function and psychomotor function, respectively. Genomic, epigenomic, cerebrovascular, metabolic and environmental factors are potentially involved in the pathogenesis of most NDDs.[3] The age- and sex-related syndromic profiles of NDDs reflect, at least, a tetravalent phenotype: (i) a specific neuropathological component associated with each NDD; (ii) a neurobehavioral component: cognitive deterioration, behavioral changes, functional decline; (iii) an age-related biological component (directly-, indirectly-, and un-related biochemical, hematological and metabolic phenotypes); and (iv) gender-related phenotypes.[4–6] According to this heterogeneous, complex clinical picture, therapeutic intervention in most NDDs is polymodal in order to modify the expression of all these complex phenotypes.[7]

NDDs are age-dependent processes causing premature neurodegeneration many years before the onset of the disease. In this context, post-symptomatic intervention is of poor therapeutic value and less than 30% of patients respond moderately to conventional drugs in early stages of the disease.[8] Therefore, NDDs pose two major challenges to the scientific community: (i) the characterization and validation of specific biomarkers for the early identification of people at risk in susceptible populations; and (ii) the discovery and assessment of novel compounds with preventive activity and/or pharmacological properties able to halt disease progression at a pre-symptomatic stage.[8,9]

Major determinants of therapeutic outcome in NDDs include age- and sex-related factors, pathogenic phenotype, concomitant disorders, treatment modality and polypharmacy, and pharmacogenetics. Different categories of genes are potentially involved in the pharmacogenetic network responsible for drug efficacy and safety. Pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes represent the major genetic determinants of response to treatment in NDDs.[10–12] The expression of genes involved in the pharmacogenetic cascade is under the regulation of the epigenetic machinery. By-products of these genes are integrated in transcriptomic, proteomic and metabolic networks which are disrupted in NDDs and represent potential targets for therapeutic intervention (Figure 5.1).[9,11,13–16]

5.2 Age-Related Pheno-Genotypes

NDD-related polymorphic phenotypes (neuropathological, neurobehavioral, biochemical, hematological) require multifactorial interventions (combined treatments) in over 60–70% of the cases, this contributing to increasing the risk of ADRs and drug–drug interactions in these complex disorders.[17] For instance, AD patients present concomitant disorders including hypertension (20–30%), overweightness or obesity (20–40%), diabetes (20–25%), hypercholesterolemia (>40%), hypertriglyceridemia (20%); excess of urea (>80%), creatinine (6%) and uric acid (5%); alterations in transaminases (ASAT, ALAT, GGT) (>15%), alkaline phosphatase (14%), bilirubin (17%), and ions (>10%); deficits of iron (5%), ferritin (3%), folate (5%), and vitamin B_{12} (4%); thyroid dysfunction (5–7%), and reduced levels of RBC (3%), HCT (33%), and