

LOOSE CONNECTIONS

What Are Ehlers-Danlos Syndromes?

I am #ZebraStrong

My Ehlers-Danlos Story

My #ZebraStrong Story

Questions, Answers, and the Scientific Method

Global Learning Conference 2016 and #ZebraStrong Rally • Photo Essay

Vascular type Ehlers-Danlos syndrome is associated with platelet dysfunction and low vitamin D serum concentration



The
**Ehlers
Danlos**
Society.

Your Magazine About Living With EDS
Autumn 2016



TABLE OF CONTENTS

| | |
|---|----|
| What Are Ehlers-Danlos Syndromes? | 4 |
| I am #ZebraStrong / Bridgette Connelly Howe | 6 |
| My Ehlers-Danlos Story / Kayleen Williams | 8 |
| My #ZebraStrong Story / Sarah Bekins Tompkins | 10 |
| From the Editor's Desk: | |
| Questions, Answers, and the Scientific Method / Mark C. Martino | 12 |
| Global Learning Conference 2016 and #ZebraStrong Rally | 15 |
| Vascular type Ehlers-Danlos syndrome is associated with platelet dysfunction and low vitamin D serum concentration | 23 |
| Board of Directors, Medical & Scientific Board, Publisher Information | 31 |

THE EHLERS-DANLOS SOCIETY

The Ehlers-Danlos Society is a global community of patients, caregivers, medical professionals, and supporters, dedicated to saving and improving the lives of those affected by the Ehlers-Danlos syndromes and related disorders.

We support collaborative research initiatives, awareness campaigns, advocacy, community-building, and care for the EDS population.

Our goals are worldwide awareness – and a better quality of life for all who suffer from these conditions. Research is at the center of what we do, so that one day we will have a cure.

Our strength begins with hope.

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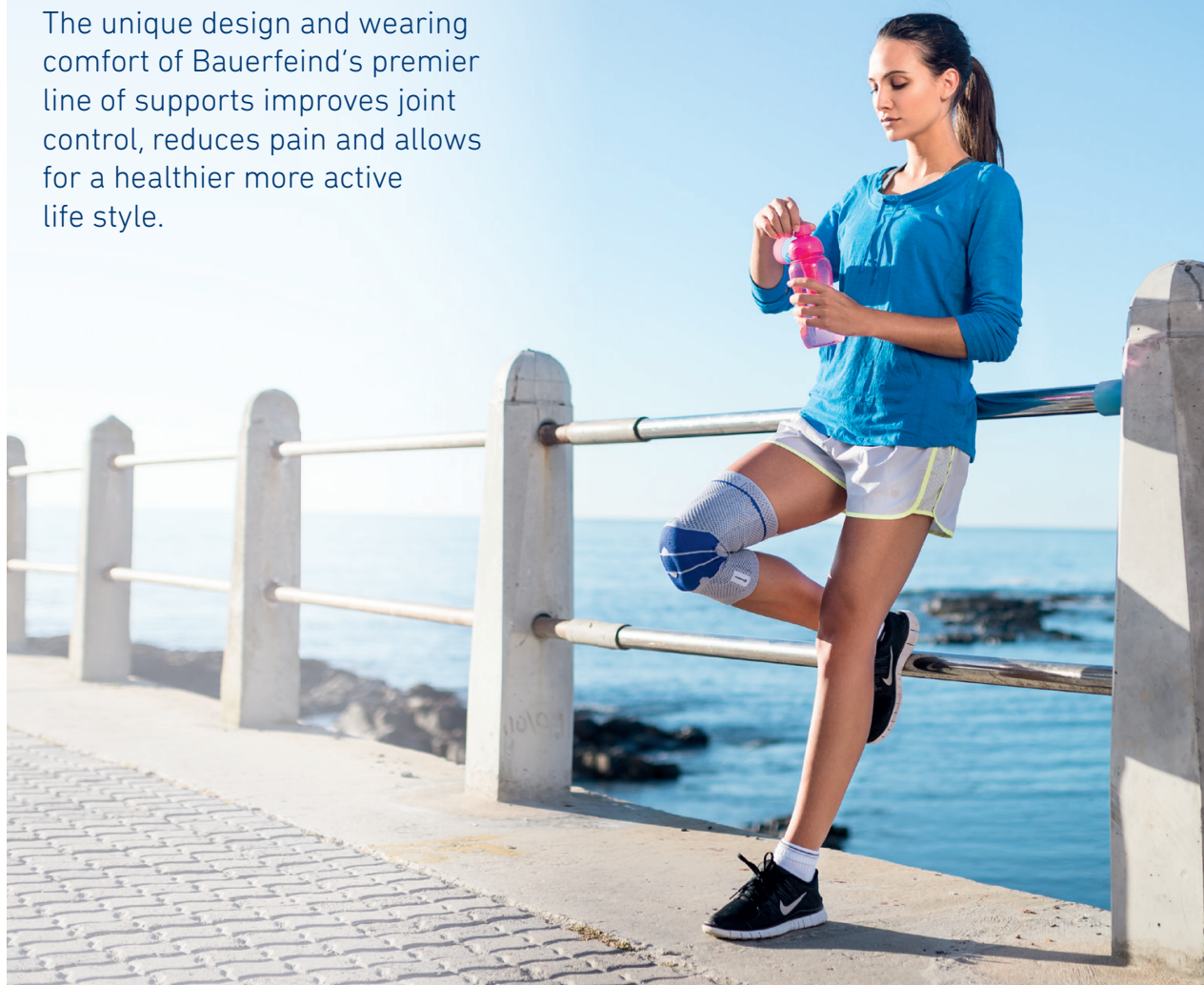
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What Are Ehlers–Danlos Syndromes?

Note: This is from a new tri-fold flyer, available free on ehlers-danlos.com, for awareness and education.

These are Ehlers–Danlos syndromes

Ehlers–Danlos syndromes (EDS) are a group of connective tissue gene disorders that alter collagen, producing complex problems across multiple systems of the body. With badly-constructed or processed collagen, tissue in the EDS-affected body can be pulled beyond normal limits, causing repeated damage. Collagen is the most abundant protein in the body and can be found almost anywhere; the problems resulting from a protein that doesn't behave the way it should can be widespread, in a wide range of severities, and affect areas that might seem otherwise unrelated to each other. There is no cure.

There are at least six types of EDS; each type of EDS has certain physical traits and with notable exception to the most common form, the hypermobile type of EDS, most types have a known disease-causing gene. The physical characteristics that are common to all types of EDS include hypermobile joints (joints that move in greater amounts than expected) and skin involvement (soft, stretchy, saggy, too thin, easy bruising, easy wounding, poor wound healing, or atrophic scarring). EDS is known to affect more than one in 2,500 men and women, of every race and ethnicity.

Early diagnosis is crucial to positive patient health.

Symptoms can be treated as they arise. Care is largely preventative, to support and manage EDS with the intent of keeping damage as minimal as possible. Specifics have to be tailored to those symptoms exhibited in the person with EDS. Even knowing what type EDS one has, each case of EDS is individual; while knowing what might happen is helpful, probably only a subset of symptoms will cause problems, not the whole set.

These are the types of Ehlers–Danlos

Most but not all of the genes responsible are identified, and new genes are still being identified in rare forms of EDS. Current diagnostic information for each type can be found on www.ehlers-danlos.com/eds-types. Diagnostic criteria don't define what the experience of EDS will be, as there are many more symptoms than criteria.

HYPERMOBILE [distinctive cause unidentified]: Most prevalent EDS type; Hypermobile EDS may be the most common heritable disorder of connective tissue, perhaps affecting more than one in 1000 people. Generalized joint hypermobility, skin involvement (possible hyperextensibility or smooth/soft skin), chronic joint pain, recurrent joint dislocations.

CLASSICAL [*COL5A1*, *COL5A2*, *COL1A1*]: Rare; second-most prevalent. Variable skin hyperextensibility, widened atrophic scars (tissue fragility), joint hypermobility, easy bruising; ± mulluscoid pseudotumors, subcutaneous spheroids; occasional internal organ fragility.

VASCULAR [*COL3A1*]: Rare. Thin, translucent skin, arterial/intestinal/uterine fragility or rupture, extensive bruising, characteristic facial appearance; ± acrogeria, hypermobility of small joints, early onset varicose veins, and pneumothorax. Vascular EDS is the most serious type due to the possibility of arterial or organ rupture. Minor trauma can lead to extensive bruising and skin tears. Arterial rupture is the most common cause of sudden death; life expectancy is shortened. Complications occur during and after surgery.

KYPHOSCOLIOTIC [*PLOD1*]: Very rare. Generalized joint laxity, severe muscle hypotonia at birth, scoliosis at birth (progressive), scleral fragility and rupture of the ocular globe; ± tissue fragility, easy bruising, arterial rupture and osteopenia.

ARTHROCHALASIA [*COL1A1, COL1A2*]: Very rare. Severe generalized joint hypermobility with recurrent subluxations, congenital bilateral hip dislocation; \pm skin hyperextensibility, tissue fragility (atrophic scars), easy bruising, muscle hypotonia and osteopenia.

DERMATOSPARAXIS [*ADAMTS2*]: Extremely rare. Severe skin fragility, sagging redundant skin; \pm soft doughy skin texture, easy bruising, premature rupture of fetal membranes, and large hernias (umbilical and inguinal).

Other known rare forms of EDS include, among others, *TNX*-deficient, progeroid, musculocontractual, spondylocheirodysplastic, *FKBP22*-deficient, periodontitis, and brittle cornea syndrome.

These are complications of Ehlers-Danlos

Autonomic Disorders and Fatigue: At least two-thirds of people with EDS struggle with body processes that are supposed to happen automatically, like breathing, blood pressure and heart rate, body temperature, and digestion. In EDS, this most often is postural tachycardia syndrome (PoTS)—when we stand up, we can find a range of problems like lightheadedness, high heart rate, weakness, even fainting. Fatigue can be a bigger problem than even our constant pain. Many of us have what's called “brain fog” — feelings of confusion, forgetfulness, and a lack of focus and mental clarity.

Cardiovascular Issues: These can include easy, possibly extensive bruising; varicose veins and blood pooling; prolonged bleeding; and spontaneous rupture of large arteries. Vascular EDS has particularly severe effects.

Chronic Pain Disorders: For many of us with EDS, widespread pain is a constant companion. Our bodies never get a chance to heal; when our joints move too far (which can happen many times in a day), all the tissue connected to those joints is stretched too far, so we endure a chronic acute pain as we injure ourselves over and over — which makes treating our pain a challenge.

Dental and Jaw Issues: The temporomandibular joint connecting the jaw to the skull can dislocate too. A

slipping TMJ can be painful, restrict eating, and affect major nerves. Many with EDS are prone to dental problems, some resulting from fragile gum tissue and periodontitis, others from the teeth themselves, including enamel fractures and tooth mobility.

GI Functional Disorders: The gut is one of the largest organs, and is made of connective tissue. EDS can cause functional disorders like delayed stomach emptying and gastric reflex, irritable bowel syndrome, and less obvious problems such as nutrient absorption and food allergies.

Immune System Complications and Allergy: There is an unexplained correlation between EDS and mast cell problems — half of mast cells reside in connective tissue. Mast cell disorders affect functions in potentially every organ system. When they abnormally release chemical mediators, a range of chronic symptoms results: skin rashes, flushing, nausea, vomiting, asthma, vascular instability, and sometimes anaphylaxis or near-anaphylaxis attacks.

Joint and Spine/Orthopedics: Hypermobile joints cause injury and long term wear. This includes the junction where the spine joins the skull, leading to a variety of problems with stability that may include Chiari malformation. Neck muscles and ligaments can irritate, compress, or pull on the nerves and blood vessels around the base of the skull, referring pain elsewhere. Those with EDS often have low bone density, starting much earlier in life than most would suspect.

Obstetrics and Gynecology: Issues are reported by women with EDS at a much greater rate than general. Depending (as almost always) on the type of EDS, these can include irregular menses, rapid progression of labor and delivery, pelvic prolapse, and premature membrane and uterine rupture.

Skin and Tissue: Skin can be soft and velvety; stretch further than it should; be translucent and fragile, tearing and bruising easily; and scar severely. Wounds may heal slowly and poorly.

EDS can also lead to many other complications, including metabolic, neurological, psychosocial, and sleep issues.



I am #ZebraStrong

THEY SAY THAT EVERY GOOD STORY has a beginning, middle and an end. As a Vascular Ehlers-Danlos (Type 4) zebra with daily complications, every day I fight to change my ending.

Blissfully unaware, I've been Zebra Strong from day one. Born almost two months premature, I fought to survive and as I grew, specialists remarked on how despite my time on the respirator and in the NICU as a preemie, I was perfectly healthy. As an adolescent I was actively involved in sports and was nicknamed "bruiser" because, as I'd like to think, I was not only tough but I was constantly bruised. My parents, both alarmed, had my blood tested for cancer, blood disorders, and anemia; this investigation only concluded that I was merely accident prone and probably practicing too much. As a late teenager making good grades and desiring to get into a competitive college, I frequented dermatologists for thinning hair and was told it was stress. I also suffered from migraines, something common in women and in my family. I was healthy, happy, and needed to relax.

None of this seemed out of the ordinary and now looking back I can clearly see that all my life I was never really sick enough.

During my second year in my professional career, I developed chronic sinusitis and a red eye that persisted. I was tested for swine flu, pink eye, diabetes, allergies, given eye drops, throat spray, nasal strips and endless scripts to rid myself of the sinus pressure. I once vomited so profusely that I developed a hard lump over my eye. It dissipated with ice and was quickly dismissed.

Bouncing from one specialist to another, it wasn't until my vision changed that an ophthalmologist requested specific imaging that showed something unusual and unheard of: a carotid cavernous fistula behind my left eye. I was urged to follow up at a major medical center. At the time, not even Google could explain to me what this was or why that I had it. I was slightly concerned but not really – after all I was young and seemingly healthy.

The surgeon suggested a routine procedure to examine the fistula and fix it. At this point my eye pain was extremely unsettling, I was still sick, and most of all, exhausted from a wild goose chase of seemingly unrelated symptoms and no answers. I chose to get this procedure done the following day.

When I awoke weeks later in the hospital, barely coherent and in tremendous pain, I was told what everyone else had already endured. During the routine procedure, my major femoral arteries including my aorta tore. In the weeks prior to me waking up, I had undergone dozens of emergency surgeries, fighting for every inch of my life, and just when it was thought that I was in the clear, another problem would unravel. The team of surgeons marveled at how the connective tissue behaved unlike anything they had seen. Through further testing and once stabilized, the unreal news was shared with my family and friends. A rare illness with no cure, even though my entire life I had been called perfectly healthy.

The middle of my story turned my world upside down. I had no inclination of how much the effects of this illness would change my life. Having gone into surgery without knowing of this condition, I was left with a myriad of ailments: a bypass which would later occlude, an abdomen left open, unexplained transient neurological attacks, bowel



obstructions, and routine ambulance rides. I had to learn to sit up, to walk, to eat differently, to deal with not knowing, to be in pain, to not give up.

Although I have been diagnosed with Vascular EDS for the last six years, I know that no matter how my story ends, the middle is where I do daily battles with my illness, unwilling to let it control me. I continue to do things I once loved – differently, slower, with limitations – but with more enjoyment, more love. I got married, adopted a dog. I look forward to doing things that I miss, and taking part in new experiences. I don't take my friends for granted or waste a beautifully sunny day inside staring at

a screen. My life is scarier, but that is what makes it even more precious. The strangest thing I hear now is, "wow you look so healthy."

As I turned 30 this year, watching the minute hand on my cellphone speed passed midnight I shed a single tear. I know that I have not just reached a rite of passage as a woman, but as a survivor of this disease. No matter where you are in your story, you can change the ending. That's what I aspire to do, I hope I can. I am #ZebraStrong.

BRIDGETTE CONNELLY HOWE



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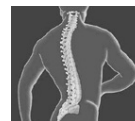
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My Ehlers-Danlos Story

AT BIRTH, IN 1964, MY MOTHER WAS asked by her doctors what she had taken, drank, or smoked to have made her baby be born like I was. My mother went into a kind of denial that anything was wrong with me; she refused to pick me up or carry me when I wasn't walking by age 2, thinking I was just lazy. I finally learned to walk without extra support by age 7.

The one and most amazing thing my mother did do was enroll us in "Baby and Me" swimming classes at the local YMCA. I was already swimming at six months! Swimming was the only way I was able to exercise and build enough strength to finally be able to walk, run, and play. My mother was still in denial that anything was wrong, and when I would complain about pain or be my usual clumsy self, she would call me "Ms. Sarah Bernhardt" because I was obviously over-exaggerating. She even said I was self-abusing when I was still hospitalized six weeks after having my tonsils removed (the sites were still bleeding) and when hospitalized for a fallopian tube abscess for two weeks. Oddly, since she refused to believe that anything was really wrong, I wasn't sheltered or kept from dangers that a diagnosis would have kept me from. This gave me a strengthened immune system that has pretty much saved my life since then.

So I lived a life of constant dislocations. I was told my many what wonderfully soft skin I had. I refused to claim that I had any pain (I knew I was just over-acting). And every time I went to a doctor, I was treated for the specific symptom I went in for, and never diagnosed. I was treated for: spastic esophagus, spastic colon, ulcerative colitis, irritable bowel syndrome, hiatal hernia, stomach ulcers, asthma, collapsed veins and arteries, constant bruising, scarring from anything that broke the skin, neuropathy, and allergies (i.e., soap,

fragrance, so many foods, corn, non-natural-fiber clothes, cigarette smoke, marijuana, ibuprofen, iodine, adhesive tape, and most human touch). Never did any of my doctors ever put together a list of symptoms as having any connection with any other one. The only thing they could agree on was that I was probably not going to be able to live a "quality life" past the age of 40 and would probably be dead by 45 from organ failure.

I was referred from my gastroenterologist to a general practitioner who was just starting his practice in 1994. Dr. Valdez was learning about prolotherapy, and thought this might help my painful joints. We spent the next two years having me get shots three times weekly (shoulders or elbows on Mondays, hips or knees on Wednesdays, and back on Fridays). After two years, my husband changed insurance plans, and we could no longer continue treatment. Other than a slight tightening in my knees, the therapy was unproductive in either helping my "bad joints" or relieving my pain.

In 1997, I was pretty much bed-ridden, having dislocated my back in 1993, and living a life where I denied there was an explanation for me to be in pain at all. My husband and I contacted a lawyer to see if I could get Social Security Disability. I had doctor reports of all my medical issues, but of course, "didn't look ill, sick, or disabled" so was denied. My husband later told me that he even stopped believing that anything was wrong with me. He filed for divorce in January of 1999. We reconciled, and resolved to start living life a bit differently.

In the summer of 2000, my mother was getting a degree in nursing and stumbled across a diagnosis of Ehlers-Danlos syndrome. It all made sense to her finally. She called me and said to ask my doctor to check it out. When I went to Dr. Valdez (still my



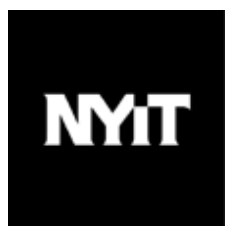
doctor today), he was ashamed that he had not realized that I obviously had EDS and was both apologetic and ecstatic. He contacted all my other doctors and they discussed a comprehensive treatment plan to keep me healthy. The team of doctors I already had were excited to finally feel they could treat me. This team included my original gastroenterologist, my OB/GYN, my rheumatologist, my dentist, my ophthalmologist, and Dr. Valdez. They are in constant contact with each other and consult with each other whenever one of them sees me. While this means I'm kind of stuck living in Houston for the rest of my life, I have a "rest of my life" to live.

I'm 52 years old now, and past my "expiration date" by almost eight years. I have a lot of bad

days, but more good ones than bad. I have a lot of pain, random bleeding internally, bruising and dislocations daily, but I'm still fighting. My doctors say that I'm living longer than most with EDS as bad as I have it, and they are determined to fight with me. Most days I'm fairly mobile, and to the average person I'm normal. My saving grace is that I can still swim. It's my comfort and joy.

Don't ever give up thought that things can get better. While "mind over matter" doesn't solve the problem, it can help keep it at bay enough to lead a meaningful life.

KAYLEEN WILLIAMS



*College of
Osteopathic
Medicine*

THE EHLERS-DANLOS SYNDROME TREATMENT PROGRAM

Our EDS program is a team approach for diagnosing and making treatment recommendations for our patients with Ehlers-Danlos Syndrome. The program takes comprehensive steps to evaluate and design an individualized program. These steps include:

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My #ZebraStrong Story

MY STORY AND MY SYMPTOMS started at 15, and took ten years before receiving an accurate diagnosis of EDS. Earlier at Seattle Children's Hospital, it had been complex regional pain syndrome, reflex sympathetic dystrophy, and fibromyalgia. Then after years and tears looking for answers and doctors, finally in 2011 I saw a geneticist at University of Washington who diagnosed me as Hypermobile Ehlers-Danlos syndrome.

That weekend at my first support group, I met my best friend Kellie Doyle, and she and I were bonded at the hip for three years. We related to one another from our experiences at Children's, hers in Kansas and mine in Seattle. Kellie's wedding was a month after Troy proposed to me. I was in awe of her wedding planning skills given the very painful symptoms Kellie was simultaneously experiencing. I counted on her strength for one day helping me with my wedding. In fact, I was going to ask her to be one of my bridesmaids.

But on her way to the National Institutes of Health for research on her case of Ehlers-Danlos syndrome, she stopped in Kansas to join up with family and fell ill. No one could have guessed that Kellie would never make it to Baltimore and the NIH. Kellie passed away January 8, 2014. Not a second passes that I don't miss her with all of my heart. We'd spent hours on the phone, like we were long-distance friends, and we'd hang out in person as often as possible.

My outdoor pool now sings with birds where she and I would sit with our friend Kathryn, bonding over our syndrome and relationships with our supportive significant others/caregivers; though the three men had never signed up for the latter role, they took the job with full hearts once we

were in need. Kellie taught me to not cater to what I thought because of my symptoms I needed to be like, look like, or act. She taught me to just be me—to smile if I wanted, cry if I needed—that I wasn't responsible for making others understand me or be comfortable with my disability and its many painful symptoms.

Even though she couldn't be at my wedding October 3, 2015, I knew she was there with us all, celebrating, just as I knew for the many surgeries since her passing that she's been there for me, and still is, in her own way, my guardian angel. Kellie was a voice for the voiceless, that one patient that wouldn't take what they were told without an explanation why it was right. She was brilliant and a smart aleck in just the right mix.

Even after her passing, she inspired me to learn more and ask more questions, particularly as none of us had understood why Kellie died. The lack of resolution over her death drew me to the EDNF Conference in 2014 in Houston. There I spoke with my hand surgeon and happily explained to others how easy the operations were and how incredible the results, and how talented Dr. William Ericson is. It was my first taste of advocacy and I loved the feeling of helping others, especially being able to help someone like me.

I also was able to print Kellie's name and a few pictures that would be memorialized at The Ehlers-Danlos Society Center for Clinical Care and Research in Baltimore, Maryland, where EDS patients may go to seek treatment. She's also part of a never-ending quilt, made to memorialize zebras lost. It was my first experience in ten years of feeling like a normal member of society again. Troy and I reveled in it, and it was at this conference I made my goal



to do as much EDS awareness as possible. So my next target would be Rare Disease Day 2015.

Kellie truly inspired me in 2015 to go to Olympia to advocate for a Washington State Rare Disease Day for February 28; and to my surprise, after my first public speech about EDS, we won an acclamation for Rare Disease Day—a huge thanks to Jay Inslee for this effort. This was my first step into awareness and bringing the world to recognize EDS. My next had to be advocacy, where Kellie would have gone next if she could have.

So starting this past spring, I've been attending Rare Disease Legislation Advocacy (RDLA) Conferences for In-District Lobby Days, to help make the legislation called the 21st Century Cures Act be brought to the Senate floor and passed. It has already passed the House but needs support to be brought to the Senate floor and passed. This act will double the treatments available to rare diseases, and hopefully also include the OPEN ACT which gives pharmaceutical companies incentives to develop treatments for the 95% of rare disease without a cure, including Ehlers-Danlos syndrome.

While I've only begun my start into being a patient advocate for the RDLA, my dream is to volunteer for The Ehlers-Danlos Society so I can represent as many zebras as possible in my advocacy for EDS and all rare diseases through the RDLA.

In the immediate future I'm hoping to start a family with my husband this fall. Should we be successful or not, I want to work to make every effort to find a cure for EDS. I want to change our society to one that doesn't see the disabled as a minority group, but people worthy of more than sub-minimum wage who are thrown into poverty by SSDI. I want this world to see disabled people as some of its strongest and brightest underused resources. We as disabled patients have huge potential.

While I may sound idealistic, it's because I'm lying in bed for what is the tenth day after a complete hip repair using cadaver parts to stabilize what I was had into an actually functional hip. My greatly experienced surgeon noted that I had the most hypermobile hip he'd ever seen. My recovery will

be at least five weeks long, just enough time to prepare for my meetings with both Senators Maria Cantwell and Patty Murray to discuss the 21st Century Cures Act and the OPEN ACT, as well as the necessary funding to the NIH and FDA for the desperately needed research and approvals.

An example of the need for funding to both NIH and FDA is for medicine to be available to those who benefit from it, not necessarily just those needs the FDA has approved the medication for, which would open many treatments for rare diseases and increase the treatments available by allowing medication prescribed off-label to be covered by insurance.

My EDS story may have started in sadness and grief for the life I thought I dreamt of; to the monumental loss of losing someone I love so dearly; to taking inspiration from Kellie from awareness to advocacy. There's been a lot of loss, but never without growth. It's been a never-ending journey, but I am always positive and I believe things happen for a reason. I am so proud of The Ehlers-Danlos Society for continually inspiring hope and awareness for a community desperate for both. My hope is to be a part of it one day, and have a family that can feel proud of my role as a zebra. Thank you all for your time and listening to our stories!

SARAH BEKINS TOMPKINS



From the Editor's Desk: Questions, Answers, and the Scientific Method

SUSPECT YOU ARE ALL AWARE BY NOW OF the EDS International Symposium 2016 held in May. For the first time since 1996, how EDS are diagnosed is being examined, and for the first time, there is an attempt to reach an agreement about how symptoms should be treated. Both are enormously important. But it is an ongoing process, not an end. Medicine is a search for answers, as all science is; sometimes the answers are universally true, sometimes they are the best we know until we find better.

This search for answers usually follows the path of scientific method, which Oxford Dictionaries Online defines as “a procedure that has characterized natural science since the 17th century, consisting of systematic observation, measurement, and experiment, and the formulation, testing, and modification of hypotheses.”

It is the way we start learning the world as children. We see something, wonder what it does or why it exists, and test that thing to find out if we were right. The more we learn, the better we are at guessing what something new might do, and we find out if our guesses were accurate, which gives us more information to work with the next time.

Scientific method is rooted in this very human behavior. We see something that needs to be explained, and the method provides a structure for us to learn something about our universe, and to re-examine what we have learned to reach deeper understanding.

It starts with an observation, which leads to questioning why. Someone comes up with ideas that might explain the questions, called hypotheses. A good hypothesis leads to expectations and predictions that can be tested.

Then comes tedious work: gathering information that tests the predictions: from other researchers and their publications; further observations; experiments. Testing to see if the results are what was predicted, refining the predictions with new information if the results aren't quite what was expected, or finding out the predictions are just wrong. Then testing again to be sure.

Once there is enough information gathered to make reasonable conclusions, the original hypothesis is refined, altered, expanded, or rejected. Unless the hypothesis is completely unsound, then a new round of predictions and testing is started, until the hypothesis is either set aside or is producing results that others are reaching, too.

“The first law of science is that the truth has not been found. The laws of science are working hypotheses. The scientist knows that at any moment facts may be found that make the present theory obsolete; this is happening now constantly....

“There’s a continuous movement onward. So there’s no law, no Rock of Ages on which you can rest. There’s nothing of the kind. It’s fluid. And we know that rocks are fluid too, though it takes them a long time to flow. Nothing lasts. It all changes.”

Joseph Campbell, "Pathways to Bliss"
(© 2004 Joseph Campbell Foundation)

Eventually, there may be enough reliable information coming from the initial observation and subsequent testing of predictions to form a general theory—a comprehensive explanation that fits all or at least most of the available data, and is consistent with other current theories.

This is very much the history of Ehlers-Danlos syndromes. Observations of people who very much fit what would eventually be EDS can be found throughout history, starting in 400 B.C. with the founder of medicine, Hippocrates. In 1657 a Dutch surgeon noted a case history of a boy with hyperextensible skin. I know I am not the only person told they had the family joints, which for me can be found in the origins of my family in 15th century Lithuania and Poland.

But no one put together any of the diverse symptoms until Chernogubov, who in 1892 first associated hypermobile joints to skin. Edvard Ehlers in a 1901 case study defined a still unnamed disorder that included lax joints, hyperextensible skin, and a tendency to bruise. In 1908, Henri-Alexandre Danlos published a second case history, helping confirm the hypothesis that there was a distinct disease. In 1936, English dermatologist Frederick Parkes-Weber suggested the disorder

be named Ehlers-Danlos syndrome (although in Russia, it remains Chernogubov syndrome).

Naming the syndrome helped researchers gather data, with the irreplaceable guidance of clinicians, to test the likelihood that EDS was in fact a unique disorder, and gradually there emerged a picture of the symptoms that might define EDS. Enough experience and information was put together to describe a collection of disorders that shared a common set of symptoms, and the first classification of EDS types—the numbers system—sprung up starting in the late 1960s and formalized in 1988 as the Berlin nosology. A list of criteria was proposed that would distinguish each type of EDS not only from each other but from other connective tissue disorders as well.

The Berlin nosology is at heart an hypothesis, refined from those turn-of-the-century case studies; it is essentially a set of predictions about these disorders and how they could be diagnosed. New research and clinical experience was subsequently published that explored how well the nosology defined the EDS types, what was useful and what was unimportant, and asking new questions for investigation.

The Scientific Method as an Ongoing Process

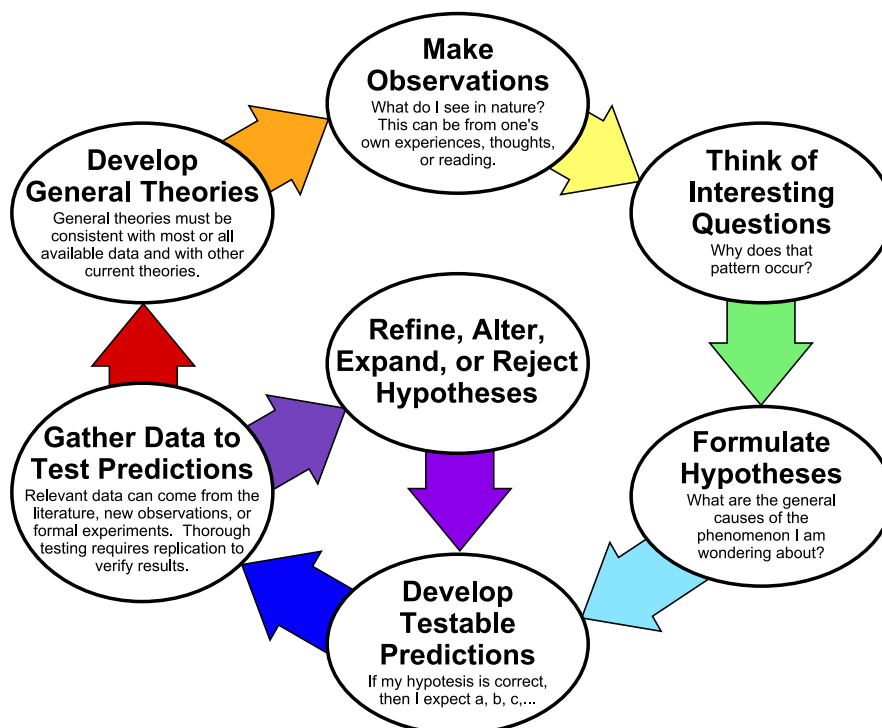


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The next diagnostic criteria were discussed in 1997 – the Villefranche nosology – and published in 1998 in the *American Journal of Medical Genetics*. This was a revised hypothesis, taking into account the interim research and trying to answer new questions. The first step was removing the numbers for the types, instead taking on new, descriptive names. A few types were taken out of the nosology, with a couple of those given their own disease names. Two were combined, and a couple of subtypes were given their own names; and the first attempts at testing for some of the responsible genes were included.

But what we know about EDS has grown enormously since 2000, eclipsing everything known previously by a wide margin, and calling into question the assumptions in the 1998 nosology. The ways in which clinicians applied the criteria and what they observed after diagnosis, along with the results of research, have tested the definitions of EDS, which is to be expected. So in late 2014 a collection of the world's leading EDS doctors and researchers began talking with each other about how to respond to the new data and integrate it into how EDS are defined.

At the EDS International Symposium this past May in New York, the first drafts of the revised set of diagnostic criteria and new recommendations for managing EDS were presented. For the first time, the results of the committees and working groups were up for debate, not only with the other groups but a larger assembly of clinicians, researchers, and representatives from EDS patient groups from around the world. The discussions were lively, and for many of the works-in-progress, new viewpoints and concerns were brought up that needed to be integrated. Revisions were undertaken, and some accomplished by the July Learning Conference in Baltimore when the public saw and heard the results for the first time. The working groups and committees continue to try to reach a consensus. All their work will be peer-reviewed before the final (for this round) papers are published, which is expected in spring, 2017.

There are very few final answers in science or medicine. For any given disease, what was the best possible treatment a decade ago might have

had repercussions we never foresaw, and we may have learned much more about the causes, so the treatment today might be very different than yesterday. The same uncertainty applies to EDS and the New York nosology: we have a better understanding of what we know, and what we have yet to explore, and the published papers will reflect all that.

But it is guaranteed we do not have all the questions, much less the answers. What we think is right today will change over time. We deserve the best possible diagnosis and care, so we will keep gathering data, asking new questions, and re-examining the state of EDS every two years until there are cures.

MARK C. MARTINO

“Science is not about certainty. Science is about finding the most reliable way of thinking at the present level of knowledge. Science is extremely reliable; it's not certain. In fact, not only is it not certain, but it's the lack of certainty that grounds it. Scientific ideas are credible not because they are sure but because they're the ones that have survived all the possible past critiques, and they're the most credible because they were put on the table for everybody's criticism.

“At any moment we have a vision of reality that is effective, it's good, it's the best we have found so far. It's the most credible we have found so far; it's mostly correct.”

Carlo Rovelli, *The Universe: Leading Scientists Explore the Origin, Mysteries, and Future of the Cosmos*, © 2014 by Edge Foundation, Inc.



Global Learning Conference 2016 and #ZebraStrong Rally

AT 3:00 PM ON JULY 14, DR. PETER Byers began kicked off The Ehlers-Danlos Society Global Learning Conference 2016 with the first-ever Thursday session. The conference was held over three days at the Hilton Baltimore in Maryland. The venue was familiar; the programming was not. Replacing the usual mixed format, presentations were made to all of the more than 500 attendees.

Material from the EDS International Symposium 2016 was unveiled for the first time to an eager public. After 18 months of work by committees and working groups leading up to the symposium and subsequent revisions, the sessions in Baltimore laid out new recommendations for diagnosis of all the EDS types, as well as guidelines for treatment. Along with the general sessions, there were two revamped Junior Zebras programs, one for teens and one for kids.

Conference sponsors and exhibitors offered services and products for our EDS audience, and their presence contributed much to the success of the conference. Platinum Sponsor Bauerfeind had a very busy booth; Bauerfeind sponsored the expanded welcome reception Thursday evening. The booth for our Exclusive Gold Sponsor Silver Ring Splints helped underwrite Friday's lunch, and their booth was very popular, as it is every year. Bronze Sponsors were EDSawareness.com and New York Institute of Technology helped fund the breaks. The conference was supported by an education grant from Acer Therapeutics, and other supporting sponsors were Genelux and ohmyarthritis.

During the lunch on Saturday, Board of Directors chair Sandy Chack presented Volunteer of the Year awards to Shani Weber and Mark Martino,

and held an auction for one of the prints of New York City signed by doctors and researchers at the International Symposium.

The first-among-firsts of the conference was the ZebraStrong Rally. Before the conference, the Society's co-executive directors, Lara Bloom and Shane Robinson, spoke in a press release about the need for the rally.

Ms Bloom said, "This is our time to take action. We want the world to understand the suffering Ehlers-Danlos causes and the need for greater awareness, expanded research, earlier diagnosis, and better treatment – worldwide."

Mr. Robinson responded, "This is a movement. To cut through the noise in an election year, we are taking our cause to directly to the public. Through patient testimonies, interactive experiences, and our media campaign, we seek to build real, first-hand awareness across the U.S. and throughout the world."

Ms Bloom added, "ZebraStrong will be a demonstration of our hope, our strength, and our resolve to show the world that while we are stronger than our ailments – and we are unwilling to let our pain steal another moment from our lives. Our pain is real, relentless and demanding of treatment wherever we live in the world!"

A little after four in the afternoon on Saturday after final discussion groups, about 100 of us gathered in front of the Hilton Baltimore, dressed mostly in the rally T-shirts, sponsored by Bauerfeind, GBMC, and The ILC Foundation. Sandy Chack arrived dressed as a glittering zebra. The society provided zebra balloons, and we marched—and rolled—down Pratt Street to the plaza in front of McKeldin Fountain,



across the street from the USS Constellation and the Inner Harbor. We were a beautiful crowd, truly feeling strong.

The rally started with Ms Bloom leading the crowd in chants. Mr. Robinson welcomed everyone, talking about why the rally was held. "Raising awareness of Ehlers-Danlos syndrome will encourage people to go to their doctors and spread the word in larger communities. We want to get more people diagnosed. We want to change the world. This change starts here. If we need more people to learn about Ehlers-Danlos syndrome, we have to get out there and bring it to the people."

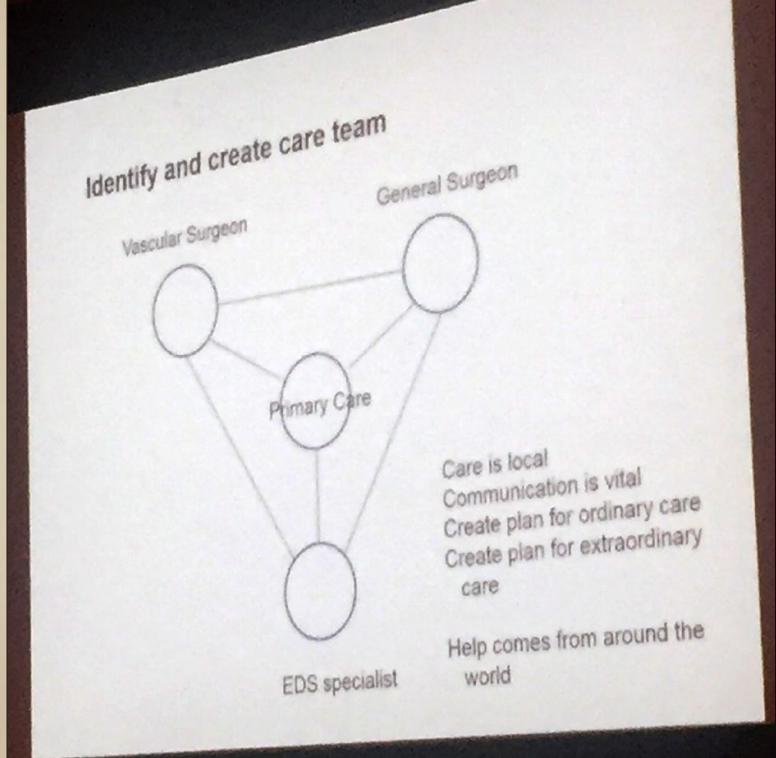
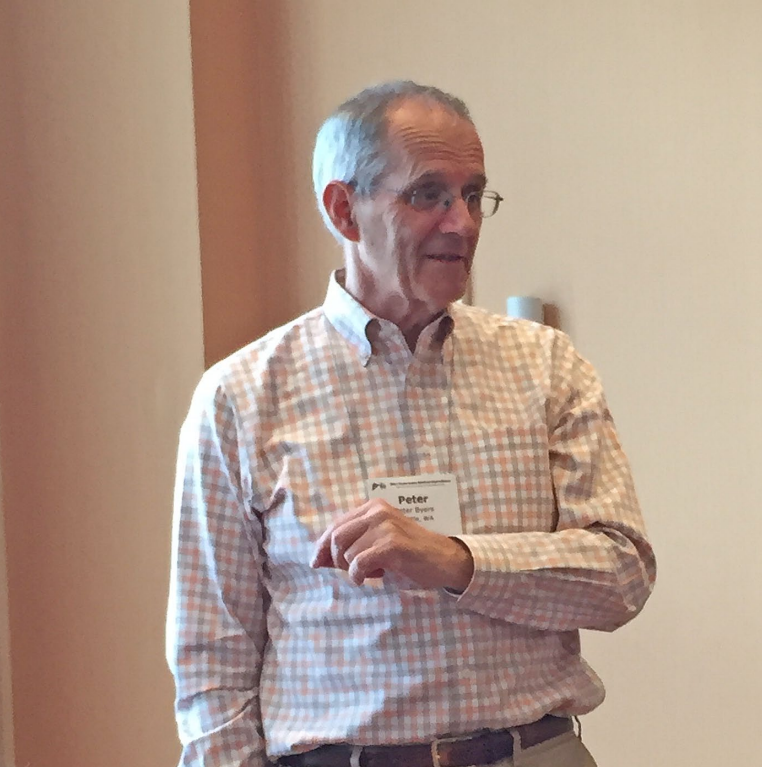
Ms Bloom followed. "EDS hurts every day. It hurts our bodies and it's starting to hurt our minds. It's stopping our quality of life because nobody is listening to how important it is for awareness of this condition. EDS is more prevalent than people

think. You probably know someone living with this who doesn't know it themselves.

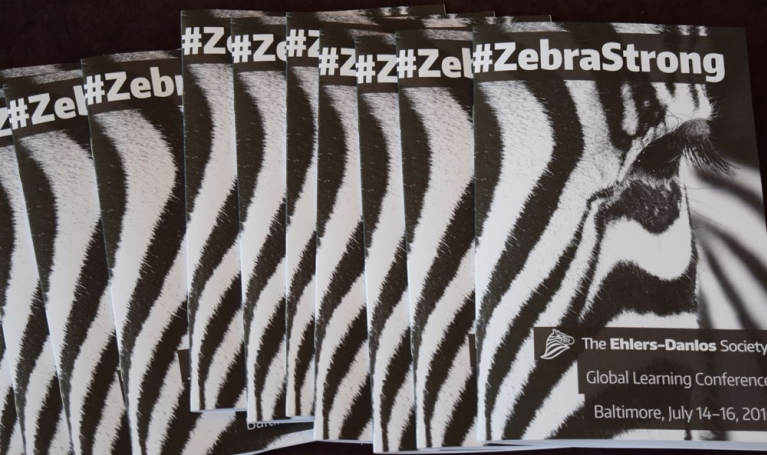
"We are a neglected and damaged community and that's not fair. We deserve so much more. There are people in this crowd who, if they'd received the right diagnosis at the right time, might not have needed to be in a wheelchair. We don't want to be trapped in our bodies anymore. We deserve diagnosis, we deserve management and we deserve validation."

Several EDSers in the rally, including Victoria Graham (Miss White Oak), spoke beautifully and urgently about their lives with EDS and their hopes for a better future. More than a few onlookers were introduced to EDS for the first time, as the rally intended; but perhaps the greatest result was the fellowship and excitement brought out in those of us participating.



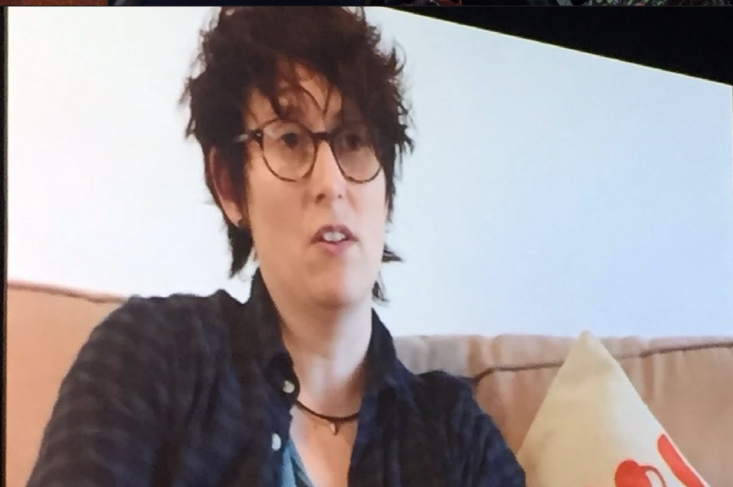








*Issues with My
Tissues*
Director's Cut



In 2011 Lara Bloom became the first known person to attempt the London Marathon with Ehlers-Danlos Syndrome. A documentary 'Issues with my Tissues' was made following her journey and raising awareness of this under diagnosed condition.







RESEARCH

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Vascular type Ehlers-Danlos syndrome is associated with platelet dysfunction and low vitamin D serum concentration

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Abstract

Background: The vascular type represents a very rare, yet the clinically most fatal entity of Ehlers-Danlos syndrome (EDS). Patients are often admitted due to arterial bleedings and the friable tissue and the altered coagulation contribute to the challenge in treatment strategies. Until now there is little information about clotting characteristics that might influence hemostasis decisively and eventually worsen emergency situations.

Results: 22 vascular type EDS patients were studied for hemoglobin, platelet volume and count, Quick and activated partial thromboplastin time, fibrinogen, factor XIII, von Willebrand disease, vitamin D and platelet aggregation by modern standard laboratory methods. Results show a high prevalence of over 50 % for platelet aggregation disorders in vascular type EDS patients, especially for collagen and epinephrine induced tests, whereas the plasmatic cascade did not show any alterations. Additionally, more than half of the tested subjects showed low vitamin D serum levels, which might additionally affect vascular wall integrity.

Conclusion: The presented data underline the importance of detailed laboratory screening methods in vascular type EDS patients in order to allow for targeted application of platelet-interacting substances that might be of decisive benefit in the emergency setting.

Keywords: Vascular type Ehlers-Danlos syndrome, EDS, Bleeding disorder, Platelet dysfunction, Vitamin D

Background

Ehlers-Danlos syndrome (EDS) is a rare connective tissue disorder with multitude heterogeneous symptoms. The estimated overall incidence is approx. 1:5000 [1]. Mutations of fibrillar collagens (I, II, III, IV, V, VI, IX and XII) or enzymes involved in their biosynthesis (i.e. *PLOD1*, *CHST14*) are responsible for the multi-systemic affection involving skin, ligaments, muscles, vessels, hollow organs, eyes and teeth [2, 3]. The rarity, although good in itself, impedes both, evidence or eminence-guided treatment, especially in emergency situations.

Classifications of EDS based on symptoms in the Berlin Nosology from 1986 aimed to facilitate diagnosis

and genetic counseling and to provide treatment suggestions. In the currently applicable Villefranche Classification from 1997 these were additionally linked to the respective genetic mutations [3, 4].

Vascular type EDS, formerly known as EDS type IV, comprises approximately 8 % of all EDS patients [5]. Mutations in *COL3A1* cause stigmata like thin translucent skin with visible venous pattern, congenital clubfoot or hip dislocation and characteristic facial appearance. However, vascular fragility and abnormal vessel structure, cause the characteristic symptoms like easy bruising, severe varicosities, arterial dissection or aneurysm formation and eventual arterial or intestinal rupture, that can lead to fatal consequences and a reduced life span of patients [2, 5, 6].

Current treatment is symptomatic only, since no causal therapy exists. The gold standard “conservative first” is,

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however, of limited advice, for most admissions are due to emergency bleedings, involving mid-size and big arteries in thoracic or abdominal position, including the aorta [7, 8]. Accordingly, mortality rates after emergency surgery are high and have only modestly declined from 40–60 % to around 30–40 % with evolving endovascular arterial repair [8–10].

Moreover, secondary intervention rates up to 50 % due to access site, as well as unrelated secondary bleeding complications add to an unacceptable morbidity and mortality rate in this subset of patients [8, 9, 11, 12]. The critical points impairing surgical outcome are vascular fragility, probably worsened by circulating collagenases during acute events of bleeding, and a deficient coagulation cascade impairing primary healing [13, 14]. Therefore, desmopressin administration prior to surgery was recommended in EDS patients [15]. But whether defects of pro-coagulant factors or misleading platelet-collagen-interactions are causative for deficient coagulatory properties is still unclear and little is known about the coagulation cascade in vascular type EDS in particular [16].

We therefore aimed to investigate hemostasis in vascular type EDS patients under normal conditions by standard laboratory means in order to reveal coagulation defects, eventually allowing a targeted therapy to breach the fatal course of acute bleedings in this subset of patients.

Methods

Patient identification and sample analysis

Vascular type EDS patients were identified and invited with support of a nationwide patients' self-help group, the German National EDS Initiative, in accordance with the national regulations for protection of data privacy. Inclusion criterion was affection by vascular type EDS. All participants were in good condition (Karnofsky Index >90 %). The study was in accordance with the declaration of Helsinki and approved by the local ethics committee (University Hospital of Würzburg) and with patients' informed and written consent. The study was conducted between January 1st and December 31st 2015.

Blood was drawn from a cubital vein with free flow after initial stasis. In order to allow immediate analysis of the samples, seven different laboratories (affiliations no. 3, 4, 5, 6, 9, 10, 11) across Germany participated in the study. All tests are standardized, commercially available products with defined and validated normal ranges and criteria for pathologic results. Normal measurement ranges and availability of single test methods varied slightly among the participating laboratories (Additional file 1: Table S1 and Additional file 2: Table S2). All laboratories are subject to routine quality control and daily/weekly calibration of their test series.

Basic test methods

Automated analyzers did hemograms, which delivered hemoglobin (Hb), platelet count and optional thrombocyte volume. C-reactive protein (CRP) serum concentration was measured as a reference value to interpret test results and exclude acute inflammatory processes. Prothrombin time according to Quick and activated partial thromboplastin time (PTT) for the extrinsic and intrinsic coagulation pathway were measured by a turbidimetric assay. Depending on the laboratory Fibrinogen was measured either by the Clauss-method or as prothrombin time derived fibrinogen (all Quick values were within normal range, Additional file 1: Table S1).

Factor XIII

Factor XIII (FXIII) was measured either by a chromogenic assay or ELISA (enzyme linked immunosorbent assay) since it is not detected elsewhere, yet has a distinctive function in fibrin crosslinking.

Von Willebrand diagnostics

Von Willebrand factor (vWF) was assessed by two different assays. Latex Immunoassay or ELISA-methods were applied to measure vWF-antigen (vWF:ag) and vWF-activity (vWF:act). Reduced vWF (low vWF:ag) and reduced activity (low vWF:act) in synopsis with a clinical bleeding phenotype was thus defined as possible von Willebrand syndrome (vWS). The patients' blood group was determined in order to allow correct assess correct normal ranges.

Vitamin D

Vitamin D concentration was measured from plasma samples by high performance liquid chromatography (HPLC) or enzyme immunoassay (EIA).

ROTEM®

The ROTEM® is a haemostasis analyzer, that measures kinetic changes of the clot elasticity of whole blood samples [17]. It is provided by the TEM group (Basel, Switzerland) (<http://www.rottem.de/en>) and allows quantitative and qualitative assessment by measuring different parameters of the clot status of the blood sample. In our study we applied the in-tem® (fast assessment of clot formation, fibrin polymerization and fibrinolysis via the intrinsic pathway), ex-tem® (fast assessment of clot formation, fibrin polymerization and fibrinolysis via the extrinsic pathway), fib-tem® (fast analysis without platelets; qualitative assessment of fibrinogen status) and ap-tem® (fast detection of lysis when compared with ex-tem via fibrinolysis inhibition).

PFA100®

The PFA-100® analyzes platelet function from citrate blood by aspiration at high shear rates through disposable cartridges containing an aperture within a membrane coated with collagen (Col) plus either epinephrine (EPI) or ADP (ADP). These agonists induce platelet adhesion, activation and aggregation and lead to occlusion of the membrane and cessation of the blood under normal conditions. The resulting time until cessation is called closure time (CT) (<http://www.practical-haemostasis.com/Platelets>). CT-Prolongation is thus suggestive of deranged primary hemostasis such as thrombocyte dysfunction by impaired activation and cross-linking or vWS. Requirements are a thrombocyte count $>80 \times 10^6/\text{mm}^3$ and a hematocrit $>35\%$.

Light transmission aggregometry by Born

Born aggregometry is based on the principle of light transmission aggregometry. Platelet rich plasma is stirred in a cuvette and different agonists are added to induce aggregation. Aggregated platelets absorb less light and transmission detected by a photocell thus increases (<http://www.practical-haemostasis.com>). Agonists are collagen (Col), epinephrine (EPI), adenosinetriphosphate (ADP) and ristocetin (Rist). Additionally, thrombin, thromboxaneA2 and different agonist concentrations can be used. This multiple testing allows measurement of aggregation, shape change of platelets whilst activation and degranulation.

Values are normally displayed in percentage of transmitted light compared to a control probe (blank) with platelet poor plasma set to 100 % light transmission. Results below the normal range thus indicate disturbed aggregation of platelets.

Results

Vascular type EDS patients have heterogeneous symptoms and genetics

22 individuals with the diagnosis of vascular type EDS were enrolled in the study, including fourteen females and eight males (median age 37 ± 16 years). Among them ten patients descended from three families (family A: ID5 and 6; family B: ID16-19; family C: ID11-14) and another three participants reported EDS symptoms in first-degree relatives not enrolled in the study (Table 1).

Major and minor symptoms varied tremendously, with abnormal bleedings, aneurysm formation, unusual hemorrhage and also non-vascular EDS symptoms. Eleven participants had defined mutations in *COL3A1*, three were diagnosed with an EDS specific skin biopsy by electron microscopic examination and eight were diagnosed by clinical evaluation of a geneticist (Table 1).

Blood count and plasmatic coagulation are not altered in vascular type EDS

Hemograms showed no alterations for Hb (13.6 ± 1.1 mg/dL; different normal ranges for males and females were respected – data not shown) and platelet count ($276 \pm 55.4 \times 10^6/\text{mm}^3$). Platelet volume (9.9 ± 0.4 fL) was available from eleven individuals, and only one patient (ID8) showed an aberrant volume of 5.8 fL. CRP was under the threshold of 0.5 mg/dL in all patients (Additional file 1: Table S1).

Prothrombin time, PTT, Fibrinogen and FXIII-levels represented plasmatic coagulation. Measurements were performed in almost every patient. Quick ($97.4 \pm 14.3\%$) and PTT (30.6 ± 3.4 s) showed normal results for almost all participants. Fibrinogen (2.8 ± 0.6 g/L) and FXIII (114.7 ± 23.5 µg/dL) showed borderline levels for only one patient each, but were within normal ranges otherwise (Additional file 1: Table S1). Additional ROTEM® analysis was performed to study clot formation and fibrinolysis within the first subjects enrolled in the study – was, however, abandoned due to high costs or un-availability (data not shown).

Von Willebrand factor diagnostics were available for thirteen patients (Additional file 3: Figure S1/Additional file 2: Table S2). One patient (ID8) showed reduced values and along with a clinical bleeding diathesis was assumed to suffer from a mild form of vWS. Patient ID3 showed abnormally high values and was supposed to eventually suffer from a collagen-receptor associated platelet disorder (assumption by the respective laboratory consultant). The laboratory diagnosis of subnormal vWF-values was thus made in only 1 out of 13 patients.

Platelet function is impaired in vascular type EDS

All enrolled individuals were screened for thrombocyte function by either PFA100® or light transmission aggregometry according to Born, depending on availability. For eight patients both were available.

In total, eleven of 22 patients (50 %) showed impaired aggregation, especially after induction with epinephrine (EPI) and collagen (Col) in at least one of two methods (Fig. 1). Additional four patients showed abnormal results of unclear significance. Six patients showed aberrant values in ADP interaction. From eight patients, in whom both test methods were available, six showed coherent results.

Vascular symptoms and thrombocyte dysfunction vary within families

Three families with more than one member were enrolled. Families A and C had mutations in *COL3A1*, identically found in all affected members (Table 1). The index person in family B was diagnosed by clinical phenotype by a

Table 1 Characteristics of the study population: method of diagnosis shows either the mutation in COL3A1 if found, diagnosis by EDS specific electron microscopy of antebrachial skin biopsy or clinical phenotype evaluated by a geneticist. Major and minor symptoms include EDS and especially vascular type EDS specific symptoms based patients' reports. Familial involvement shows positive family history (yes) in patients and A, B, C refer to distinct families, where more than one member participated in the study (Fig. 2). Medication shows daily and occasional drugs at the time of investigation. (y = years, f = female, m = male, SAB = subarachnoidal bleeding)

| ID | Sex | Age (y) | Method of EDS diagnosis | Major symptoms | Minor symptoms | Familial involvement | Medication |
|----|-----|---------|--|----------------------------|---|----------------------|----------------------------------|
| 1 | f | 39 | clinical | - | (uncomplicated delivery) | yes | Celiprolol |
| 2 | f | 45 | c3508G > A (p.G1170S) | hemorrhage | (mother/sister had lethal internal bleedings) | yes | - |
| 3 | f | 44 | Col3A1 c.1804C > A | hemorrhage, hypermenorrhea | (sister/niece have same vasc EDS mutation) | yes | Thyroxine, Venlafaxine |
| 4 | m | 52 | skin biopsy | cranial aneurysm, SAB | - | - | ASS, Metoprolol, Amiodarone |
| 5 | m | 43 | COL3A1:c.[973G > T] ₁ {=} | cranial aneurysm | - | A | - |
| 6 | m | 13 | COL3A1:c.[973G > T] ₁ {=} | - | hypermobility | A | - |
| 7 | f | 22 | c.2295_2312delTCTATTGGTCTCTCTGG, p.[Le767_Pro772del] | vertebral aneurysm | hypermenorrhea | - | evl Tranexamic acid |
| 8 | f | 36 | clinical | - | hypermobility | - | Thyroxine |
| 9 | m | 53 | clinical | - | multiple hernia | - | - |
| 10 | f | 25 | skin biopsy | internal bleeding | hypermobility, kissing spleen, varicose veins, valve insuffic | - | Tramadol, Bisoprolol, Duloxetine |
| 11 | f | 75 | COL3A1:IVS16 + 1G > A | cervical av-fistula | hemorrhage, varicose veins, hypermobility | C | - |
| 12 | f | 46 | COL3A1:IVS16 + 1G > A | kidney infarction, SAB | hemorrhage, hematoma lower extremity, hypermobility | C | - |
| 13 | f | 55 | COL3A1:IVS16 + 1G > A | SAB | hypermobility | C | - |
| 14 | f | 29 | COL3A1:IVS16 + 1G > A | - | spina bifida, hydrocephalus, hypermobility | C | - |
| 15 | f | 41 | clinical | atrial septum aneurysm | hemorrhage, hypermobility, mitral valve reflux | - | Nebivolol, Kodein, Prednisolon |
| 16 | f | 50 | skin biopsy, negative Col5A/Col3A testing | hemorrhage | (six uncomplicated deliveries) | B | - |
| 17 | m | 19 | clinical | gastric perforation | hemorrhage | B | - |
| 18 | m | 8 | clinical | hemorrhage | impaired wound healing | B | - |
| 19 | m | 9 | clinical | - | facial stigmata of EDS | B | - |
| 20 | m | 50 | Col3A1 c.3544G > A | retroperitoneal hemotoma | - | - | - |
| 21 | f | 25 | Col3A1 c.1258G > C | carotid dissection, stroke | contralateral asymptomatic dissection | - | - |
| 22 | f | 49 | skin biopsy | hemorrhage | gestational bleeding | - | - |

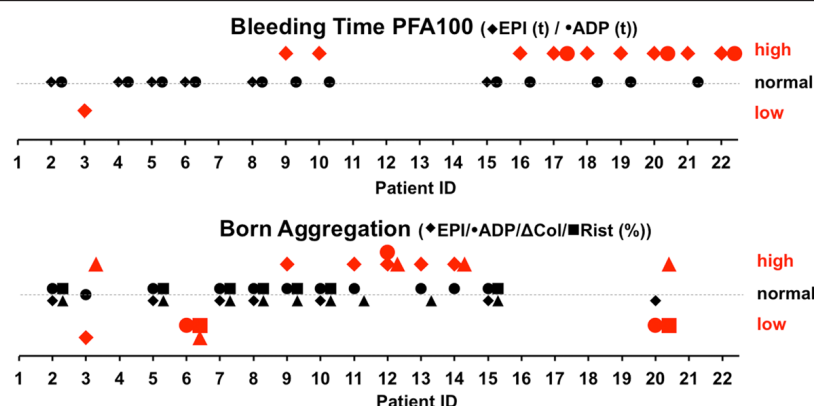


Fig. 1 Platelet function diagnosis: The graphs show qualitative alterations in platelet function diagnosis by PFA100® (upper) or light transmission aggregometry (lower). Bold red signs demonstrate deviation from the normal range (dotted line). Bleeding time is reported in seconds (s), higher values thus indicating an abnormal long time till aggregation. Born Aggregation is reported in percentage of a normal probe with no aggregation and complete light transmission, higher values thus indicating impaired aggregation. Abbreviations in brackets indicate stimulating substances for test: EPI = epinephrine, ADP = adenosintriphosphate, Col = collagen; Rist = ristocetin; The quantitative values for each patient and test are depicted in Additional file 2: Table S2

geneticist, as screening for *COL3A1/COL5A1* mutations and analysis of skin biopsy did not show clear results.

Symptoms or alterations in coagulation parameters varied substantially, even within genetically uniform families. In family A the phenotype of EDS by facial appearance was much more pronounced in the son than the father along with clear signs of platelet dysfunction in the offspring (Fig. 1). In contrast, members of family B were more similar in phenotype and symptoms and showed similar alterations in PFA100® measurements (Additional file 2: Table S2). PFA100® measurements, with prolongation of closure-time after EPI induction, were also very similar in family C, symptoms and phenotype, however, differed notably between generations.

Low Vitamin D serum levels were found in vascular type EDS patients

Serum Vitamin D level was additionally available in fourteen individuals investigated. 57 % were found to have low and critically low values (Fig. 3). One patient (ID8) was below threshold, despite current oral substitution (Additional file 2: Table S2). No patient reported any form of kidney or liver disease that might influence Vitamin D biosynthesis.

Discussion

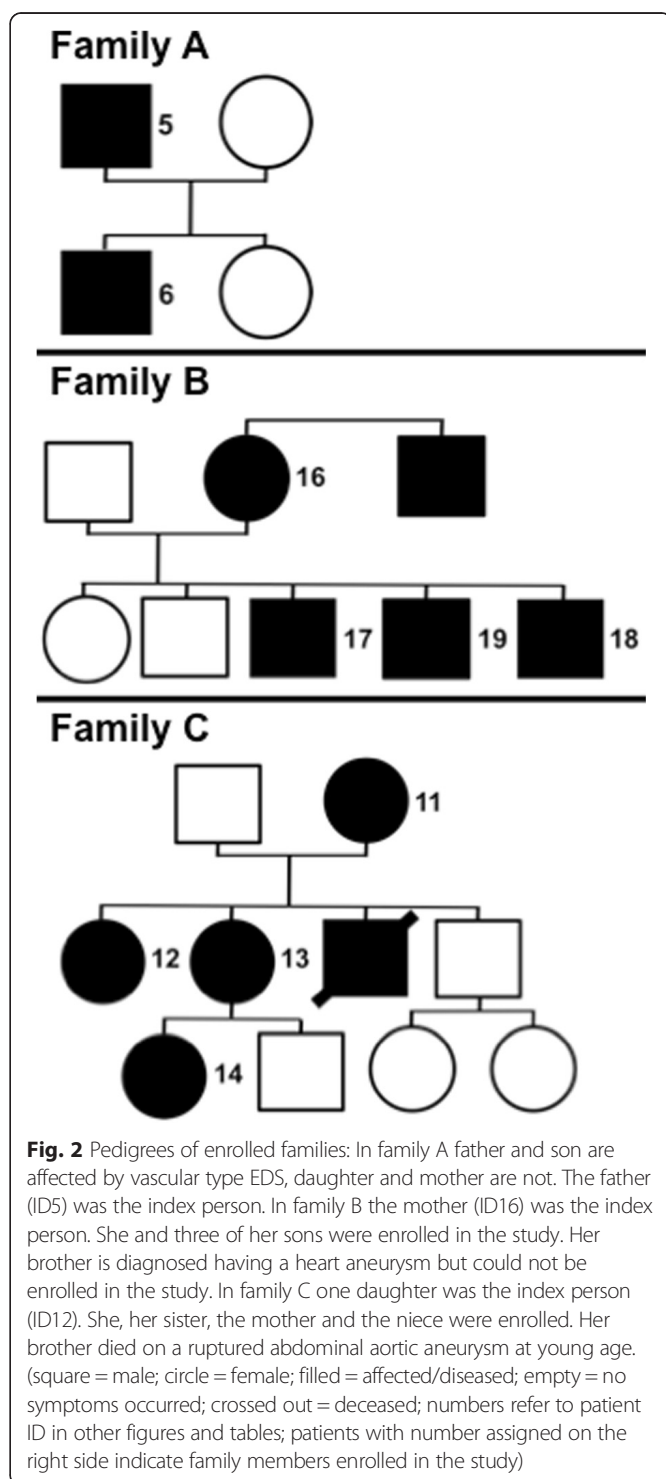
This is, to our best knowledge, the first study to analyze plasmatic and cellular coagulation in a unique number of 22 vascular type EDS affected individuals.

EDS reports are generally based on case scenarios and very few studies include bigger number of patients, generally from different EDS subtypes [11, 15, 16, 18, 19]. Concordantly, evidence for coagulation disorders associated with the disease comes from surgical cases and variances in the female reproduction cycle [20–22]. In 1991

Anstey et al. conducted a study in 51 patients of different EDS types and revealed heterogeneous abnormalities in platelet aggregation and plasmatic coagulation [16]. Here, we investigated exclusively vascular type EDS and reveal dysfunctional platelets as the most prominent disorder with a prevalence of 50 % based on single time-point blood analysis and a corresponding clinical hemorrhagic diathesis (Table 1). Especially thrombocyte stimulation by collagen, epinephrine and ADP was altered (Fig. 1/Additional file 2: Table S2). Epinephrine is a weak agonist itself, but an important catalyzer of aggregation after initial degranulation. Thus prolongation of stable aggregates might be seriously affected.

The study's biggest limitation is the observational character based on single time-point measurements at different laboratories. Nationwide inclusion of patients and immediate sample analyses demand the participation of diverse institutes, and the use of modern, standardized test methods with clearly defined pathological ranges copes with this limitation, as the validation of results for eight patients with two functional platelet tests could demonstrate. Confounding bias in pre-analytics was tried to exclude as much as possible by evaluation of disturbing values. Additionally, analysis should be broadly available and not restricted to specialized laboratories or experimental methods.

Our findings are coherent with previously published EDS cases [16, 18, 23]. In pilot studies from the 1970s Deliyannis et al. and Karaca et al. were able to show reduced aggregation of platelets from control patients with collagen from affected patients and vice versa. Arneson et al. could restore impaired aggregation by addition of soluble fibronectin, an extracellular matrix glycoprotein, in experimental studies [24–26]. Electron microscopic examination of platelets has suggested



altered distribution and function of granules [27–29]. Additionally, thrombocyte derived growth factors might influence *COL3A1* expression in non-vascular tissues [30]. Whether our results are due to dysfunctional receptor expression or impaired degranulation could not be verified in this study, yet warrants further dedicated research.

Based on the cohort size we can safely exclude other factors to noticeably influence coagulation, like thrombocyte volume, FXIII deficiency, vWS, or plas-matic coagulation, as reflected by normal Quick and PTT [15, 31–33]. Normal screening tests, however, cannot exclude mild deficiencies or functional impairment [34, 35].

Since detailed coagulation analysis is not available in emergency situations, evidence for targeted substitution must come from investigations under normal conditions. Our study provides evidence for the application of thrombocyte- and clot-formation-directed substances in case of arterial bleedings. The use of desmopressin, tranexamic acid, activated factor VII, factor VIII and platelet transfusion have been reported in EDS [15, 18, 33, 36]. Experimental data, however, only exist for desmopressin, shown to restore normal bleeding time in a total of 21 children with undefined types of EDS in two studies [15, 37]. This effect is most likely due to an increase in FVIII and vWF from endothelial reservoirs, although in-vitro experiments have also suggested a direct effect on thrombocyte granules [29, 38].

A clear clinical type assignation in EDS is very difficult since the peculiarity of symptoms varies notably among patients and is only partly reflected by the genotype, as observed in our cohort (Table 1, Fig. 2). Variability within families has been described before, but until now not for coagulation defects [2, 3]. Our results from three different families with a total of ten members suggest, that there is no correlation of genotype, clinical symptoms and eventual coagulation disorder, are, however, limited by the small number (Fig. 2). Nevertheless a dedicated family evaluation is advisable whenever an index person is diagnosed.

Of special interest are the low serum levels of Vitamin D in 8 of 14 tested individuals, which has never been investigated in EDS before (Fig. 3/Additional file 2: Table S2).

Vitamin D serum level (µg/l)

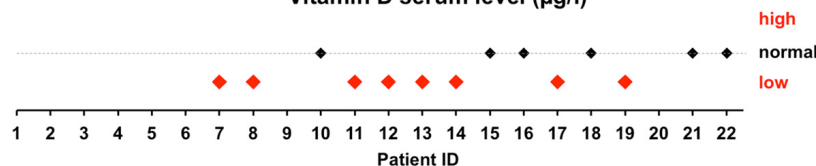


Fig. 3 Vitamin D serum levels: The graph shows qualitative alterations in Cholecalciferole serum levels. Bold red signs indicate deviation from the normal range (dotted line). The quantitative values for each patient and test are depicted in Additional file 2: Table S2

There is clear evidence for impaired bone mineralization and abnormal osseous structure by bone mineral density and x-ray examination from independent studies [39–41]. Furthermore, characteristic EDS-symptoms, like chronic pain, tendon weakness and myopathy, are closely related to bone integrity [42, 43]. Deficiency has been epidemiologically associated with cardiovascular disease, clear molecular mechanisms are, however, missing [44]. Diagnosis of Vitamin D is fairly cheap and oral substitution with cholecalciferol well tolerated. Thus screening of EDS patients for Vitamin D deficiency seems advisable, albeit proof of principle for oral substitution affecting the vascular phenotype has yet to be done in a bigger cohort. Additional benefit of oral substitution in vascular type EDS patients might result from anti-inflammatory and regenerative effects on chronic low-grade inflammation of the vasculature [31, 45].

Conclusion

In a detailed functional analysis of plasmatic and cellular coagulation in a cohort of 22 patients with vascular type EDS we found a high prevalence of 50 % for thrombocyte dysfunctions. This might severely affect hemostasis in emergency bleeding situations and require targeted therapy. Elaborate coagulation screening is thus advisable in every, especially vascular type EDS patient, as well as their relatives and should include modern platelet aggregation tests. Additionally, we have analyzed Vitamin D serum levels for the first time in EDS, showing a deficiency in a respectable number of patients that might be associated with EDS characteristic symptoms.

Additional files

Additional file 1: Table S1. Blood count and plasmatic coagulation laboratory results: The table shows the results for each patient, listed to patient ID according to Table 1, with unit and normal measurement range. Bold red values show deviation from the normal range. Stroked out values are not available in the specific laboratory of examination. (DOCX 74 kb)

Additional file 2: Table S2. von Willebrand, Vitamin D and platelet diagnostics: The table shows the results for each patient, listed to patient ID according to Table 1, with unit and normal measurement range in brackets depending on the respective laboratory where the analysis was performed. For Vitamin D and functional platelet analysis, normal ranges differ among those depending on the commercial test used. Bold red values show deviation from the normal range. Stroked out values are not available in the specific laboratory of examination (n.a.d. = no applicable disease). (DOCX 111 kb)

Additional file 3: Figure S1. von Willebrand Syndrome diagnostics: The graph shows qualitative alterations in vWF diagnosis. Bold red signs demonstrate deviation from the normal range (dotted line). (TIF 213 kb)

Abbreviations

ADP, adenosinetriphosphate; CHST14, gene name: carbohydrate sulfotransferase 14; COL, collagen; COL3A1, gene name: collagen type III alpha 1 chain; CRP, C-reactive protein; CT, closure time in PFA100® measurement; EDS, Ehlers-Danlos syndrome; EIA, enzyme immunoassay; ELISA, enzyme linked immunosorbent assay; EPI, epinephrine; FVIII, Factor VIII in the coagulation

cascade; FXIII, Factor XIII of the coagulation cascade; Hb, hemoglobin content; HPLC, high performance liquid chromatography; ID, identification number; PFA, platelet function analyzer; PLOD1, gene name: procollagen-Lysine-2-Oxoglutarate 5-Dioxygenase 1; PTT, activated partial thromboplastin time; vWF, von Willebrand factor; vWS, von Willebrand syndrome

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Availability of data and materials

All data from this study is included in figures and tables of the manuscript.

Authors' contributions

AB and RW designed the study and AB, CTG and RW acquired funding for the study. AB, BH, FB, DH, JK, HT and ES performed the research. SH, HJ, AT, YK and CTG helped with patient recruitment and genetic counseling. AB, BH, DH, JK, HT and ES analyzed the data. AB and RW wrote the manuscript. All authors approved the final version of the manuscript.

Competing interests

The authors have no competing interests concerning the manuscript.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was in accordance with the declaration of Helsinki and approved by the local ethics committee (University Hospital of Würzburg; no number assigned) and with patients' informed and written consent.

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