DELTA ECG: A GENETIC PERSPECTIVE

Zachary Levine
Faculty of Mathematics and Computer Science
Weizmann Institute of Science
Rehovot, Israel
{zachary.levine}@weizmann.ac.il

Hagai Rossman
Pheno.Ai
Tel Aviv, Israel
{hagai}@pheno.ai

Eran Segal
Faculty of Mathematics and Computer Science
Weizmann Institute of Science
Rehovot, Israel
{eran.segal}@weizmann.ac.il

METHODS

We analyzed 12-lead ECGs from The Human Phenotype Project, sampling each 10 s recording at 1000 Hz and segmenting each ECG into two four-second windows. In keeping with current state-of-the-art, we trained a contrastive convolutional/transformer neural network to embed ECG segments, enforcing similarity between embeddings from the same individual (both across and within visits) while maximizing separation from different individuals Kiyasseh et al. (2021); Diamant et al. (2022). Training curves are shown in Figure 1. As illustrated, embeddings from an individual's two visits cluster distinctly from a null distribution of unmatched visits, confirming that the self-supervised model learns individualized ECG signatures. After model validation, we computed a per-patient scalar by taking the cosine similarity between baseline and follow-up embeddings, defining this as *Delta ECG*—a single scalar quantifying patient-specific ECG changes over two years.

As input for genetic analyses, we used an imputed (from 0.6x) SNP array by the external third-party Gencove, removing first-degree relatives and adjusting for population structure through the use of the top 10 principal components as covariates. For transcriptomics, PBMC RNA-seq data from the same samples were normalized to counts-per-million per gene, per sample. A genome-wide association study (GWAS) on *Delta ECG* identified five genome-wide significant loci, highlighting a genetic basis for individual cardiovascular state changes (Fig. 2ii). Notably, none of these SNPs had been previously reported in any GWAS.

Among these, we identified variants in ***ARID5B*** (rs139222531, $P < 4 \times 10^{-9}$), previously associated with CVD, suggesting that *Delta ECG* may capture genetic predisposition to long-term cardiovascular risk Kichaev et al. (2019). ***SLC30A8*** (rs117871919, $P < 3 \times 10^{-8}$), a gene encoding a zinc transporter linked to glycemic variability, HbA1c, and BMI Masahiro et al. (2018); Saxena et al. (2007), was also identified. Given the established link between type 2 diabetes (T2D) and CVD Pearson-Stuttard et al. (2021), these findings suggest that *Delta ECG* shares genetic associations with both CVD and its key risk factors.

To further assess the biological relevance of *Delta ECG*, we examined its predictive capacity for gene expression using overrepresentation analysis of PBMC RNA-seq data. In men, our embeddings significantly predicted the expression of 57 genes ($P < 0.05$), with nine genes meeting a stricter threshold ($P < 0.01$). Predictions in women were weaker, with only nine genes associated at $P < 0.05$, and no significantly enriched pathways after multiple hypothesis correction. Notably, results in men these included genes encoding mitochondrial respiratory chain components (*MT-RNR1*, *MT-RNR2*, *MT-TV*), which agrees with previous work implicating oxidative phosphorylation in cardiovascular function Chistiakov et al. (2018).

Overall, by integrating deep learning-derived ECG representations with genetic and transcriptomic data, *Delta ECG* provides a scalable and label-free framework for quantifying temporal changes in cardiac health. Our findings demonstrate that leveraging deep learning for multi-omic analysis can uncover clinically relevant cardiovascular dynamics, offering a path toward personalized risk

assessment and monitoring. Future work should validate this approach across diverse populations to maximize its utility in precision cardiovascular medicine.

RESULTS

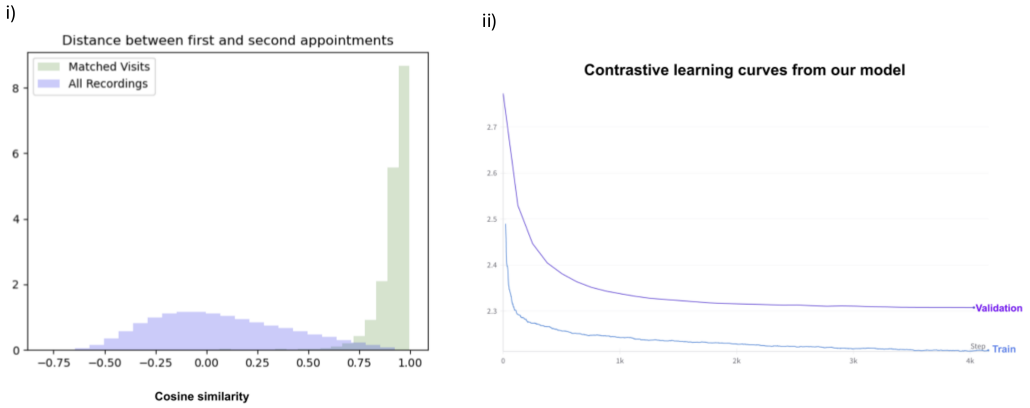
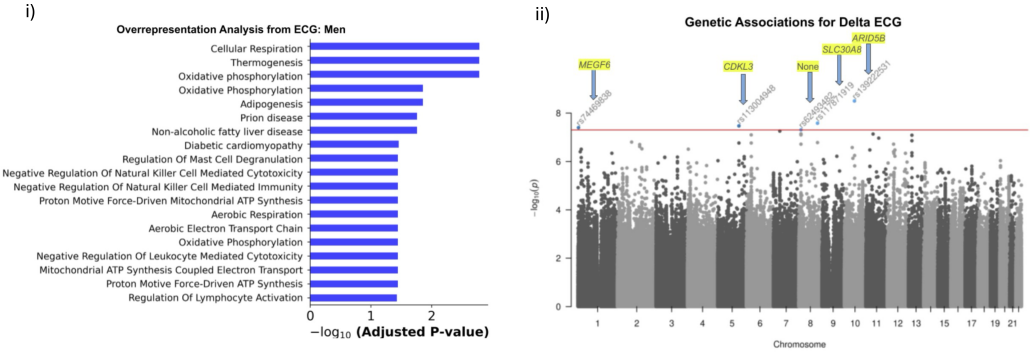


Figure 1: **Validating delta ECG** (i) Distribution of cosine similarity (Delta ECG) for matched vs. all unmatched visits, indicating a strong patient-specific signal. (ii) Contrastive learning curves, showing training (blue) and validation (purple) losses converging over steps.



iii)

Table 1: Significant Hits for Delta ECG. Delta ECG shares a genetic basis with CVD and its known risk factors and correlates.

SNP	Chromosome	P	Gene	Previous Associations
rs139222531	10	3.2e-9	*ARID5B*	CVD
rs117871919	8	2.66e-8	*SLC30A8*	A1C, BMI, T2D
rs113004948	5	3.42e-8	*CDKL3*	Eosinophil count
rs74469838	1	4.13e-8	*MEGF6*	Systemic mastocytosis
rs62493482	8	4.9e-8	*N.C.*	None

Figure 2: **Genetic Analyses. (i)** Overrepresentation analysis of genes significantly predicted by our ECG embeddings in men demonstrates enrichment for metabolic and immune-related pathways (e.g., mitochondrial respiration, mast cell degranulation). **(ii)** A Manhattan plot reveals five genomic loci surpassing the genome-wide significance threshold for *Delta ECG*, including *ARID5B* (associated with CVD), *SLC30A8* (glycemic control), *CDKL3* (eosinophil count), and *MEGF6* (mast cell pathways). **(iii)** A table highlighting these key variants, reinforcing that longitudinal ECG changes (captured via our self-supervised *Delta ECG* measure) share genetic underpinnings with CVD risk factors and immune processes.

MEANINGFULNESS STATEMENT

The genetic basis of cardiovascular disease remains largely unresolved. Existing deep-learning applications to electrocardiograms (ECGs) focus on single phenotypes or isolated timepoints Radhakrishnan et al. (2023); Libiseller-Egger et al. (2022); Wang et al. (2023), introducing biases. Here, we present *Delta ECG*, a metric based on pairs of embeddings that captures patient-specific changes in cardiovascular state over time. We demonstrate that this measure reliably differentiates within-patient variation from population-level differences and aligns with genome-wide significant loci for cardiovascular disease (CVD) and its risk factors.

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