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Metabolic Differences in Monozygotic Twins: Evidence of Epigenetic Modulation in Lipid, Inflammatory and Hormonal Markers

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ABSTRACT

Monozygotic twins share identical genomes but frequently present relevant phenotypic differences throughout development. Such differences have been attributed to epigenetic mechanisms that modulate gene expression in response to environmental exposures. In this study, we analyzed 21 pairs (42 individuals) of monozygotic twins, evaluating intra-pair discrepancies in anthropometric, metabolic, hormonal, and lipid variables. After standardization, the largest differences were found in metabolic and lipid markers. The results strengthen the role of epigenetics in shaping phenotypic difference between genetically identical individuals.

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Introduction

Monozygotic twins share nearly 100% of their deoxyribonucleic acid (DNA) sequence and therefore constitute a unique natural model for disentangling the relative contributions of genetic inheritance and environmental influences on human phenotypes. Because they originate from a single fertilized ovum that subsequently splits, monozygotic twins are genetically almost identical at birth. This biological characteristic allows researchers to control for genomic variability when investigating complex traits, making twin studies a cornerstone in epidemiology, genetics, and systems biology.

Despite their shared genotype, monozygotic twins frequently exhibit marked phenotypic discordance across multiple domains, including metabolic regulation, hormonal balance, inflammatory responses, cognitive performance, and behavioral patterns. Such differences challenge the deterministic view of genetics and highlight the importance of gene-environment interactions. Increasing evidence suggests that these phenotypic differences are largely mediated by epigenetic mechanisms, which regulate gene expression without altering the underlying DNA sequence [1-5].

Key epigenetic processes include DNA methylation, histone modification, and the regulation of gene expression by non-coding ribonucleic acid (RNAs) such as microRNAs and long non-coding RNAs. These mechanisms are dynamic and responsive to environmental exposures across the lifespan, including nutrition, stress, physical activity, infections, and intrauterine conditions. Consequently, monozygotic twins provide an ideal framework for studying how environmental and stochastic factors shape biological variability through epigenetic modulation. Prior studies have demonstrated that epigenetic profiles diverge progressively with age, contributing to increasing phenotypic discordance over time [1-5].

Methods

Data were obtained from 21 pairs of monozygotic twins residing in Itapetininga, Brazil, representing a total sample of 42 individuals. The study population included both male and female participants across a range of ages, allowing for the assessment of variability across different life stages. All participants underwent standardized clinical and laboratory evaluations, including metabolic, lipid, inflammatory, and anthropometric measurements.

To enable comparability across variables with different scales and units, all numerical variables were standardized using z-scores. This normalization process ensured that each variable had a mean of zero and a standard deviation of one, allowing for direct comparison of effect sizes across different biological domains.

For each twin pair, the absolute intra-pair difference was calculated for every measured variable. This approach quantifies

the magnitude of discordance independently of direction, focusing on the extent of difference rather than which twin had higher or lower values. Summary statistics, including means, standard deviations, and ranges, were computed for all variables. Additionally, mean standardized intra-pair differences were calculated to identify which biological markers exhibited the greatest difference across twin pairs.

Sample Characteristics

The study sample consisted of 42 individuals forming 21 monozygotic twin pairs. Participants displayed a broad range of clinical and biochemical profiles, reflecting natural variability within the population. Anthropometric measures such as body mass index, weight, and height showed moderate dispersion, while laboratory markers demonstrated varying degrees of heterogeneity.

Table 1 presents the descriptive statistics for all numeric variables included in the analysis, including central tendency and dispersion measures. Overall, the sample reflects a heterogeneous but representative group, suitable for examining intra-pair variability. Importantly, no systematic bias was observed between co-twins at the population level, supporting the validity of intra-pair comparisons as a measure of difference rather than directional change.

Table 1: Descriptive Statistics of Main Variables

Variable	N	Mean	Standard Deviation	Min	Q1 Hip	Median	Max
ID number	42	272.238	155.273	45.000	149.250	266.500	430.750
Age	42	9.381	3.832	3.000	6.000	10.000	13.000
Weight	42	31.836	16.016	11.000	18.625	25.000	47.750
Height (m)	42	1.314	0.255	0.900	1.103	1.300	1.568
Waist	41	59.293	10.115	45.000	50.000	56.000	71.000
Hip	41	69.317	14.643	47.000	58.000	67.000	82.000
Head circumference	41	52.805	2.626	48.000	51.000	53.000	54.000
Birth weight	36	2459.444	512.021	1240.000	2137.500	2475.000	2712.500
Height at birth	35	46.429	2.468	40.000	45.000	47.000	48.000
Systolic blood pressure	41	93.049	11.983	70.000	90.000	90.000	100.000
Diastolic blood pressure	41	62.439	6.626	50.000	60.000	60.000	60.000
Total cholesterol	41	152.780	22.080	113.000	139.000	148.000	169.000
Low-density lipoprotein	41	91.537	18.032	56.000	81.000	89.000	105.000
High-density lipoprotein	41	46.610	9.038	34.000	41.000	44.000	50.000
Very-low-density lipoprotein	41	14.629	4.932	5.200	11.400	13.600	17.200
Triglycerides	41	73.146	24.660	26.000	57.000	68.000	86.000
Blood sugar	41	85.829	8.209	72.000	81.000	85.000	91.000
Uric acid	41	4.354	0.803	2.900	3.900	4.400	4.700
Fibrinogen	33	234.752	112.610	68.580	139.380	250.700	311.510
Apolipoprotein A	41	129.366	20.859	97.000	118.000	124.000	137.000
Apolipoprotein B	41	82.122	15.818	43.000	70.000	83.000	94.000
Body mass index	42	17.063	2.656	12.950	14.915	16.705	19.875
Renda per capita	42	148.421	105.938	24.000	70.000	129.200	182.200
Testosterone	16	120.812	135.712	16.000	34.000	40.000	246.250
Estradiol	25	51.904	36.860	19.000	28.000	42.000	60.000
Anti-low-density lipoprotein	39	0.337	0.090	0.170	0.285	0.330	0.370

Results

Following standardization and computation of intra-pair differences, substantial variability was observed across several biological domains. The highest discrepancies were identified in metabolic, inflammatory, and lipid-related markers. In particular, anti-low-density lipoprotein (LDL) antibodies, total cholesterol, fibrinogen levels, Apolipoprotein A, and LDL exhibited the greatest mean standardized intra-pair differences.

These findings indicate that even in genetically identical individuals, pathways related to lipid metabolism and systemic inflammation are highly susceptible to difference. Additional variability was also observed in high-density lipoprotein (HDL), very-low-density lipoprotein (VLDL), and Apolipoprotein B, although to a lesser extent.

Table 2 summarizes the mean standardized intra-pair differences for all variables, highlighting those with the highest levels of discordance. Notably, the distribution of differences was not uniform, suggesting that certain biological systems are more sensitive to environmental modulation than others. Anthropometric measures showed comparatively lower difference, whereas biochemical markers exhibited higher variability, reinforcing the role of dynamic regulatory processes.

Table 2: Standardized Intra-Pair Differences (Z-Scores)

Rank	Variable	Mean Standardized Difference
1	Anti-low-density lipoprotein	1.1523
2	Total cholesterol	0.8605
3	Fibrinogen	0.8373
4	Apoliprotein A	0.8078
5	Low-density lipoprotein	0.7792
6	High-density lipoprotein	0.7026
7	Blood sugar	0.6151
8	Apoliprotein B	0.6132
9	Estradiol	0.5648
10	Height at birth	0.5318
11	Birth weight	0.5239
12	Uric acid	0.4980
13	Triglycerides	0.4805
14	Very-low-density lipoprotein	0.4805
15	Diastolic blood pressure	0.3018
16	Body mass index	0.2936
17	Head circumference	0.2856
18	Testosterone	0.2674
19	Waist	0.1829
20	Hip	0.1741
21	Systolic blood pressure	0.1460
22	Height (m)	0.0971
23	Weight	0.0925
24	Renda per capita	0.0686
25	ID number	0.0092
26	Age	0.0000

Discussion

The present findings demonstrate that the largest intra-pair differences among monozygotic twins occur in biological variables that are strongly influenced by environmental exposures and epigenetic regulation. Lipid metabolism markers - including anti-LDL, total cholesterol, LDL, HDL, VLDL, Apolipoprotein A, and Apolipoprotein B - showed substantial difference, consistent with previous evidence indicating that hepatic lipid metabolism is highly responsive to dietary intake, physical activity, and metabolic stress.

Epigenetic modulation plays a central role in regulating genes involved in lipid transport, synthesis, and clearance. DNA methylation patterns in liver and adipose tissue, as well as histone modifications affecting transcriptional activity, have been shown to vary significantly even between genetically identical individuals. These differences can lead to altered expression of key metabolic genes, ultimately resulting in measurable phenotypic difference [2,3].

Inflammatory markers such as fibrinogen also demonstrated high variability, suggesting that immune and inflammatory pathways are similarly influenced by environmental and stochastic factors. Chronic low-grade inflammation is known to be modulated by lifestyle factors, including diet, stress, and exposure to pathogens, all of which may differ between twins over time.

Importantly, neonatal differences - including birth weight and birth length - were also observed and may represent early indicators of intrauterine asymmetry. Such differences are critical, as the intrauterine environment plays a fundamental role in shaping long-term epigenetic programming. Variations in placental function, nutrient availability, and fetal positioning can lead to differential gene expression patterns that persist into adulthood, a concept central to the developmental origins of health and disease hypothesis [1,4,5].

Over time, the accumulation of environmental exposures further amplifies these initial differences, leading to progressive difference in epigenetic profiles and associated phenotypes. This dynamic process underscores the importance of considering both early-life and lifelong influences when interpreting variability among monozygotic twins.

Conclusion

In conclusion, monozygotic twins exhibit significant metabolic and physiological difference despite their genetic identity. The magnitude and distribution of intra-pair discrepancies observed in this study strongly support the hypothesis that epigenetic mechanisms - shaped by both intrauterine conditions and postnatal environmental exposures - play a central role in driving phenotypic variation [1-5].

These findings reinforce the concept that genetic determinism alone is insufficient to explain human biological diversity. Instead, the interaction between genes and environment, mediated through epigenetic regulation, emerges as a key determinant of health and disease. Future research integrating longitudinal epigenetic profiling with environmental and clinical data will be essential to further elucidate the mechanisms underlying difference in monozygotic twins and to translate these insights into precision medicine approaches.

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None.

Conflicts of interest

No conflict of interest.

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