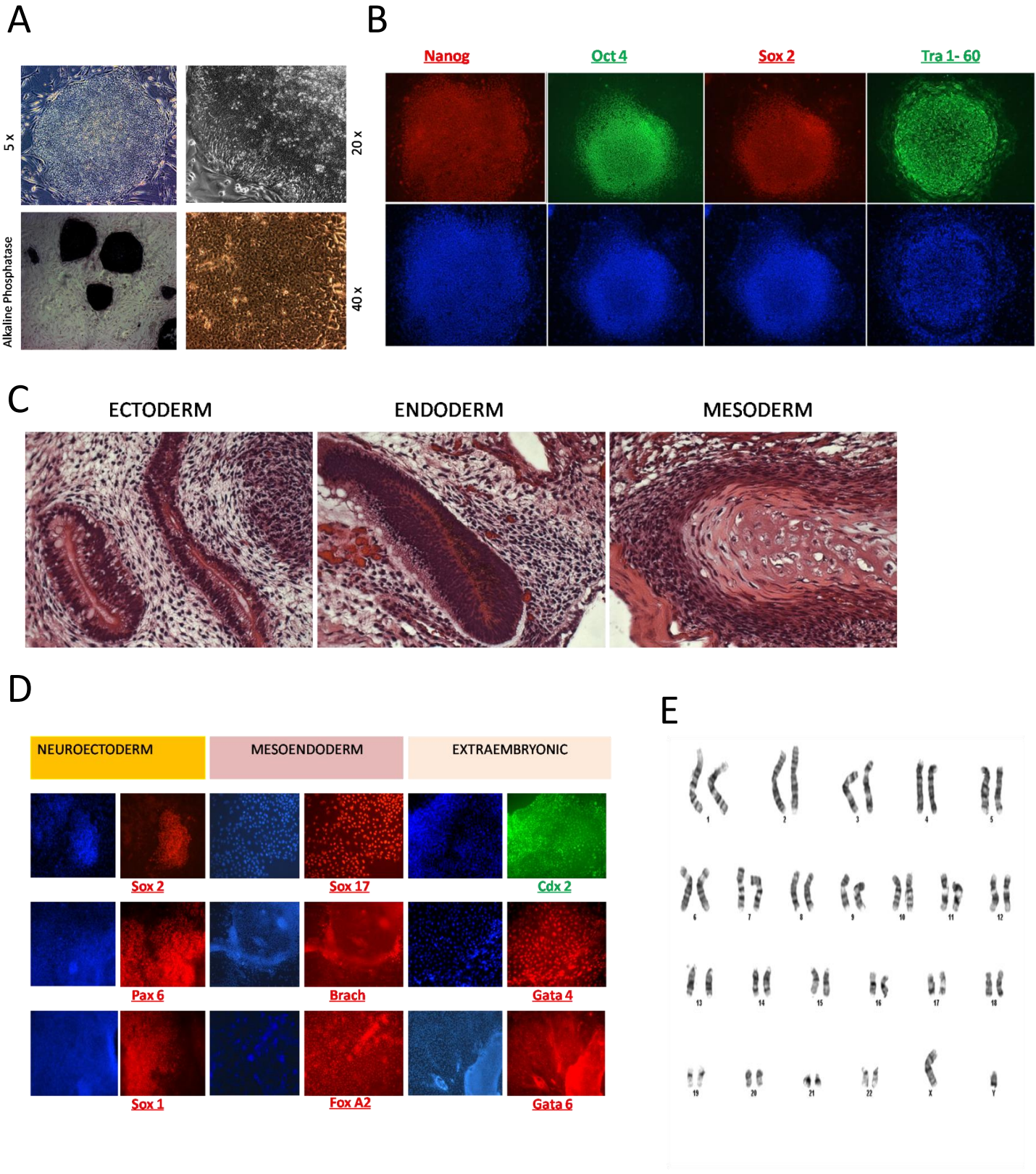
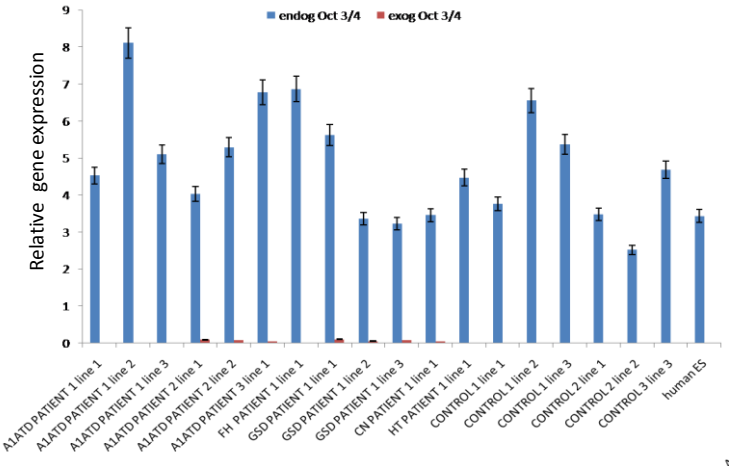
Disease	Clinical features	Genotype
Alpha 1 Antitrypsin deficiency (A1ATD)	Patient 1 – 65 year old caucasian male, liver transplant recipient, explant biopsy confirmed A1ATD induced liver cirrhosis Patient 2 – 55 year old caucasian male with clinical symptoms & liver biopsy confirming intrahepatic α1-antitrypsin polymer accumulation Patient 3 – 16 week old caucasian male with liver disease, biopsy confirmed diagnosis. of A1ATD	Homozygous Glu342Lys (Z mutation) Homozygous Glu342Lys (Z mutation) Homozygous Glu342Lys (Z mutation)
Glycogen storage disease type 1a (GSD1a)	25 year old caucasian male with clinical features of excess glycogen deposition confirmed by enzyme functionality assay.	Absent hepatic glucose – 6 – phosphatase enzyme
Familial Hypercholesterolaemia (FH)	Caucasian adult male patient with symptoms of early onset atherosclerotic disease secondary to hypercholesterolemia and strong family history. Diagnosis confirmed by LDL receptor dysfunction assay.	Autosomal dominant mutation in LDL receptor
Crigler Najjar Syndrome (CN)	2 month old caucasian male with clinical features of CN.	Homozygous for a 13 bp deletion in exon 2 of the UGT1A1 gene.
Hereditary Tyrosinaemia Type 1 (HT)	2 month old caucasian male with clinical features of HT.	One allele carries a missense mutation in codon 166 of fumarylacetoacetate hydrolase (FAH) gene: T>G in base 553 (553T>G) causes a GTC(val) to GGC(gly) substitution [Val166Gly (V166G)]; the other allele is unknown
Control	Asymptomatic 50 and 55 year old males Asymptomatic 60 year old female	Not tested

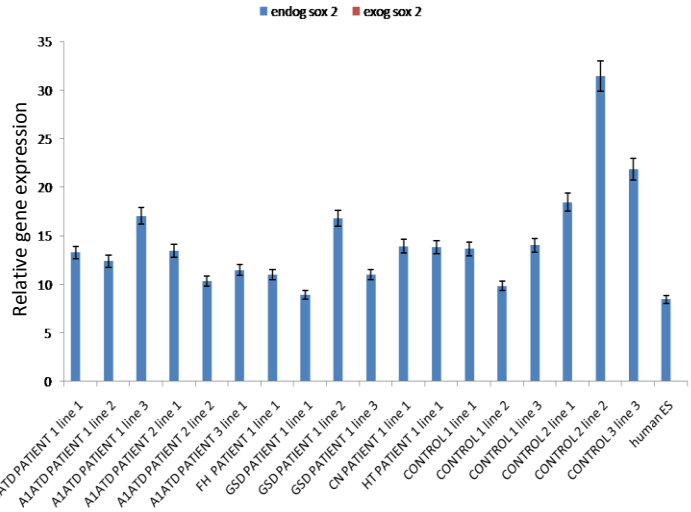
Supplementary Table 1 – Further clinical details of patients from whom disease specific hIPSC library was generated

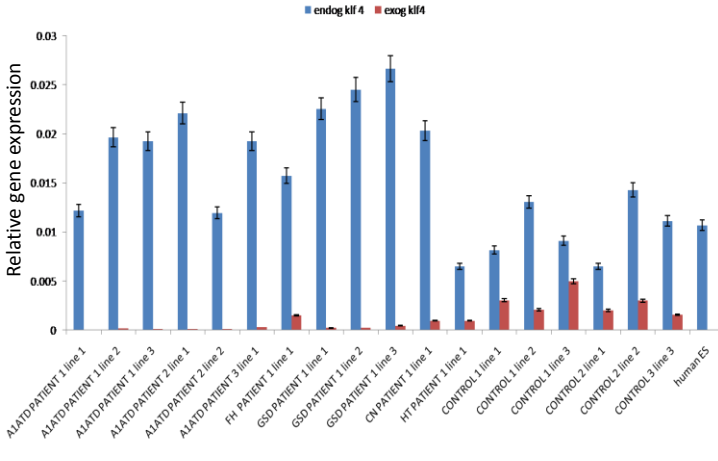


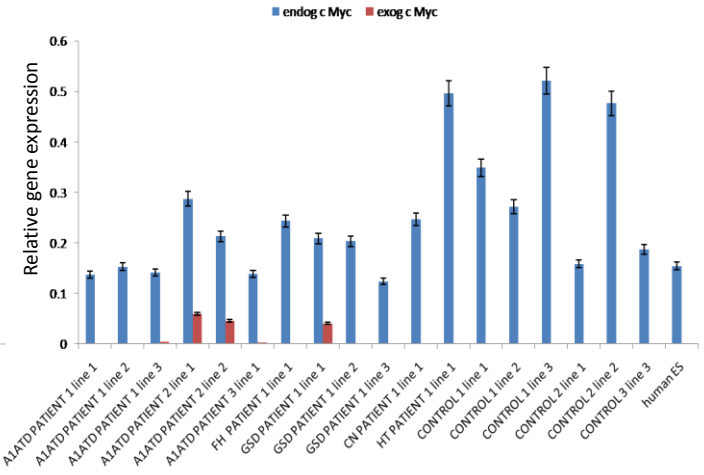
Supplementary Figure 1 - Generation of patient specific Human iPS cells (data shown is taken from one d hIPSC line but is representative of all lines characterized from the dhIPSC library –see Table 1) (A) Bright field pictures depicting the characteristic hESC like morphology of dhIPSC colonies (5X, 20X) and dhIPSC cells (40X). The colonies also displayed the alkaline phosphatase activity that is characteristic of pluripotent stem cells. (B) Immunostaining demonstrating dhIPSCs expressed proteins characteristic of pluripotency – Nanog, OCT3/4, SOX2 and Tra1-60 (Top panels green fluorescence, Bottom panels: DAPI stained nuclei blue fluorescence). (C) hematoxylin and eosin stained sections of teratomas formed following the injection of dhIPSCs into immune deficient mice showing the formation of cell types characteristic of all three germ layers including pigment cells (Ectoderm), goblet cells (endoderm) and cartilage (mesoderm). (D) Immunostaining demonstrating that dhIPSCs could be differentiated *in vitro* into derivatives of the three germ layers and into extra-embryonic tissues: neuroectoderm (SOX-2, PAX6, SOX-1), mesendoderm (SOX17, Brachyury, FOXA2) and extraembryonic (CDX-2, GATA-4,GATA-6). (E) G banding analysis confirming normal karyotype of dhIPSCs.

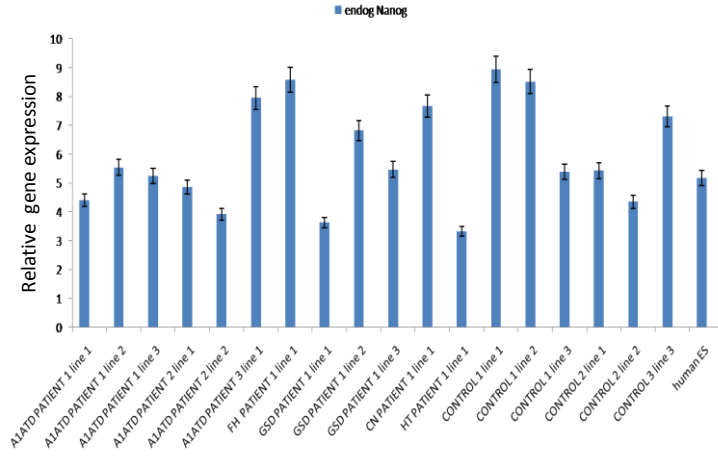
F





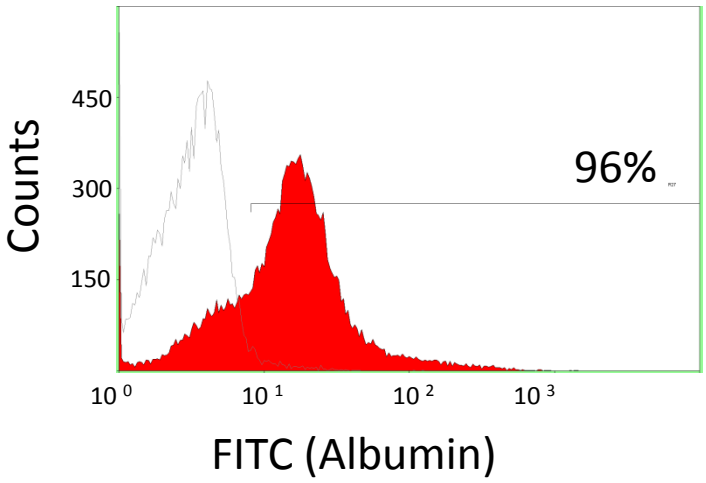




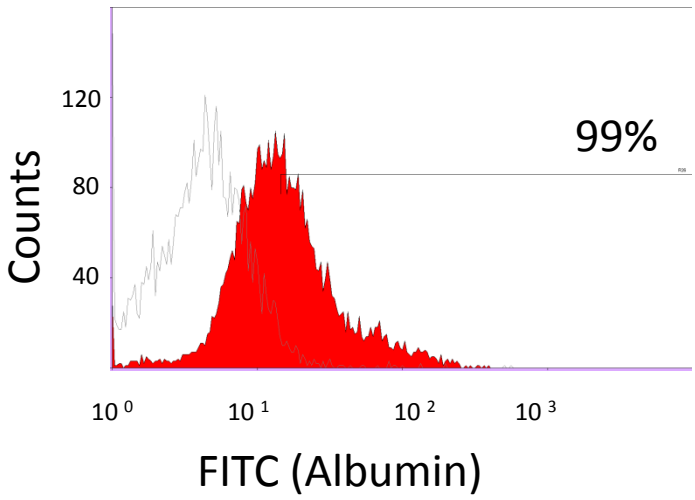


Supplementary Figure 1 contd. - (F) Real Time PCR analyses for the expression of endogenous and exogenous Oct-4, Sox2, Klf-4, C-Myc and Nanog in 18 dhIPSCs lines derived from 9 individuals. Human embryonic stem cells (human ES; H9) were used as a positive control.

G

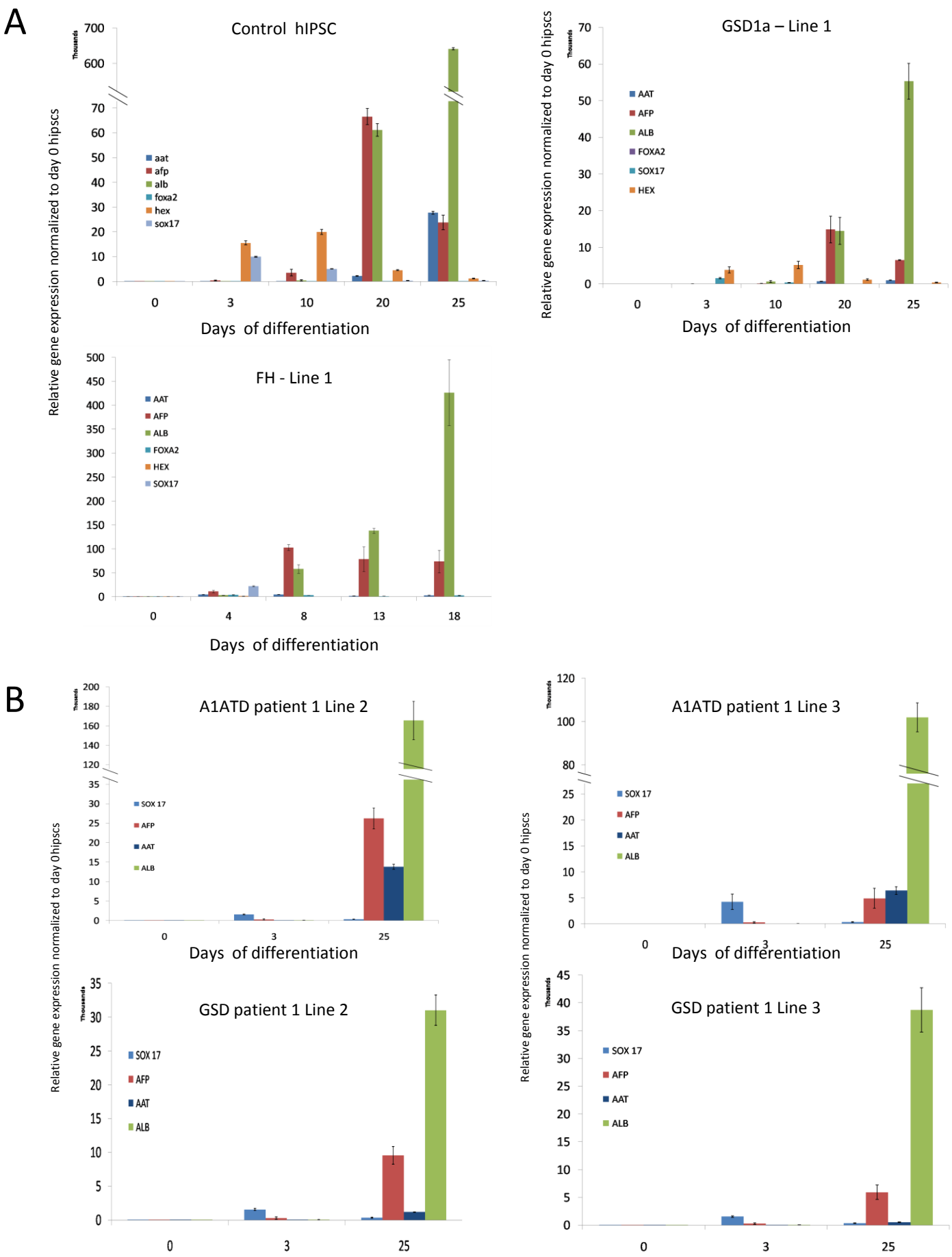


FOETAL



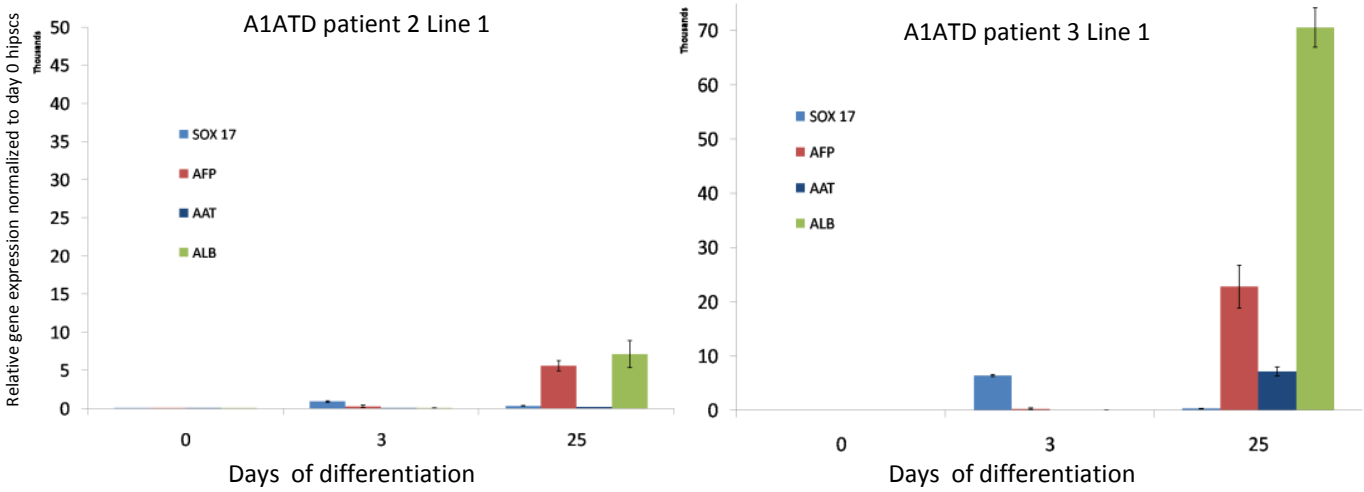
ADULT

Supplementary Figure 1 contd. - (G) Fraction of cells expressing albumin in late first trimester foetal liver (top panel – FOETAL) and adult liver (bottom panel - ADULT) as shown by FACS analyses .

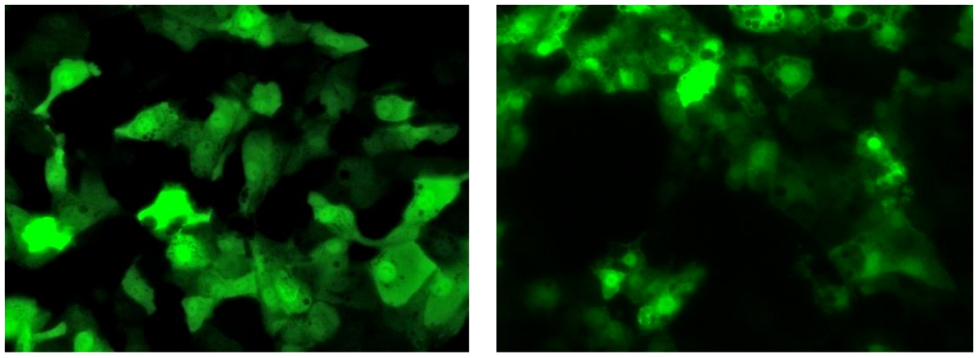


Supplementary Figure 2 – Hepatic differentiation of dhIPSCs (A - B) Real Time PCR analyses for the expression of specific markers of liver development during differentiation of dhIPSCs into hepatocytes.

C



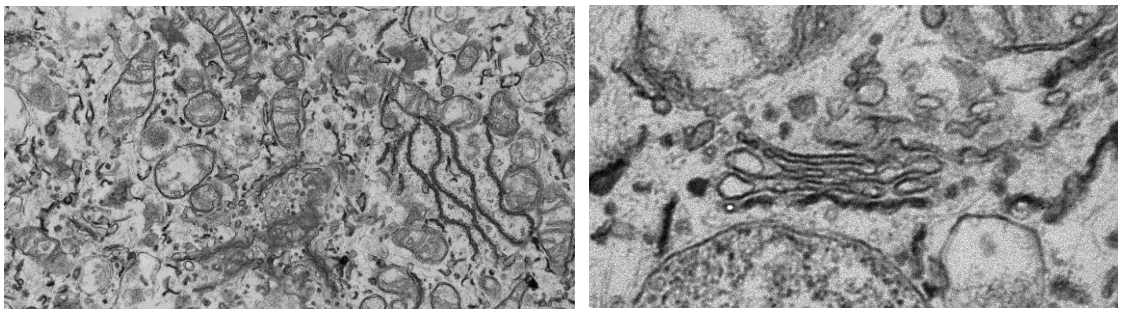
D



dhIPSC derived hepatocytes

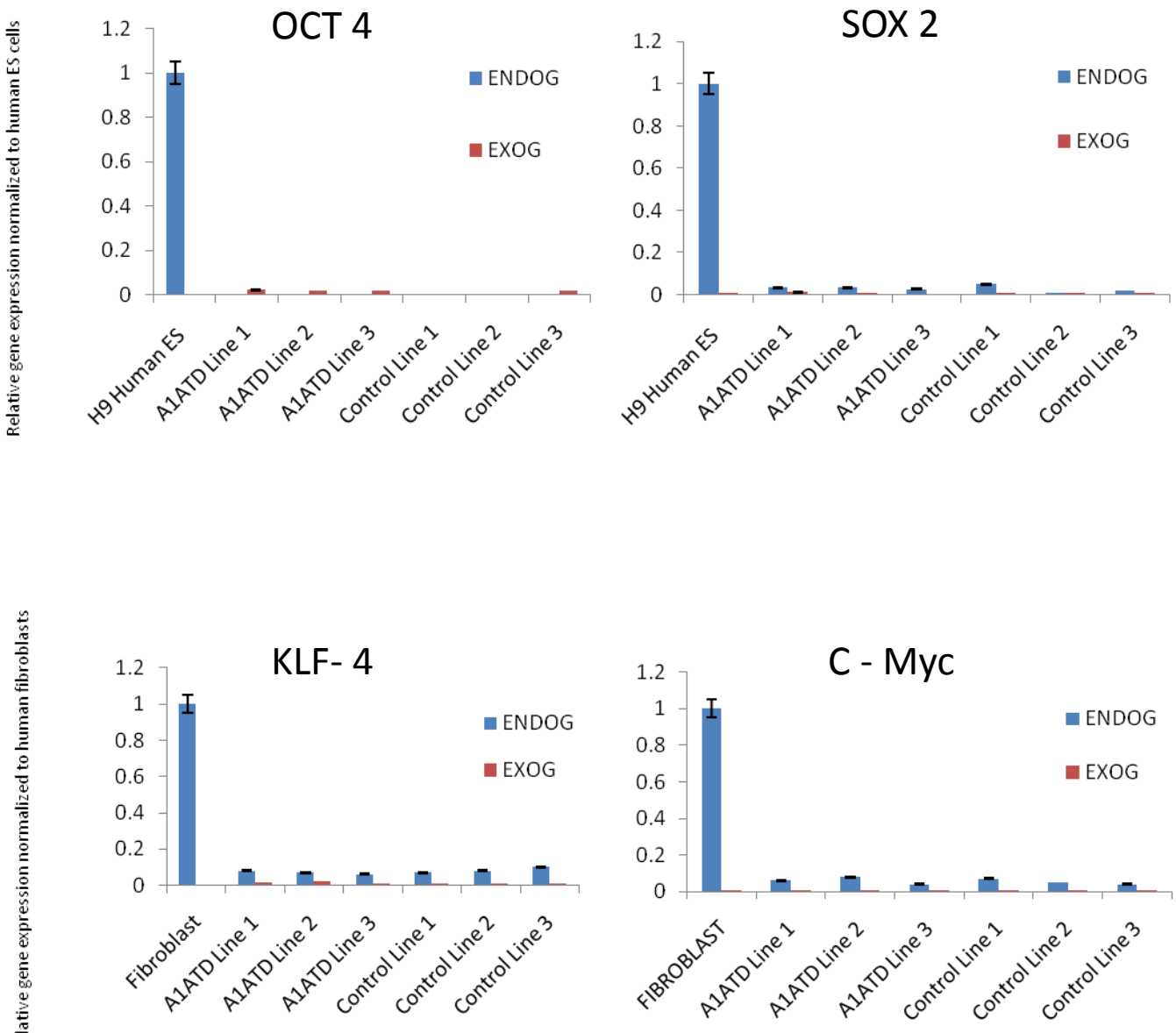
CONTROL hiPSC derived hepatocytes

E



Supplementary Figure 2 contd - (C) Real Time PCR analyses for the expression of specific markers of liver development during differentiation of dhIPSCs into hepatocytes. (D) Immunostaining showing that A1ATD-dhIPSC derived heptocytes were able to express GFP following transduction of a viral vector containing GFP reporter under the control of the liver specific ApoAII promoter. (dhIPSC)- cells derived from same A1ATD line characterized in Figure 1, (control) - cells from non diseased hIPSC derived hepatocytes. (E) Transmission electron microscopy demonstrating that dhIPSC derived hepatocytes display typical hepatocyte features such as prominent nuclear (sometimes binuclear) structures, Golgi body and rough and smooth endoplasmic reticulum.

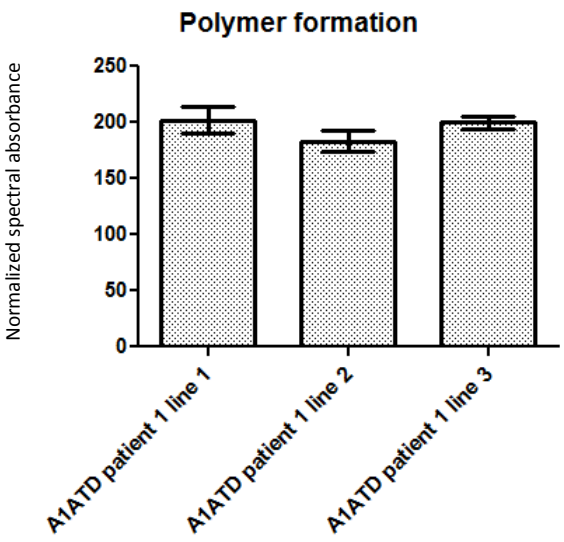
F



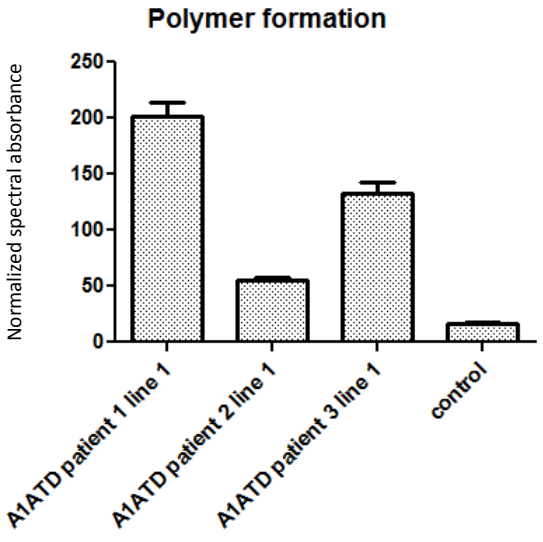
Supplementary Figure 2 contd - (F) Real Time PCR analyses for the expression of exogenous Oct-4, Sox2, Klf-4 and C-Myc in 3 dhIPSC derived hepatocyte lines and 3 controls . Relative expression was normalized to either Human embryonic stem cells (human ES; H9) or fibroblast

G

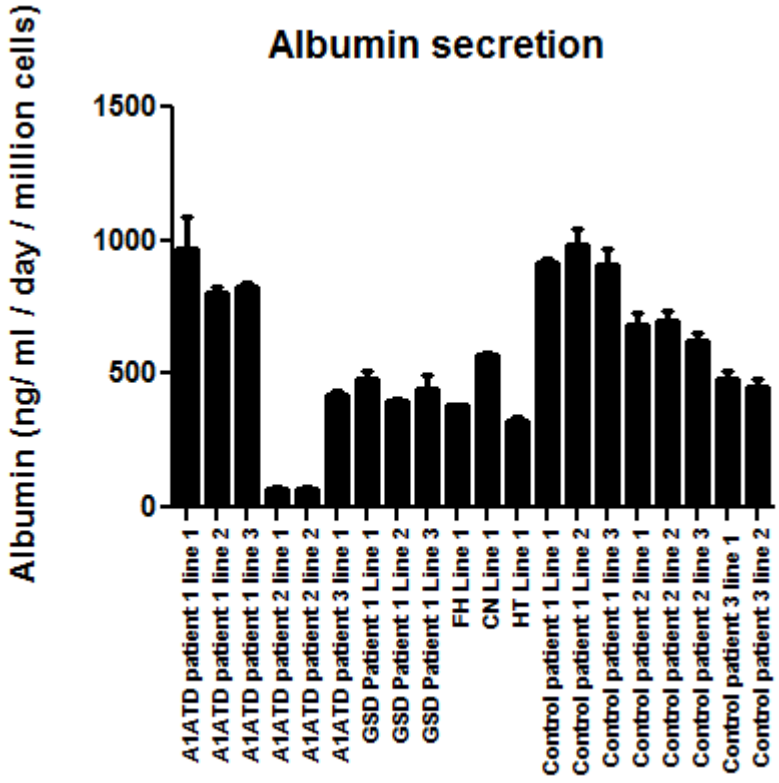
Variability between lines from the same patient



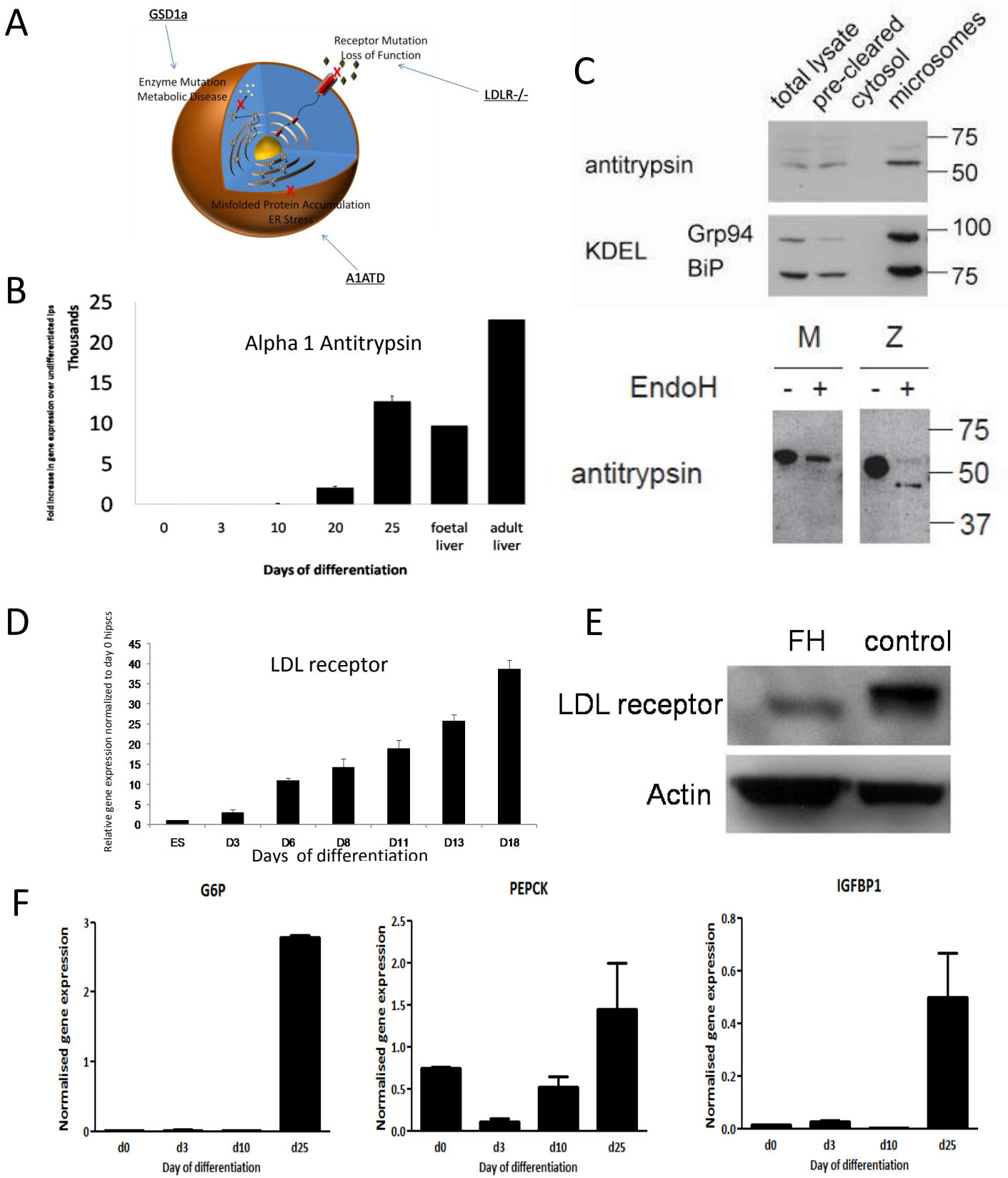
Variability between lines from different patients



H



Supplementary Figure 2 contd - (G) ELISA to assess the intracellular expression of polymeric α_1-antitrypsin protein in patient specific (A1ATD) and control hIPSC derived hepatocytes (control) following overnight proteosomal inhibition by MG132. n = 3. (H) ELISA to assess Albumin secretion from each of the 20 hIPSC derived hepatocyte lines.



Supplementary Figure 3 – Disease modelling using dhIPSCs (A) Schematic depicting the rationale for choosing A1ATD, GSD-1a and FH to explore the capacity of dhISPCs for *in vitro* disease modelling. (B) Real Time PCR analyses comparing the level of expression of AAT in A1ATD-dhIPSCs differentiating into hepatocytes (Day 0, 3, 10, 20 and 25) and in late first trimester human foetal liver (foetal) and in adult liver (adult). (C) Subcellular fractionation of dhIPSC derived hepatocytes from an A1ATD patient co-enriches for markers of the endoplasmic reticulum (GRP94 and BIP) and α_1-antitrypsin as analyzed by western blot.(upper panel). Subsequent Endoglycosidase H (*Endo H*) digestion of A1ATD dhIPSC derived hepatocyte microsomal subcellular fraction (Z) or fraction from control patient hIPSC derived hepatocyte (M) confirms specificity of misfolded polymeric α_1-antitrypsin retention within the endoplasmic reticulum to A1ATD patient line (Z) (lower panel). n = 3 (D) Increase in the expression of LDL receptor during hepatic differentiation (Day 0, 6, 8, 11, 13, 18) of FH-dhIPSCs as shown by Real-Time PCR analyses. (E) Western blot analysis for the expression of Low Density Lipoprotein receptor confirming relative absence of LDL receptor in FH-dhIPSC derived hepatocytes (FH) compared to non diseased hIPSC derived hepatocytes (control). (F) Real time PCR analyses showing the expression of G6P, IGFBP1 and PEPCK during hepatic differentiation of GSD-1a dhIPSCs (Day 0, 3, 10, 25).