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Urogenital Findings in Ehlers-Danlos Syndrome Correlate with Underlying Tissue Laxity Mechanisms

Sahil S. Tonk[1], Golder N. Wilson[2*]

[1]School of Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, USA
[2]Department of Pediatrics, Texas Tech University Health Sciences Center, Lubbock and Kinder Genome Genetics Private Practice, Dallas, TX, USA
Email: *golder.wilson@ttuhsc.edu

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Abstract

Urogenital complications of Ehlers-Danlos syndrome are highlighted in an example patient and documented in 1261 others of whom 566 had DNA variants judged relevant by whole exome sequencing. Females with the condition had frequencies of menorrhagia, endometriosis, ovarian cysts, and bladder issues of 70, 21, 34, and 41%, respectively; under-represented males had a 16% frequency of bladder issues. Less common complications like pelvic floor slippage (7.2%), umbilical (3.5%) or inguinal (2.7%) hernias, polycystic ovarian syndrome (5.6%), or vulvodynia (0.56%) were mentioned by women, frequent urination (6.1%), inguinal hernias (5.6%), and cryptorchidism (1.5%) the only ones recurring in men. The pattern of skeletal and neuro-autonomic findings, their age-related occurrence, and their few unique gene changes suggested that patients with more urogenital findings were a more severe version of the typical condition, their recognition adding therapeutic options like mesh surgery, pelvic vein embolism, or urodynamic optimization to the exercise, hydration, and medications known to benefit patients with Ehlers-Danlos syndrome. Recognition of underlying connective tissue dysplasia-dysautonomia mechanisms as the cause of these urogenital complications can optimize patient care and increase clinical genetic understanding of disorders like interstitial cystitis, dysmenorrhea, pelvic floor/congestion, and polycystic ovarian syndrome.

Keywords

Ehlers-Danlos Syndrome, Urogenital Complications, Bladder Issues, Pelvic Congestion, Hernias, Interstitial Cystitis, Polycystic Ovarian Syndrome, Collagen Gene Change

1. Introduction

Ehlers-Danlos Syndrome (EDS), traditionally defined by hypermobile joints and hyperelastic skin [1], is increasingly recognized as a multisystemic disease [2] associated with significant orthopedic [3] neuro-autonomic [4]-[7], and urogenital [8]-[10] complications. Recognition of the latter problems is particularly important given the greater hypermobility in women [2] and their 4 to 5-fold majority when EDS is systematically evaluated [11]. Their pain [12] from recurring urinary tract infections/cystitis [8], pelvic/lower limb varicosities (congestion, [9] [10]), and vulvodynia [13] is too often attributed to hypersensitivity or psychiatric disease [6] in a reprise of historical dismissals of female symptoms as hysteria [14] [15].

Previously described but inadequately quantified are the menorrhagia, endometriosis, and ovarian cysts of females with EDS and their bladder complications (urgency, leakage, susceptibility to urinary tract infection) that parallel those in affected males [8]-[10]. Better detailing of these urologic symptoms is needed in order to facilitate timely recognition and referral by patients and healthcare workers with development of evaluation and treatment guidelines by specialists.

Here we document the frequencies of urogenital complications by focusing on their prevalence in 1261 patients who were holistically diagnosed [1] [2] and systematically evaluated [2] [11], 906 of them shown by whole exome sequencing to have a range of DNA [11] [14] and particularly of collagen gene [16] changes that relate urogenital and reproductive abnormalities to general effects of tissue laxity and vessel distensibility. The results suggest mechanisms for common complications like interstitial cystitis, emphasize the importance of early acknowledgement and treatment of pain [17], and document low pregnancy risks for the average EDS patient that reverses the aura of hazard promoted by focus on rare EDS types [18] [19].

2. Methods

Prior reports [2] [11] describe the systematic evaluation of 1261 out of 1899 EDS patients diagnosed in a medical genetics private practice from July 2011 through October 2020. Severe EDS types like periodontal [18] or vascular [19] were easily recognized clinically by their severe periodontitis [18], chiseled facies with tight skin, prominent eyes [19], and their frequent bowel and vessel ruptures [18] [19] and excluded from this population. Included patients were shown by evaluation of 80 histories and 40 physical findings to meet criteria for the hypermobile or classical EDS types [20].

These clinical findings and results from 967 undergoing DNA testing (906 by commercial whole exome sequencing using standard methods—[11] [21]) were entered into a password-protected MS Excel© GW patient database approved by the North Texas IRB (centered at Medical City Hospital, Dallas) in 2014 (exempt protocol number 2014-054). Deidentified Excel tables containing the clinical/DNA data reported in this article are available in the Supplementary Materials

of the recent article [11]. Average frequencies, standard deviations, and significant differences at the $p < 0.05$ level were determined using Excel functions and online resources [22], the latter comparing means by two-tailed t and proportions by N-1 chi-squared tests.

3. Results

3.1. Example Patient Presentation

A 30-year-old female was referred from cardiology for evaluation of EDS after having multiple urogenital and Postural Orthostatic Tachycardia Syndrome (POTS) symptoms with minimal evidence of hypermobility. More severe symptoms began at puberty when painful and prolonged periods began along with intermittent pain from ovarian cysts. Later, a partial hysterectomy was needed for endometriosis and the patient had recurrent bladder problems before and after her two pregnancies which included frequency, urgency, and frequent urinary tract infections. She also developed severe migraines in her teens, subsiding somewhat in her 20 s but accompanied by daily headaches with posterior neck pain and poor balance. Head MRI studies showed a 3 - 4 mm Chiari herniation that was not deemed to require surgery. Adolescent fatigue became more severe in her mid-twenties and was exacerbated during her first pregnancy, which was related to POTS by positive tilt-table testing and improved by hydration and salt protocols. Additional symptoms of bowel irregularity, stomach pain, reflux, and reactive airway disease with food-medicine intolerances provided additional indications of dysautonomia.

The patient was not noted to be a flexible baby and was not aware that she was more flexible as a child. She developed pain in her R hip and L leg after her second pregnancy and at evaluation reported some looseness of her R shoulder that may be mild subluxation. She realized upon questioning that her joints do pop with movement and she had scoliosis diagnosed in junior high, wearing a lift in her shoe that may have corrected the problem. An increase in joint pain after pregnancy led to rheumatology evaluation with a diagnosis of fibromyalgia; she had a transient positive ANA and was begun on Synthroid© for a diagnosis of hypothyroidism. Significant in view of her DNA testing were normal echocardiograms and aneurysm screens; pelvic ultrasound did show dilated veins with some downward and backward tilting of the uterus.

The family history included a son aged 10 who was tall and thin with his ankles turning in, having knee and foot pain with occasional headaches. A daughter 7 did not yet have EDS-dysautonomia complications; these were only pregnancies having no complications besides some worsening of fatigue and joint pain. A brother was the only sibling among three who had symptoms (joint pain), her mother had diagnoses of lupus and fibromyalgia with a hip replacement.

Physical examination showed her height and weight to be proportionate at the 60th centiles for age. This fit build likely minimized the patient's joint complications along with her lower-than-average Beighton score [23] of 3 over 9 (she could

only hyperextend her elbows somewhat and could touch her palms flat to the floor without bending her knees). She was able to perform large joint maneuvers by joining hands, one arm around her back and one over her shoulder, do the prayer sign behind her back, and reach her arm around her back to touch her umbilicus. Her face did not have a thin or chiseled aspect, her skin was velvety without unusual scars and slightly elastic (jaw and forearm stretches of 1.5 inches with fleshy rather than thin epidermal folds). She had mild lordosis but no scoliosis, flat feet, or gait changes, and her balance assessed by the tandem walk maneuver was normal.

The impression was a form of AAD/EDS-D with 36 findings by history (more than 50% of EDS patients her age) and 16 by physical (more than 40% of EDS patients her age) on the standard forms [11], see Methods). The patient had more prominent dysautonomia, urogenital, and neurologic rather than joint laxity/injury symptoms but would best fit the hypermobile type with her lack of scarring and her pelvic organ and brain-stem slippage. She also had evidence of mast cell activation with her food-medication intolerances and transient anti-nuclear antibody elevation, likely inheriting her EDS and autoimmune predispositions from her mother who had hip arthritis and a diagnosis of lupus. Whole exome with mitochondrial DNA sequencing found a change in the collagen type III gene that substituted a linear nonpolar leucine amino acid for the kink-producing proline that can have a positive charge (*COL*3 c.24889C > T p.Pro830Leu). Though qualified as a variant of uncertain significance by the testing company, this gene change was interpreted as making a significant contribution to her symptoms and rated as having the highest grade (MDna4+) of clinical diagnostic utility [11]. The medically qualified DNA diagnosis (MDna 1-4+) emphasizes biochemical factors like amino acid structural change, degree of symptom and gene mechanism compatibility with the putative clinical diagnosis, concordance of the gene change and with symptoms in relatives, and prior association of the altered gene with the disease spectrum in question [11]. The dramatic amino acid structural change, presence of the DNA variant in the patient's mother and son, and multiple associations of *COL*3 gene mutations with severe [19] and milder EDS patients [11] justified qualification of this variant as having 4+ diagnostic utility.

3.2. Overview of Urogenital Findings in EDS

Among the 80 historical findings registered during evaluations of patients like the example are five genitourinary findings—the menorrhagia, endometriosis, ovarian cysts, bladder issues, and hernias listed as shaded frequencies in **Table 1**. Patients were asked to add details to each finding—e.g., pelvic congestion/slippage, inguinal, or femoral in the hernia category—but these details were not systematically ascertained. As a consequence, frequencies of the shaded findings in **Table 1** (e. g., bladder issues, ovarian cysts) are fairly accurate while their particular manifestations (e.g., leakage, polycystic ovarian syndrome) are under-reported. Rarer findings like rectal prolapse or premature delivery are even more dependent on

voluntary information, pregnancy problems sometimes mentioned but not systematically documented on the family-natural history form [2] [11] including hematuria, increased urinary frequency, sense of urgency, difficulty initiating stream, incomplete emptying, incontinence, and bladder diverticula.

Better-documented frequencies of EDS female complications, deriving from the approximate 5 to 1 (1064 to 197) excess of women over men in **Table 1**, provide better guidance for therapy. Heavy periods or menorrhagia (70%) can be treated with hormonal regulation (birth control measures) as can endometriosis (21%), both with additional surgical or pain medication options. Ovarian cysts (34%) as single occurrences can be reassuringly differentiated from other causes of abdominal pain but may herald polycystic ovarian syndrome that occurs in 5.6% of female patients. These gynecologic manifestations mirror the high frequencies of menorrhagia, dysmenorrhea, and chronic pelvic pain described in other EDS cohorts [10]. Other pelvic problems in women, slippage of the uterus and bladder needing mesh surgery [24] [25] and blood pooling [pelvic congestion, 9], are not addressed by the history or physical forms [2] [11].

Complications affecting structures occurring in both sexes are still influenced by anatomic differences, bladder issues (41% female; 16% male) including urinary tract infections (9.3%; 0.5%), polyuria (7.6%; 6.1%), leakage (4.8%; 0%), urgency (4.1%; 1.0%), and delayed emptying (3.8%; 2.0%) reflecting the shorter female urethra and estrogen-mediated reduction in collagen crosslinking and pelvic floor integrity [26]-[28]. EDS-associated tissue laxity, mast cell alteration, and urothelial signaling also contribute to interstitial cystitis in women [29]-[32], a complication undoubtedly more common than its volunteered frequency of 4.4% in **Table 1**.

Table 1. Urogenital complications in females and males.

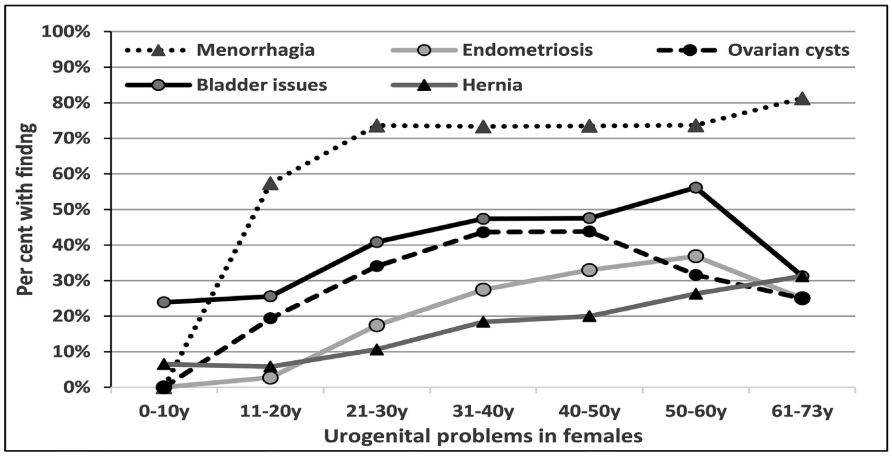
Complication—Group	Females (1064 pts)			Males (197 pts)		
Age group	All	0.3 - 30y	31 - 73y	All	0.7 - 30	31 - 63
Patients pts	1064	538	526	197	158	39
Any urogenital finding pts (%)	883 (83)	404 (75)	479 (91)	42 (21)	30 (19)	12 (31)
Common genital issues pts (%)	808 (76)[1]	360 (67)	448 (85)	17 (8.6)	12 (7.6)	5 (13)
Menorrhagia[2]	70%			--		
Endometriosis[2]	21%			--		
Ovarian cysts[2]	34%			--		
Bladder issues[2]	41%	33%	48%	16%	14%	23%
Urinary tract infection	9.3%			0.5%		
Frequent urination	7.6%			6.1%		
Leakage-night or day	4.8%			0%		
Interstitial cystitis	4.4%			0%		
Urgency	4.1%			1.0%		

Continued

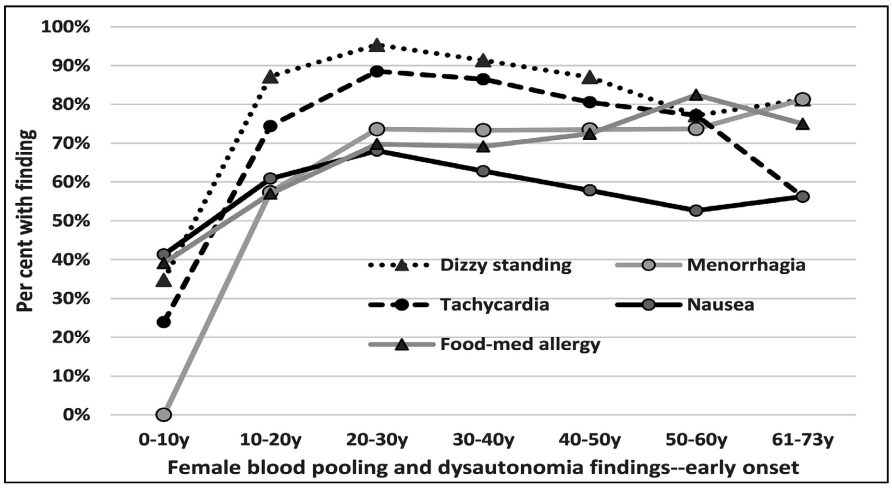
Delayed emptying	3.8%			2.0%		
Hernias[2]	15%	9.3%	21%	7.1%	5.7%	13%
Pelvic floor slippage	7.2%			--		
Umbilical hernia	3.5%			1.5% (3 pts)		
Inguinal hernia	2.7%			5.6% (11 pts)		
Less usual genital issues	13%	15%	11%	1.5%	1.9%	0
Polycystic ovarian syndrome	5.6%			--		
Hysterectomy	2.6%			--		
Dyspareunia	0.85% (9 pts)			--		
Vulvodynia	0.56% (6 pts)					
Tilted uterus	0.38% (4 pts)			--		
Cryptorchidism				1.5% (3 pts)		
Reproductive/pregnancy issues[3]						
Premature delivery	14 pts			--		
Severe postpartum bleeding	4 pts			--		
Early labor	2 pts			--		
Uterine rupture during delivery	2 pts			--		
Infertility	1 pt			0		

General complications are shaded, types of that complication in the unshaded rows below; frequencies in categories may not be additive since a patient may have more than one complication; [1]94 females had 4 or 5 of the 5 urogenital findings that were systematically evaluated, *i.e.*, on the standard history form; [2]systematically evaluated, [3]percentages not precisely calculated since the number of pregnancies is not known—the 900 or so estimated from my family history forms would suggest that the 14 premature deliveries amount to 0.15% of the total pregnancies.

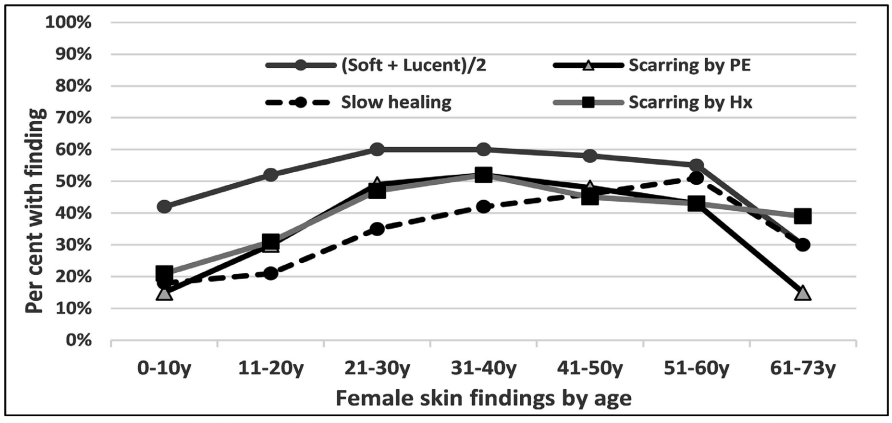
Also contributing to female bladder issues is the pelvic slippage or prolapse that occurs in 7.2% of women, resulting in pressure on the bladder and its distortion by pelvic descent increasing all of the listed complications and paralleling normal increases during pregnancy. Although EDS connective tissue fragility should increase hernia formation, the frequencies in **Table 1** for umbilical (3.5% of females; 1.5% of males) or inguinal (2.7%: 5.6%) hernias do not greatly exceed those for the general population, the former 2% for both sexes [33] [34], the latter ranging from 0.43% female; 1.4% male in Denmark [35] to 0.53% female, 6.8% male in the United States [36]. Frequencies of hernias increase dramatically with obesity [33]-[36] or with abdominal complications like cirrhosis [34], pregnancy (0.8% umbilical, [37]), or post-surgery (1%, [34]). Under-reporting of hernias in **Table 1** likely reflects incompleteness of examination and historical recall since the documented skin lacerations and sutural dehiscence in EDS [1] [2] [11] must be accompanied by spontaneous and post-operative hernias; lifetime risks for spontaneous or secondary inguinal hernias are 3% for females and 27% for males in the general population [36].



(A)



(B)



(C)

Figure 1. Female urogenital (A), blood pooling (B), and skin laxity (C) findings by age. Numbers are from systematic evaluation of 1064 female patients as described in Methods; Hx, History; PE, Physical Examination; y, years.

3.3. Urogenital Findings by Age

Warranting notice in Table 1 are the substantial prevalences of urogenital issues

in younger EDS patients: All urogenital (female 75% versus 91%, male 19% versus 31%), common genital (female 67% versus 85%, male 7.6% versus 13%), urinary tract (female 33% versus 48%, male 14% versus 23%) when those under 30 versus those over are compared. More detailed relations to age are shown in panel A of Figure 1, menorrhagia increasing dramatically with puberty, ovarian cysts and bladder issues somewhat later, endometriosis and hernias (including pelvic slippage) having more delayed increases with age (panel A of Figure 1). Not shown on the very gradual and parallel increases of bladder issues and hernias in EDS males that would likely be more striking if more in the 41 to 50-year (18 patients) or 51 to 63-year (6 patients) groups were included.

Relevant to the pathogenic mechanisms causing these urogenital complications in female EDS patients are increases parallel to those of menorrhagia in panel B--the dizziness, tachycardia, and food-medicine intolerances that reflect the sympathetic stimulation producing postural orthostatic tachycardia and mast cell activation syndrome [5], the nausea reflecting the parasympathetic suppression manifest as low bowel motility/irritable bowel syndrome [7]. That these symptoms of autonomic imbalance in panel B as well as the increases in bladder issues and hernias with age in panel A reflect tissue laxity is suggested by the parallel increase in skin fragility (softness, scarring, slow healing) in panel C of Figure 1; bleeding tendencies reflected by easy bruising (not shown) that are relevant to menorrhagia showed had a similar age profile to the other findings in Figure 1(C).

3.4. Reproductive Issues

Also in need of better documentation are the prevalence of reproductive and sexual issues in EDS females, the more involved EDS subspecialists like cardiologists, rheumatologists, or medical geneticists rarely perform pelvic examinations. Labial and vaginal introitus pain can occur with yeast and other infections, but such pain with no obvious cause that lasts 3 months or more is called vulvodynia. This complication was mentioned incidentally by only 6 female patients with EDS in Table 1, the dyspareunia caused by this and other pelvic issues was mentioned only by 9 women but is much more common in literature reports [8]-[10]. Not systematically queried but voluntarily mentioned were male concerns about penile sensitivity or sexual dysfunction in their smaller cohort.

More optimistic for reproduction is the low prevalence of pregnancy and delivery problems volunteered by women, premature delivery occurring in 14 patients (1.3%), premature labor reported by 2, severe complications like severe postpartum bleeding or uterine rupture occurring in only 4 (Table 1). Although plausible to some degree from laxity of the genital ducts or pelvic blood pooling, mention of infertility was made by one woman and none of the men (bottom row of Table 1).

3.5. Clinical and DNA Variant Profiles of EDS Patients with More Urogenital Findings

The 42 of 197 male patients with bladder issues or hernias and the 94 of 1064

female EDS patients with 4 or 5 urogenital findings were grouped as Urogenital+ and compared with the Other group (1125 patients) having systematic evaluations and fewer urogenital findings in Table 2 and Table 3.

Note first in Table 2 the expected difference in average number of urogenital findings between the male and female groups selected for more (UroGenital+) or less (Other), males scored for only bladder issues and hernias, females for those and three others (menorrhagia, endometriosis, ovarian cysts). Those having more urogenital problems have significantly more findings in most categories, indicating that increased genitourinary issues parallel increases in joint-tissue laxity—Beighton score, childhood findings (awareness of hypermobility, performing double-jointed tricks), joint (subluxations, pain, injury) plus skeletal deformations (scoliosis, flat feet), and skin elasticity (stretching, scarring)—and neural (migraines, muscle aches) or dysautonomia findings (chronic fatigue, tachycardia, anxiety of POTS; reactive skin, food-medicine intolerances of MCAS; irregularity, bloating, nausea of IBS). Parallel increases of urogenital and other EDS findings with age in Figure 1 are mirrored here by increased numbers of findings in male or female urogenital-frequent and other groups.

Table 2. History and physical finding profiles in patients with more or less urogenital findings.

Trait/category	M-UroGenital+	M-Other	F-UroGenital+	F-Other
Patients	42	155	94	970
Age (years)	23 ± 14	20 ± 13	38 ± 9.3*	30 ± 13
Age distress (years)	14 ± 14	14 ± 9.9	18 ± 9.1	17 ± 9.0
Total Hx findings of 80	31 ± 6.8*	24 ± 7.8	46 ± 8.1*	35 ± 9.4
Total PE findings of 40	17 ± 5.0	16 ± 4.7	20 ± 5.1	19 ± 4.5
Beighton score (PE) of 9	5.4 ± 2.1*	4.2 ± 1.9	7.0 ± 1.9*	5.1 ± 1.9
Childhood (Hx) of 10	4.7 ± 1.4*	1.7 ± 1.2	5.8 ± 2.1*	1.4 ± 1.1
Joint (Hx)-Sk (Hx + PE) of 21	7.9 ± 2.5*	6.4 ± 2.6	11 ± 2.9*	8.4 ± 2.9
Skin (Hx + PE) of 11	4.4 ± 2.4	4.3 ± 2.2	6.9 ± 2.0*	5.5 ± 2.3
Genitourinary (Hx) of 2M-5F	1.1 ± 0.3*	0.0 ± 0.3	4.1 ± 0.3*	1.6 ± 1.0
Neuromusc (Hx + PE) of 16	4.7 ± 2.3*	3.6 ± 2.4	7.5 ± 2.4*	5.5 ± 2.6
Dysautonomia (Hx) of 20	11 ± 3.3*	8.5 ± 3.8	15 ± 3.1*	12 ± 3.7
Build-Face-Sk (PE) of 18	6.2 ± 3.0	5.7 ± 2.9	6.5 ± 3.2*	5.8 ± 2.8

*Significantly different at $p < 0.05$ level; Hx, History, PE, Physical Examination; Sk, Skeletal; there were 12 history and 7 physical categories on the standard evaluation forms, each category having 4 to 12 findings [see the Supplementary Materials of reference for all findings]; mean number of findings for several categories are added, e.g., joint history + skeletal history + skeletal physical or dysautonomia (POTS, MCAS, and IBS categories).

The upper left cells of Table 3 show that the 136 patients with more urogenital findings had similar yields to the 1125 (1261-136) with less, 91% or 67% having DNA testing and 61 (67%) having positive results with 98 DNA variants judged potentially significant by commercial report (see Methods). A similar 78% of the 1125 other EDS patients had DNA testing (>95% of both groups by whole exome

sequencing), 507 having significant variants by commercial report. Although only 20 of the 568 results were qualified as definitely contributory to the EDS diagnosis (pathogenic, likely pathogenic) by commercial report, 565 were qualified by clinical protocol as having 2-4+ diagnostic utility for EDS, one of 1+ (uncertain) diagnostic utility, and with 4 incidental and one of 1+ uncertain diagnostic utility).

The lower left cells of **Table 3** compare the 68 genes altered in the UroGenital+ with the 330 in the Other groups, 16 genes with 1 variation in the entire EDS cohort being unique to the urogenital group (see legend). The overall profile of gene change is remarkably similar, with proportions of voltage-gated calcium channel (*CACNA*1/2), connexin or gap junction 2 (*GJB*2), and ankyrin (*ANK*2/3) genes the only ones significantly higher in the urogenital group. These genes, respectively associated with neurologic, skin-deafness, and cardiac diseases do not provide any obvious correlation with urogenital issues unless the reactive and ulcerating skin of the *GJB*2-related Keratitis-Ichthyosis-Deafness (KID) syndrome (entry 148210 in http://www.omim.org/) indicates predisposition to vulvodynia. Listed symptoms characteristic of mucosal/skin fragility (conjunctivitis with corneal ulceration, fissured tongue, inflammatory erythroderma, absence of foreskin) and of connective tissue dysplasia (elbow-knee contractures, flat feet) suggest potential impact of GJB2 gene changes on the urogenital connective tissue and mucosa if adequately investigated [38].

Similarity between the tissues impacted or types of gene product associated with the gene variations in the urogenital and other groups is shown to the right of **Table 3**, of the 17 of 98 variants affecting immune-inflammatory functions based on their associated diseases, is more striking in the former group. Significantly fewer variants in genes encoding transcription factors were found in the urogenital group, such changes predicting that the 40% or so of EDS patients not having DNA variants found by whole exome sequencing will be found when whole genome sequencing can meaningfully analyze the non-exonic or dark genome.

4. Discussion

4.1. Clinical Management

Documenting the pattern of genitourinary complications in patients with EDS has several implications for medical care, particularly in the area of women's health given their disproportionate affliction. Foremost is appreciation that the combination of dysmenorrhea (menorrhagia, 70% of women; ovarian cysts 34%; endometriosis 21%), bladder issues (41% of women with various urodynamic changes and interstitial cystitis), and other causes of pelvic pain like pelvic floor slippage (7.2% of women) can be part of a tissue laxity-dysautonomia, multisystem syndrome (**Table 1**). The parallel increase of urogenital complications with those of adrenergic stimulation (e.g., tachycardia), cholinergic suppression (e.g., low bowel mobility/nausea), and tissue/skin laxity (e.g., scarring, slow healing) around the time of puberty in **Figure 1** cements these relationships and adds a natural history element for EDS consideration. The data of **Table 2** and their eventual recognition

in our example patient reinforce the consonance of urogenital problems with other EDS complications, their presence associated with more severe EDS expression as shown by significantly more hypermobility, childhood, joint-skeletal, and neuromuscular symptoms in males and females.

Table 3. Comparison of DNA testing results in EDS patients with and without more urogenital findings.

Group	UroGenital+	Other	Variant gene impact on tissue/function	UroGenital+	Other
	No. (%)			% of 98	% of 795
EDS patients	**136 (100)**	**1125 (100)**	Neural	27	33
DNA tested[1]	**91 (67)**	**876 (78)**	Heart	12	13
DNA change	**61 (67)**	**507 (58)**	Autonomic	13	14
Total variants	98 (100)[2]	795 (100)[2]	Muscle	6.1	12
All COL[3]	10 (10)	58 (7.3)	Immune-Inflammatory	17*	7.7
All Mito.	15 (15)	143 (18)	Bone	7.1	6.9
FBN1	5 (5.1)	17 (2.1)	Joints	7.1	6.2
MT-CYB	5 (5.1)	18 (2.2)	Clotting	5.1	4.0
FLG	5 (5.1)	35 (4.4)	Skin	5.1	3.3
*CACNA*1/2	4 (4.1) *	2 (0.25)	**Gene product**	**% of 98**	**% of 795**
*GJB*2	4 (4.1) *	2 (0.25)	Structural	30	24
*COL*1*A*1/*A*2	4 (4.1)	11 (1.4)	Enzyme	27	28
*MT-ND*1/2/4/5/6	4 (4.1)	27 (3.4)	Membrane channel	15	10
*SCN*9*A*	3 (3.1)	8 (1.0)	Signal	15	12
HFE	3 (3.1)	13 (1.6)	Receptor	6.1	9.5
VWF	3 (3.1)	15 (1.9)	Adhesive	3.1	6.7
*ANK*2/3	2 (2.0)*	1 (0.13)	Transcription factor	2.0*	9.0

[1]95% by WES; [2]98 or 893 DNA variants found in the 61 or 568 patients, many having more than one variant; [3]C*OL*1*A*1/*A*2, *COL*3*A*1, *COL*6*A*1/2/3, *COL*7*A*1, *COL*12*A*1 were the collagen genes, *ABCA*4, *COL*27*A*1, *FOXP*2, *KCNH*2, *IFIH*1, *IGF*1*R*, *LAMA*5, *MED*12, *MEFV*, *MYLK*, *NLRP*3, *PPT*1, *PRKAG*2, *SCN*2*B*, *THRB*, and *TIMP* the genes with single variations found only in the urogenital group; gene names, the nature of their protein product, and diseases associated with their variation can be found at http://www.omim.org/; findings of the principal associated disease determined the contribution of that gene change to a particular tissue (neural, bone) or function (autonomic, clotting). *, significantly different at $p < 0.05$ level. Data on the overall EDS patient population is from Wilson and Tonk [11].

The approach to the woman with multiple urogenital problems, particularly when pelvic pain, pelvic floor/organ slippage, and lower body blood pooling [pelvic congestion, 9; varicosities] are present, should assess hypermobility (large joint flexibility as with the reverse prayer or palms to floor signs of the example patient is easy to examine) and then look for accompanying symptoms of orthostatic intolerance (dizziness, feeling faint, brain fog), adrenergic stimulation (tachycardia, chronic fatigue, anxiety), and cholinergic suppression (bowel irregularity, bloating-reflux) that further the diagnosis of EDS-dysautonomia [1]-[10]. Knowledge

of these underlying tissue laxity/vessel distensibility/lower body blood pooling mechanisms will in turn encourage evaluation of women with more common bladder issues (7.6%, 4.8%, and 4.1%/3.8% of EDS women had frequent urination, leakage, or urgency/delayed emptying in **Table 1**) for problems like pelvic congestion [9] [39] or pelvic organ/floor slippage [8]-[10].

Recognition that these common urologic symptoms may be part of a broader EDS pattern adds treatment measures like mesh surgeries [24] [25], pelvic vein embolization [40], or bladder exercise/stimulation (in these women who likely need urodynamic study after failing conservative management, [41]). Benefits for osteoporosis by estrogen replacement after menopause [28] must be balanced with its increase of tissue laxity [26] [27]. Relating urogenital symptoms to EDS mechanisms also gives insight into cause and therapy, interstitial cystitis seen as a thinning and fragility of bladder adnexal tissue; polyuria, urgency, delayed emptying, and stress incontinence [41] seen as part of the adrenergic imbalance [5]; hernias and pelvic organ/floor slippage reflecting the general tissue laxity/skeletal instability of EDS [1]; vulvodynia [8] perhaps reflecting its skin fragility [2] [11]. Note that our example patient waited until age 30 for EDS diagnosis despite the occurrence of treatable urogenital symptoms with puberty.

Highlighting a major flaw of this study that counterbalances its virtue of systematic evaluation is its minimal insights into urogenital problems of the EDS male, with only 21% of them having urogenital findings in **Table 1**. Of these, frequent urination and inguinal hernia at 6.1% and 5.6% were the only substantive contributors at levels not convincingly more than those of the average male. Frequencies of penile irritation/dyspareunia, erectile dysfunction/infertility, and prostate/urinary tract problems in EDS males are of particular importance based on the well-documented complications of skin-mucosal fragility, pelvic blood pooling/slippage, and ureteral/urethral laxity/reflux in affected females [1] [2] [8] [9]. This and existing surveys [8]-[10] would be improved by prospective and systematic documentation conducted by urologic and gynecologic specialists in concert with those knowledgeable about the genetics and DNA contributors to EDS.

4.2. Research Implications

Genomic testing of a substantial fraction (906) of the 1261 EDS patients having systematic evaluation along with preliminary data showing low levels of pregnancy or fertility problems (**Table 1**) provides a major benefit needing further documentation: The overwhelming majority of EDS patients and their physicians can discount concerns from rare EDS types [18] [19] and look forward to low reproductive risks. Screening of all genes for mutations through exome and mitochondrial DNA sequencing [11] emphasizes that the clinical finding pattern and not changes in a particular gene determine EDS type, our example patient having a change in the oft-associated collagen type III gene but none of the vessel-bowel ruptures or chiseled facial features of vascular EDS [18] [19].

Clinical interpretation of genomic change using grades of diagnostic utility ra-

ther than qualifications of uncertain significance [11] will encourage physician use of this testing and the accumulation of clinical-DNA correlations that are needed to know if genes altered preferentially in EDS patients with more urogenital symptoms (Table 3) are prefiguring a unique type of that disease. More likely, in view of the 286 nuclear and 31 mitochondrial genes showing changes in the 566 of 1261 EDS patients having a DNA variant relevant to EDS, the gene network proposed to produce the EDS-dysautonomia panoply of symptoms [11] also acts on the urogenital system. The few genes found exclusively in EDS patients with urogenital symptoms in Table 3 will likely be accompanied by many others as genomic testing becomes commonplace. This view would fit with the clinical data in Table 1, Table 2 which frame EDS patients with urogenital symptoms as having a more severe version of the same EDS profile; it also accords with the actions and product functions of genes changed in urogenital-impacted versus usual EDS patients that significantly differ only in immune-inflammatory action and transcription factor function (Table 3).

A more focused example of research issuing from the association of urogenital complications with EDS concerns the 34% of women who reported ovarian cysts, most with single and painful ones that rarely required excision but 5.6% with the multiple cysts of polycystic ovarian syndrome or PCOS (Table 1). Recent studies [42] suggest a higher incidence of sleep-disordered breathing in PCOS that is somewhat independent of the higher rate of obesity (~75%) in women with that condition, both of these problems (disordered sleep, 66%; obesity 17% - 30%) being frequent in EDS [2] [11] [14]. Another direction is suggested by the 10% of 426 patients with acute and 43 with long COVID-19 who had urogenital symptoms [43], the latter disorder and EDS showing remarkable overlap of joint-skeletal and neuroautonomic symptoms [14] [44].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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