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Heritable disorders of connective tissue: description of a data repository and initial cohort characterization

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Abstract

We describe a data repository on the heritable disorders of connective tissue (HDCT) assembled by the National Institutes of Health's National Institute on Aging (NIA) Intramural Research Program between 2001 and 2013. Participants included affected persons with a wide range of heritable connective tissue phenotypes, with clinical diagnoses updated in 2015, and unaffected family members. Elements include a comprehensive history and physical examination, standardized laboratory data, physiologic measures and imaging, standardized patient-reported outcome measures centered on overall health, pain, sleep and fatigue and an extensive linked biorepository. The NIA made a commitment to make the repository available to extramural investigators and deposited samples at the Coriell Tissue Repository ($N=126$) and GenTAC registry ($N=132$). The clinical dataset ("HDCT NIA Dataset v.2016") was transferred to Penn State University College of Medicine Clinical and Translational Science Institute in 2016, and data elements and structure inventoried. The consented cohort of 1009 participants averaged 39 ± 18 years (mean $\pm$ SD, range 2-95) at consent; gender distribution is 71% F and 29% M, and 83% self-report Caucasian ethnicity. Diagnostic categories include Ehlers-Danlos Syndrome (Classical $N=50$, Hypermobile $N=99$, Vascular $N=101$, Rare Types and Unclassified $N=178$), Marfan Syndrome ($N=33$), Stickler Syndrome ($N=60$), Fibromuscular Dysplasia ($N=135$), Other HDCT ($N=72$). Unaffected family members ($N=218$) contributed DNA for the molecular archive only. We aim to develop further discrete data from unstructured elements, analyze multi-symptom HDCT manifestations, encourage data use by other researchers and thereby better understand the complexity of these high-morbidity conditions and their multifaceted effects on affected persons.

Keywords

Ehlers-Danlos syndromes; heritable connective tissue disorders; data repository

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1 | INTRODUCTION

The heritable disorders of connective tissue (HDCT) are a heterogeneous group of conditions caused by defects in the structure and synthesis of extracellular matrix elements such as collagen, elastin, muco-polysaccharides and related biomolecules (McKusick, 1973). The genetic causes of many disorders of connective tissue have been identified (Beyens et al., 2018; Byers et al., 2017; Dietz et al., 1991; Francomano, 2010; Francomano et al., 1987; Lee, Vitale, Superti-Furga, Steinmann, & Ramirez, 1991; Liberfarb et al., 2003; Malfait et al., 2017). However, others are not well understood at the molecular level, most notably the hypermobile form of Ehlers-Danlos Syndrome. Diagnostic criteria for this diverse family of disorders have evolved over the years since the present study was initiated (Beighton, 1970; Malfait et al., 2017). Affected persons often present with features that do not clearly fit into a neat diagnostic category.

Defining the disease phenotypes for these rare disorders is a continuing challenge. Because connective tissue is ubiquitous in the human body, the hereditary disorders of connective tissue affect multiple organ systems. Also challenging is the variability between individuals with the same diagnosis and among family members (inter- and intra-familial variability). A third challenge is the evolving nature of the phenotype in a single individual over the lifespan, as patients report considerable temporal variation in symptoms. Early clinical studies suggested common features across the individual syndromes, but typically focused on a particular organ system manifestation. More recent studies have begun to document the multi-system nature of EDS (Castori et al., 2017), but robust cluster analyses of large cohorts, ascertained using consistent methods, are needed. Another continuing need is for evaluation of the multi-organ system aspect of these disorders, and for comparison across HDCT diagnoses using standardized instruments.

To address the necessity for deeper characterization of these disorders, a cohort study was initiated in 2001 at the National Institute on Aging (NIA). Enrollment in the study continued through 2013. Recruitment focused on identifying patients across the spectrum of HDCT with clinical classification at the time of recruitment, extensive phenotyping and collection and banking of bio-samples. Personnel and programmatic changes led to an end of the NIA intramural study in 2013, and patient organizations advocated for the development of a process to release the accumulated data to investigators in the academic community.

Our long-range program goals are to perform analyses of the complex multi-symptom manifestations in the HDCT, to further enrich the data repository by developing discrete data from unstructured elements (e.g. narrative history and imaging), and to encourage the use of the data by other researchers. This paper will provide a description of the full HDCT cohort and existing data elements, as well as the process by which data have been prepared for release.

2 | METHODS

The National Institute on Aging study “*Clinical and Molecular Manifestations of Heritable Disorders of Connective Tissue*” was designed to investigate the natural history of the most common HDCT. Emphasis was placed on the cardiovascular, musculoskeletal and neurological complications of HDCT and the natural history of these complications. The original study protocol was designed to collect clinical and family history data, and to use this information to clarify the clinical distinctions between diagnoses. Through mutational analysis for genes known to cause the HDCT and identification of new genes, the study aimed to assess the relationship between specific mutations and their associated phenotypes, an effort that is ongoing (Shalhub et al., 2014). The 2003–086 protocol aggregated previous individual protocols addressing Ehlers-Danlos syndrome, Marfan syndrome, Stickler syndrome, fibromuscular dysplasia, and other “overlap” phenotypes.

Dr. Clair Francomano was the original Principal Investigator (2001–2005), and the study continued under the leadership of Dr. Nazli McDonnell after 2005. Following closure of enrollment in 2013, the cohort data was migrated to a comprehensive relational database. In November 2015, the NIA convened a workshop and introduced the database to stakeholders including leaders in the genetics community, interested investigators and leaders in the patient community. The workshop’s purpose was to discuss the database with interested scientists and consider how this resource might best serve the investigators and patient support groups who are eager to see advances in the field. The attendees endorsed the plan to make the database available in an accessible format to investigators with an interest in HDCT research. Discussion focused on diverse strategies to address the many clinical and basic science questions in this diverse population.

2.1 | Study design

This is primarily a cross-sectional dataset of participants seen between 2001–2013, initially at the Johns Hopkins Bayview Clinical Research Unit and subsequently at the NIA Advanced Studies in Translational Research (NIA-ASTRA) unit at Harbor Hospital in Baltimore. The scope of participation ranged from a detailed in-person assessment and biological sample contribution accomplished during a multi-day visit to contribution of biological samples with limited clinical assessment. Participants included individuals with HDCT and unaffected family members. A subset of participants completed second and third assessments.

2.2 | Institutional review board jurisdiction

The National Institute on Aging study “*Clinical and Molecular Manifestations of Heritable Disorders of Connective Tissue*” began by assembling consented cohorts with a wide range of heritable disorders of connective tissue, under an umbrella protocol (Protocol 2003–086, later changed to 03-AG-N330). After the study was closed to enrollment, the Institutional Review Board approved the reorganization and migration of the data into a relational database repository and approved re-contacting participants to determine if they would be interested in participating in future research. The HDCT cohort data are provided in SAS

datasets, PDF, Excel, MRI DICOM file formats and are now under the umbrella of protocol 11-AG-N079, “*Sample and Data Repository Protocol for NIA Studies.*”

2.3 | Recruitment and consent methods

Participants were recruited from the pool of patients previously seen by the Principal Investigators and from patient support groups nationally. Most participants were diagnosed by a clinical geneticist prior to participating in the study. In a small number the diagnosis was suggested by the primary care doctor or a specialist such as an orthopedic surgeon or a rheumatologist. Specific efforts were made to recruit minority participants. Recruitment letters were sent to minority medical institutions and practitioners who practice in areas with high minority populations. Efforts were made to collect biological samples from individuals with connective tissue disorders of unknown genetic cause. An authorized guardian provided consent for minor participants, with age-appropriate assent by the minor.

Participants were re-contacted by a coauthor (SM) to ascertain their willingness to be approached for participation in follow-up assessments and future studies. All but one contacted participant agreed to be re-contacted in the future.

2.4 | Inclusion criteria

2.4.1 | Demographics—Both genders were recruited for participation. Full clinical assessments were performed beginning at age 12 with no upper age limit. Biological samples were contributed by participants as young as age 2.

2.4.2 | Clinical eligibility

Affected individuals: Determination of eligibility was made by review of prior medical records. In some cases, a screening evaluation at the NIA was used to establish a basis for inclusion. Individuals were eligible for participation if they had an established or suspected diagnosis of EDS, Marfan syndrome, Stickler syndrome, fibromuscular dysplasia, or a heritable connective tissue disorder without a specific diagnosis. Review criteria included personal or family history features suggestive of a heritable connective tissue disorder such as: Marfanoid body habitus, aortic dilation and/or dissection, ectopia lentis, detached retina, vitreous degeneration and/or early onset high myopia, posterior cleft palate, joint laxity and/or recurrent dislocation, premature osteoarthritis, skin fragility, striae, easy bruising and/or dural ectasia, Chiari malformation, high frequency sensorineural hearing loss, fibromuscular dysplasia of arteries, and/or arterial aneurysm.

Relatives: Both affected and unaffected relatives contributed biological samples. These were primarily first degree relatives of the probands but in some cases more extended family members were included.

2.5 | Exclusion criteria—The major exclusion criterion was the inability to provide informed consent or the absence of a guardian who was authorized to provide informed consent in the case of minor subjects. Pregnant and nursing women were limited in their participation in some aspects of the study (e.g., ionizing radiation exposure or MRI) during

the time they were pregnant/nursing. This study did not enroll individuals with cognitive disabilities or with cytogenetic findings establishing an alternative diagnosis.

2.6 | Clinical evaluation—Affected participants were admitted to the NIA-ASTRA unit for up to three days for testing and sample collection. The scope of clinical assessment for affected and unaffected individuals is catalogued in Results. Data collection forms for the following study elements are provided in the online supplement:

2.6.1 | Demographics: Age at visit, gender, self-reported ethnicity/race. *Narrative History:* Detailed narrative history, including medical and surgical histories and medication use. Verification of patient history through independent review of medical records was not routinely performed.

2.6.2 | Physical examination: The physical examination included orthostatic blood pressure and pulse measurements, a standardized Beighton score for joint hypermobility and a skin exam to assess for skin texture, translucency and extensibility. Elements of the diagnostic criteria for Marfan syndrome and Stickler syndrome were included if these diagnoses were suspected by the evaluating clinician. *Medical Photography:* The IRB included consent for medical photography. Images are not part of the dataset. *Laboratory studies:* Complete Blood Count Panel, Chemistry Panel, Urinalysis, Hormone Analysis. *Diagnostic Studies:* electrocardiogram, echocardiogram, holter monitoring during wakefulness and sleep, pulse wave velocity, ankle-brachial index, dual-energy x-ray absorptiometry (DEXA) bone densitometry, Magnetic Resonance Imaging (MRI, supine, neutral position, brain, neck, chest), and Magnetic Resonance Angiography (MRA, brain). *Patient Reported Outcome Measures:* Participants completed the following standardized questionnaires: Brief Pain Inventory; Sleep Associates of Maryland (SMAM) sleep questionnaire; Pittsburgh Sleep Quality Index (PQSI); Mini-mental examination (as part of physical examination); Quality of Life Index; Multi-dimensional Fatigue Inventory (MFI-20); Short Form 36 (SF-36); Symptom Checklist-90 (SCL-90); and NEO Personality Inventory. *DNA samples:* DNA was isolated from white blood cells and stored in the NIA Biorepository. *Biosamples:* Volar forearm skin biopsies were performed and fibroblasts isolated in culture and frozen in liquid nitrogen. Plasma, saliva, and urine samples were also collected. One investigator (NM) was able to obtain a limited number of surgical samples, primarily of vascular tissue or bone. Samples were directly collected in the operating room and immediately processed and archived.

2.7 | Diagnostic assignment—Consented participants were initially classified based on diagnostic criteria in place at the time of their clinical visit at the NIA (2001–2013). Subjects contributing only biological samples were diagnosed either through a limited onsite evaluation or through review of submitted medical records.

Reclassification: Between 2013 and 2015, clinical research forms were constructed to verify the assignment to one of the following diagnostic categories: EDS (subtypes: classical, hypermobile, vascular, rare and unclassified), Marfan syndrome, Stickler syndrome, fibromuscular dysplasia, HDCT Other. These classifications were based on the diagnostic criteria that were in place when the research subjects were enrolled, as described below:

2.8 | Ehlers-Danlos Syndrome (EDS)—Extensive clinical and genetic heterogeneity characterize the 13 types of Ehlers-Danlos syndrome, but as a whole they are characterized by joint hypermobility, skin hyperextensibility, and vascular and soft tissue fragility, with varying involvement of different organ systems in the different types. At the time of their initial NIA clinical assessment, patients with Ehlers-Danlos syndrome were classified according to the Villefranche Nosology (Beighton, De Paepe, Steinmann, Tsipouras, & Wenstrup, 1998). *Classical*: The diagnosis of classical type of EDS was made on the basis of joint laxity (Beighton score ≥ 4/9), extremely hyperextensible skin, fragility of the skin with evidence of easy bruising, and the presence of thin atrophic scars. *Hypermobile*: The diagnosis of hypermobile EDS was made on the basis of a history or presence of dislocations, generalized joint laxity, and velvety texture of skin with an absence of extreme skin extensibility and profoundly abnormal scars. *Vascular*: The diagnosis of vascular EDS was made based on genetic testing showing causative variants in COL3A1, the gene encoding type III collagen. *Rare and Unclassified*: This category included patients with the rarer types of Ehlers-Danlos Syndromes. A molecular diagnosis was used for the arthrochalasia and kyphoscoliotic types. Some patients had features overlapping with two or more types of EDS, and classification proved to be difficult in those cases, and such patients were diagnosed as “EDS, unclassified”. If we had a clinical impression of EDS but they did not meet the diagnostic criteria for any of the known types, we assigned a diagnosis of “EDS, unclassified”. Participants in this group may be reclassified as new genetic causes are found (Blackburn et al., 2018; in press).

2.9 | Marfan syndrome—Marfan syndrome is an autosomal dominant systemic connective tissue disorder caused by defects in fibrillin 1, a major component of elastic tissue (Dietz et al., 1991; Lee et al., 1991). Current nosology states that the major clinical criteria are aneurysmal dilation of the ascending aorta and dislocation of the ocular lenses (Loeys et al., 2010). Affected persons may have skeletal, ocular, cardiovascular, pulmonary, and integumentary manifestations with substantial clinical variability both within and between families. The prevalence and severity of the less common clinical features have not been established. The diagnosis of Marfan syndrome was made based on the 1996 Ghent nosology (De Paepe, Devereux, Dietz, Hennekam, & Pyeritz, 1996). Patients seen after 2010 were diagnosed according to the revised Ghent nosology (Loeys et al., 2010).

2.10 | Stickler syndrome (hereditary arthro-ophthalmopathy)—This is an autosomal dominant disorder characterized by ocular, oral-facial, auditory, cardiac, and skeletal abnormalities, including premature osteoarthritis, vitreo-retinal degeneration that may lead to retinal detachment, and sensorineural hearing loss. Genetic defects have been found in the genes encoding type II collagen and type XI collagen. Substantial clinical variation within and between families is noted (Francomano, 2010; Francomano et al., 1987; Liberfarb et al., 2003). The diagnosis of Stickler syndrome was made based on clinical findings consistent with the diagnosis prior to 2005 and published diagnostic criteria after 2005 (Rose et al., 2005).

2.11 | Fibromuscular dysplasia—Fibromuscular dysplasia (FMD) is a rare, nonatherosclerotic vascular disease, originally described in 1938 (Leadbetter & Burkland,

1938), characterized by arterial dysplasia and obstruction to arterial blood flow by neointimal lesions rich with cells with a smooth muscle phenotype (Slovut & Olin, 2004). It most commonly affects the renal arteries (presenting as hypertension) and internal carotid arteries (presenting as stroke or transient ischemic attack) but has been described in virtually all arterial beds. Ganesh et al first recognized this as a generalized connective tissue disorder (Ganesh et al., 2014).

2.12 | HDCT other (overlapping connective tissue disorder)—The HDCT group is heterogenous and contains multiple diverse families. Efforts continue to further refine phenotypes and identify genetic loci. We identified a family with a new autosomal dominant connective tissue disorder with features overlapping those of Ehlers-Danlos, Marfan and Stickler syndromes, which we initially labeled “*Overlapping Connective Tissue Disorder*.” During the course of the study, a number of other families with similar features were identified. One subset of this phenotype was found by Hal Dietz and his colleagues to be caused by mutations in the TGFB2 gene and is now recognized as a subtype of Loeys-Dietz syndrome (Lindsay et al., 2012). It is likely that analyses will identify additional explanatory mutations.

2.13 | NIA repository structure—The NIA cohort data is stored in a relational database repository and SAS datasets. The datasets contain de-identified data only; study ID is the only link to the original NIA data. Data transfer agreements may be arranged with the NIA by interested investigators and de-identified data are transferable via secure file transfer protocol (sftp). Study Case Report Forms (CRFs) used in the database are provided in the Online Supplement. Demographic data is searchable as discrete data elements as are clinical HDCT Diagnosis Worksheets that provide disease-specific confirmation of diagnosis assignment as discrete data elements.

2.14 | Penn State University Clinical and Translational Science Institute PSU-CTSI repository—In 2016, a signed Data Transfer Agreement between NIA and Penn State University resulted in transfer of a copy of the HDCT NIA Dataset v.2016 data repository to the Penn State University Clinical and Translational Science Institute (PSU-CTSI). Datasets were accompanied by copies of original case report forms and SAS dataset codebook descriptions. To guide the direction of our research, we established an EDS Clinician-Patient Research Partnership, including a patient research advisory group, and have engaged these patient partners in monthly meetings to participate in our research planning and outreach, from formulating research questions to assessing the face validity of the outcome measures.

2.15 | Biorepository donations—Data and biosamples from a subset of participants were contributed to two national repositories, Corriel and GenTAC (National Registry of Genetically Triggered Thoracic Aortic Aneurysms and other Cardiovascular Conditions).

3 | RESULTS

3.1 | NIA HDCT cohort

The HDCT NIA Dataset v.2016 consented cohort includes 1009 participants with an average age of 39 ± 18 years (range 2–95, median 40). 194 participants were 18 years or younger. Demographic characteristics of the cohort by diagnostic category are shown in Table 1.

Multiple visits: Thus far we have analyzed results from 49 affected individuals who completed two visits with characteristics shown in Table 2. We also identified five individuals who completed three visits: their diagnoses and interval between first and third visits were: vascular EDS ($N=2$, 4 and 5.6 years), Marfan syndrome ($N=1$, 2.9 years), Stickler syndrome ($N=1$, 4.7 years), and Rare and unclassified EDS ($N=1$, 8.1 years).

3.2 | National repositories: Coriell and GenTAC

One hundred twenty-six samples were contributed to the Coriell Tissue Repository (<https://www.coriell.org/1/Services/Biobanking>). Participants were 45 ± 12 years old (range 15–82), and 78% were female with assigned diagnoses of Classical EDS ($N=14$), Hypermobile EDS ($N=13$), Vascular EDS ($N=26$), Rare and Unclassified EDS ($N=26$), Marfan ($N=5$), Stickler ($N=3$), Fibromuscular dysplasia ($N=31$), and other HDCT ($N=8$). Data and biosamples were also sent to the GenTAC Registry ($N=132$).

3.3 | PSU CTSI NIA HDCT data repository

Table 3 shows the data elements in the transferred repository. After reviewing the elements in the data repository, the Penn State EDS patient research advisory group identified four areas for initial focus: (1) difficulties with nighttime sleep and daytime fatigue; (2) pain, (3) differences in disease manifestations among EDS types, and (4) the multisystem nature of their condition. The datasets were cleaned and descriptive and summary statistics were computed. Various questionnaires were scored according to published guidelines. We are currently prioritizing the creation of structured data elements from the unstructured data.

3.4 | Derived projects and publications

The NIA HDCT data have contributed to advances in understanding familial hypertryptasemia (Chovanec et al., 2017; Lyons et al., 2016). Clinical characterization and molecular studies of the NIA FMD cohort were included in the publication showing clinical and biochemical profiles that suggested fibromuscular dysplasia is a systemic disease with altered TGF- β expression and connective tissue features. (Ganesh et al., 2014).

4. | DISCUSSION

The heritable disorders of connective tissue are a group of high morbidity, high-disease-burden conditions, many of which are underdiagnosed and poorly understood. The NIA HDCT research repository and the developing plans for its dissemination and use are the product of a concerted effort among researchers, clinicians, patient partners and advocacy organizations to address both the challenges and opportunities provided by this group of rare diseases.

Unlike organ-specific diseases (e.g., lung disease, heart disease) heritable disorders of connective tissue affect multiple organ systems, a reflection of the ubiquity of connective tissue throughout the body. This multi-organ system manifestation presents a particular challenge for defining and studying a disease and can slow the adoption and evaluation of diagnostic criteria. In other diseases such as cystic fibrosis, genetic analysis has shown the importance of disease modifiers, as a single genotype can be expressed very differently in two individuals depending on the presence or absence of modifier alleles (Cutting, 2010). This may also be the case in many of the HDCTs. Another continuing challenge is defining the disease phenotypes for these rare disorders because a phenotype that is thought to be a single entity, may in fact represent multiple conditions, each with a distinct, but overlapping presentation and trajectory.

The NIA HDCT repository has continuing value as diagnostic classifications evolve. The biorepository combined with the rich phenotypic data set can be used to evaluate the impact of new nosologies. For example, the 2017 International EDS Classification diagnostic criteria now recognize 13 subtypes based on clinical criteria and organize the subtypes into a pathogenetic schema based on causative protein functions (Malfait et al., 2017). The NIA repository can now be assessed to determine the impact of the reclassification and new diagnostic criteria for different types of EDS.

Construction of this dataset, and the process of making it available to interested investigators, reflects lessons from work in other rare diseases. Assembling cohorts of patients with similar presentations, albeit of unknown cause, is the first step in gene discovery, which may result in the identification of new pathogenic pathways and led to development of rational therapies where none are now available (Griggs et al., 2009; Habashi et al., 2006). Structured approaches to characterizing a rare disease with detailed phenotyping can be the first step to developing a more limited set of common data elements that form the basis for prognostic instruments and for evaluating interventions, whether pharmacotherapies or disease management strategies (Corvol et al., 2015; Cutting, 2015; NINDS Common Data Elements, n.d.).

In the case of the HDCT, especially EDS, increasing recognition of the overlap between various phenotypes and co-morbidities, has led to the development of the EDS Co-Morbidity Coalition of patient support groups addressing specific co-morbid conditions often seen in EDS (The Ehlers-Danlos Society, Chiari and Syringomyelia Foundation, Mastocytosis Society, Dysautonomia International, Spinal CSF Leak Foundation and the Penn State EDS Clinician-Patient Research Partnership).

Strengths of the cohort include the rich phenotypic dataset assembled in a diverse cohort representing the HDCT as well as the large biorepository. Over 1,000 participants took part in the protocol over time, with over 40,000 biosample aliquots, including serum, plasma, urine, fibroblasts and DNA. Clinical hematology, chemistry and/or urinalysis results are available for 299 participants and imaging data (including echocardiography and brain and spinal MRIs) are available for select groups. Another strength of the cohort is the use of multiple validated patient reported outcome measures.

Ideally, an equal number of men and women would have been enrolled in this study, however, men and ethnic minorities were under-represented in the patient population. Although gender ratio for these disorders should be 1:1, female patients with hypermobile EDS are well-known to be over-represented in genetics clinics and research cohorts (Murray, Yashar, Uhlmann, Clauw, & Petty, 2013). Affected females, on average, seem to have more severe manifestations and consequently seek medical attention more frequently than men (Malfait et al., 2017). It is possible that the female predominance beginning in adolescence reflects hormonal influences or epigenetic modification of a common genotype.

Although the original longitudinal study of the NIA cohort was not fully completed as planned, a robust cross-sectional clinical dataset has emerged, with some limited longitudinal data. Over a decade has passed since the initial clinical assessment of many participants. The persons in the cohort have been approached and are overwhelmingly willing to be re-contacted concerning future research about the HDCT. This offers the opportunity for longitudinal re-assessment of the cohort, supplementing the baseline assessment with additional phenotyping. In keeping with the goals of the original NIA study, the PSU CTSI is performing extensive analyses of the EDS Cohort (HDCT NIA Dataset v. 2016). We anticipate that this paper, which provides a basic description of the cohort and available data, is the first of many prepared by the PSU EDS study group utilizing the NIA HDCT data set.

The study of genetic materials, tissue samples, and clinical data from patients with HDCT can increase insight into common pathological conditions that affect the aging population, since specific manifestations are models of organ specific aging. These manifestations include osteopenia/osteoporosis, osteoarthritis, degenerative disc disease, arterial aneurysms, musculoskeletal disability (weakness and pain), tendon/ligament weakness and injury, tissue fragility, delayed wound healing, and other consequences of weaker connective tissue such as retinal detachment. Chronic pain resulting from musculoskeletal deformities and sleep disturbances may mimic those seen in aging and provide a useful line of inquiry. The investigation of the biology and natural history of single gene disorders may well enhance our understanding and potentially improve the quality of life for HDCT patients and the aging population as a whole.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Beighton P (1970). Ehlers-Danlos syndrome. *Ann Rheum Dis*, 29(3), 332–333. [PubMed: 5432600]

- Beighton P, De Paepe A, Steinmann B, Tsipouras P, & Wenstrup RJ (1998). Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet*, 77(1), 31–37. [PubMed: 9557891]
- Beyens A, Albuisson J, Boel A, Al-Essa M, Al-Manea W, Bonnet D, ... Callewaert B (2018). Arterial tortuosity syndrome: 40 new families and literature review. *Genet Med*. doi:10.1038/gim.2017.253
- Blackburn PR, Xu Z, Tumelty KE, Zhao RW, Monis WJ, Harris KG, ... Atwal PS (2018; in press). Biallelic Alterations in AEBP1 Lead to Defective Collagen Assembly and Connective Tissue Structure Resulting in a Variant of Ehlers-Danlos Syndrome. *American Journal of Human Genetics*, 102, 1–10.
- Buyse DJ, Reynolds CF 3rd, Monk TH, Berman SR, & Kupfer DJ (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*, 28(2), 193–213. [PubMed: 2748771]
- Byers PH, Belmont J, Black J, De Backer J, Frank M, Jeunemaitre X, ... Wheeldon N (2017). Diagnosis, natural history, and management in vascular Ehlers-Danlos syndrome. *Am J Med Genet C Semin Med Genet*, 175(1), 40–47. [PubMed: 28306228]
- Castori M, Tinkle B, Levy H, Grahame R, Malfait F, & Hakim A (2017). A framework for the classification of joint hypermobility and related conditions. *Am J Med Genet C Semin Med Genet*, 175(1), 148–157. [PubMed: 28145606]
- Chovanec J, Liu Y, Bai Y, Yin Y, Metcalfe DD, Milner JD, & Lyons JJ (2017). Correlation of alpha- and beta-specific tryptase gene expression with TPSAB1 and TPSB2 genotypes in humans. *J Immunol*, 198(1 Supplement), 59.13.
- Cleeland CS (1989). Measurement of pain by subjective report In Chapman CR & Loeser JD (Eds.), *Advances in Pain Research and Therapy* (Vol. 12, pp. 391–403). New York, NY: Raven Press.
- Corvol H, Blackman SM, Boelle PY, Gallins PJ, Pace RG, Stonebraker JR, ... Knowles MR (2015). Genome-wide association meta-analysis identifies five modifier loci of lung disease severity in cystic fibrosis. *Nat Commun*, 6, 8382. [PubMed: 26417704]
- Costa PT Jr., & McCrae RR (1985). *The NEO Personality Inventory Manual Psychological Assessment Resources*. Odessa, FL.
- Costa PT Jr., & McCrae RR (1992). *NEO Personality Inventory-Revised (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI) Professional Manual Psychological Assessment Resources*. Odessa, FL.
- Cutting GR (2010). Modifier genes in Mendelian disorders: the example of cystic fibrosis. *Ann N Y Acad Sci*, 1214, 57–69. [PubMed: 21175684]
- Cutting GR (2015). Cystic fibrosis genetics: from molecular understanding to clinical application. *Nat Rev Genet*, 16(1), 45–56. [PubMed: 25404111]
- De Paepe A, Devereux RB, Dietz HC, Hennekam RC, & Pyeritz RE (1996). Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet*, 62(4), 417–426. [PubMed: 8723076]
- Derogatis LR, & Cleary PA (1977). Confirmation of the dimensional structure of the SCL-90: a study in construct validation. *J Clin Psychol*, 33(4), 981–989.
- Dietz HC, Cutting GR, Pyeritz RE, Maslen CL, Sakai LY, Corson GM, ... et al. (1991). Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature*, 352(6333), 337–339. [PubMed: 1852208]
- Ferrans CE, & Powers MJ (1992). Psychometric assessment of the Quality of Life Index. *Res Nurs Health*, 15(1), 29–38. [PubMed: 1579648]
- Folstein MF, Folstein SE, & McHugh PR (1975). “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*, 12(3), 189–198. [PubMed: 1202204]
- Francomano CA (2010). Stickler syndrome In Cassidy SB & Allanson JE (Eds.), *Management of Genetic Syndromes* (3rd ed.). Hoboken, NJ: John Wiley & Sons, Inc.
- Francomano CA, Liberfarb RM, Hirose T, Maumenee IH, Streeten EA, Meyers DA, & Pyeritz RE (1987). The Stickler syndrome: evidence for close linkage to the structural gene for type II collagen. *Genomics*, 1(4), 293–296. [PubMed: 2896625]
- Ganesh SK, Morissette R, Xu Z, Schoenhoff F, Griswold BF, Yang J, ... McDonnell NB (2014). Clinical and biochemical profiles suggest fibromuscular dysplasia is a systemic disease with

- altered TGF-beta expression and connective tissue features. *FASEB J*, 28(8), 3313–3324. [PubMed: 24732132]
- Griggs RC, Batshaw M, Dunkle M, Gopal-Srivastava R, Kaye E, Krischer J, ... Rare Diseases Clinical Research, N. (2009). Clinical research for rare disease: opportunities, challenges, and solutions. *Mol Genet Metab*, 96(1), 20–26. [PubMed: 19013090]
- Habashi JP, Judge DP, Holm TM, Cohn RD, Loeys BL, Cooper TK, ... Dietz HC (2006). Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science*, 312(5770), 117–121. [PubMed: 16601194]
- Leadbetter WF, & Burkland CF (1938). Hypertension in unilateral renal disease. *J Urol*, 39, 611–626.
- Lee B, Vitale E, Superti-Furga A, Steinmann B, & Ramirez F (1991). G to T transversion at position +5 of a splice donor site causes skipping of the preceding exon in the type III procollagen transcripts of a patient with Ehlers-Danlos syndrome type IV. *J Biol Chem*, 266(8), 5256–5259. [PubMed: 1672129]
- Liberfarb RM, Levy HP, Rose PS, Wilkin DJ, Davis J, Balog JZ, ... Rubin BI (2003). The Stickler syndrome: genotype/phenotype correlation in 10 families with Stickler syndrome resulting from seven mutations in the type II collagen gene locus COL2A1. *Genet Med*, 5(1), 21–27. [PubMed: 12544472]
- Lindsay ME, Schepers D, Bolar NA, Doyle JJ, Gallo E, Fert-Bober J, ... Loeys BL (2012). Loss-of-function mutations in TGFB2 cause a syndromic presentation of thoracic aortic aneurysm. *Nat Genet*, 44(8), 922–927. [PubMed: 22772368]
- Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, ... De Paepe AM (2010). The revised Ghent nosology for the Marfan syndrome. *J Med Genet*, 47(7), 476–485. [PubMed: 20591885]
- Lyons JJ, Yu X, Hughes JD, Le QT, Jamil A, Bai Y, ... Milner JD (2016). Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat Genet*, 48(12), 1564–1569. [PubMed: 27749843]
- Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, ... Tinkle B (2017). The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*, 175(1), 8–26. [PubMed: 28306229]
- McKusick VA (1973). *Heritable Disorders of Connective Tissue*. St. Louis, MO: Mosby.
- Murray B, Yashar BM, Uhlmann WR, Clauw DJ, & Petty EM (2013). Ehlers-Danlos syndrome, hypermobility type: A characterization of the patients' lived experience. *Am J Med Genet A*, 161A(12), 2981–2988. [PubMed: 24254846]
- NINDS Common Data Elements. (n.d.). Chiari I malformation. Retrieved from https://www.commondataelements.ninds.nih.gov/CM.aspx#tab=Data_Standards
- Rose PS, Levy HP, Liberfarb RM, Davis J, Szymko-Bennett Y, Rubin BI, ... Francomano CA (2005). Stickler syndrome: clinical characteristics and diagnostic criteria. *Am J Med Genet A*, 138A(3), 199–207. [PubMed: 16152640]
- Shalhub S, Black JH 3rd, Cecchi AC, Xu Z, Griswold BF, Safi HJ, ... McDonnell NB (2014). Molecular diagnosis in vascular Ehlers-Danlos syndrome predicts pattern of arterial involvement and outcomes. *J Vasc Surg*, 60(1), 160–169. [PubMed: 24650746]
- Slovut DP, & Olin JW (2004). Fibromuscular dysplasia. *N Engl J Med*, 350(18), 1862–1871. [PubMed: 15115832]
- Smets EM, Garssen B, Bonke B, & De Haes JC (1995). The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*, 39(3), 315–325. [PubMed: 7636775]
- Tan G, Jensen MP, Thornby JI, & Shanti BF (2004). Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain*, 5(2), 133–137. [PubMed: 15042521]
- Tombaugh TN, & McIntyre NJ (1992). The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc*, 40(9), 922–935. [PubMed: 1512391]
- Ware JE Jr., & Sherbourne CD (1992). The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual Framework and Item Selection. *Medical Care*, 30(6), 473–483. [PubMed: 1593914]

TABLE 1

NIA cohort demographics

Category	Diagnostic Assignment	N	Age	Demographics		
				# 18	Gender F:M	% Caucasian
1	EDS: classical	45	39±15 (5-63)	6	39:6	89
2	EDS: hypermobile	101	37±16 (5-88)	22	82:19	89
3	EDS: vascular	109	37±15 (2-77)	16	75:34	75
4	EDS: rare and unclassified	174	35±19 (2-89)	47	128:46	83
5	Marfan syndrome	31	42±15 (15-67)	4	15:16	77
6	Stickler syndrome	61	31±19 (3-70)	24	35:26	90
7	Fibromuscular dysplasia	138	48±13 (5-75)	5	125:13	91
8	HDCT others	104	37±18 (2-72)	22	62:42	86 *
9	Family members	217	41±22 (2-95)	45	139:79	88
10	Miscellaneous **	29	41±17 (6-73)	3	18:11	83
TOTAL		1009	39±18 (2-95)	194	718:291	83

* Data shown for 104 participants for whom race was available

** Insufficient information to establish diagnosis ($N=22$); participant or relative judged not to have HDCT on final review ($N=5$); withdrew ($N=2$)

TABLE 2

Characteristics of individuals completing two visits

Diagnostic category	N	Age at first visit*	# 18 at first visit	Sex (F:M)	BMI	Years between visits*
Total	49	43±14 13-69	6	35:14	26±8 14-53	2.6±1.4 1.4-8.6
EDS: classical	7	45±15 15-61	1	7:0	31±12 21-48	2.4±0.8 1.6-3.6
EDS: hypermobile	8	43±13 15-59	1	5:3	25±4 19-30	2.1±0.4 1.6-3.1
EDS: vascular	9	42±15 13-57	1	6:3	25±5 17-29	3.7±2.0 1.4-5.8
EDS: rare and unclassified	9	42±19 13-69	2	9:0	27±9 14-39	2.1±0.7 1.4-3.7
Marfan syndrome	5	46±17 19-61	1	3:2	22±3 17-26	1.9±0.3 1.5-2.2
Stickler syndrome	1	26	0	0:1	23	2.1
Fibromuscular dysplasia	5	45±9 38-57	0	3:2	23±4 20-29	2.0±0.5 1.6-2.6
HDCT others	5	40±7 32-48	0	2:3	33±13 22-53	4.0±2.2 1.9-8.6

* Values shown are mean +SD, min-max

** 98% of these participants have laboratory studies (median 163 per participant, range 74-946 results)

TABLE 3

Data elements and structure (2016)

Data element	Data structure
Demographics	Discrete data
<u>CLINICAL DATA</u>	
Clinical HDCT Diagnosis Worksheet	Discrete data
History	Unstructured (scanned pdf reports)
Physical Exam	Structured (text)
Orthostatic blood pressure recording	Worksheet
Mini-mental examination (as necessary) (Folstein, Folstein, & McHugh, 1975; Tombaugh & McIntyre, 1992)	Structured (text)
NEO personality inventory (Costa Jr. & McCrae, 1985, 1992)	Discrete data
Serum laboratory studies	Both structured and unstructured
Urine laboratory studies	Both structured and unstructured
ECG	Unstructured (scanned pdf reports)
Holter monitor studies	Unstructured (scanned pdf reports)
Carotid ultrasound and reflected wave study	Unstructured (scanned pdf reports)
Echocardiogram	Unstructured (scanned pdf reports)
Bone densitometry	Discrete data and scanned pdf reports
<u>IMAGING DATA</u>	
MRI/MRA studies (based on participants' diagnosis)	Unstructured (PDF reports)
Cervical spine and brain MRI	Unstructured (PDF reports)
Thoracic MRI	Unstructured (PDF reports)
Lumbar spine MRI	Unstructured (PDF reports)
Brain MRA Chest, neck vessels and abdomen MRA or MRI (with or without contrast)	Unstructured (PDF reports)
Other as pertinent to the participant's diagnosis (e.g. MRI of knee joints, hips or shoulders, MRA of vessels not referenced above)	Unstructured (PDF reports)
<u>PAIN AND QUALITY OF LIFE SURVEY INSTRUMENTS</u>	
Wisconsin Brief Pain Inventory (BPI) (Cleeland, 1989; Tan, Jensen, Thornby, & Shanti, 2004)	Discrete data
Health Inventory (SF-36) Symptoms Checklist – Revised (Ware & Sherbourne, 1992)	Discrete data
Psychological Inventory (SCL-90) (Derogatis & Cleary, 1977)	Discrete data
Ferrans and Powers Quality of Life Inventory (QLI) (Ferrans & Powers, 1992)	Discrete data
Multidimensional Fatigue Inventory (MFI-20) (Smets, Garssen, Bonke, & De Haes, 1995)	Discrete data
Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989)	Discrete data
<u>BIOREPOSITORY</u>	
Blood, saliva, urine, buccal and fibroblast samples; limited surgical samples	Samples stored at NIA