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Beyond Coronary Obstruction: Genome-Wide Copy Number Variation Profiling in MINOCA and Atherosclerotic Acute Coronary Syndrome

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Abstract

Background and Objectives: The genetic architecture underlying myocardial infarction with nonobstructive coronary arteries (MINOCA) remains incompletely understood. While genetic research in coronary artery disease has largely focused on individual variants and susceptibility loci, genome-wide structural genomic alterations have received limited attention. We aimed to characterize and compare copy number variation (CNV) profiles in patients with MINOCA and atherosclerotic acute coronary syndrome (ACS) using high-resolution molecular karyotyping. *Materials and Methods:* This observational study included 83 patients with myocardial infarction, comprising 39 with MINOCA and 44 with atherosclerotic ACS. Genome-wide molecular karyotyping was performed using the CytoScan HT-CMA 1000K chromosomal microarray platform (Thermo Fisher Scientific, Waltham, MA, USA). Genomic gains and losses were systematically characterized according to their chromosomal location, recurrence, and associated gene annotations, enabling a comprehensive comparison of structural genomic patterns between the two clinical phenotypes. *Results:* Genome-wide analysis identified 221 CNV events, including 109 in MINOCA and 112 in atherosclerotic ACS. Copy number gains accounted for 65 and 78 events, respectively, whereas losses accounted for 44 and 34 events. Recurrent alterations involved 17q21.31, 19p12, and 2q37.3, revealing shared structural genomic patterns across both phenotypes. Notably, distinct CNV regions were identified exclusively in MINOCA, including 6q24.1, 4q13.3, and 17q11.2, with the latter encompassing genes involved in inflammatory and cellular signaling pathways. Other recurrent alterations, including 8q24.13 and 16q21, were observed exclusively in atherosclerotic ACS. *Conclusions:* High-resolution genome-wide molecular karyotyping revealed a complex landscape of shared and distinct structural genomic alterations in MINOCA and atherosclerotic ACS. These findings highlight candidate genomic regions that may provide new insights into the biological heterogeneity of myocardial infarction and its underlying mechanisms.

Keywords: myocardial infarction with nonobstructive coronary arteries; acute coronary syndrome; copy number variation; molecular karyotyping

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1. Introduction

Myocardial infarction with nonobstructive coronary arteries (MINOCA) is an increasingly recognized clinical entity characterized by evidence of acute myocardial infarction in the absence of obstructive coronary artery disease on coronary angiography. Although MINOCA accounts for a minority of acute myocardial infarction presentations, it represents a heterogeneous syndrome encompassing several potential mechanisms, including coronary vasospasm, coronary microvascular dysfunction, coronary thromboembolism, and disruption of nonobstructive atherosclerotic plaques. Hence, the underlying mechanisms of MINOCA are often difficult to establish, creating challenges in diagnosis, risk stratification, and individualized treatment [1].

Despite differences in coronary anatomy and clinical presentation, MINOCA and atherosclerotic acute coronary syndrome (ACS) share several pathophysiological processes, including endothelial dysfunction, inflammation, oxidative stress, and vascular injury. Previous investigations have demonstrated differences in clinical characteristics, biomarker profiles, and cardiovascular risk factors between these populations [2]. Nevertheless, the extent to which these distinct myocardial infarction phenotypes share underlying genetic determinants remains incompletely understood. Identifying genomic alterations associated with these clinical presentations may provide additional insight into their biological heterogeneity [3].

Genetic investigations of coronary artery disease and myocardial infarction have predominantly focused on single-nucleotide variants, common genetic susceptibility loci, and polygenic risk. However, genome-wide molecular karyotyping using chromosomal microarray technology enables the detection of submicroscopic genomic gains and losses that may not be identified through conventional cytogenetic approaches [4,5]. Copy number variations (CNVs), including genomic deletions and duplications, can affect gene dosage, disrupt regulatory regions, and influence gene expression [6]. Depending on their location and genomic context, these alterations may involve genes participating in inflammatory responses, lipid metabolism, oxidative stress regulation, vascular homeostasis, and cellular signaling, all of which are potentially relevant to cardiovascular disease [7,8]. Although CNVs have been investigated in several cardiovascular conditions, comparative evidence concerning their distribution in MINOCA and atherosclerotic ACS remains limited.

Unlike comparisons with healthy controls, which primarily investigate the enrichment of genetic variants in disease populations, comparing MINOCA with atherosclerotic ACS enables the exploration of shared and distinct structural genomic patterns across two clinical phenotypes of myocardial infarction. Accordingly, the present study aimed to characterize and compare genome-wide CNV profiles in patients with MINOCA and atherosclerotic ACS using high-resolution molecular karyotyping. Given the limited sample size and exploratory nature of the study, the identification of shared and potentially phenotype-associated CNV patterns was intended to generate preliminary hypotheses regarding the possible role of structural genomic variation in the heterogeneity of myocardial infarction, rather than to establish disease-specific genetic susceptibility or causal relationships.

2. Materials and Methods

2.1. Study Design and Population

This observational, cross-sectional study was conducted in collaboration between the Departments of Cardiology and Medical Genetics. Patients were consecutively recruited between March 2024 and May 2025 according to predefined clinical eligibility criteria. Coronary angiography was performed in all participants, and coronary stenosis severity was determined by visual angiographic assessment. The study included 83 adult patients (≥18 years) who presented with suspected acute coronary syndrome, fulfilled the diagnostic

criteria for acute myocardial infarction according to the Fourth Universal Definition of Myocardial Infarction, underwent coronary angiography, and had successfully completed chromosomal microarray analyses [9].

No patients underwent cardiac magnetic resonance imaging. Optical coherence tomography (OCT) and intravascular ultrasound (IVUS) were unavailable at our institution and were therefore not performed. Alternative diagnoses, including myocarditis and Takotsubo syndrome, were evaluated using the available clinical, electrocardiographic, laboratory, and echocardiographic findings. However, the absence of advanced imaging prevented definitive etiological characterization in all patients. Patients meeting the predefined exclusion criteria were not enrolled. Because a comprehensive screening log was not maintained, the total numbers of screened and excluded patients could not be reliably determined retrospectively.

Acute myocardial infarction was defined as a rise and/or fall in cardiac troponin concentrations, with at least one value exceeding the 99th percentile upper reference limit, accompanied by clinical evidence of myocardial ischemia. Patients were classified into two groups based on clinical presentation, electrocardiographic findings, serial cardiac troponin measurements, and coronary angiographic findings: 39 patients with MINOCA and 44 patients with ACS. MINOCA was defined as acute myocardial infarction in the absence of obstructive coronary artery disease, characterized by <50% luminal stenosis in all major epicardial coronary arteries. Alternative causes of myocardial injury, including myocarditis, Takotsubo syndrome, and other nonischemic conditions, were evaluated according to available clinical, laboratory, and imaging findings. Additional diagnostic investigations were performed when clinically indicated and available. The atherosclerotic ACS group consisted of patients with acute myocardial infarction and angiographically documented obstructive coronary artery disease (≥50% luminal stenosis) [9].

Exclusion criteria included procedure-related coronary complications (such as coronary dissection, coronary rupture, or acute stent thrombosis), previous cardiovascular surgery, end-stage renal or hepatic disease, malignancy, previous chemotherapy or radiotherapy, collagen vascular diseases, previous cerebrovascular events, endocrine disorders, active or chronic inflammatory diseases, moderate-to-severe valvular heart disease, Takotsubo cardiomyopathy, pulmonary embolism, and central nervous system disorders. Patients without elevated cardiac biomarkers or those who did not undergo coronary angiography were also excluded.

2.2. Clinical and Laboratory Assessments

Demographic characteristics, cardiovascular risk factors, medical history, and clinical findings were obtained from patient assessments and hospital medical records. Cardiac troponin levels were measured as part of routine clinical evaluation at hospital admission and repeated when clinically indicated. The highest recorded troponin concentration during hospitalization was defined as the peak troponin value and used for statistical comparisons.

Transthoracic echocardiography was performed to evaluate left ventricular systolic function. Left ventricular ejection fraction (LVEF) was calculated using the modified biplane Simpson's method from apical four- and two-chamber views.

2.3. Blood Sampling and Genomic DNA Isolation

Approximately 5 mL of peripheral venous blood was collected from each participant into ethylenediaminetetraacetic acid (EDTA)-containing tubes using standard venipuncture techniques. Samples were transported to the laboratory under appropriate conditions and stored at −80 °C until DNA extraction. Genomic DNA was isolated using commercially available DNA extraction kits(QIAGEN, Hilden, Germany) in accordance with the manufac-

turer's instructions. DNA concentration and purity were assessed spectrophotometrically, and samples meeting the laboratory's quality requirements were selected for molecular karyotyping. DNA purity was evaluated using the A260/A280 absorbance ratio, with an acceptable range of 1.8–2.0. DNA integrity and suitability for microarray analysis were assessed according to the laboratory's established quality-control procedures.

2.4. Genome-Wide Molecular Karyotyping and CNV Detection

Genome-wide copy number variation (CNV) analysis was performed using the CytoScan HT-CMA 1000K chromosomal microarray platform(Thermo Fisher Scientific, Waltham, MA, USA), a high-resolution SNP-based array designed for the simultaneous assessment of genomic copy number alterations and single-nucleotide polymorphisms. The platform provides genome-wide coverage with approximately 1.1 million genomic markers, including approximately 1 million SNP probes and 130,000 non-polymorphic probes, with an average probe spacing of less than 4 kb. DNA samples were processed and scanned using the Applied Biosystems GeneTitan MC Instrument(Thermo Fisher Scientific, Waltham, MA, USA).

Genomic data were analyzed using Chromosome Analysis Suite (ChAS), version 4.5(Thermo Fisher Scientific, Waltham, MA, USA), with the GRCh38/hg38 human reference genome assembly and the software's default CNV-calling parameters. Microarray quality control was performed according to the manufacturer's recommendations and the laboratory's established procedures. Sample-level quality assessment included the evaluation of SNP quality control (SNPQC) and median absolute pairwise difference (MAPD) metrics, with acceptance thresholds of $\geq$15.0 and $\leq$0.25, respectively. CNV detection was performed using the intrinsic calling criteria implemented in ChAS, without additional post-calling filtering based on CNV size, probe count, OMIM gene content, or clinical pathogenicity classification. This approach was adopted to preserve the exploratory characterization of genome-wide CNV-event distributions.

Molecular karyotyping was used to identify genomic copy number losses (microdeletions) and gains (microduplications) across the genome. For each detected CNV, the chromosome, cytogenetic location, copy number state (gain or loss), approximate genomic size, marker count, and associated gene annotations were recorded where available [10]. Detected CNVs were subsequently organized according to chromosome, cytogenetic region, and copy number state to identify recurrent alterations, regions shared between the two clinical groups, and regions observed exclusively in either MINOCA or atherosclerotic acute coronary syndrome (ACS).

Gene annotations were obtained from the microarray analysis outputs and interpreted using available genomic annotation resources, including OMIM and other established genomic databases. Because systematic breakpoint-level reassessment of individual CNVs against gene coordinates was not performed, the reported gene annotations were interpreted as regional genomic associations rather than definitive evidence of complete or partial gene disruption. Similarly, the identification of a CNV within a particular genomic region was not considered sufficient to establish its pathogenicity or a causal relationship with either clinical phenotype. A total of 221 CNV events were included in the final genomic dataset, comprising 109 events in 39 patients with MINOCA and 112 events in 44 patients with atherosclerotic ACS. All detected CNV events meeting the software's intrinsic calling criteria were retained for descriptive analysis. CNV-event distributions were summarized separately from patient-level CNV burden to distinguish the total number of genomic alterations from their distribution across individual participants.

2.5. Bioinformatic Annotation and Classification of CNVs

Detected CNVs were characterized according to their chromosomal distribution, cytogenetic location, direction of copy number change, genomic length, and associated gene annotations. Regions were grouped by chromosome, cytogenetic band, and CNV type to facilitate the identification of recurrent genomic alterations. For comparative purposes, CNV regions were classified into three categories: regions observed in both patient groups, regions detected only in the MINOCA group, and regions detected only in the atherosclerotic ACS group. Recurrent regions were defined as chromosomal region–CNV type combinations represented by more than one recorded CNV event. Gains and losses involving the same cytogenetic region were analyzed separately.

Particular attention was given to recurrent CNVs and regions containing genes with potential relevance to cardiovascular biological processes, including inflammation, vascular regulation, endothelial function, oxidative stress, and cellular signaling. Gene-level annotations were obtained from the available chromosomal microarray analysis outputs. Genes associated with individual CNV regions were recorded according to the annotations provided in the genomic analysis dataset. Because systematic breakpoint-level matching was not performed, gene annotations were interpreted as regional genomic associations rather than definitive evidence of complete or partial gene disruption.

2.6. Literature-Based Annotation of Recurrent CNV Regions

Literature-based annotation indicated that several recurrent CNV regions identified in the study cohort, including loci associated with KANSL1, GSTT1, UGT2B17, CCL3L1, and the CFH/CFHR gene cluster, have previously been reported to exhibit substantial structural variation across human populations. However, direct equivalence between published variants and the CNVs detected in our cohort could not be established because genomic coordinates and breakpoints were not systematically matched. Accordingly, these findings were considered contextual rather than evidence of disease-associated genomic alterations.

2.7. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous clinical variables were expressed as mean ± standard deviation or median with interquartile range (IQR), as appropriate, while categorical variables were presented as frequencies and percentages. Between-group comparisons of continuous clinical variables were performed using the Mann–Whitney U test, whereas categorical clinical variables were compared using Fisher's exact test. For these clinical analyses, the individual patient was the unit of observation. All clinical statistical tests were two-sided, and a p-value of <0.05 was considered statistically significant.

Genomic analyses were conducted using the finalized and verified dataset. All CNV events were definitively linked to their corresponding participants through the original molecular karyotyping records and patient identifiers. The final dataset comprised 221 CNV events identified in 83 patients, with no unmatched CNV records. Genomic findings were summarized descriptively at the CNV-event level. The total numbers of CNV events, copy number gains, and copy number losses were calculated separately for each clinical group. Aggregate CNV events per enrolled patient were calculated by dividing the number of recorded events by the corresponding group size. CNV size, marker count, OMIM-annotated gene content, and recurrent chromosomal regions were summarized using counts, percentages, and medians with interquartile ranges, as appropriate. Because multiple CNV events could originate from the same participant, event-level observations were not treated as statistically independent. Accordingly, no inferential statistical tests were applied to CNV-event-level comparisons. These genomic findings were interpreted as

descriptive and hypothesis-generating rather than as evidence of statistically established phenotype-specific associations.

2.8. Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. Patient recruitment and blood sample collection were performed under the approval of the local Clinical Research Ethics Committee (approval no. 2024/72, dated 28 March 2024). Subsequent genomic analyses of the stored blood samples were conducted under a separate ethics committee approval (approval no. 2025/161, dated 17 April 2025). Written informed consent was obtained from all participants in accordance with the applicable approved protocols.

3. Results

3.1. Baseline Demographic and Clinical Characteristics

A total of 83 patients were included in the study, comprising 39 patients with MINOCA and 44 patients with atherosclerotic ACS. Baseline demographic, clinical, and laboratory characteristics are summarized in Table 1.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population.

Characteristic	MINOCA ($n = 39$)	ACS ($n = 44$)	Overall ($n = 83$)	p-Value
Age, years	58.0 [51.0–65.0]	65.0 [59.8–70.2]	61.0 [55.0–69.5]	0.003
Male sex, *n* (%)	23 (59.0)	34 (77.3)	57 (68.7)	0.098
Hypertension, *n* (%)	22 (56.4)	23 (52.3)	45 (54.2)	0.826
Diabetes mellitus, *n* (%)	9 (23.1)	15 (34.1)	24 (28.9)	0.335
Current smoking, *n* (%)	12 (30.8)	24 (54.5)	36 (43.4)	0.045
Dyslipidemia, *n* (%)	7 (17.9)	8 (18.2)	15 (18.1)	1.000
Previous coronary artery disease, *n* (%)	4 (10.3)	16 (36.4)	20 (24.1)	0.009
LVEF, %	60.0 [60.0–60.0]	53.0 [43.0–60.0]	60.0 [50.0–60.0]	<0.001
Peak troponin, ng/L	855 [145–4222]	14,417 [4302–25,000]	4492 [771–21,865]	<0.001
CRP, mg/L	5.8 [4.2–6.7]	6.9 [2.4–12.6]	5.9 [3.1–10.6]	0.970
LDL cholesterol, mg/dL	126 [96–177]	126 [106–162]	126 [100–167]	0.813
HDL cholesterol, mg/dL	41.0 [34.8–51.5]	39.7 [34.0–47.7]	40.4 [34.1–48.6]	0.460
Creatinine, mg/dL	0.8 [0.7–1.0]	0.8 [0.7–1.0]	0.8 [0.7–1.0]	0.661

Table note: Data are presented as median [interquartile range] or *n* (%), as appropriate. Continuous variables were compared using the Mann–Whitney U test and categorical variables using Fisher's exact test. Abbreviations: ACS, acute coronary syndrome; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MINOCA, myocardial infarction with nonobstructive coronary arteries.

Patients with MINOCA were significantly younger than those with atherosclerotic ACS (median age, 58.0 [51.0–65.0] vs. 65.0 [59.8–70.2] years; $p = 0.003$). Current smoking (30.8% vs. 54.5%; $p = 0.045$) and previous coronary artery disease (10.3% vs. 36.4%; $p = 0.009$) were less frequent in the MINOCA group. The proportion of male patients was numerically lower in MINOCA, although the difference was not statistically significant (59.0% vs. 77.3%; $p = 0.098$).

Left ventricular ejection fraction was higher in patients with MINOCA than in those with atherosclerotic ACS (60.0 [60.0–60.0]% vs. 53.0 [43.0–60.0]%; $p < 0.001$), whereas peak troponin levels were substantially lower (855 [145–4222] vs. 14,417 [4302–25,000] ng/L; $p < 0.001$). No statistically significant differences were observed in the prevalence of hypertension, diabetes mellitus, or dyslipidemia, or in C-reactive protein, lipid parameters, and serum creatinine levels (all $p > 0.05$).

3.2. Overall CNV Burden and Distribution

A total of 221 copy number variation (CNV) events were identified across the study population, including 109 events in the MINOCA group and 112 events in the atherosclerotic ACS group. Overall, 143 events (64.7%) were copy number gains and 78 (35.3%) were losses. Detailed event-level characteristics of the identified CNVs, including chromosomal and cytogenetic locations, copy number states, genomic sizes, marker counts, and available gene annotations, are presented in Supplementary Table S2.

The aggregate number of CNV events per enrolled patient was 2.79 in the MINOCA group and 2.55 in the atherosclerotic ACS group. Copy number gains accounted for 65 events (59.6%) in MINOCA and 78 events (69.6%) in atherosclerotic ACS, corresponding to 1.67 and 1.77 gain events per enrolled patient. In contrast, copy number losses accounted for 44 events (40.4%) in MINOCA and 34 events (30.4%) in atherosclerotic ACS, corresponding to 1.13 and 0.77 loss events per enrolled patient.

Copy number gains were proportionally more frequent in atherosclerotic ACS and losses were proportionally more frequent in MINOCA. These findings suggest descriptive differences in CNV event distribution without establishing statistically significant differences in patient-level genomic burden (Table 2).

Table 2. Copy Number Variation Burden, Size, and Gene Content in MINOCA and Atherosclerotic ACS.

Characteristic	MINOCA (n = 39)	ACS (n = 44)	Overall
Total CNV events, n	109	112	221
Copy number gains, n (%)	65 (59.6)	78 (69.6)	143 (64.7)
Copy number losses, n (%)	44 (40.4)	34 (30.4)	78 (35.3)
Total CNV events per patient	2.79	2.55	2.66
Gain events per patient	1.67	1.77	1.72
Loss events per patient	1.13	0.77	0.94
CNV size, kb, median [IQR]	149.3 [118.4–230.3]	159.2 [124.3–278.3]	—
Marker count per CNV, median [IQR]	44 [28–56]	48 [32.75–77.5]	—
OMIM genes per CNV, median [IQR]	1 [0–2]	1 [1–2]	—
CNVs containing ≥ 1 OMIM gene, n (%)	69 (63.3)	89 (79.5)	158 (71.5)
Total CNVs per patient, median (IQR)	3 (1.5–4)	2 (1–4)	2 (1–4)
CNV gains per patient, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)
CNV losses per patient, median (IQR)	1 (0–2)	0.5 (0–1)	0.5 (0–1)

Table note: Data are presented as CNV-event counts, percentages, aggregate events per enrolled patient, or median [interquartile range (IQR)], as appropriate. Percentages were calculated using the total number of CNV events within each group (109 for MINOCA and 112 for ACS). Aggregate CNV events per patient were calculated by dividing the total number of CNV events by the number of enrolled patients in each group. All CNV records were linked to their corresponding participants in the verified final dataset. CNV-event-level comparisons are descriptive; no inferential statistical tests were applied to these comparisons. Abbreviations: ACS, acute coronary syndrome; CNV, copy number variation; IQR, interquartile range; MINOCA, myocardial infarction with nonobstructive coronary arteries; OMIM, Online Mendelian Inheritance in Man.

In addition, the median CNV size was 149.3 kb (IQR, 118.4–230.3) in MINOCA and 159.2 kb (IQR, 124.3–278.3) in atherosclerotic ACS. The median number of markers per CNV was 44 (IQR, 28–56) and 48 (IQR, 32.75–77.5). The median number of OMIM-annotated

genes per CNV was 1 (IQR, 0–2) in MINOCA and 1 (IQR, 1–2) in atherosclerotic ACS. At least one OMIM-annotated gene was present in 69 CNV events (63.3%) in MINOCA and 89 events (79.5%) in atherosclerotic ACS. The sizes and gene annotations of selected recurrent CNV regions are presented in Supplementary Table S1.

3.3. Shared and Recurrent CNV Regions

The distribution of recurrent CNV regions according to chromosomal location and copy number status is presented in Table 3. The most frequently recorded region was 17q21.31 gain, accounting for 23 events (10.41% of all CNV events), including 7 in MINOCA and 16 in atherosclerotic ACS. This was followed by 19p12 loss (22 events; 12 in MINOCA and 10 in ACS) and 2q37.3 loss (17 events; 10 in MINOCA and 7 in ACS).

Table 3. Shared and Recurrent Copy Number Variation Regions in MINOCA and Atherosclerotic ACS.

Chromosomal Region	CNV Type	MINOCA (109 Events), *n* (%)	ACS (112 Events), *n* (%)	Overall (221 Events), *n* (%)
17q21.31	Gain	7 (6.42)	16 (14.29)	23 (10.41)
19p12	Loss	12 (11.01)	10 (8.93)	22 (9.95)
2q37.3	Loss	10 (9.17)	7 (6.25)	17 (7.69)
16p11.2–p11.1	Gain	2 (1.83)	4 (3.57)	6 (2.71)
8q24.23	Loss	4 (3.67)	1 (0.89)	5 (2.26)
10q26.3	Gain	1 (0.92)	4 (3.57)	5 (2.26)
10p11.1	Gain	1 (0.92)	3 (2.68)	4 (1.81)
6q24.1	Loss	3 (2.75)	0 (0.00)	3 (1.36)
22q11.23–q12.1	Loss	2 (1.83)	1 (0.89)	3 (1.36)

Table note: Data are presented as CNV-event counts and percentages. Percentages were calculated using the total number of CNV events in each group (109 for MINOCA, 112 for ACS, and 221 overall), rather than the number of patients. Regions were categorized according to chromosomal location and CNV type. These findings represent descriptive event-level distributions and should not be interpreted as statistically established phenotype-specific associations. Abbreviations: ACS, acute coronary syndrome; CNV, copy number variation; MINOCA, myocardial infarction with nonobstructive coronary arteries.

Other recurrent regions included 16p11.2–p11.1 gain (2 vs. 4 events), 8q24.23 loss (4 vs. 1 event), 10q26.3 gain (1 vs. 4 events), and 10p11.1 gain (1 vs. 3 events) in MINOCA and atherosclerotic ACS, respectively. Losses involving 22q11.23–q12.1 were also identified in both groups (2 vs. 1 event).

Although gains involving 17q21.31 were numerically more frequent in atherosclerotic ACS and losses involving 8q24.23 were more frequent in MINOCA, these patterns were descriptive and did not establish region-specific associations with either clinical phenotype.

3.4. Group-Exclusive CNV Regions

Several recurrent CNV regions were observed exclusively in one clinical group within the study cohort (Table 4). Among patients with MINOCA, losses involving 6q24.1 were recorded in three events and were not observed in the atherosclerotic ACS group. Additional MINOCA-exclusive regions, each represented by two events, included gains at 4q13.3, 10q21.1, 17q11.2, and Xp22.31, as well as losses at 7p12.1. Annotated genes within these regions included COX18 and ANKRD17 at 4q13.3, CCL3L1 and KSR1 at 17q11.2, and PUDP at Xp22.31.

In contrast, three recurrent regions were observed exclusively in the atherosclerotic ACS group, each represented by two events: gains at 8q24.13 and 16q21 and losses at 10p12.1. Representative gene annotations included FAM83A at 8q24.13 and PTCHD3 at 10p12.1.

Table 4. CNV Regions Detected Exclusively in MINOCA or Atherosclerotic ACS.

Chromosomal Region	CNV Type	Representative Genes	MINOCA (109 Events), *n* (%)	ACS (112 Events), *n* (%)	Overall (221 Events), *n* (%)
6q24.1	Loss	—	3 (2.75)	0 (0.00)	3 (1.36)
4q13.3	Gain	COX18, ANKRD17	2 (1.83)	0 (0.00)	2 (0.90)
7p12.1	Loss	—	2 (1.83)	0 (0.00)	2 (0.90)
10q21.1	Gain	—	2 (1.83)	0 (0.00)	2 (0.90)
17q11.2	Gain	CCL3L1, KSR1	2 (1.83)	0 (0.00)	2 (0.90)
Xp22.31	Gain	PUDP	2 (1.83)	0 (0.00)	2 (0.90)
8q24.13	Gain	FAM83A	0 (0.00)	2 (1.79)	2 (0.90)
10p12.1	Loss	PTCHD3	0 (0.00)	2 (1.79)	2 (0.90)
16q21	Gain	ESB3, LIPB	0 (0.00)	2 (1.79)	2 (0.90)

Table note: Data are presented as CNV event counts and percentages calculated relative to the total number of CNV events in each group. Only regions with at least two events in one group and none in the other are displayed. A dash indicates unavailable gene annotation. Abbreviations: ACS, acute coronary syndrome; CNV, copy number variation; MINOCA, myocardial infarction with nonobstructive coronary arteries.

4. Discussion

The present study provides an exploratory, genome-wide characterization of structural genomic variation in patients with MINOCA and atherosclerotic ACS. Three principal descriptive observations emerged. First, the aggregate CNV-event burden was numerically similar between the groups, although differences in the relative distribution of gains and losses were observed. Second, several recurrent chromosomal regions were identified in both groups, while other regions were recorded exclusively in one clinical group within the study cohort. Third, a greater proportion of CNV events in atherosclerotic ACS contained at least one OMIM-annotated gene; however, this observation reflects an event-level distribution and does not establish a difference in patient-level carrier prevalence. These findings describe overlapping and potentially differing structural genomic patterns across two myocardial infarction populations. They should not be interpreted as evidence of independent phenotype-specific genetic susceptibility, functional genomic effects, or causal mechanisms.

An important strength of this study was the application of high-resolution genome-wide molecular karyotyping rather than an analysis restricted to selected genes or polymorphisms. This approach enabled the characterization of CNV frequency, chromosomal distribution, physical size, and gene content. Although CNV size and the number of OMIM-annotated genes per event were broadly comparable between groups, a greater proportion of CNV events in atherosclerotic ACS contained at least one OMIM-annotated gene. This finding may indicate differences in the genomic content of structural alterations but should be interpreted cautiously because the event-based analysis did not account for multiple CNVs originating from the same patient. Moreover, the presence of an annotated gene within a CNV does not necessarily imply functional disruption or pathogenicity. Genome-wide CNV profiling therefore provides complementary information for exploring structural genetic variation, particularly in clinically heterogeneous conditions such as MINOCA, while remaining limited in its ability to detect single-nucleotide variants and balanced rearrangements. However, differences in age, smoking status, previous coronary artery disease, left ventricular ejection fraction, and peak troponin levels between the two groups should be considered when interpreting these genomic observations. Given the observational design and the absence of adjusted genomic analyses, potential confounding and selection

effects cannot be excluded, and the observed CNV distributions should not be attributed independently to myocardial infarction phenotype.

The possibility of a distinct genetic contribution to MINOCA represents an important consideration in understanding its heterogeneous pathophysiology. Unlike atherosclerotic ACS, in which inherited susceptibility interacts with established cardiovascular risk factors and progressive coronary atherosclerosis [5], MINOCA encompasses several mechanisms that may occur without significant epicardial coronary obstruction. This raises the hypothesis that genetic alterations affecting vascular reactivity, endothelial function, inflammation, or microvascular regulation could contribute to selected MINOCA phenotypes [11]. However, our findings did not demonstrate a greater overall CNV burden in MINOCA compared with atherosclerotic ACS. Moreover, although these regions were observed exclusively in one clinical group within the present cohort, their absence from the other group does not establish disease specificity. Given the limited sample size and lack of an independent validation cohort, these observations may reflect chance variation, population-specific structural polymorphisms, technical factors, or differences in the clinical composition of the study groups. Therefore, these regions should be regarded as exploratory genomic observations requiring replication rather than as established or candidate diagnostic markers for either myocardial infarction phenotype.

Among the recurrent regions, 17q21.31 gains and losses involving 19p12 and 2q37.3 were particularly prominent. Gains involving 17q21.31 were recorded more frequently in atherosclerotic ACS, whereas 19p12 and 2q37.3 losses were observed in both groups. The 17q21.31 locus is characterized by a complex genomic architecture involving inversion-associated haplotypes and segmental duplications, including structural polymorphisms affecting KANSL1. Previous investigations have demonstrated substantial ancestry-dependent variation in KANSL1 duplication haplotypes, indicating that recurrent gains within this region may represent common inherited structural variants rather than alterations specifically related to atherosclerotic disease [12]. Similarly, the recurrence of 19p12 and 2q37.3 losses in both clinical groups suggests overlapping regional CNV patterns, although shared cytogenetic localization does not necessarily imply identical genomic alterations or biological consequences. Importantly, the interpretation of these recurrent CNV regions is constrained by the absence of ancestry-matched healthy controls and systematic breakpoint-level comparisons. Consequently, it remains uncertain whether the alterations identified in our cohort correspond to previously described common structural polymorphisms or represent distinct genomic events. Similar cytogenetic localization does not necessarily indicate identical genomic boundaries, gene dosage effects, or biological consequences. Therefore, population-genetic evidence should be considered primarily as an interpretative framework, rather than as direct evidence of disease-related genomic alterations.

The potential relevance of inflammatory pathways should also be considered in the context of established clinical observations following myocardial infarction. Matyas et al. reported that elevated systemic inflammatory biomarkers, particularly high-sensitivity C-reactive protein and interleukin-6, were associated with higher NT-proBNP levels during the acute phase of myocardial infarction, highlighting the relationship between inflammation and post-infarction ventricular dysfunction [13]. These findings provide clinical context for considering inflammation-related biological pathways in cardiovascular disease. Several CNV regions were identified exclusively in one clinical group. In MINOCA, these included alterations involving 6q24.1, 4q13.3, 7p12.1, 10q21.1, 17q11.2, and Xp22.31, whereas alterations involving 8q24.13, 10p12.1, and 16q21 were observed exclusively in atherosclerotic ACS. Certain regions were annotated with genes potentially relevant to cardiovascular biology. For example, CCL3L1 participates in inflammatory signaling and leukocyte recruit-

ment, while KSR1 is involved in intracellular signaling pathways [14,15]. Such biological functions may be relevant to vascular inflammation and endothelial regulation, although the presence of these genes within an affected region does not establish altered expression or a causal contribution to myocardial infarction. These group-exclusive findings may help identify candidate genomic regions for further investigation, but their occurrence in only one clinical group should not be interpreted as evidence of disease specificity.

The interpretation of these findings requires consideration of the extensive structural genomic diversity observed across human populations. Several loci identified in our cohort, including KANSL1, GSTT1, UGT2B17, CCL3L1, and the CFH/CFHR gene cluster, have previously been associated with substantial population-dependent variation. GSTT1 is involved in glutathione-dependent detoxification, whereas UGT2B17 participates in glucuronidation and the metabolism of endogenous compounds [16,17]. CCL3L1 is involved in chemokine-mediated inflammatory signaling, while the CFH/CFHR gene family contributes to regulation of the complement system [18,19]. These pathways are biologically relevant to cardiovascular disease, particularly oxidative stress, vascular inflammation, and endothelial injury. However, the established structural variability of these loci indicates that their recurrence in a clinical cohort may reflect common inherited polymorphisms rather than disease-associated genomic alterations.

Published population studies have demonstrated marked geographical differences in GSTT1 null-genotype prevalence, UGT2B17 deletion polymorphisms, CCL3L1 copy number, and CFHR3/CFHR1 deletion frequencies. Notably, CCL3L1 copy numbers differ substantially across European, Asian, and African populations, while structural variation within the CFH/CFHR cluster also exhibits considerable ancestry-dependent variability [16–19]. These observations highlight the importance of population background when interpreting genomic findings. Furthermore, several previously reported population frequencies concern deletions or null genotypes, whereas corresponding alterations in our cohort included gains. For other recurrent regions, including 19p12, 2q37.3, 6q24.1, and 8q24.23, directly comparable population frequencies were not established. Therefore, the available population-genetic evidence provides an interpretative framework but cannot establish equivalence between previously reported structural variants and the CNVs identified in our patients.

From a clinical perspective, the present findings support further investigation of structural genomic variation as a potential contributor to the heterogeneity of myocardial infarction. Although the study did not demonstrate a greater overall CNV burden in MINOCA, the identification of recurrent and group-exclusive regions raises the possibility that specific genomic alterations, rather than the total number of CNVs, may be relevant to different ischemic mechanisms. Future studies incorporating larger cohorts, ancestry-matched healthy controls, detailed MINOCA phenotyping, and functional genomic analyses may help determine whether particular CNVs influence coronary vasomotor function, endothelial responses, inflammatory pathways, or susceptibility to myocardial injury. Such investigations are necessary before structural genomic findings can be incorporated into clinical risk assessment or precision cardiovascular medicine.

Study Limitations

Several limitations should be acknowledged. Advanced diagnostic investigations, including cardiac magnetic resonance imaging and intracoronary imaging, were not systematically performed in all patients with MINOCA. Therefore, MINOCA should be regarded as a working diagnosis rather than an etiologically confirmed diagnosis, and potential diagnostic misclassification cannot be excluded. In addition, the relatively small, single-center cohort limited statistical power and generalizability, while the absence of a healthy and

ancestry control group prevented assessment of CNV enrichment relative to the general population. Differences in baseline clinical characteristics between groups may also have influenced the observed patterns. Furthermore, MINOCA represents a heterogeneous clinical entity encompassing several distinct ischemic mechanisms, including coronary vasospasm, microvascular dysfunction, plaque disruption, and coronary embolism. As these underlying mechanisms could not be systematically characterized in all patients, potential differences in CNV profiles across individual MINOCA subtypes could not be investigated. This phenotypic heterogeneity may have attenuated or obscured associations between specific genomic alterations and underlying ischemic mechanisms. Therefore, the observed CNV patterns should be interpreted as exploratory findings associated with angiographically defined myocardial infarction phenotypes rather than as genetic signatures of specific MINOCA mechanisms. In addition, although all CNV events were linked to their corresponding participants in the finalized dataset, multiple CNVs could originate from the same patient. Therefore, CNV-event-level findings were presented descriptively without inferential statistical testing, and the observed differences should not be interpreted as statistically established associations between the clinical groups. The recurrent CNVs were not independently validated using orthogonal molecular techniques, which limits confidence in these findings, particularly given the small number of events supporting several of the observed regional patterns. Therefore, these findings should be regarded as exploratory and interpreted alongside the patient-level CNV burden analysis. Finally, the absence of independent molecular validation, functional analyses, and systematic genomic breakpoint matching prevented definitive conclusions regarding the biological consequences or pathogenicity of the identified CNVs. Nevertheless, the genome-wide approach provides preliminary evidence on the distribution of structural genomic alterations across two distinct myocardial infarction phenotypes and identifies candidate regions for future investigation.

5. Conclusions

This exploratory study identified shared, recurrent, and apparently group-restricted copy number variation (CNV) patterns among patients with MINOCA and atherosclerotic ACS. Although differences in the distribution and genomic characteristics of CNV events were observed between the two groups, these findings are descriptive and do not establish phenotype-specific genetic associations or causal relationships with myocardial infarction. In particular, the presence of annotated genes within the identified CNV regions does not demonstrate functional alterations or involvement in disease pathogenesis. Given the limited sample size, absence of ancestry-matched healthy controls, and lack of independent genomic validation, the observed patterns should be considered hypothesis-generating. Larger, well-characterized cohorts with appropriate control populations, detailed genomic characterization, and functional validation are required to determine their potential clinical and biological relevance.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/medicina62112152/s1: Table S1: Genomic characteristics and gene annotations of selected recurrent copy number variation regions; Table S2: Event-level genomic characteristics of copy number variations identified in patients with MINOCA and atherosclerotic acute coronary syndrome.

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Informed Consent Statement: Written informed consent was obtained from all participants involved in the study.

Data Availability Statement: The individual-level clinical and genomic data generated and analyzed during the current study are not publicly available due to patient confidentiality and ethical restrictions. Requests for access to appropriately de-identified data may be directed to the corresponding author and will be considered subject to applicable ethical and institutional approvals.

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