BACE1-AS, *NAT-Rad18*, *17A*, *GDNFOS*).[172] Examples of miRNAs directly linked to AD pathogenesis include miR-34a (1p36.22), miR-34b/c (11q23.1), miR-107 (10q23.31), miR-124 (8p23.1/8p12.3/20q13.33), miR-125b (11q24.1/21q21.1), and miR-137 (1p21.3); and examples of epigenetically regulated miRNAs with targets linked to AD pathogenesis are let-7b (22q13.1), miR-9 (1q22/5q14.3/15q26.1), miR-132/212 (17p13.3), miR-146a (5q34), miR-148a (7p15.2), miR-184 (15q25.1), and miR-200 (miR-200b/200a/429, 1p36.33; miR-200c/141, 12p13.31).[171] AD-related SNPs interfere with miRNA gene regulation and affect AD susceptibility. The significant interactions include target SNPs present in seven genes related to AD prognosis with the miRNAs- miR-214, -23a & -23b, -486-3p, -30e*, -143, -128, -27a & -27b, -324-5p and -422a. The dysregulated miRNA network contributes to the aberrant gene expression in AD.[173–175]

5.5 Pharmacoepigenomics

Pharmacogenetics alone does not predict all phenotypic variation in drug response.[12,13] The genes involved in the pharmacogenomic network are under the regulatory control of the epigenetic machinery (DNA methylation, histone modifications, miRNA regulation), this configuring the novel pharmacoepigenomic apparatus.[12,13]

Epigenetic regulation is also responsible for the tissue-specific expression of genes involved in pharmacogenetic processes, and epigenetics plays a key role in the development of drug efficacy, safety and resistance. Epigenetic changes affect CYP expression, major transporter function, and nuclear receptor interactions.[176–179] Variable methylation patterns have been detected in genes encoding phase I–III enzymes (Table 5.4). Although this is a still poorly explored field, epigenetic regulation of genes encoding drug-metabolizing enzymes (*CYP1A1*, *1A2*, *1B1*, *1A6*, *2A13*, *2B6*, *2C8*, *2C9*, *2C18*, *2C19*, *2D6*, *2E1*, *2J2*, *2F1*, *2R1*, *2S1*, *2W1*, *3A4*, *3A5*, *3A7*, *3A43*, *UGT1*, *GSTP1*), drug transporters (*ABCB1*/*MDR1*/*P-gp*, *ABCC1*/*MRP1*, *ABCC11*/*MRP8*, *ABCG2*/*BCRP*, *SLC19A1*, *SLC22A8*), and nuclear receptors (*RARB2*, *ESR1*, *NR1I2*, *HNF41*) has been documented in pioneering studies of pharmacoepigenetics.[12,13,176–179]

Epigenetic modifications are also associated with drug resistance.[12,13,178,180] The acquisition of drug resistance is tightly regulated by post-transcriptional regulators such as RNA-binding proteins (RBPs) and miRNAs, which change the stability and translation of mRNA-encoding factors involved in cell survival, proliferation, epithelial–mesenchymal transition, and drug metabolism.[178] In the complex cascade of pharmacoepigenetic events, the epigenetic factory may act as a promiscuous, redundant security system in which several miRNAs target genes encoding epigenetic regulators. For example, miR-29, -29c, -370, and -450A target DNMT3A, and miR-29, -148, and -29b target DNMT3B, inducing hypomethylation and expression of tumor suppressor genes; let-7a, miR-26a, -101, -138, and -124 target EZH2, decreasing histone methylation and increasing expression of tumor suppressor genes; miR-449 and -874 target *HDAC1*, inducing growth arrest by decreasing histone