, are strategic against population stratification and/or false-positive associations, and offer superior quality control.

The gene disrupted-in-schizophrenia 1 (*DISC1*) is also a risk factor for mental illness due to dopamine dysregulation, as DISC1 interacts with other dopamine-system proteins (Dahoun, Trossbach, Brandon, Korth, & Howes, 2017). Of interest, DISC1 disrupts pancreatic betacell function, decreases beta-cell proliferation, and promotes apoptosis and glucose intolerance in transgenic mice (Jurczyk et al., 2016); thus *DISC1* is a T2D-candidate gene. Per SCZ-T2D GWAS overlapping data, there are several other candidate genes for SCZ-T2D comorbidity (Lin & Shuldiner, 2010). However, the causality hypothesis may more strongly

impact the comorbidity of SCZ with T2D and MetS than the pleiotropic gene theory, since an impaired pathway in early-onset SCZ may lead to T2D and/or MetS over time. However, some risk genes will have pleiotropic effects (Figure 1). Hence, there is a need to address current scientific gaps of the neuro-psycho-metabolic pathways involved in SCZ, T2D, and their comorbidity. New gene pathways will possibly be detected in a comorbidity-focused study.

3.5 | MDD and metabolic-genetic overlap

GWAS meta-analyses and candidate gene studies have reported genetic variants associated with cardio-metabolic diseases and mood disorders. Even if most studies have traditionally focused on a single disorder, a literature study looking at both cardio-metabolic and mood disorders (e.g., T2D, CAD, hypertension, obesity, lipids, insulin, glucose, MDD, and bipolar disorder) identified several potential pleiotropic risk genes (e.g., methylenetetrahydrofolate reductase [*MTHFR*], *FTO,* adrenoceptor-beta-1 [*ADRB1*], 5-hydroxytryptamine receptor 1A [*HTR1A*], adrenoceptor-alpha-2A [*ADRA2A*], cAMP responsive element binding protein 1 [*CREB1*], proopiomelanocortin *[POMC],* brain-derived neurotrophic factor [*BDNF*], *TCF7L2,* melatonin receptor 1B [*MTNR1B*], and insulin-like growth factor-1 [*IGF1*]), likely co-shared between cardio-metabolic and mood disorders, revealing comorbid pathways (e.g., corticotrophin-releasing hormone signaling, serotonin or dopamine receptors signaling, circadian rhythm, and leptin signaling; Amare et al., 2017).

A recent bioinformatics study, per analysis of large-scale GWAS statistics, explored the co-shared genetics of T2D and MDD and identified 496 significant risk SNPs for both disorders, and highlighted, via functional enrichment analysis, that immune responses (e.g., T cell and B cell receptors signaling, Fc gamma R-mediated phagocytosis), lipid metabolism, cancer-related pathways, and cell signaling (Wingless-type [Wnt] signaling, mitogen-activated protein kinase 3 [MAPK]) are the most enriched common pathways (Ji, Zhuang, & Shen, 2016; Figure 1).

In addition, a study in Danish and Swedish twins demonstrated significant genetic overlap between T2D and MDD and reported qualitative genetic sex differences (Kan et al., 2016).

Of interest, most recently, a study showed that patients with MDD and increased appetite and/or weight carried a higher number of risk variants for BMI and levels of C-reactive protein and leptin, whereas the decreased appetite and/or weight subgroup showed an inverse correlation with BMI. The authors concluded that the association may derive from shared immune-metabolic dysregulations (Milaneschi et al., 2017).

We highlighted the possible gene pathways and mechanisms related to the neuro-endocrine cortisol pathway impairment contributing to the clinical association of MDD and T2D (Gragnoli, 2012a, 2014a). As previously mentioned, we also reported *PSMD9* in linkage with T2D (Gragnoli, 2010a), depression (Gragnoli, 2012c), and the depression-associated mental traits of generalized anxiety disorder (Gragnoli, 2014b), and insomnia (Hao et al., 2015). PSMD9 is a highly concentrated ubiquitous PDZ-domain-containing chaperone of the 26S proteasome complex assembly and is an insulin gene transcription coactivator highly transcribed in pancreatic islets (Thomas, Yao, Tenser, Wong, & Habener, 1999).

Pancreatic overexpression of the homologous *PSMD9* gene in transgenic mice causes insulin deficiency, diabetes, and hypertriglyceridemia (Volinic, Lee, Eto, Kaur, & Thomas,2006). Gene transcription inhibition in vitro reduces insulin secretion (Thomas et al., 1999). *PSMD9* variants may impair insulin transcription and cause beta-cell dysfunction and T2D (Thomas et al., 1999). We found that *PSMD9* causes T2D by rare unique mutations (Gragnoli & Cronsell, 2007), and is also significantly linked, beyond T2D, to maturity-onset diabetes of the young type 3 (MODY3) (Gragnoli, 2010a, 2010b). PSMD9-associated 26S proteasome complex contributes to intracellular proteins degradation in antigenic peptides in the immune response to antigens by MHC-class I cells. Thus, one potential PSMD9 role in the phenotypes associated with T2D, MDD, and atherosclerosis relates to the pathogenesis of inflammation as an autoimmune process (Wick, Millonig, & Xu, 2001). Furthermore, PSMD9 regulates ligand-dependent retinoid-target genes transcription. Thus, impaired PSMD9 function due to gene variants affecting protein sequence and/or dosage may alter dosage and/or effects of several downstream genes. Given the complex network of transcription and coactivator factors to which PSMD9 is associated, both a PSMD9 reduced or increased protein dose may contribute to phenotypes that may be either different or have a common underlying contributing factor. Of interest, PSMD9 influences both basal-and tumor necrosis factor-alpha (TNF-alpha)-mediated nuclear-factor-κB (NF-κB) activation through inhibition of nuclear-factor-κBα (κBα) proteasomal degradation. The nuclear-ribonucleoprotein-A1 (hnRNPA1) is one of the novel interacting partners of PSMD9. PDZ-domain point mutations or deletion of hnRNPA1 C-terminal residues disrupt the two proteins interaction which is directly influencing NF-κB activity. The interactions between κBα, hnRNPA1, and PSMD9 elucidate a possible mechanism for degradation of κBα by the proteasome, in which hnRNPA1 and PSMD9 may be, respectively, a shuttle receptor and a subunit acceptor (Sahu, Sangith, Ramteke, Gadre, & Venkatraman, 2014). In summary, PSMD9 role in modulating inflammation may explain the link between MDD, and/or SCZ with T2D.

A GWAS study of bipolar disorder, which is associated with MDD, tested the SNPs-interaction effects with BMI and identified a risk intronic SNP of *TCF7L2*, the strongest T2D risk gene. The data indicate that the bipolar disorder risk SNP is dependent on BMI (Winham et al., 2014). A cross-sectional study performed in a multiethnic population reported that the association between obesity and MDD may, at least in part, be explained by shared genetic factors (Samaan et al., 2015).

A study performed in the Scottish population reported that the alleles-effect increasing BMI was greater in the subjects with MDD, current psychological distress, or high neuroticism. Thus, MDD, neuroticism, and current psychological distress amplify BMI-polygenic risk score effects on BMI. Thus, subjects with MDD having a greater polygenic load for obesity have a greater risk of obesity compared to control subjects (Clarke et al., 2015).

4 | PRL-PATHWAY GENES, MENTAL DISEASES, AND METABOLIC GENETIC OVERLAP

4.1 | PRL-pathway in SCZ, MDD, T2D, and MetS

PRL mediates personal-social bonding, attachment-related behaviors (Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010; Neumann,2009), and anti-depressant response (Faron-Gorecka et al., 2013) as well as contributes to insulin secretion and action, and beta-cell mass. To support the theory that the comorbidity of T2D-and/or MetS-associated psychological–mental traits is due to shared gene variants, we hereby highlight the candidate genes correlated and implicated in the PRL-pathway: prolactin-releasing hormone receptor (*PRLRH*), prolactin receptor (*PRLR*), oxytocin (*OXT*), oxytocin receptor (*OXTR*), and neuropeptide Y (*NPY).* In fact, an inherited PRL-pathway dysfunction such as manifesting with reduced OXT levels, and/or PRLR, PRLRH, OXTR dysfunction, and/or impaired NPY may contribute to the following: (a) impairment of basal and stress-related PRL-secretion (Insana & Wilson, 2008; Torner, Toschi, Pohlinger, Landgraf, & Neumann, 2001); (b) abnormal personal and social attachment-styles and communication skills; inadequate mental-behavioral-development and mood, and psychopathology (Cochran, Fallon, Hill, & Frazier, 2013; Gordon et al., 2010; Neumann, 2009; Veenema & Neumann,2008); and (c) reduction of insulin secretion, insulin action (Balbach et al., 2013; Huang, Snider, & Cross, 2009; Sorenson & Brelje, 2009; Sorenson, Johnson, Parsons, & Sheridan, 1987), and beta-cell mass (Nielsen et al., 2001). Any of these effects may lead to SCZ, MDD, as well as impaired glucose metabolism, T2D, and MetS. Our premise is based on the following evidence.

SCZ-psychosis is partly due to increased dopamine and/or activity of DRD_2 activity (Howes & Kapur, 2009), and dopamine inhibits PRL-secretion via DRD_2, which is an SCZ-risk gene (Chien et al., 2013; Glatt et al., 2009); thus DRD_2 dysfunction may alter the PRL-pathway. As we previously highlighted (Gragnoli, Reeves, Reazer, & Postolache,2016), the PRL-pathway genes (PRL, *PRLHR, PRLR, OXT, OXTR,* and *NPY*) may thus contribute to SCZ, T2D, and/or MetS. Several studies suggest that the PRL-pathway may contribute to SCZ-mental traits: (a) male-PRL levels are reduced compared to female-PRL levels, and SCZ has earlier onset in males (Hafner, Maurer, Loffler, & Riecher-Rossler, 1993); (b) PRL levels have been reported decreased (Meaney & O'Keane, 2002; Rao et al., 1994) as well as increased in SCZ drug-naive patients (Gonzalez-Blanco et al., 2016), and decreased in depression (Depue et al., 1990); (c) PRL increases with anti-depressant (Faron-Gorecka et al., 2013) and typical anti-psychotic action (Oberweis & Gragnoli, 2012); (d) a more severe SCZ first-episode is associated with decreased PRL (Gorobets & Matrosova,2010); (e) PRL is an anxiolytic secreted during stress response (Insana & Wilson, 2008; Torner et al., 2001) and enhances bonding, social interaction, and attachment (Gordon et al., 2010; Neumann, 2009); and (f) PRL-levels changes are associated with dissociative symptoms of depression (Bob et al., 2008). Thus, PRL-levels changes are associated with SCZ; however, association does not imply causality.

As early-life stressful life events (e.g., parental abuse, neglect) predisposes to SCZ (Rubino, Nanni, Pozzi, & Siracusano, 2009) and MDD (Rubino et al., 2009; Young & Dietrich, 2015),

and as PRL is essential for social and personal stress-coping ability, subjects with impaired PRL-pathway and inadequate stress-related PRL-secretion early in life may be susceptible to inadequate mental development and become mentally impaired.

Of interest, psychosis is comorbid with MDD (Bozkurt et al., 2015; Lim et al., 2015), and while low PRL is involved in depression (Depue et al., 1990) and PRL elevation is an effect of anti-depressants (Faron-Gorecka et al., 2013), PRL also plays a role in feeding and sleep-wake cycles (Ben-Jonathan, LaPensee, & LaPensee, 2008), which are disrupted in depression. Thus, PRL-pathway and related-genes disruption may confer risk for T2D-and Mets-mental traits comorbidity (Figure 2). We hereby summarize what is known about the PRL-pathway genes.

4.2 | PRL

PRL lies on locus 6p22.3, which is strongly associated with pre-diabetes traits in a genome-wide linkage scan (An et al., 2005), T2D in the replication of GWAS data (Lu et al., 2012; Zeggini et al., 2007), T2D risk (Lu et al., 2012), SCZ, including a dense genome-wide linkage scan (Gornick et al., 2005; Maziade et al., 2005), and bipolar disorder in a genome-wide linkage study (Marcheco-Teruel et al., 2006). Of note, genetic overlap exists between bipolar disorder and MDD (Pregelj, 2009). PRL is relevant to SCZ pathogenesis. *PRL* is associated with SCZ (Rybakowski, Dmitrzak-Weglarz, Kapelski, & Hauser, 2012). Prolactin-regulatory-element (*PREB*) is associated with eating disorders (Gratacos et al., 2009). A variant near *PRL* is associated with male obesity (Nilsson et al., 2011), a finding not confirmed in a GWAS-meta-analysis (den Hoed et al., 2013) and glycemic traits in a replication study of GWAS data (Kong et al., 2014). *PRL* variants have not been associated with childhood depression (Strauss et al., 2010).

Furthermore, PRL plays a role in beta-cell mass (Nielsen et al.,2001), islet proliferation (Nyblom et al., 2009), insulin secretion and action, glucose regulation (Balbach et al., 2013; Huang et al., 2009; Sorenson et al., 1987; Sorenson & Brelje, 2009), metabolic risk factors (Glintborg et al., 2014), feeding-and sleep-wake cycles (Ben-Jonathan et al., 2008). Reduced PRL levels can lead to T2D and/or MetS and their comorbidity with mental traits (Balbach et al., 2013; Corona et al., 2014).

PRL-secretion requires PRLRH function as PRLRH is the PRL-releasing hormone; PRL action requires PRLR function. PRLHR and PRLR are implicated in eating behavior, obesity, insulin resistance, beta-cell mass, MetS, and SCZ-T2D (Auffret et al., 2013; Balbach et al., 2013; Corona et al., 2014; Gu, Geddes, Zhang, Foley, & Stricker-Krongrad, 2004; Watanabe et al., 2005).

4.3 | PRLR

PRLR lies on 5p13.2, which is a locus linked to C-reactive protein (Lakka et al., 2006), and strongly linked to SCZ (Bespalova et al.,2005). To the best of our knowledge, there are no human genetic studies on T2D, MetS, MDD, and SCZ. *PRLR* knockout mice show reduced beta-cell mass during embryogenesis and the postnatal period. PRLR is essential for pancreas ontogenesis in the perinatal time (Auffret et al., 2013). PRLR dysfunction may lead

to T2D, MetS, or T2D- and/or MetS-mental traits comorbidity (Balbach et al., 2013; Corona et al., 2014).

4.4 | PRLRH

PRLRH lies on 10q26.13, locus linked to T2D (Vionnet et al., 2000), including in our Italian T2D dataset (Milord & Gragnoli, 2007), bipolar disorder (Smith et al., 2009), and SCZ (K. B. Bulayeva, Glatt, Bulayev, Pavlova, & Tsuang, 2007). PRLRH is the PRL-releasing hormone. *PRLRH* knockout mice overeat, are obese, and insulin-resistant (Gu et al., 2004). In rats, a mutated *PRLRH* (alias GPR10) is responsible for hyperphagia, obesity, and dyslipidemia (Watanabe et al., 2005). There are no human *PRLRH* studies in T2D, MetS, MDD, and SCZ.

Also, OXT, OXTR, and NPY modulate the dopamine-PRL pathway and may confer risk for PRL-pathway disruption and T2D and/or Mets-mental traits comorbidity.

4.5 | OXT

OXT lies on 20p13, a locus linked and/or associated with small atherogenic LDL-particles, large VLDL-particles in diabetic subjects (Divers et al., 2010), T2D (Ghosh et al., 2000), MDD (K. Bulayeva et al., 2012), and SCZ (Fanous et al., 2008; Teltsh et al., 2008; Teltsh et al., 2012). *OXT* is not associated with childhood depression (Strauss et al., 2010) and is associated with postpartum depression (Jonas et al., 2013) and SCZ (Montag et al., 2013; Teltsh et al., 2012). There are no *OXT* studies in T2D and/or MetS. OXT stimulates via OXTR lactotrophs' PRL-secretion and an OXT injection induces in rats PRL release as per copulation; OXT antagonism inhibits lactotroph activity (Egli et al., 2006; Kennett & McKee, 2012) and PRL influences via PRLR hypothalamus OXTergic neurons (Egli et al., 2006). An OXT-impaired system may lead to social cognitive-behavioral dysfunction and paranoid delusions (Cardoso, Kingdon, & Ellenbogen, 2014; Holka-Pokorska & Jarema, 2014; Peters, Slattery, Uschold-Schmidt, Reber, & Neumann, 2014). Of note, OXT attenuates the stress-cortisol pathway; the OXTergic system has a role in emotional and cognition regulation and OXT reduces anxiety in mice (Cardoso et al., 2014; Peters et al., 2014).

OXT is elevated in SCZ, social avoidance for negative emotions (Brown et al., 2014), MDD (Parker et al., 2010), and is activated during stress (Brown et al., 2014; Scantamburlo, Ansseau, & Legros, 2001). OXT is essential in pair-bond formation, human social behaviors (e.g., social decision making, social stimuli evaluation and response, social interaction, and social memories formation; Cochran et al., 2013; Neumann, 2009; Veenema & Neumann, 2008). OXT is involved in various neuropsychiatric functions and mental disorders (e.g., SCZ and affective and anxiety disorders; Cochran et al., 2013). Thus, PRL-OXT pathway dysfunction may lead to mental pathology. While OXT is increased in MDD (Parker et al., 2010), OXT administration improves depression (Scantamburlo, Hansenne, Geenen, Legros, & Ansseau, 2015) and has antipsychotic and anxiolytic effects, and improves social cognition in SCZ (Frost et al., 2014; Mercedes Perez- Rodriguez, Mahon, Russo, Ungar, & Burdick, 2015; Woolley et al., 2014).

OXT nasal spray increases trust in healthy subjects, modulates emotion recognition, social memory, prosocial, and altruistic behaviors; OXTergic system dysregulation may cause incorrect meaning attribution of emotional information from the environment, leading to social cognition dysfunction and abnormal social behavior (e.g., withdrawal from social contact, isolation, and paranoid delusions) (Holka-Pokorska & Jarema, 2014), all SCZ features.

OXT plays a role in rat pancreatic islets (Johansson et al., 1991) and in alpha- and beta-cell secretion in diabetic and control subjects, by augmenting insulin secretion (Paolisso et al., 1988), and has a role in obesity and IGT (Camerino, 2009; Johansson et al., 1991; Paolisso et al., 1988). *OXT* knockout mice develop obesity, decreased insulin sensitivity, and glucose intolerance (Camerino, 2009). OXT administration over 8-weeks reduces food intake in men, causes weight loss and lipolysis, and reverses pre-diabetes in rats and patients (Zhang et al.,2013). Central OXT infusion in high-fat-diet-induced obese rats causes a dose-dependent weight loss, increases lipolysis, and reduces glucose intolerance and insulin resistance (Deblon et al., 2011).

4.6 | OXTR

OXTR lies on 3p25, a locus strongly associated with SCZ (Zintzaras & Ioannidis, 2005), T2D (Voight et al., 2010), MetS, CAD (Bowden et al.,2006), and depression (Breen et al., 2011). There are no *OXTR* studies in T2D and MetS. *OXTR* is associated with SCZ (Montag et al., 2013), empathy in SCZ (Montag et al., 2012), and modulates fear by social memory (Guzman et al., 2014). Heterozygous *OXTR* knockout mice have impaired social behavior (Sala et al., 2013) and are obese (Takayanagi et al., 2008). *OXTR* variants increase risk for anxiety, stress, and depression (Myers et al., 2014). OXT is activated during stress (Scantamburlo et al., 2001), thus *OXTR* dysfunction may cause stress hyper-response leading to the comorbidity of MDD with T2D and/or MetS.

4.7 | NPY

NPY lies on 7p15.1, a locus strongly associated to T2D (Voight et al., 2010; Zeggini et al., 2007), and linked to T2D (Wiltshire et al., 2001), MetS (Bosse et al., 2007), and SCZ (Fallin et al., 2003). NPY variant is associated with MDD (Y. Wang et al., 2013) and was replicated in another study (Bosker et al., 2011). NPY association studies in SCZ are conflicting (Duan et al., 2005; Hall et al., 2007; Inoue et al., 2009; Itokawa et al., 2003; Lindberg et al., 2006; H. S. Wang et al., 2005). NPY intensifies dopamine inhibition of PRL-secretion (Hsueh, Cheng, & Pan, 2002; C. Li, Chen, & Smith, 1999; J. Wang, Ciofi, & Crowley, 1996). Suckling induces PRL and, in tuberoinfundibular dopaminergic (TID) neurons, NPY (C. Li et al., 1999), which inhibits PRL-secretion (Ciofi et al., 1993). In female mice, lactotroph-DRD_2 selective disruption increases via PRL NPY hypothalamic expression, food intake, and adiposity (Perez Millan et al., 2014). During fasting, up-regulated NPY stimulates TID neurons and inhibits PRL-secretion (Hsueh et al.,2002). NPY is implicated in the SCZ-T2D pathway and/or comorbidity (Lin & Shuldiner, 2010; Liu et al., 2013). NPY is less expressed in the dorsolateral prefrontal cortex in psychosis (Choi et al., 2008) while cerebrospinal fluid NPY levels correlate to social competence, psychosis, and SCZ outcome (Choi et al., 2008; Lin & Shuldiner, 2010; Liu et al., 2013; Stalberg, Ekselius, Lindstrom,

Larhammar, & Boden, 2014). NPY has beneficial effects on mood, stress coping ability, food intake, and metabolism (Farzi, Reichmann, & Holzer, 2015). *NPY*-positive rat-islet-cells increase with high-fat-diet or T2D (Ruipan et al.,2014); NPY levels correlate with body weight changes (Alkemade et al., 2012) and increase with insulinemia in T2D (Ilhan et al., 2010; Katsiki, Mikhailidis, Gotzamani-Psarrakou, Yovos, & Karamitsos, 2011). NPY is significantly elevated in chronically stressed women vulnerable to diet-related abdominal fat, oxidative stress, and metabolic risk; women with higher NPY have a stronger association of highly palatable food (high sugar and fat) with abdominal adiposity (Aschbacher et al., 2014).

Thus, NPY role in appetite, diet-related fat, oxidation, and metabolic risk (Alkemade et al., 2012; Aschbacher et al., 2014; Ilhan et al., 2010; Katsiki et al., 2011; Pankov, Chekhranova, & Karpova, 2008) may increase appetite-related effects, thereby leading to T2D and Mets (Pankov et al., 2008). NPY is associated with inflammation in T2D (Jaakkola et al., 2010), T2D (Nordman et al., 2005), MetS (Pesonen, 2008), atherosclerosis (Kakko, Jaakkola, Raitakari, & Kallio,2011), and MetS-CAD (Parizadeh et al., 2015).

A search in PubMed using the following set of terms did not identify any GWAS **meta-analysis** reporting these genes: "*PRL*", "*PRLR*", "*PRLHR*", and the keyword "prolactin" or "*OXT*", "*OXTR*", "*NPY*" and "GWAS" and "metanalysis" (or "meta-analysis") and "type 2 diabetes" (or "T2D"), "metabolic syndrome" (or "MetS"), "schizophrenia" (or "SCZ"), and/or "major depressive disorder" (or "MDD", or "depression").

However, as described above, *PRL*/6p22.3, PRLR/5p13.2, *PRLHR*/10q26.13, *0XT*/20p13, *OXTR*/3p25, and *NPY*/7p15.1 genes/loci have all been variably linked and/or associated with prediabetes traits, SCZ, bipolar disorder, MDD, postpartum depression, T2D, C-reactive protein, T2D-atherogenic particles, MetS, and CAD (An et al., 2005; Bespalova et al., 2005; Bosse et al., 2007; Bowden et al., 2006; Breen et al., 2011; K. Bulayeva et al., 2012; Divers et al., 2010; Fallin et al., 2003; Fanous et al., 2008; Ghosh et al., 2000; Gornick et al., 2005; Jonas et al., 2013; Kong et al., 2014; Lakka et al., 2006; Lu et al., 2012; Marcheco-Teruel et al., 2006; Maziade et al., 2005; Montag et al., 2013; Myers et al., 2014; Nilsson et al., 2011; Rybakowski et al., 2012; Smith et al., 2009; Teltsh et al., 2012; Teltsh et al., 2008; Voight et al., 2010; Y. Wang et al., 2013; Wiltshire et al., 2001; Zeggini et al., 2007; Zintzaras & Ioannidis, 2005). Furthermore, the *PRL*, *PRLR*, *PRLHR, OXT, OXTR,* and *NPY* genes play a key role in the PRL-pathway and may, if impaired, confer risk for T2D, Mets, associated traits, and the SCZ-T2D and/or -MetS comorbidity. Hence, since we lack studies of PRLR and PRLHR in SCZ, T2D, MetS, and *OXT* and *OXTR* in T2D and MetS, these PRL-pathway genes should be investigated in these disorders.

The PRL-pathway-related genes' SNPs should be amplified in homogenous population families, enriched for the mental and metabolic traits phenotypes, and they should be tested for linkage and/or association with T2D and/or MetS and/or associated metabolic and mental traits.

The PRL-pathway-related genes' significant SNPs from the linkage and/or association family study should be tested in a case-control group for association with T2D and/or MetS

and/or associated metabolic and mental traits. Finally, the PRL-pathway-related rare and uncommon variants potentially underlying the significant linkage and/or association should be identified and tested in family members with significant linkage to determine possible linkage and/or association with T2D and/or MetS and/or associated metabolic and mental traits.

5 | INVESTIGATIONAL EXPECTATIONS, NEEDS, AND NEW IDEAS

We do not expect that only a single gene pathway or a few genes in a specific pathway will explain SCZ, MDD, T2D, and MetS, or their comorbidity. Not all SCZ and/or MDD patients develop T2D and/or MetS, and only few T2D and/or MetS patients present with SCZ pre-symptoms and several T2D and/or MetS patients present with MDD. We believe that an impaired pathway in early-onset SCZ as well as MDD may over time determine T2D and/or MetS.

Consequently, we expect a genetic stratification of disease-predisposition correlated with phenotype heterogeneity for both SCZ (Arnedo et al., 2015) as well as MDD. Phenotype(s) gene correlation, or lack of thereof, should help identify the genetic basis of the clinical association of SCZ and MDD with T2D and/or MetS and should be the basis for future studies. Thus, it is essential to study SCZ and MDD with T2D and MetS in a polygenic genome-wide variants context.

We propose that it is necessary to perform genetically enriched family-based studies, using family datasets from homogeneous populations, especially from an island and/or a peninsula, ascertained ideally for family enrichment with at least SCZ, MDD, T2D, or MetS, and preferably both a mental and a metabolic phenotype, thereby carrying increased familial-disease risk and possibly increased genetic risk for the mental-metabolic comorbidity as well. The need is for detailed phenotyping of metabolic and mental traits (including T2D, MetS, MDD, and the associated traits of anxiety and primary insomnia, as well as SCZ and related-traits). In addition, to empower gene identification, the families' samples selected for the study should ideally be from populations which traditionally follow a healthy lifestyle and nutrition, so that they will have a reduced environmental-disease burden and thus be genetically more informative.

Investigation in these types of families should explore the potential genetic predisposition to neuroendocrine dysfunction; the linkage and association of genome-wide variants (including low frequency and rare coding variants and CNVs) to SCZ, MDD, T2D, MetS, their sub-phenotypes, associated metabolic-mental traits; the comorbidity of metabolic and mental traits, with and without anti-psychotic and antidepressant treatment; the variant role within different traits (Andreassen et al., 2013; Liu et al., 2013; Zhang, Hui, et al., 2013); and, via NGS, the genes and common and rare variants underlying linkage and association signals.

The goal would be to genetically risk stratify patients based on phenotypes contributing to the T2D and/or MetS-mental traits association.

6 | NOVELTY OF MENTAL-METABOLIC FOCUSAND OUTCOME

Our hypothesis challenges the concept that T2D and MetS are merely metabolic disorders and SCZ and MDD are purely mental disorders; we hypothesize that untreated mental traits, abnormal neuroendocrine mental and behavioral compensatory traits leading to SCZ and/or MDD may contribute to prediabetes-T2D and/or MetS with genetic predisposition to beta-cell failure, and abdominal obesity. Such a study would be novel because: (a) there are no genome-wide family-based studies exploring jointly SCZ and T2D and/or MetS or MDD and T2D and/or MetS; (b) there are scarce *PRL-PRLRH-PRLR-OXT-OXTR-NPY* genetic data in human T2D, MetS, and mental traits; (c) linkage and association tests would be performed not only in patients with T2D and/or MetS or SCZ and/or MDD or mental traits but also with the associated traits and endo-phenotypes, and in genetically homogeneous families datasets; (d) the richness of the patient phenotypes would allow defining new trait categories and improving risk genes identification power; this phenotypes-focused strategy is a powerful new methodology, and the study performance in homogeneous-phenotypes and clinical-based family groups is advantageous when the families are derived from either a peninsula or an island (Andersen et al., 2016); (e) it would explore a new avenue in T2D and/or MetS, SCZ and/or MDD, and mental traits human genetics—the study of the impact of single, complex, and polygenic variants, and their interaction, in major traits and sub-phenotypes of two apparently distinct disorder groups, T2D-MetS, and mental traits; (f) it would focus on gene haplotypes, diplotypes, and multilocus alleles, rare and uncommon variants beyond genotypes and alleles and would prove the complex gene variants risk effects in common disorders; and (g) it should apply innovative statistical models to study genetic actions and interactions among genome-wide gene variants and examine the role of genetic imprinting in disease risk.

Our suggested interdisciplinary approach would integrate genome-wide human genetics and the study of candidate genes for the mental–metabolic comorbidity with the clinical phenotyping of these diseases not commonly studied jointly. The results would prompt new research for associated mental–metabolic disorders creating a new focus on the mental–metabolic dysfunctions characterizing predisease states. By considering the joint pathogenesis of apparently different disorders, it would dramatically advance these diseases' research. As a result, attention would be shifted toward psychological traits in subjects at risk for T2D and MetS and metabolic phenotypes in subjects at risk for SCZ and/or depression. The detection of genetic predisposition would lead to primary integrated prevention (e.g., cognitive-behavioral and nutritional) in at-risk subjects and molecular targeted therapies in patients.

Hence, a need to stratify the genetic risk for T2D and MetS comorbidity with mental traits sub-phenotypes. Phenotype(s) gene correlation, or its absence, would help identify the genetic basis for T2D and/or MetS and T2D-and/or MetS-mental traits association; and would be the basis for future hypotheses and pathogenic theories. Identifying genetic risks for T2D, MetS, and associated mental traits would allow us to explain the shared genetic pathogenesis and/or comorbidity; know the disorders' and comorbidity genetic risks; focus new research on relevant genes, proteins, correlated pathways; and increase family homogeneity and detection power for future studies.

In summary, the proposed novel strategy should be based on phenotype-based family groups and on testing common and rare genetic variants, complex gene variants, and their interaction in distinct disorder groups and associated traits, as well as gene imprinting effects. The richness of the family phenotypes would lead to new trait categories and improve risk genes identification power, as a phenotypes-focused strategy is powerful and innovative. Performing polygenic linkage and association tests and NGS may disclose common and rare risk variants for SCZ, MDD, T2D, MetS, and their associated traits and comorbidity.

Furthermore, T2D, MetS, and mental traits and/or disorders increase cardiovascular risk and pathology, reduce life quality and expectancy, and dramatically increase health costs. Thus, possible family-health burden prevention and secondary interventions would significantly reduce health costs.

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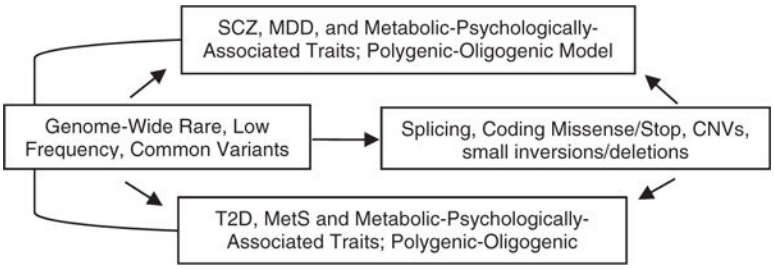

FIGURE 1.

Hypothesized causal genome-wide variants of different frequencies and nature under a possible polygenic-oligogenic disease model for SCZ, MDD, T2D, MetS, metabolic-psychologically associated traits, and their comorbidity. SCZ, schizophrenia; MDD, major depressive disorder; T2D, type 2 diabetes; MetS, metabolic syndrome

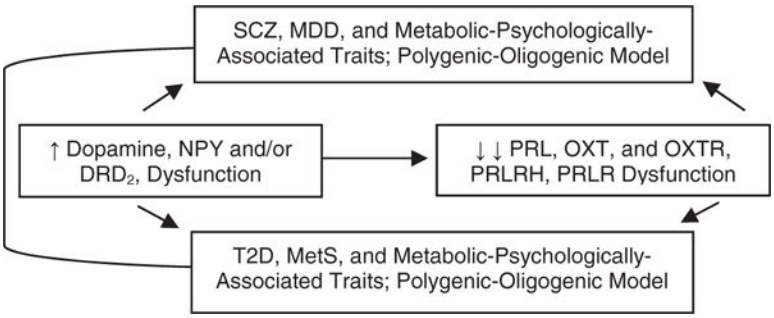

FIGURE 2.

Hypothesized relationship between increased dopamine, NPY, and/or DR_2 dysfunction, decreased PRL, OXT, and OXTR, PRLRH, PRLR dysfunction, and resultant SCZ, MDD, T2D, MetS, and metabolic-psychologically associated traits, and their comorbidity. SCZ, schizophrenia; MDD, major depressive disorder; T2D, type 2 diabetes; MetS, metabolic syndrome