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Vascular Ehlers Danlos Patient Clinical History and Generation of an Induced Pluripotent Stem Cell (iPSC) Line

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ABSTRACT

Vascular Ehlers-Danlos Syndrome (vEDS) is a rare autosomal dominant connective tissue disorder caused by a mutation in collagen 3A1 (COL3A1). The disorder is characterized by tissue friability and age-related susceptibility to arterial aneurysm, dissection, and rupture, as well as uterine and bowel tears. Here we describe the clinical history of a vEDS patient. We generated an induced pluripotent stem cell (iPSC) line derived from a vEDS patient carrying a missense mutation in the COL3A1 gene (c.1762G>A, p. Gly588Ser). The stem cells were generated from a male who presented at 48 years of age with an aortic dissection, with a subsequent genetic diagnosis and familial history established. The line exhibited typical iPSC morphology, expression of pluripotent markers, and normal karyotype. Normal and vEDS-derived stem cells exhibited differences in Collagen III processing. Extracellular PIIINP (amino-terminal propeptide of type III procollagen) is elevated in vEDS cells and subject urine samples. The iPSC line can provide valuable insight into the underlying biochemical mechanisms of vEDS pathophysiology.

Keywords

Vascular Ehlers Danlos Syndrome, Collagen III, COL3A1, Aortic Dissection, Extracellular Matrix, iPSC.

Introduction

vEDS is caused by an autosomal dominant mutation that encodes the pro-alpha1 chains of type III collagen (COL3A1), which is found in blood vessels, skin, and internal organs. This mutation, therefore, compromises the durability of vessels and internal organs, causing a variety of pathologies such as organ ruptures, vascular dissections/ruptures, and gastrointestinal perforations/ hernias [1]. Many of these pathologies typically require surgery to correct, but because of vessel fragility, individuals with vEDS have a higher incidence of postoperative bleeding and graft-related complications. For this reason, surgical approaches to pathologies are generally reserved for life-threatening situations [2,3]. Currently, there are no medications that target the underlying collagen defect or gene mutation. Thus, disease management typically relies heavily on lifestyle modification, blood pressure control, and addressing complications as they arise [4].

Generation of patient-specific iPSCs allows for complex and targeted in vitro study of a particular vEDS phenotype with a known gene mutation and clinical presentation. Characterization then opens the door to a wider understanding of mutation-specific vEDS pathophysiology and targeted therapeutics that address the underlying causality. The cell line can be differentiated into endothelial and vascular smooth muscle cells to further model vEDS vascular complications and interventions in a lab setting [5].

Here, we generated an induced pluripotent stem cell (iPSC) line from a vEDS patient carrying a missense mutation in the COL3A1 (c.1762G>A, p. Gly588Ser) gene. The 48-year-old male presented with an aortic dissection, which prompted subsequent genetic diagnosis and the establishment of familial history. Understanding specific vEDS gene mutation expressivity can assist in the development of in vitro iPSC characterization assays and eventual patient-specific interventions.

The objective of this study is to establish iPSCs for both wild-type and those containing the vEDS mutation. Subsequent experimentation can then be done to analyze the difference between

the two lines and genetically manipulate the vEDS cells to correct the faulty mutation. These modified cells could then be used to treat the disorder using the strategy of gene-corrected autologous stem cell therapy. There are recent examples of this approach. In a recently approved therapy for Dystrophic epidermolysis bullosa (DEB), researchers used genetically modified autologous grafts to treat a Collagen VII skin disease. They were able to genetically modify the iPSCs to correct the COL7A1 mutation and then create viable grafts on human skin [6]. Therefore, creation and characterization of iPSCs for regenerative medicine applications is a promising approach for vEDS and other connective tissue diseases.

Results

Clinical History

A 48-year-old white man with no history of smoking or hypertension was admitted to the emergency department due to a Stanford Type A (ascending) aortic dissection, which extended down to his descending aorta (Debakey Type 1). Unlike a type B (descending) aortic dissection, a type A requires surgery, which is performed in an emergency setting. A type A surgery requires a median sternotomy to allow detachment around the aortic arch and the surrounding vessels [2]. If the patient's aortic valve is damaged, it is replaced. A synthetic graft is then placed at the site of damage. The surrounding vessels are then anastomosed and reinforced with felt and biological glue. Blood factors and platelets are then thoroughly replaced to ensure adequate hemostasis. The patient of interest's dissection surgery was successful with no postoperative complications. While there is an increased likelihood for vEDS patients to have complications during surgery, some may not. This is believed to be because some vEDS mutations have minimal effect on the fragility of the vessel [3].

Subsequently, the patient underwent genetic testing and was found to have vEDS. Specifically, he was found to be heterozygous for the p.G588S (c.1762G>A) pathogenic mutation in the coding exon 25 of the COL3A1 gene. The mutation was novel and not found in the data set, and was later annotated as pathogenic, considering the clinical history and characterization of the mutation. The serine substitution seen in this patient has been shown to exhibit the longest survival amongst glycine triple helix missense mutations, with a median survival of 66 years, as compared to 41 years for a valine substitution [7]. Nevertheless, the genetic testing was important because almost 80% of individuals with vEDS have a vascular complication by age 40 [8]. The patient's diagnosis prompted other family members to test for vEDS. This family pedigree for vEDS can be seen in Figure 1, with the patient of interest being individual number 3 highlighted in red. VEDS is an autosomal dominant trait; therefore, each progeny of affected individuals has a 50% chance of inheriting the condition.

Four years later, at age 52, the patient had an abdominal aortic aneurysm near the left common iliac artery. The aneurysm was large enough to elicit surgical repair by placing a synthetic graft at the site of injury. Open abdominal aortic aneurysm (AAA) surgery is a procedure that repairs a widened section of the aorta. A large incision is made in the abdomen to access the vessel, and then a synthetic graft is used to replace the damaged part of the aorta.

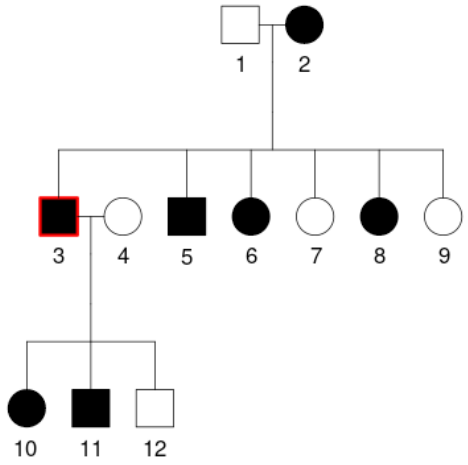

Figure 1: The family pedigree for vEDS autosomal dominant mutation inheritance, with the patient of interest being individual number 3 highlighted in red.

By age 54, the patient presented with multiple abdominal hernias, including umbilical (belly button), incisional (surgical scar), and ventral (general abdominal wall) hernias. Robotic-assisted hernia repair is a minimally invasive surgical technique where a surgeon uses a robotic system to repair hernias, offering enhanced precision, dexterity, and visualization compared to traditional methods [9]. It involves small incisions, a camera for visualization, and robotic arms with specialized instruments controlled by the surgeon from a console. This approach can lead to less pain, faster recovery, and potentially lower recurrence rates compared to open surgery.

The patient's condition is managed by maintaining blood pressure and heart rate using the angiotensin II receptor blocker (ARB), Losartan, and the beta-1 selective beta blocker, Metoprolol [10]. Frequent imaging includes CT, MRI, and Echocardiogram to monitor existing or emergent aneurysms or other conditions related to vEDS [11].

Generation of iPSCs

The vEDS patient derived iPSC lines provide valuable insight into the underlying biochemical mechanisms of vEDS pathophysiology. Reprogramming of vEDS patient derived PBMCs (p.G588S (c.1762G>A)) was performed using a non-integrative Sendai virus vector containing Oct3/4, Sox2, Klf4, and c-Myc (Yamanaka factors). Prior to reprogramming the isolated PBMCs underwent pathogen screening using PCR. The donor cells were negative for all screened pathogens, including HAV, HBV, HCV, HTLV-1, HIV-1, HIV-2 and mycoplasma. The colonies with typical iPSC morphology were selected and expanded for 6 passages before cryopreservation. Three clones were selected for quality control

analysis. The final three clones were tested for recovery from cryopreservation on matrigel coated plates. Phase-contrast images taken 6 days after recovery show characteristic morphology, including high density growth with well defined edges (Figure 2A). In addition, Alkaline Phosphatase (AP) stained the iPSCs, and is a universal marker for pluripotency, highly active in undifferentiated but not in differentiated cells (Figures 2B).

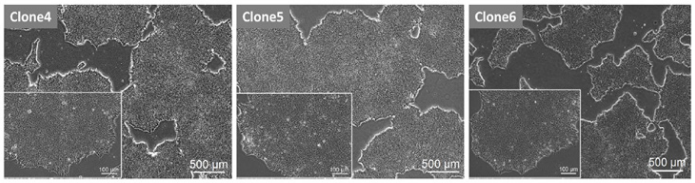

Figure 2A: Phase contrast images of three iPSC clones (#4-6) following recovery from cryopreservation. Stem cells are grown on Matrigel Coated 6-well plate.

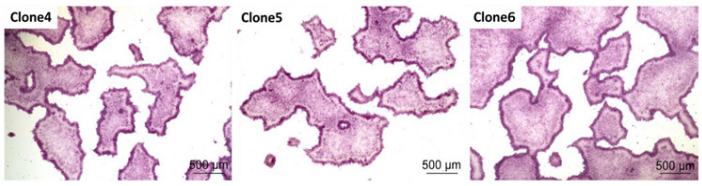

Figure 2B: Alkaline Phosphatase (AP) staining performed on day 6 after recovery of iPSC clones #4-6. Clones have typical iPSC morphology and abundant AP staining.

The defining characteristic of pluripotent stem cells (PSCs) is their ability to differentiate into any of the body's cell types. Pluripotency markers, such as the transcription factors and cell surface markers OCT-3/4, NANOG, and Tra-1-60, act as master regulators and pluripotency biomarkers. Their expression indicates that the cells are in their undifferentiated state. The vEDS patient derived iPSCs were cultured in mTeSR Plus medium on 24 well Matrigel-coated plates and immunofluorescence stained for OCT-3/4, NANOG, and Tra-1-60. DAPI is a fluorescent DNA stain used for visualizing and counting cell nuclei in stem cells, and is the counterstain in immunofluorescence (Figure 3, A-C).

The iPSCs underwent karyotype testing. The results showed normal male karyotype without aberration in the chromosomes (XY, 46) performed at band resolution of 425-450 per haploid set of chromosomes (Figure 4). The vEDS subject had a site specific genetic analysis of COL3A1 (Ambry Genetics). The pG588S variant (also known as c.1762G>A), is located in coding exon 25 of the COL3A1 gene, and results from G to A substitution at codon position 588. The glycine at codon 588 is replaced by serine. Approximately two-thirds of COL3A1 mutations identified to date have involved the substitution of another amino acid for glycine within the triple helical domain. This alteration inserts a bulky side chain into a sterically constrained region [12]. Two alterations in the same codon p.G588D and p.G588V have been reported previously in individuals with vEDS [13].

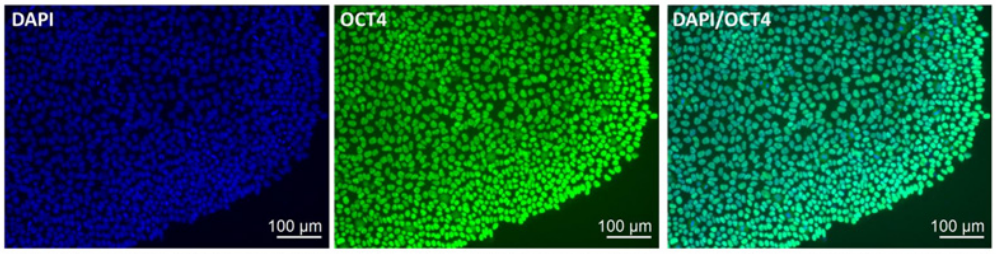

Figure 3A: The hiPSCs were cultured in mTeSR Plus medium on 24-well Matrigel-coated plates before immunofluorescent staining using the Oct4 antibodies. >90% cells were expressing stem cell marker OCT4.

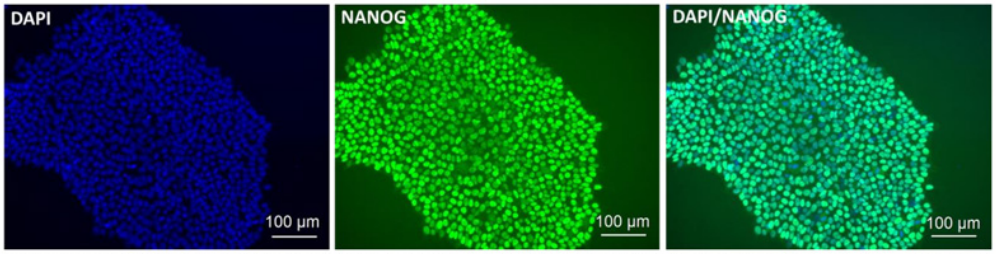

Figure 3B: The hiPSCs were cultured in mTeSR Plus medium on 24-well Matrigel-coated plates before immunofluorescent staining using the Nanog antibodies. >90% cells were expressing stem cell marker NANOG.

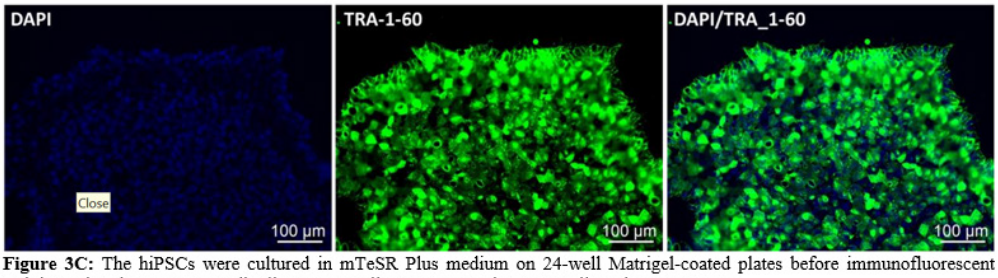

Figure 3C: The hiPSCs were cultured in mTeSR Plus medium on 24-well Matrigel-coated plates before immunofluorescent staining using the Tra-1-60 antibodies. >85% cells were expressing stem cell marker TRA-1-60.

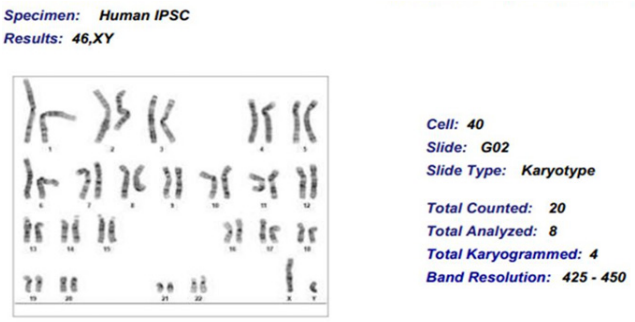

Figure 4: Human iPSC clones underwent karyotyping testing. The result showed normal karyotypes without aberration in chromosomes.

The vEDS derived iPSCs (Clone#5) were compared to a Normal human iPS cell line. The normal iPSCs were derived from PBMCs of a 56-year-old male donor (iXCells Cat#30HU-002). The stem cell lines were grown side by side on Vitronectin coated 6 well plates. After 3 days growth (day 3 post media change), the conditioned media was collected and the cells lysed in RIPA buffer. Normal and vEDS derived stem cells samples were tested for differences in Collagen III protein and PIIINP (the amino-terminal propeptide of type III procollagen). No difference in intact Collagen III was measured between the normal and vEDS iPSCs under these conditions (data not shown). However, processed Collagen III, in the form of PIIINP showed an increase in vEDS conditioned media versus normal iPSCs conditioned media. Additional analysis of PIIINP in urine samples from normal individuals versus vEDS donor indicate a similar trend, with nearly 2-fold increase in PIIINP in vEDS subject samples (Figure 5). PIIINP is a biomarker that is relevant to vEDS pathology and indicative of fibrosis in other Collagen III related diseases (14). These results indicate that increased processing and turn-over of COL3A1are measurable in vEDS patient derived iPSCs as well as patient urine samples.

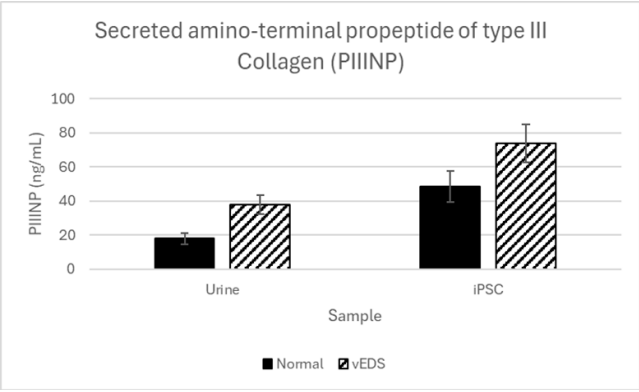

Figure 5: PIIINP ELISA comparing Normal (solid bars) and vEDS (hashed bars) samples from urine and iPSC conditioned media.

Materials and Methods

Cell Source and Reprogramming

A 48-year-old male was diagnosed with Vascular Ehlers Danlos following an aortic dissection and repair. Genetic testing (Ambry Genetics) resulted in a pathogenic variant of COL3A1 detected (p.G588S, c.1762G>A). The individual provided informed consent to supply health information, as well as whole blood, serum and urine samples. PBMCs were isolated from whole blood and used for iPSC reprogramming using Sendai virus (iXCells Biotechnologies). Transduced PBMCs were plated onto Sigma-Corning Matrigel-coated plates and cultured in mTeSR Plus media (StemCell Technologies Cat#100-0276). Post transduction colonies with characteristic iPSC morphology were selected and expanded for 6 passages before cryopreservation. The Human Normal iPSC Line was provided by iXCells Biotechnologies (Cat#30HU-002) and were derived from PBMC of a 56-year-old male donor. The iPSC lines were maintained on Matrigel coated plates (or Vitronectin VTN-N, Gibco Cat# A14700) with mTeSR Plus media changed every 2-3 days.

Pathogen Screening

Pathogen screening of PBMCs isolated from patients' blood was submitted for screening using PCR. All parental lines are negative from all screened pathogens, including HAV, HBV, HCV, HTLV-1, HTLV-2, HIV-1, HIV-2, and mycoplasma (IDEXX Bioanalytics).

Pluripotency Marker Analysis

The iPSCs were seeded onto Matrigel coated 6 well plates and Phase-Contrast images taken 6 days after recovery from cryopreservation to assess morphology. Alkaline Phosphatase Live Stain (Molecular Probes, Cat#A14353) was used to identify pluripotent stem cells. Pluripotency makers Oct3/4 (eBioscience Cat#EM92), Nanog (eBioscience Cat#23D2-3C6), and TRA-1-60 (Invitrogen Cat#Tra-1-60) were used for immunofluorescent staining on iPSCs cultured in mTeSR Plus media on 24-well Matrigel-coated Plates. DAPI nucleic acid stain (Thermo Cat#62248) was used as a counter stain to determine total cell number.

Karyotyping and Genomic Analysis

The iPSC clone #5 was collected and analyzed for chromosomal abnormalities with a band resolution of 425-450 per haploid set of chromosomes (KaryoStat Assay, Thermo). Genetic testing was performed by Ambry Genetics (Aliso Viejo, CA).

Collagen 3A1 and PIIINP ELISA on iPSCs and Urine

The vEDS and Normal iPSCs were grown side by side on Vitronectin coated 6 well plates. After 3 days growth (day 3 post media change), the conditioned media was collected and the cells lysed in RIPA buffer. Urine from vEDS patient sample was compared to normal individual pooled sample. The samples were diluted 10-fold in assay buffer and tested for differences in Collagen III protein and PIIINP (the amino-terminal propeptide of type III procollagen). Human N-Terminal ProCollagen III Propeptide ELISA Kit (Invitrogen Cat#EEL204) is a solid phase sandwich enzyme-linked immunosorbent assay (ELISA). Human COL3A1 ELISA kit (Aviva Systems Biology, Cat#OKCD01159) is a standard sandwich ELISA using an antibody specific for COL3A1 pre-coated onto the 96-well plate. Samples were tested in triplicate in 2-3 separate experiments according to manufacturers instructions.

Discussion

Stem cell therapy, specifically using induced pluripotent stem cells (iPSCs), holds significant importance for vascular Ehlers-Danlos Syndrome (vEDS) due to its potential to address the underlying genetic defect. Patient-specific iPSCs allow for in-depth in vitro study of vEDS phenotypes with known gene mutations and clinical presentations. Characterization of these cell lines opens doors for developing targeted therapeutics that address the root cause of the disease. The stem cells can be differentiated into endothelial and vascular smooth muscle cells, which are directly affected in vEDS, allowing for modeling of vascular complications and testing interventions in a lab setting [15].

The objective is to establish iPSCs from both wild-type and vEDS patients, analyze their differences, and genetically manipulate the vEDS cells to correct the faulty mutation. These gene-corrected autologous stem cells could then be used to treat the disorder. Similar approaches have shown success in other connective tissue diseases, such as Dystrophic epidermolysis bullosa (DEB), where Beremagene Geperpavec-svdt (B-VEC) is a modified, herpes simplex virus type 1-based gene therapy vector that topically delivers COL7A1 to dystrophic epidermolysis bullosa wounds. In a phase III study, B-VEC significantly improved wound healing at 3 and 6 months compared with placebo [16].

Our studies show that vEDS-derived iPSCs exhibit increased processing and turnover of COL3A1, measurable as elevated PIIINP (amino-terminal propeptide of type III procollagen) in both conditioned media and patient urine samples. Dysregulation of Collagen, and other extracellular matrix proteins have been previously reported in primary human fibroblasts from vEDS subjects [17]. PIIINP is released during the conversion of procollagen type III to mature collagen fibers. PIIINP is a relevant biomarker for vEDS pathology, tissue remodeling, wound healing, and other fibrotic diseases [14].

In summary, iPSC therapy offers a powerful platform for understanding vEDS, developing targeted treatments, and potentially providing a gene-corrected autologous stem cell therapy to address the critical needs of vEDS patients.

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