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Review Article

Twin metabolomics: the key to unlocking complex phenotypes in nutrition research

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Twin studies are a valuable resource for studying phenotypes and their underlying biology. Heritability estimates based on the classic twin model show that genes influence human traits including health, diet, and food choice. Metabolomics is a promising tool in nutrition and health research where complex metabolite profiles reflect the metabolic effects of foods and diets as well as the biological pathways associated with diet-related diseases. In recent years, publications arising from twin research have incorporated metabolomic analysis, providing insights into genetic and environmental influences on metabolomic profiles. This article reviews the application of metabolomics in twin research with a particular focus on nutrition and diet-related diseases. The review begins by describing the classic twin study design, followed by a look at its application in nutrition research. Indeed, there is clear evidence for a genetic influence on dietary intake, regardless of the outcome measure: energy, macronutrients, dietary patterns, or food choice. The latter part of the review introduces metabolomic research showing how twin studies can separate aspects of the metabolome that are strongly influenced by genetics vs those that are more influenced by environment. The combination of metabolomics and twin research brings the promise of untangling gene-environment effects on complex phenotypes such as the metabolome, obesity, and diet-related diseases. For example, metabolomics is used in nutrition research to identify metabolites associated with particular dietary patterns. When combined within a twin study design, heritability of metabolite–dietary pattern associations can be established allowing further insight into complex gene-environment interactions that shape individual metabolomes.

1. Introduction

Twin studies provide a valuable resource for studying phenotypes and their underlying biology. Interindividual variation on heritable traits differs between monozygotic (MZ) and dizygotic (DZ) twins, providing the perfect platform for separating genetic and environmental influences. Indeed, classic twin studies have reported the proportion of variance

Abbreviations: BMI, body mass index; DZ, dizygotic; GC, gas chromatography; GSEM, genetic structural equation modeling; LC, liquid chromatography; MS, mass spectrometry; MZ, monozygotic; NMR, nuclear magnetic resonance; NTR, Netherlands Twin Registry.

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attributed to genes vs environment for a broad range of traits, from physical measurements such as body composition [1] to behavioral attributes such as physical activity or eating behaviors [2-4]. Since the introduction and widespread application of omics-based technologies, researchers have become increasingly interested in interindividual variation; in particular, what factors influence health status, disease development, and an individual's response to interventions. Metabolomics, which involves measuring the complete complement of metabolites, has been particularly influential in this respect. In fact, the concept of an individual metabolic phenotype or "metabotype" was coined with the introduction of metabolomics-based research [5,6]. Metabolomics has already proved its worth in nutrition research revealing the complex metabolic effects of foods and diets from observational and intervention studies, as well as identifying metabolite profiles and biological pathways associated with diet-related diseases [7]. Furthermore, the identification of metabotypes associated with lifestyle practices [8] and response to interventions [6] has changed how we approach data analysis in nutrition research and will ultimately impact nutrition recommendations.

One of the key questions to be addressed for metabolomics is to fully understand how genes, environmental factors, and their interactions influence metabotypes. Twins are naturally matched and share similar environments; therefore, twin studies offer unique opportunities to reduce the impact of potential confounders in nutrition research. In recent years, publications arising from twin research have begun to incorporate metabolomic analysis. This review will address the application of metabolomics in twin research with a particular focus on nutrition and diet-related diseases. English-language articles that report results from twin studies focused on nutrition, diet-related diseases, and metabolomics were obtained through searches in PubMed. The review will begin by describing the classic twin study design and its application in nutrition research and will finish by focusing specifically on studies that have incorporated metabolomic methodologies.

2. The classical twin design

Classically, twin research compares the phenotypic resemblance of MZ twin pairs to DZ twin pairs to estimate how much of the diversity of a phenotypic trait is a result of genetic differences [9]. Twin research is based on the knowledge that MZ twins originate from 1 zygote and subsequently inherit nearly identical genetic material, whereas DZ twins arise from 2 separate zygotes and share approximately 50% of their genes. The comparison of the twin intraclass correlation allows the analysis of phenotypes of interest, for example, weight or eye color. Phenotypes are the composite of a person's observable characteristics or traits [10] and are influenced by additive genetic effects (A), shared environmental effects (C), and nonshared environmental effects (E). This is the foundation of the ACE model, which is the input for genetic structural equation modeling (GSEM), a technique that obtains maximum likelihood estimates of variance components using twin data. Genetic structural equation modeling calculates the expected MZ and DZ covariances and compares the result to the covariances observed in the data to estimate the genetic and environmental influences causing phenotypic variation in a trait [11].

In general, twin studies focus on the additive genetic effect, which refers to the sum of those genetic effects that influence an individual's phenotype [12]. However, nonadditive genetic effects that result from interactions between alleles at a locus or among genes at different loci and that influence a phenotype can also be examined. The source of nonadditive genetic effects includes dominance, where 1 allele contributes as much as 2 of the same alleles or epistasis where alleles act differently depending on the presence of other alleles. Nonadditive genetic effects can be modeled when the MZ twin intraclass correlation is greater than twice the DZ twin intraclass correlation for a particular trait. When examining dietary intake, nonadditive genetic effects are demonstrated for some food groups. For example, Hasselbalch et al [13] reported nonadditive genetic effects for fat intake as well as some individual food groups, such as juice and eggs.

The twin design is based on 2 main assumptions: the first is the "equal environments assumption," which states that MZ and DZ twins share equally similar environments [14]. It means that greater similarity between MZ twins than DZ twins is due to a genetic influence. This assumption can be challenged by the fact that the postnatal environment is more similar for MZ twins than for DZ twins; however, researchers have demonstrated that early environmental differences are driven by "genetic influence" [15,16]. The Minnesota Study of Twins Reared Apart controlled for environmental treatment and found no major differences in phenotypes between MZ twins reared apart and MZ twins reared together, thus validating this assumption [17]. Another assumption is that twins are comparable to the general population and similar to singletons. Twin pregnancy is deemed higher risk than singleton pregnancy (particularly for MZ twins). As a result, differences in gestation and early life have been reported, including higher risk of premature labor and lower birth weight [18]. However, evidence exists to suggest that these disadvantages disappear by early to middle childhood [14]. Therefore, based on these assumptions and the genetic relatedness of twins, we can determine the influence of nature vs nurture on any trait.

Twin research is based on the foundation that all human traits are heritable and influenced by genetic differences [19]. Heritability is the amount of observed variation in a particular trait that can be attributed to inherited genetic factors rather than environmental factors. Some characteristics, such as height, are strongly influenced by genes; others such as personality traits are moderately influenced, whereas more complex heritability is a product of different genes affecting different aspects of 1 trait [19]. However, the role of environmental factors in determining phenotypic variation can also be demonstrated from twin research. For example, Pimpin et al [20] reported correlations of 0.96 and 0.93 for total energy intake for MZ and DZ twin children. The close correlation for both groups suggests that energy intake of children is strongly influenced by shared environment.