Gene therapy restores the transcriptional program of hematopoietic stem cells in Fanconi anemia

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Supplementary Materials for

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Supplementary Methods

Analysis of lentiviral vector copy numbers in total BM and purified CD34⁺ cells

The number of proviral copies per cell (VCN/cell) was analyzed after genomic extraction of the DNA using the DNA easy blood and tissue kit (Qiagen) or by proteinase K lysis as previously described (2). Duplex qPCR was conducted to detect the Psi sequence of the provirus and the Albumin, as a control gene. To amplify Psi sequence: Psi forward (Psi.F): 5' CAGGACTCGGCTTGCAGAG 3' and Psi reverse (Psi.R): 5' TCCCCCGCTTAATACTGACG detected with the Tagman probe *Psi*.P primers were used and 5'CGCACGCAAGAGGCGAGG3'. To normalize to endogenous *Albumin*, specific primers for Albumin were used: Alb forward (Alb.F): 5' GCTGTCATCTCTTGTGGGCTG 3' and Alb reverse (Alb.R.): 5' ACTCATGGGAGCTGCTGGTTC 3' together with a Taqman probe Alb.P VIC: 5' CCTGTCATGCCCACACAAATCTCTCC 3'. qPCR was conducted in an Applied 7500 Fast Real Time PCR system (Thermo Fisher Scientific), as previously described (2). Percentages of gene correction in PB and BM were directly deduced from the number of copies of the therapeutic provirus in these cells, (eg. 20% corrected cells is deduced from the presence of 0.2 copies per PB or BM cells), given that the VCN per transduced CD34⁺ cell was consistently lower than 1.0 (2).

Single-cell RNA-sequencing (scRNA-seq)

The transcriptome of BM CD34⁺ cells was investigated using NEXTGEM Single Cell 3' Reagent Kits v3.1 (10X Genomics) according to the manufacturer's instructions. Between 2.000 and 6.000 CD34⁺ cells were loaded at a concentration of 700-1,000 cells/μL on a Chromium Controller instrument (10X Genomics) to generate single-cell gel bead-in-emulsions (GEMs). In this step, each cell was encapsulated with primers containing a fixed Illumina Read 1 used to sequence a cell-identifying 16 bp 10X barcode for each cell and a 12 bp Unique Molecular Identifier (UMI) for each transcript. Upon cell lysis, reverse transcription yielded full-length, barcoded cDNA. This cDNA was then released from the GEMs, PCR-amplified and purified with magnetic beads (SPRIselect, Beckman Coulter). Enzymatic Fragmentation and Size Selection was used to optimize cDNA size prior to library construction. Fragmented cDNA was then end-repaired, A-tailed and ligated to Illumina adaptors. A final PCR-amplification with barcoded primers allowed sample indexing. Library quality control and quantification was performed using Qubit 3.0

Fluorometer (Life Technologies) and Agilent's 4200 TapeStation System (Agilent), respectively. Sequencing was performed in a NextSeq500 (Illumina) (Read1: 28 cycles; Read 55 cycles; i7 index: 8 cycles) at an average depth of 20,000 reads/cell. According to these analyses CD34⁺ cell populations were classified as *corrected* (FANCA⁺) and *uncorrected* (FANCA⁻) cells, considering that FANCA⁻ is enriched with cells that only express the endogenous mutated *FANCA* mRNA, while FANCA⁺, that includes cells with higher FANCA expression, is enriched with cells that express both the endogenous mutated *FANCA* plus the ectopic functional *FANCA* mRNA.

scRNA-seq: bioinformatics

Data filtering and normalization: Sequenced libraries were demultiplexed, aligned to human transcriptome (hg38) and quantified using Cell Ranger (v_3.0.1). Ongoing analysis was conducted using Seurat (V_3.2.0)(15) in R (V_3.5.2) (16). Quality control filters based on the number of detected genes, number of UMIs and percentage of mitochondrial UMIs were performed to each one of the samples. The thresholds were defined based on the distribution of the previously mentioned parameters and visual inspection of quality control scatter plots. After filtering of low quality cells, a total number of 14,208 (FA-02002), 720 (FA-02004), 1,438 (FA-02006), 1,995 (FA-02008), and 12,549 (HD) cells were retained.

Each single cell dataset was individually normalized, using the Normalize Seurat function. Feature counts for each cell were divided by the total counts for that cell and multiplied by the scale factor. This was then natural-log transformed. The data was regressed out by cell cycle stadium, number of features and number of counts. Uniform Manifold Approximation and Projection (UMAP) was performed to plot the data of each sample. PCA was defined as dimensional reduction to use in the UMAP graph. Each of the FA samples was integrated with the healthy donor sample.

<u>Cell annotation</u>: For cell annotation, we use the annotation conducted in three additional human samples of healthy young individuals (3YI). The isolation protocol of 3YI includes the cell types in the 4 FA patients and the HD: Ficoll-Paque Plus (GE healthcare) density gradient centrifugation and stained using CD34 (clone 8G12; BD bioscience) CD64 (clone 10.1; Biolegend) CD19 (clone SJ25C1; Biolegend) CD10 (clone HI10A; Biolegend) CD3 (clone OKT3; Biolegend) CD36 (clone CLB-IVC7; Sanquin Plesmanlaan) CD61 (clone RUU-PL7F12; BD bioscience) for 15 min at RT. And finally, CD34+ CD64- CD19- CD10- CD3-CD36+CD61+ cells were then sorted in a BD FACSAria II (BD Biosciences) as previously shown. The data-analysis processing of those

samples was conducted as the protocol described for FA samples. Next, we performed unsupervised clustering with the Louvain algorithm as implemented in Seurat¹⁶. We tested several resolution values and assessed the results by calculating the average silhouette for each cluster. We determined the cluster markers using the Seurat function FindAllMarkers, with the MAST method. Finally, we annotated the clusters in 3YI by manually inspecting the most specific markers and looking for curated markers in the literature. Using the robust annotation conducted in 3YI, the "label transfer function" from Seurat was used to annotate the four FA and the HD samples(15). It is important to note that while the annotation of the 3YI is valid for the annotation of FA and HD samples, we decided not to include the 3YI samples in the analysis as the cell proportions may be different based on the isolation protocol.

<u>Differential expression analysis</u>: The differential expression analysis was conducted using FindMarkers function in the Seurat package. Genes were considered differentially expressed if |logFC|>0.25 and adjusted p-value<0.05.

GSEA analysis: Gene set enrichment analyses were conducted using ClusterProfiller (version 3.10.1) (17) in R(16). The normalized data of each sample and cell type was ranked by the logFC value and the analysis was run comparing our data with GO biological processes. A gene set was considered significantly enriched if GO adjusted p-value<0.05.

Pathway visualization

After GSEA analysis two core pathways were selected (Cell cycle and FA/BRCA) for visualization purpose using Cytoscape (version 3.8.2.)(18). The values of logFC were for each one of the samples and different contrast using omic visualizer package. The pathways are shown as imported in the Cytoscape package; for two genes an alternative gene symbol is shown (MHF, RPA).

Analysis of the sensitivity of hematopoietic colony forming cells to the genotoxic agent mitomycin C

To assess the influence that gene therapy had in the response of FA hematopoietic progenitors to mitomycin C (MMC), the number of colonies generated in the absence and the presence of this agent was assessed. In these experiments a total number of 2.5×10^5 nucleated BM cells fractionated with Hydroxyethylstarches (HES; Grifols) were plated in plates containing 1 mL methylcellulose medium (MethocultTM #H4434) supplemented with 10 µg/mL anti-TNF α and 1 mM N-

acetylcysteine, in the absence and the presence of 10 nM MMC (Sigma-Aldrich). Cells were then cultured for 14 days at 37°C, 5% CO₂ and 5% O₂, and colonies were then scored under an inverted microscope.

Telomere length studies

DNA was extracted from patient's blood samples and the telomere length was determined by quantitative PCR as previously described(20). In this method the amount of telomere DNA (T) and of the single copy 36B4 reference gene (S) were determined by quantitative PCR for each blood sample. The ratio between these two parameters (T/S) was a measure of the relative telomere length. A control DNA isolated from the cultured cell line MCF-7 was used as an internal control in each experiment to normalize the T/S ratio obtained for the experimental samples. The telomere length of each sample was calculated from the normalized T/S ratios using the formula: telomere length in Kbp = T/S x 3.86 + 1.89. Three independent experiments with triplicates were conducted for each sample.

Basic statistical tests

<u>Proportion test</u>: In each FA sample and cell type, a two-proportion statistical test was conducted to investigate significant differences in cell type proportion between FANCA⁺ and FANCA⁻ cells in each CD34⁺ subpopulation.

<u>Anova test</u>: We conducted a two-tail ANOVA test to investigate the differences of FANCA expression between therapy treated patients among the FANCA⁺ set for each CD34⁺ cell subpopulation.

<u>Wilcoxon test</u>: The comparison of the expression of the FANCA gene between FANCA⁺ cells in FA integrated samples and HDs was performed using a two-sided Wilcoxon test for each CD34⁺ cell subpopulation. In HD, only cells with >0 FANCA gene expression value were considered.

<u>Binomial Test</u>: We conducted a binomial test to investigate if the shared directionality of changes for two contrasts, "FANCA⁺ vs FANCA⁻" and "HD vs FANCA⁺", was significantly overrepresented. To this end, the genes sharing the same directionality for both contrasts were classified as 1, and 0 otherwise; the binomial was conducted considering a probability of 0.5,

number of experiments of 382 and a one-tail p-value associated to values larger than the observed. The analysis was conducted separately for each cell type and sample.

<u>Binary Correlation</u>: We conducted a binary correlation analysis between the directionality of the same genes in the two contrasts, "FANCA⁺ vs FANCA⁻" and "HD vs FANCA⁺". All the upregulated genes were classified as 1 and the downregulated as 0. A binary correlation test was conducted using R.

General considerations: To perform all the statistical tests R(15) was used. In all the cases the multiple testing was addressed using Bonferroni; and for any analysis the null hypothesis was rejected if adjusted p-value <0.05.

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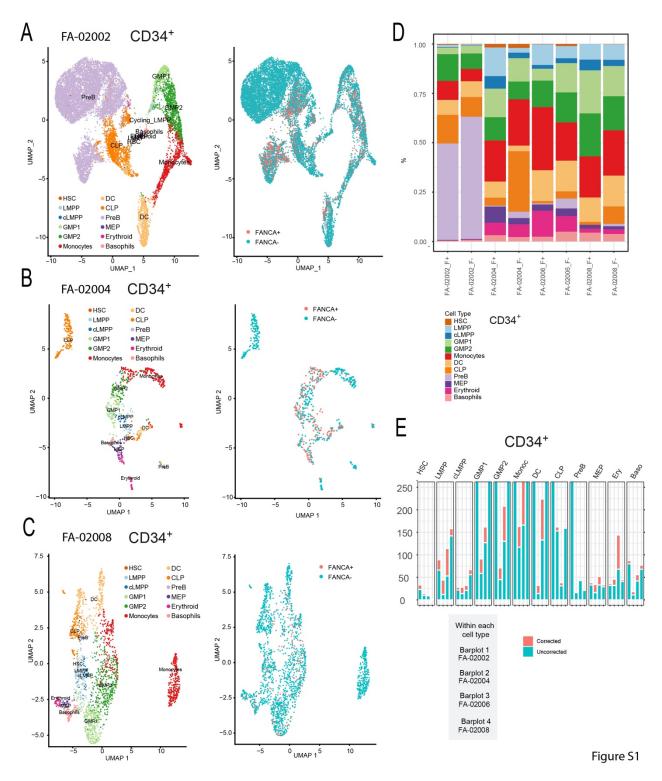


Figure S1. (A) <u>Left panel</u>: UMAP plot showing the clustering analysis for CD34⁺ BM cells from the FA-02002 patient undergoing FANCA gene therapy. A total of 12 clusters were identified, spanning the different HSPC subpopulations. Identified clusters include an HSC cluster

(hematopoietic stem cell; brown). Clusters with megakaryocytic-erythroid identity include MEP (erythroid-megakaryocyte progenitor; purple), Erythroid (erythroid progenitor; pink), and Basophils (basophil progenitor; light pink). Clusters with lympho-myeloid identity include LMPP (lymphoid-primed multipotent progenitor; light blue), Cycling-LMPP (blue), CLP (common lymphoid progenitor; orange), GMP1 and GMP2 (granulocyte-monocyte progenitor; light green and green), Monocytes (monocyte progenitor; red), DC (dendritic cell progenitor; nude), and PreB (B cells progenitor; light purple). Right panel: Distribution of FANCA positive cells (corrected cells; red) versus FANCA negative cells (uncorrected cells; blue). (B,C) Same as (A), including the analysis of the FA-02004 and FA-02008 respectively patient. (D) Cell type proportions for each individual separating in each case FANCA+ and FANCA- cells. (E) Barplot showing the total number of cells in the different HSPC populations corresponding to the four gene therapy treated patients. In each case, the number of FANCA+ (red) and FANCA- (blue) cells is shown. Panel E is a zoom over low prevalent cells that complements Fig. 2C.

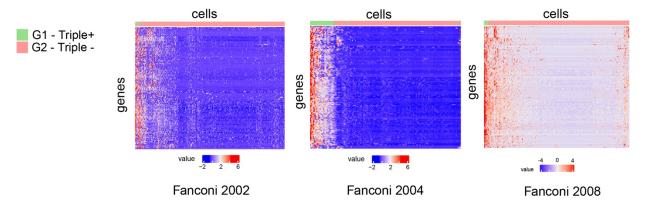


Figure S2

Figure S2. Fingerprint validation. Comparison of gene expression of fingerprint between G1 (cells with reads mapping to FANCA, poly-A sequence of the viral vector, and PGK1) and G2 (cells with no reads mapping to FANCA, neither to viral vector's poly-A sequence, neither to PGK1). For each sample, cells have been selected, and expression plotted separately. In addition, values have been z-scored within each of the samples. In the case of patient FA-02006, no cell in G1 was identified.

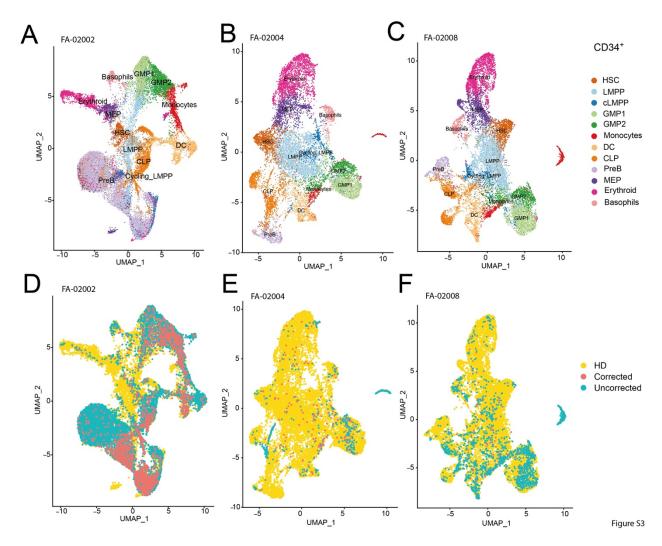


Figure S3. (A) UMAP plot showing the clustering analysis for CD34⁺ BM cells from the FA-02002 patient undergoing FANCA gene therapy and the healthy donor. A total of 12 clusters were identified, spanning the different HSPC subpopulations. Identified clusters include an HSC cluster (hematopoietic stem cell; brown). Clusters with megakaryocytic-erythroid identity include MEP (erythroid-megakaryocyte progenitor; purple), Erythroid (erythroid progenitor; pink), and Basophils (basophil progenitor; light pink). Clusters with lympho-myeloid identity include LMPP (lymphoid-primed multipotent progenitor; light blue), Cycling-LMPP (blue), CLP (common lymphoid progenitor; orange), GMP1 and GMP2 (granulocyte-monocyte progenitor; light green and green), Monocytes (monocyte progenitor; red), DC (dendritic cell progenitor; nude), and PreB (B cells progenitor; light purple). **(B, C)** Same as (A), including the analysis of the FA-02004 and FA-02008 respectively patient. **(D)** Distribution of cells classified as cells derived from the healthy

donor (yellow), $FANCA^+$ cells (red) and $FANCA^-$ cells (blue) for FA-02002 patient. (E, F) Same as (D) including the analysis of the FA-02004 and FA-02008 respectively patient.

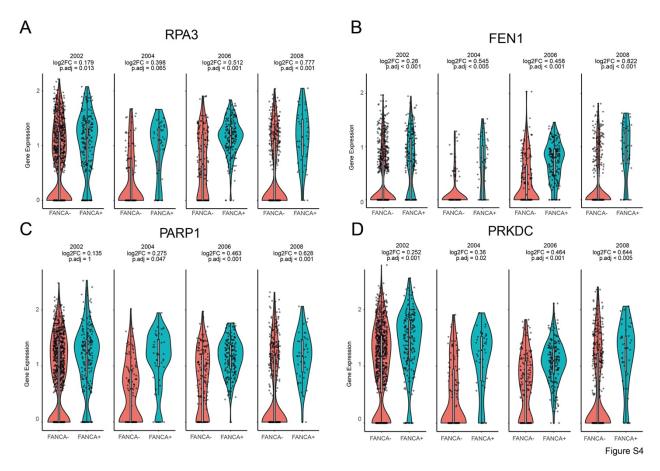


Figure S4. Gene expression differences between FANCA+ and FANCA- for selected Telomere related genes in CD34+ progenitor monocytes. The violin plots depict normalized gene expression for each patient separately in CD34+ progenitor monocytes for FANCA- (red, left) and FANCA+ (light-blue, right). Log2FC denotes logarithmic fold-change, and p.adj denotes adjusted p-value for each FANCA+ vs. FANCA- contrast. Panels A, B, C, and D show the information for RPA3, FEN1, PARP1, and PRKDC respectively.

Cell type	FA-02002 p.adjust	FA-02004 p.adjust	FA-02006 p.adjust	FA-02008 p.adjust
HSC	1.000	1.000	1.000	1.000
LMPP	0.211	0.000	0.206	1.000
Cycling_LMPP	1.000	1.000	1.000	1.000
GMP1	1.000	1.000	0.000	1.000
GMP2	0.000	1.000	1.000	1.000
Monocytes	0.000	1.000	0.000	1.000
DC	1.000	0.125	1.000	1.000
CLP	0.000	0.000	0.399	0.022
PreB	0.000	1.000	0.000	1.000
MEP	1.000	0.342	1.000	1.000
Erythroid	1.000	1.000	0.099	1.000
Basophils	1.000	1.000	1.000	1.000

Table S1. Results of the statistical test comparing the proportion of FANCA⁺ vs FANCA⁻ HSPCs. For each HSPC type and each patient's sample the adjusted p-value is shown. Bonferroni was used to correct for multiple testing.

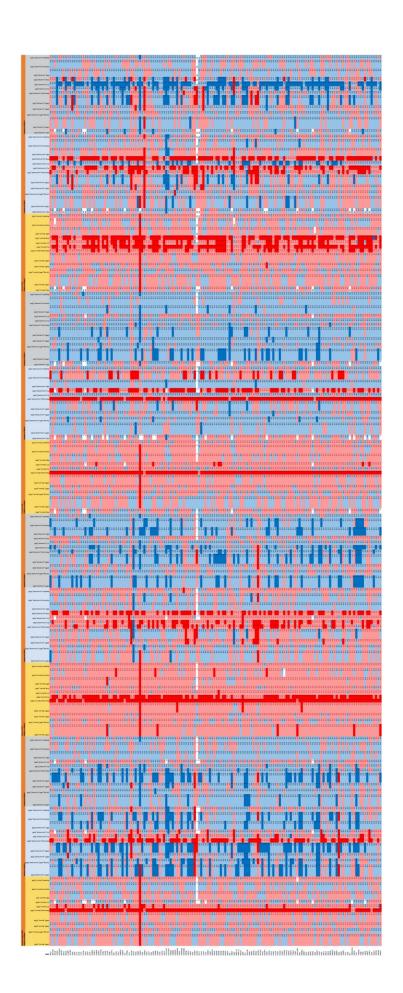


Table S2. Differential FANCA⁺ signature derived from Fig.1F. The genes included in the list are those that for at least one cell type are identified as differentially expressed (abs(logFC)>0.25 and adjusted p-value<0.05) in "at least three patients", and "showing the same direction of the change for the three patients", when considering the contrast FANCA⁺ vs FANCA⁻ HSPCs (n=152). FANCA was excluded from the analysis. For each gene the information is provided for each individual, for each contrast (FANCA⁺ vs FANCA⁻ and Healthy vs FANCA+) conducted for each cell type. There is a color/number code that denotes: 1/red upregulated and statistically significant; 0.5/light-red upregulated and not statistically significant; 0 no changes; -1/blue downregulated and statistically significant; 0.5/light-blue downregulated and not statistically significant.

	Binomial Test								Correlation					
Cell type	FA-02002 FA-02004					FA-02006		-02008	FA-02002	FA-02004	FA-02006	FA-02008		
Cen type	p.adjust	#of genes	p.adjust	# of genes	p.adjust	# of genes	p.adjust	# of genes	p.adjust	p.adjust	p.adjust	p.adjust		
HSC	1.0000	73	0.0000	107	NA	NA	NA	NA	0.8340	0.0000	NA	NA		
LMPP	1.0000	76	0.1410	90	1.0000	77	1.0000	50	1.0000	0.0006	0.0453	0.3469		
Cycling_LMPP	0.0007	100	1.0000	74	1.0000	73	1.0000	66	0.0005	1.0000	1.0000	1.0000		
GMP1	0.0434	93	1.0000	58	0.0000	127	1.0000	60	0.1230	1.0000	0.0059	1.0000		
GMP2	1.0000	64	1.0000	78	1.0000	68	1.0000	48	1.0000	0.0001	1.0000	1.0000		
Monocytes	0.0000	130	0.0000	152	0.0000	141	0.0000	145	1.0000	0.0839	1.0000	1.0000		
DC	0.0000	143	1.0000	79	0.0000	144	0.0001	103	0.0000	0.0029	0.0015	1.0000		
CLP	1.0000	21	0.0000	138	0.0000	137	1.0000	73	0.0005	0.4071	1.0000	1.0000		
PreB	0.0000	148	NA	NA	0.0000	135	NA	NA	0.0000	NA	0.1257	NA		
MEP	0.0004	101	1.0000	41	1.0000	45	1.0000	53	1.0000	1.0000	1.0000	1.0000		
Erythroid	1.0000	81	0.0000	127	1.0000	73	0.0022	98	1.0000	0.0000	0.0479	0.0947		
Basophils	0.0154	95	1.0000	80	0.0000	123	0.8386	85	0.2829	0.0092	0.0059	0.4477		

Table S3. Comparison of the directionality of the following two contrasts: "FANCA+ **vs. FANCA**-", and "Healthy vs. FANCA-". "# genes tot", denotes the total number of genes per individual and cell-type considered for the analysis. For the two analysis the genes sharing the same directionality for both contrasts were classified as 1, and 0 otherwise (see Methods). "Binomial test": the analysis was executed independently by cell type and sample. The adjusted p-value after Bonferroni multiple testing correction is provided. NA denotes that it was not possible to compute the p-value due to the limited number of cells. "# of genes" denotes the number of genes with the same directionality in both contrasts. Correlation: binary correlation.

ID						
	Description	enrichmentSc	pvalue	p.adjust	Cell_type	Contrast
GO:0009262	deoxyribonucleotide metabolic process	0.71817658	0.00174825	0.01525153	Monocytes	FA-02008 (FAI)
GO:0032212	positive regulation of telomere maintenance via telomerase	0.70294651	0.00174825	0.01525153	Monocytes	FA-02008 (FAI)
	negative regulation of mRNA processing	0.67199855	0.00174825	0.01525153	Monocytes	FA-02008 (FAI)
	positive regulation of telomerase activity			0.01525153		FA-02008 (FAI)
	protein peptidyl-prolyl isomerization			0.01525153		FA-02008 (FAI)
	maturation of 5.8S rRNA			0.01525153		FA-02008 (FAI)
	DNA replication initiation			0.01525153		FA-02008 (FAI)
GO:0019692	deoxyribose phosphate metabolic process	0.68523953	0.00175439	0.01525153	Monocytes	FA-02008 (FAI)
GO:0033119	negative regulation of RNA splicing	0.71547714	0.00175439	0.01525153	Monocytes	FA-02008 (FAP
GO:0051984	positive regulation of chromosome segregation	0.67395754	0.00175439	0.01525153	Monocytes	FA-02008 (FAI)
GO:0070198	protein localization to chromosome, telomeric region	0.8256152	0.00175439	0.01525153	Monocytes	FA-02008 (FAI)
GO:1904358	positive regulation of telomere maintenance via telomere lengthening	0.70946365	0.00175747	0.01525153	Monocytes	FA-02008 (FAI)
	purine nucleotide catabolic process			0.01525153		FA-02008 (FAI)
GO:0006297	nucleotide-excision repair, DNA gap filling			0.01525153		FA-02008 (FAI)
	mismatch repair 2'-deoxyribonucleotide metabolic process			0.01525153		FA-02008 (FAI)
				0.01525153		FA-02008 (FAI)
	apoptotic nuclear changes kinetochore organization			0.01525153		FA-02008 (FAI)
	xinetocnore organization cellular component disassembly involved in execution phase of apoptosis	0.72093834	0.00176678	0.01525153	Monocytes	FA-02008 (FAI)
	Cellular Component oi assessemby involved in execution phase of apoptosis telomere maintenance via semi-conservative replication on	0.67510528	0.00177305	0.01525153	Monocytes	FA-02008 (FAP
	telomere maniferance via Semi-conservative repincation establishment of protein localization to chromosome			0.01525153		FA-02008 (FAI)
	estationalities of protein to activation to circomosome pyrimidine nucleotide catabolic process	0.84350003	0.00177303	0.01525153	Monocytes	FA-02008 (FAI)
	pyrimine instructive autority process blinding of sperm to zona pellucida blinding of sperm to zona pellucida	0.8780535	0.0017702	0.01525153	Monocytes	FA-02008 (FAI)
60:0007333	binding or spent to Zona periculas Chromosome condensation	0.71905504	0.0017762	0.01525153	Monocytes	FA-02008 (FAI)
	protein localization to nuclear body	0.71503304		0.01525153	Monocytes	FA-02008 (FAI)
	positive regulation of establishment of protein localization to telomere	0.91541891		0.01525153		FA-02008 (FAI)
	protein localization to Cajal body			0.01525153		FA-02008 (FAI)
	cristae formation			0.01525153		FA-02008 (FAI)
	burine nucleobase biosynthetic process			0.01525153		FA-02008 (FAI)
	deoxyribonucleotide biosynthetic process	0.80297149	0.00178253	0.01525153	Monocytes	FA-02008 (FAI)
GO:0070203	regulation of establishment of protein localization to telomere	0.89752693	0.00178253	0.01525153	Monocytes	FA-02008 (FAI)
	positive regulation of cyclin-dependent protein kinase activity	0.72451391	0.00178253	0.01525153	Monocytes	FA-02008 (FAI)
GO:1904816	positive regulation of protein localization to chromosome, telomeric region	0.91707246	0.00178253	0.01525153	Monocytes	FA-02008 (FAI)
GO:0000466	maturation of 5.85 rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.85 rRNA, LSU-rRNA)	0.73017046	0.00178571	0.01525153	Monocytes	FA-02008 (FAI)
GO:0022616	DNA strand elongation	0.72251057	0.00178571	0.01525153	Monocytes	FA-02008 (FAI)
	RNA localization to Cajal body			0.01525153		FA-02008 (FAI)
GO:0090671	telomerase RNA localization to Cajal body	0.86556636	0.00178571	0.01525153	Monocytes	FA-02008 (FAI)
GO:0090672	telomerase RNA localization	0.86556636	0.00178571	0.01525153	Monocytes	FA-02008 (FAI)
GO:0090685	RNA localization to nucleus			0.01525153		FA-02008 (FAI)
GO:0000469	cleavage involved in rRNA processing	0.68247898	0.00179211	0.01525153	Monocytes	FA-02008 (FAI)
GO:0010499	proteasomal ubiquitin-independent protein catabolic process	0.7724766	0.00179211	0.01525153	Monocytes	FA-02008 (FAI)
GO:1902751	positive regulation of cell cycle G2/M phase transition	0.69333963	0.00179211	0.01525153	Monocytes	FA-02008 (FAI)
GO:0034080	CENP-A containing nucleosome assembly	0.73328797	0.00179533	0.01525153	Monocytes	FA-02008 (FAI)
GO:0061641	CENP-A containing chromatin organization			0.01525153		FA-02008 (FAI)
GO:0000291	nuclear-transcribed mRNA catabolic process, exonucleolytic	0.6166161	0.00179856	0.01525153	Monocytes	FA-02008 (FAI)
GO:0006261	DNA-dependent DNA replication	0.64754021	0.00179856	0.01525153	Monocytes	FA-02008 (FAI)
GO:0007088	regulation of mitotic nuclear division	0.47897688	0.00179856	0.01525153	Monocytes	FA-02008 (FAI)
GO:0022900	el- el-ectron transport chain	0.50166408	0.00179856	0.01525153	Monocytes	FA-02008 (FAI)
	mitotic chromosome condensation			0.01525153		FA-02008 (FAI)
GO:0009148	pyrimidine nucleoside triphosphate biosynthetic process	0.73505206	0.0018018	0.01525153	Monocytes	FA-02008 (FAI)
GO:0009154	purine ribonucleotide catabolic process	0.74979727		0.01525153		FA-02008 (FAI)
	sperm-egg recognition	0.74796493		0.01525153	Monocytes	FA-02008 (FAI)
GO:0044788	modulation by host of viral process	0.78415702	0.0018018	0.01525153	Monocytes	FA-02008 (FAI)
GO:0070202	regulation of establishment of protein localization to chromosome	0.87601141		0.01525153		FA-02008 (FAI)
GO:0070987	error-free translesion synthesis	0.70132774	0.0018018	0.01525153	Monocytes	FA-02008 (FAI)
GO:1904814	regulation of protein localization to chromosome, telomeric region	0.90333773	0.0018018			FA-02008 (FAI)
GO:1990173	protein localization to nucleoplasm			0.01525153		
		0.82728175	0.0018018	0.01525153	Monocytes	FA-02008 (FAI)
GU:0006260	DNA replication	0.82728175	0.0018018	0.01525153 0.01525153 0.01525153	Monocytes	FA-02008 (FAI) FA-02008 (FAI)
GO:0006403	DNA replication RNA localization	0.82728175 0.59545381 0.49356949	0.0018018 0.00180505 0.00180505	0.01525153 0.01525153 0.01525153	Monocytes Monocytes Monocytes	FA-02008 (FAI)
GO:0006403 GO:0010948	DNA regilication RNA localization negative regulation of cell cycle process	0.82728175 0.59545381 0.49356949 0.38099218	0.0018018 0.00180505 0.00180505 0.00180505	0.01525153 0.01525153 0.01525153 0.01525153	Monocytes Monocytes Monocytes Monocytes	FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI)
GO:0006403 GO:0010948 GO:0016072	DNA regilectation RNA localization registrier regulation of cell cycle process refixAn regulation process	0.82728175 0.59545381 0.49356949 0.38099218 0.53085252	0.0018018 0.00180505 0.00180505 0.00180505 0.00180505	0.01525153 0.01525153 0.01525153 0.01525153 0.01525153	Monocytes Monocytes Monocytes Monocytes Monocytes	FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI)
GO:0006403 GO:0010948 GO:0016072 GO:0051438	DNA regileration RNA localization negative regulation of cell cycle process rRNA metabolic process regulation of unity protein transferase activity	0.82728175 0.59545381 0.49356949 0.38099218 0.53085252 0.57920637	0.0018018 0.00180505 0.00180505 0.00180505 0.00180505 0.00180505	0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153	Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes	FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI)
GO:0006403 GO:0010948 GO:0016072 GO:0051438 GO:0006335	DNA regilectation RNA localization negative regulation of cell cycle process regulation of other control of the	0.82728175 0.59545381 0.49356949 0.38099218 0.53085252 0.57920637 0.76647602	0.0018018 0.00180505 0.00180505 0.00180505 0.00180505 0.00180505 0.00180832	0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153	Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes	FA-02008 (FAM FA-02008 (FAM FA-02008 (FAM FA-02008 (FAM FA-02008 (FAM FA-02008 (FAM FA-02008 (FAM
GO:0006403 GO:0010948 GO:0016072 GO:0051438 GO:0006335 GO:0006414	DNA regileration RNA localization negative regulation of cell cycle process rRNA metabolic process rgulation of bulguith protein transferase activity DNA regilection - dependent nucleosome assembly translational dependent nucleosome assembly translational dependent nucleosome assembly	0.82728175 0.59545381 0.49356949 0.38099218 0.53085252 0.57920637 0.76647602 0.63650416	0.0018018 0.00180505 0.00180505 0.00180505 0.00180505 0.00180505 0.00180832 0.00180832	0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153	Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes	FA-02008 (FAM FA-02008 (FAM FA-02008 (FAM FA-02008 (FAM FA-02008 (FAM FA-02008 (FAM FA-02008 (FAM FA-02008 (FAM FA-02008 (FAM
GO:0006403 GO:0010948 GO:0016072 GO:0051438 GO:0006335 GO:0006414 GO:0009141	DNA replication RNA ccalization negative regulation of cell cycle process regulation of tell cycle process regulation of bullquitin-protein transferase activity DNA replication-benedent nucleosome assembly translational elongation nucleoside triphophate metabolic process	0.82728175 0.59545381 0.49356949 0.38099218 0.53085252 0.57920637 0.76647602 0.63650416 0.54743047	0.0018018 0.00180505 0.00180505 0.00180505 0.00180505 0.00180505 0.00180832 0.00180832	0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153	Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes	FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI) FA-02008 (FAI)
GO:0006403 GO:0010948 GO:0016072 GO:0051438 GO:0006435 GO:0006414 GO:0009141 GO:0010389	DMA regilectation RMA ccalization RMA ccalization registive regulation of cell cycle process rMAM necablotic process regulation of obliquitin-proces regulation of obliquitin-process regulation of obliquitin-process regulation of obliquitin-process regulation of CMA transferase activity regulation of CMA transferase obligation of the regulation of CMA transferase obligation of CMA transferase regulation of CMA transferasion of more regulation of CMA transferasion of the regulation of CMA transferasion of the regulation of CMA transferase regulation regul	0.82728175 0.59545381 0.49356949 0.38099218 0.53085252 0.57920637 0.76647602 0.63650416 0.54743047 0.46025685	0.0018018 0.00180505 0.00180505 0.00180505 0.00180505 0.00180832 0.00180832 0.00180832	0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153	Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes	FA-02008 (FAM FA-02008 (FAM
G0:0006403 G0:0010948 G0:0016072 G0:0051438 G0:0006414 G0:0009141 G0:0010389 G0:0015985	DNA regilectation RNA ccalization negative regulation of cell cycle process regulation of trell cycle process regulation of trell cycle process regulation of ubliquitin-protein transferase activity DNA regulation-dependent nuclessome assembly translational elongation nucleoside triphophate metabolic process regulation of GZ/M transition of mitotic cell cycle energy coupled proton transport, down detrochemical gradient	0.82728175 0.59545381 0.49356949 0.38099218 0.53085252 0.57920637 0.76647602 0.63650416 0.54743047 0.46025685 0.75720046	0.0018018 0.00180505 0.00180505 0.00180505 0.00180505 0.00180505 0.00180832 0.00180832 0.00180832 0.00180832	0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153	Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes	FA-02008 (FAM FA-02008 (FAM
G0:0006403 G0:0010948 G0:0016072 G0:0051438 G0:0006335 G0:0006414 G0:00019141 G0:001038 G0:0015985	DMA regilectation RMA ccalization RMA ccalization regarder regulation of cell cycle process rifflam metabolic process rifflam metabolic process rifflam metabolic process rifflam metabolic process regulation of Judiquitin-protein transferase activity DMA regilection-dependent nucleosome assembly runcleoside triphosphate metabolic process regulation of GZMA transition of mitotic citycle energy coupled proton transport, down electrochemical gradient ATP synthesis coupled proton transport, down electrochemical gradient ATP synthesis coupled proton transport	0.82728175 0.59545381 0.49356949 0.38099218 0.53085252 0.57920637 0.76647602 0.63650416 0.54743047 0.46025685 0.75720046	0.0018018 0.00180505 0.00180505 0.00180505 0.00180505 0.00180505 0.00180832 0.00180832 0.00180832 0.00180832 0.00180832	0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153	Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes	FA-02008 (FAM FA-02008 (FAM
G0:0006403 G0:0010948 G0:0016072 G0:0051438 G0:0006335 G0:0006414 G0:00101389 G0:0015986 G0:0015986 G0:0031935	DNA regilectation RNA ccalization negative regulation of cell cycle process regulation of trell cycle process regulation of bullquitin-protein transferase activity DNA regilectano-dependent nucleosome assembly translational elongation nucleoside triphophate metabolic process regulation of GZ/M transition of mitotic cell cycle energy coupled proton transport, down electrochemical gradient ATP synthesis coupled proton transport, down	0.82728175 0.59545381 0.49356949 0.38099218 0.53085252 0.57920637 0.76647602 0.63650416 0.54743047 0.46025685 0.75720046 0.75720046	0.0018018 0.00180505 0.00180505 0.00180505 0.00180505 0.00180505 0.00180832 0.00180832 0.00180832 0.00180832 0.00180832 0.00180832	0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153	Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes	FA-02008 (FA)
G0:0006403 G0:0010948 G0:0016072 G0:0051438 G0:0006414 G0:0001389 G0:0015985 G0:0015985 G0:0034723	DNA regilectation RNA ccalization RNA ccalization regarder regulation of cell cycle process rRNA necabolic process regulation of bullquitin-protein transferase activity DNA regulation-dependent nucleisome assembly RNA regulation of SQLA Transition of mitotic cycle regulation of SQLA Transition of mitotic cell cycle energy coupled proton transport, down dectrochemical gradient ATP synthesis coupled proton transport, down dectrochemical gradient ATP synthesis coupled proton transport regulation of CAP on the regulation of RAP of the RA	0.82728175 0.59545381 0.49356949 0.38099218 0.53085252 0.57920637 0.76647602 0.63650416 0.54743047 0.46025685 0.75720046 0.752720046 0.76265508 0.76647602	0.0018018 0.00180505 0.00180505 0.00180505 0.00180505 0.00180832 0.00180832 0.00180832 0.00180832 0.00180832 0.00180832 0.00180832 0.00180832	0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153	Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes Monocytes	FA-02008 (FA)
G0:0006403 G0:0010948 G0:0016072 G0:0051438 G0:0006335 G0:0006414 G0:0009141 G0:0015985 G0:0015985 G0:00319935 G0:0034935 G0:0034925	DMA regilectation RMA localization negative regulation of cell cycle process regulation of trell cycle process regulation of of unit cycle process regulation of ubliquitin-protein transferase activity DMA regilectano-dependent nucleosione assembly translational elongation uncleoside triphophate metabolic process regulation of GZ/M transition of mitotic cell cycle energy coupled proton transport, down electrochemical gradient ATP synthesis coupled proton transport, down electrochemical gradient ATP synthesis coupled proton transport, down of mitotic cell cycle regulation of chronatin silencing DMA regilectation-dependent nucleosome organization ngative regulation of nRMA spicincia, via spilicosome	0.82728175 0.59545381 0.49356949 0.38099218 0.53085252 0.57920637 0.76647602 0.63650416 0.54743047 0.46025685 0.75720046 0.75720046 0.76265508 0.76647602 0.77236926	0.0018018 0.00180505 0.00180505 0.00180505 0.00180505 0.00180505 0.00180832 0.00180832 0.00180832 0.00180832 0.00180832 0.00180832 0.00180832 0.00180832	0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153 0.01525153	Monocytes Monocy	FA-02008 (FA)
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Table S4. Gene Set Enrichment Analysis. Results of Gene Set Enrichment Analysis conducted for each FA patient, for cell type and for each of the contrasts of interest. Only top 100 results are provided; such threshold allows the insertion of the table in the supplement document requested (other thresholds may require a tab-supplementary file).