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Connective Tissue and Related Disorders and Preterm Birth: Clues to Genes Contributing to Prematurity

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Abstract

To identify candidate genes contributing to preterm birth, we examined the existing literature on the association between known disorders of connective tissue synthesis and metabolism and related diseases and prematurity. Our hypothesis was that abnormal matrix metabolism contributes to prematurity by increasing risk of preterm premature rupture of membranes (PPROM) and cervical incompetence. Based on this review, we identified gene mutations inherited by the fetus that could predispose to preterm birth as a result PPRM. The responsible genes include *COL5A1*, *COL5A2*, *COL3A1*, *COL1A1*, *COL1A2*, *TNXB*, *PLOD1*, *ADAMTS2*, *CRTAP*, *LEPRE1* and *ZMPSTE24*. Marfan syndrome, caused by *FBN1* mutations, and polymorphisms in the *COL1A1* and *TGFB1* genes have been associated with cervical incompetence. We speculate that an analysis of sequence variation at the loci noted above will reveal polymorphisms that may contribute to susceptibility to PPRM in the general population.

Keywords

Connective tissue; Genes; Preterm Birth; PPRM; Cervical incompetence

Introduction

Preterm birth has multiple etiologies but among these, preterm premature rupture of membranes (PPROM) is the leading identifiable cause, occurring in 1% of all pregnancies [1]. The human fetal membranes are composed of an inner layer, the amnion, and an adherent outer layer, the chorion. The amnion has five distinct layers (the epithelium, basement membrane, compact layer, fibroblast layer, and an intermediate layer), while the chorion is made up of a reticular layer, basement membrane, and trophoblast cells. Although the chorion is thicker than the amnion, the amnion is the main contributor to structural integrity [1-3]. The strength of the fetal membranes is thought to be influenced by both synthesis and degradation of the components of the extracellular matrix [4,5]. The fibrillar collagens (type I, III and V), are presumed to be the critical components lending tensile strength to the amnion [5,6]. However, other extracellular membrane proteins are also present including type IV collagen, type VI collagen, elastic components, fibronectin and laminin [6-8]. Consequently, connective

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tissue disorders that involve defects in fibrillar collagen synthesis or altered collagen or other extracellular matrix protein structure may affect fetal membrane tensile strength and result in preterm birth from unscheduled rupture. Cervical incompetence is another cause of preterm birth [9]. Since the extracellular matrix is critical to cervical function, and its remodeling, a necessary event in normal parturition, abnormalities in maternal matrix metabolism affecting cervical integrity could also contribute to prematurity.

Women with connective tissue disorders and related diseases are at an increased risk for complications during pregnancy. These complications include rupture of maternal viscera, including blood vessels, bowel and uterus, defects in fetal connective tissue formation, recurrent miscarriage and PPRM leading to preterm delivery. Heritable disorders associated with preterm delivery include Ehlers-Danlos syndrome, osteogenesis imperfecta and restrictive dermopathy. Some of these disorders are caused by mutations that affect fibrillar collagen synthesis or structure.

We reasoned that a critical analysis of the existing literature on pregnancy outcomes in disorders affecting extracellular matrix, particularly those involving known matrix components of the fetal membranes and cervix, could be informative in that disorders of matrix metabolism with known genetic causes would implicate or exclude the respective genes as candidates for PPRM and cervical incompetence [9]. Indeed, studies on pregnancy outcome in women with Ehlers-Danlos syndrome have reported an increased risk of PPRM and preterm birth if the fetus is affected [10,11]. Case reports of pregnancies in which the fetus is affected with restrictive dermopathy [12-14] and epidermolysis bullosa [15-17] have also described instances of PPRM or preterm birth. However, studies that reported on pregnancy outcome in women with Marfan syndrome, another heritable connective tissue disorder, found no increase in risk of PPRM or preterm birth whether or not the fetus was affected [18,19].

The purpose of this work was to assess the effect that heritable connective tissue disorders and related diseases in pregnancy have on preterm birth, and derive, based on the established genetics of these conditions, a list of candidate molecules and genes critical to fetal membrane and cervical integrity and risk of preterm birth. Many of the mutations in these disorders are newly identified, and the list may expand as more information regarding these diseases becomes known. The list of candidate genes for preterm birth derived from our analyses is based on what is currently known about these collagen and related disorders and does not preclude the involvement of other genes and pathways such as mutations in pro-inflammatory cytokine and matrix degrading metalloproteinases genes that are associated with preterm birth.

Methods

Medline and Google Scholar searches of studies and case reports on pregnancy outcome in heritable connective tissue disorders and related diseases were conducted. Disorders examined were Ehlers-Danlos syndrome, Marfan syndrome, osteogenesis imperfecta, epidermolysis bullosa, restrictive dermopathy and cutis laxa. For each condition different combinations of the search words 'in pregnancy', 'preterm birth', 'prematurity' and 'case reports', in addition to the name of the condition were used.

Results

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome encompasses a group of heritable connective tissue disorders characterized by hyperelasticity of the skin, joint hypermobility, tissue fragility and cardiac valvular defects [20]. There are six major types of Ehlers-Danlos syndrome – Classical (types I and II) in which there is a defect in type V or rarely type I collagen; Hypermobility (type III)

in which the cause is still largely considered unknown, however a defect in the extracellular matrix protein tenascin X (*TNXB*) has been reported in a subset of patients; Vascular (type IV) where there is defect in type III collagen; Kyphoscoliosis (type VI) where there is deficiency of lysyl hydroxylase; Arthrochalasia (a subgroup of type VII) where there is deficiency of type I collagen caused by mutations in the *COL1A1* and *COL1A2* genes that affect recognition sites for the processing enzyme ADAMTS2; and Dermatosparaxis (also a subgroup of type VII) in which there is deficiency of the enzyme ADAMTS2, which excises the N-propeptide of type I, type II and type V procollagens [21-23] (Table 1). The prevalence for all types of Ehlers-Danlos syndrome is estimated to be 1 in 5000 [24]. People of all racial backgrounds are equally affected [25].

Data collected from members of Ehlers-Danlos Associations/Foundations have consistently revealed higher rates of preterm birth and PPROM [11,26,27] (Table 1). A 1966 study of birth outcome among mothers with Ehlers-Danlos syndrome provided strong evidence of an increased risk for PPROM and preterm delivery, if the fetus is affected [10]. Among 18 patients with Ehlers-Danlos syndrome whose birth histories were available 14 (77.8%) were born prematurely. In 13 of the 14 preterm births, labor was preceded by PPROM [10].

In a survey of patients in the Ehlers-Danlos Foundation, Ainsworth and Aulicino [26] reported premature rupture of membranes rates of 26-75%, depending on the type of Ehlers-Danlos syndrome. Ehlers-Danlos syndrome types I and III had the highest and lowest incidences, respectively. Premature rupture of membrane rates for types II and IV were 40% and 58%, respectively. The incidence of PPROM in these subjects exceeds the prevalence of PPROM in the general population of 1-3%, supporting the notion that the defects in extracellular matrix predispose to unscheduled fetal membrane rupture [1].

Lind and Wallenburg 2002 [11] reported a preterm birth rate of 22% among 45 Dutch women affected with Ehlers-Danlos syndrome. In cases where both mother and fetus were affected with Ehlers-Danlos syndrome, 35% of the deliveries were preceded by PPROM. In affected women with a non-affected fetus, the preterm delivery rate was 12.5%. Among non-affected mothers who delivered an infant with Ehlers-Danlos syndrome, the preterm delivery rate was 40%, with one-half of all preterm cases preceded by PPROM.

In a clinical survey of obstetric histories of 43 women affected with Ehlers-Danlos syndrome, Sorokin et al. [27] reported a preterm delivery rate of 23.1% (22/95). Fifteen of the infants (15.7%) were small-for-gestational age. Yen et al. [28] reviewed the medical records of 16 Ehlers-Danlos patients and reported a preterm delivery rate of 19% (3/16). The prevalence of premature rupture of membranes was also 19% (3/16).

Most articles on pregnancy outcome in Ehlers-Danlos patients are case reports or reviews of case reports. These case reports are prone to publication bias yet, review of the articles listed in Table 1 shows that a pregnancy with an unaffected child [29-40] may proceed to term whereas offspring affected with Ehlers-Danlos syndrome [41-44] are more likely to be born preterm following PPROM. Table 1 also lists reports where the diagnosis in the offspring was either unknown at time of delivery or confirmed to be Ehlers-Danlos syndrome, and yet the pregnancy proceeded to term [33,45]. Cases where maternal complications necessitated earlier delivery [46,47] are also reported. Morales-Roselló et al. [34] reviewed the obstetric outcome in 39 published cases of Ehlers-Danlos syndrome type III and reported a preterm/premature rupture of membranes rate of 15% (6/39).

In 32 out of 36 healthy women who presented with recurrent miscarriage following PPROM, using immunohistochemical and electron microscopic studies, changes in the dermal collagen architecture similar to those in patients with Ehlers-Danlos syndrome were found [48]. A control group that comprised of 33 women with uneventful pregnancies and 33 non-pregnant

women showed no differences in dermal matrix structure. The findings, according to the authors, suggest a link between recurrent preterm premature rupture of membranes and connective tissue abnormalities.

Based on the observations that PPROM rates are highest when the fetus is affected with classical Ehlers-Danlos syndrome (types I and II) and type IV, the *COL5A1*, *COL5A2* and *COL3A1* genes are implicated as contributors to PPROM risk. Mutations leading to a nonfunctional *COL5A1* allele, leading to haploinsufficiency of type V collagen, or mutations that result in a structural alteration in the type V collagen proteins are among the more common causes of classical Ehlers-Danlos syndrome [49]. Mutations in the *COL3A1* gene causing type IV (vascular) Ehlers-Danlos syndrome encompass multiple exon deletions, skipping of a single exon or a point mutation resulting in the substitution of a glycine by another amino acid [50]. While PPROM appears to be a significant obstetrical complication when the fetus is affected, maternal Ehlers-Danlos syndrome is widely thought to facilitate vaginal delivery due to more compliance of the birth canal.

Osteogenesis imperfecta

Osteogenesis imperfecta is a heterogeneous group of inherited connective tissue disorders. Among the most common signs of the disorder are increased bone fragility, blue sclera and thin skin [51]. The disease has an overall incidence of approximately 1 in 10,000 births [52]. It is usually inherited in an autosomal dominant pattern, but rare, severe forms of osteogenesis imperfecta are transmitted as autosomal recessive traits. Most patients (90%) with osteogenesis imperfecta have a mutation in *COL1A1* or *COL1A2*, the genes encoding collagen type I. Autosomal recessive forms of osteogenesis imperfecta result from mutations in the *CRTAP* and *LEPRE1* genes [53-56]. The prolyl 3-hydroxylase 1 (P3H1) protein is encoded by *LEPRE1*, which together with cartilage associated protein encoded by the *CRTAP* gene, and cyclophilin B forms an intracellular complex required for efficient 3-hydroxylation of the fibrillar collagen prolyl residues. Osteogenesis imperfecta has traditionally been classified into four main clinical types, Osteogenesis imperfecta I – IV [57]. This classification has recently been expanded to include four other distinct types (V, VI, VII and VIII) [58,59] (Table 2).

Osteogenesis imperfecta type I, the most common type, is due to a quantitative defect of collagen type I protein [51,59]. Clinical presentation in these individuals is mild with most attaining normal height, though fractures of long bones and vertebral compression fractures are common [58,59]. Osteogenesis imperfecta type II results in death in the perinatal period. These infants have multiple bone deformities and fractures and many are born prematurely [57] and are small-for-gestational age [60]. Most of the mutations that cause this form of the disease involve substitutions for one of the invariant glycine residues in the *COL1A1* and *COL1A2* genes, which disrupts formation of the helical structure of the molecules [61]. Cases of perinatal lethal osteogenesis imperfecta with mutations in the *CRTAP* gene have recently been reported [56]. Among the features that distinguish these infants from osteogenesis type II infants with a structural collagen defect is their white or light blue sclera. Osteogenesis imperfecta type III, the most severe form compatible with survival after the perinatal period, presents with multiple long bone fractures and deformities at birth. The infant's length and birth weight are often lower than normal for gestational age [51]. Patients with osteogenesis imperfecta type IV have mild to moderate bone deformities and may not have fractures at birth. Osteogenesis imperfecta types V-VIII also present with moderate to severe bone fragility but do not have mutations in the collagen genes [59].

In a review of birth outcomes in 15 mothers affected with osteogenesis imperfecta of varying severity, Key and Horger [62] reported preterm birth in one of six infants affected with the disorder (Table 2). Table 2 also shows case reports of apparently healthy mothers delivering affected infants at term [44,63-66]. There are also cases of affected mothers with affected

offspring [67], as well as affected mothers with unaffected infants [62] delivered at term. In other cases, early delivery was necessitated by maternal or fetal complications [68-70]. In two reported cases where the infant was affected with both osteogenesis imperfecta and arthrogryposis multiplex congenita one pregnancy ended in preterm delivery [71] while the other [66] proceeded to term.

In an epidemiologic and genetic study, Sillence et al. [57] reported that babies with type II osteogenesis imperfecta had many features in common, among which were prematurity, and low birth weight. A review of birth records of 16 babies and 5 stillbirths, all diagnosed with osteogenesis imperfecta type II, showed 19 instances where delivery was preterm. All had low crown-heel length at birth and the majority had low birth weight.

In a report on three pregnancies in healthy mothers carrying fetuses affected with osteogenesis imperfecta type II, Cole et al. [72] reported PPRM and preterm birth in two out of the three pregnancies. A 2008 case report [60] also reported preterm birth in a pregnancy where the fetus was affected with osteogenesis imperfecta type II. Rodriguez et al. [73] reviewed eight cases of lethal osteogenesis imperfecta, and reported a high rate of small-for-gestational age and prematurity. One-half of all the babies were born preterm (gestational ages ranging from 31-34 weeks) and six had low birth weight (weights ranging from 950 – 2150 g). Thus, there seems to be an increased risk of PPRM and premature birth when the fetus is affected with type II osteogenesis imperfecta. The impact that the CRTAP-deficient lethal osteogenesis imperfecta has on gestation is not known at this time. Mutations in the *COL1A1* and *COL1A2* genes result in defects in the structure of collagen in type II osteogenesis imperfecta. In osteogenesis imperfecta type I, however, the gene defects result in production of lower than normal quantities of collagen [51].

Epidermolysis bullosa

Inherited epidermolysis bullosa is a clinically and genetically heterogeneous group of diseases characterized by fragility of the skin and mucous membranes. Minor trauma results in erosions and blister formation. Fragility may extend to some of the internal organs and the surface of the cornea [74]. Inherited epidermolysis bullosa has an overall incidence of 19 in every 1 million births in the United States population [74]. There are four major types of epidermolysis bullosa – intraepidermal (epidermolysis bullosa simplex (EDS)), junctional epidermolysis bullosa (JEB), dermolytic (dystrophic epidermolysis bullosa (DEB)), and mixed (Kindler syndrome) (Table 3) [75]. Each major type is further classified into major and minor subtypes, but clinical variation may occur within each subtype. Inherited epidermolysis bullosa may be transmitted as an autosomal dominant or recessive trait. The blistering tendency in inherited epidermolysis bullosa results from mutations in at least 10 distinct genes, which encode structural proteins within the epidermis or the basement membrane zone separating the epidermis from the underlying dermis [74,76].

When the mother has the disorder but the fetus is not affected, the pregnancy usually ends in term delivery [77-81] (Table 3). There have, however been instances where the baby is delivered prematurely through caesarian section [82], or the pregnancy ends in preterm delivery following PPRM [83].

In instances where a healthy mother carried an affected fetus, the pregnancies have either proceeded to term [84-88] or ended in premature delivery [15-17,87-91]. In the rare instances where the fetus has pyloric atresia in addition to epidermolysis bullosa, the pregnancy commonly ends prematurely [15-17,87,88,90,91]. Polyhydramnios has been reported in some of these cases, which may contribute to risk of fetal membrane rupture beyond the impact of any extracellular matrix abnormality [16,17,90]. In 37 cases of JEB with pyloric atresia, Shaw et al., [16] reported the mean birth weight at the 30th percentile for gestational age.

Overall, epidemolysis bullosa, uncomplicated by pyloric atresia, does not seem to increase the risk for preterm delivery. In a study that compared birth weights of children affected by recessive DEB (N = 66) to a sibling control group (N = 44), 30% of the children with epidemolysis bullosa were found to be small-for-gestational age compared with 12% of controls (p = 0.02). There was, however no difference in gestational age. The mean gestational ages (in weeks) for the children born with epidemolysis bullosa and from the control group were 39.8, and 39.7, respectively [92].

Restrictive dermopathy

Restrictive dermopathy is a rare and lethal genetic disorder inherited in an autosomal recessive pattern. Clinical features include intrauterine growth retardation, shiny, tight and rigid skin with prominent vessels, enlarged fontanels, multiple joint contractures and characteristic facial features (small mouth, small pinched nose, and micrognathia) [12]. Affected babies are born prematurely and are either stillborn or die during the first few weeks of life from respiratory insufficiency [12-14,93-96] (Table 4).

In a review of 31 published cases of restrictive dermopathy, Mau et al. [13] found all the babies to be born prematurely (Table 4). PPRM was reported in all cases where information on spontaneous membrane rupture was provided. Most pregnancies were complicated by polyhydramnios.

A 2008 review of 58 cases of restrictive dermopathy reported PPRM in 24 of 30 cases where information on spontaneous membrane rupture was provided [96]. Polyhydramnios was reported as a complication in 21 out of 26 pregnancies with the remaining reports making no reference to the condition. Smitt et al. [97] reviewed 12 cases of restrictive dermopathy and reported polyhydramnios and premature membrane rupture rates of 50-85%. Cases of restrictive dermopathy complicated by chorioamniotic membrane separation have also been reported [98].

The cause of restrictive dermopathy has previously been reported as unknown, but mutations in the *ZMPSTE24* gene have recently been implicated [95,99,100]. *ZMPSTE24* encodes a zinc metalloproteinase involved in the two step post-translational proteolytic cleavage of carboxy terminal residues of farnesylated prelamin A to form mature lamin A [101,102]. Mutations in the *ZMPSTE24* gene cause accumulation of prelamin A in the nuclear envelope resulting in abnormalities in nuclear architecture [101,102].

Histological examination of the skin in restrictive dermopathy cases shows a thickened epidermis, thin dermis, parallel alignment of collagen bundles and absence of elastic fibers [12,13,96]. The precise cause of premature rupture of membranes in restrictive dermopathy is uncertain but abnormal collagen structure and absence of, or reduction in elastic fibers in the fetal membranes may be contributory factors.

Other connective tissue disorders and preterm

Marfan syndrome—Marfan syndrome is an autosomal dominant connective tissue disorder with manifestations in skeletal, ocular and cardiovascular systems [103]. The disorder is caused by mutations in the *FBN1* gene that encodes the extracellular matrix protein fibrillin-1 [104]. The pathophysiology underlying Marfan syndrome is now recognized to encompass excessive TGF β signaling as a consequence of the *FBN1* mutations. Marfan syndrome has an estimated prevalence that ranges between 1 in 5,000 and 1 in 10,000 [105].

Retrospective and prospective studies on pregnancy outcome in women affected by Marfan syndrome reported preterm birth and PPRM rates similar to rates in the general population [18,19,106], but a high rate of spontaneous abortion has been reported in these women

[107-110], possibly associated with cervical incompetence. There are no reports of an association between preterm birth and the Loeys Dietz Syndrome, a recently discovered syndrome that is caused by mutations in the *TGFBR2* and *TGFBR1* genes and has many features similar to Marfan syndrome.

Congenital cutis laxa—Congenital cutis laxa is a rare heterogeneous group of connective tissue disorders characterized by loose, sagging, inelastic skin. Both autosomal dominant and recessive forms of cutis laxa have been described [111]. A form of congenital cutis laxa with deficiency in lysyl oxidase, an extracellular copper enzyme, had been reported as a X-linked trait [112] but in 1991, Hämmäläinen et al. [113] mapped the lysyl oxidase gene to chromosome 5. The X-linked form is now recognized to be a disorder of copper transport [114].

Pulmonary and cardiovascular involvement, are common in the recessive form of cutis laxa [111]. The dominant form is relatively benign, and usually confined to the skin [111] but cases of dominant cutis laxa with systemic involvement have been reported [115,116]. Mutations in the *FBNL5* and *ELN* genes have been reported in the dominant form of cutis laxa [115-118]. Mutations in the *FBNL5* gene have also been identified in the recessive form of cutis laxa [114,119], but the *FBNL5* and *ELN* gene mutations may not be the exclusive cause of the disease [116]. Preterm birth and PPROM are not common features of cutis laxa. Although instances of cutis laxa with preterm birth have been reported [117,120,121] most offsprings affected with cutis laxa have come from full-term pregnancies [111,120,122-127].

Discussion

Pregnancies hosting a fetus with Ehlers-Danlos syndrome, restrictive dermopathy or osteogenesis imperfecta Type II are associated with an increased risk of preterm birth and PPROM. Women affected by Marfan syndrome have PPROM rates similar to rates in the general population, but appear to be at greater risk for pregnancy complications associated with cervical function. When the mother or fetus is affected with cutis laxa there is no apparent increase in risk for preterm birth. Pregnancies in which the fetus is affected with epidemolysis bullosa and pyloric atresia commonly end prematurely. This may possibly be a result of multiple factors, but epidemolysis bullosa per se does not seem to increase the risk for preterm delivery. These observations create a menu of genes that contribute to prematurity. Collectively, these epidemiologic observations strongly suggest a fetal role in risk of PPROM and an excessive risk for PPROM when extracellular matrix structure or metabolism is abnormal in the fetus.

Gene mutations in Ehlers-Danlos syndrome include defects in the *COL5A1*, *COL5A2*, *COL3A1*, and *COL1A1* and *COL1A2* genes. Other mutations reported to cause Ehlers-Danlos syndrome include defects in the *TNXB*, *PLOD1* and *ADAMTS2* genes. Among the known genetic mutations in osteogenesis imperfecta type II are defects in *COL1A1*, *COL1A2*, *CRTAP* and *LEPRE1* genes. Mutations in the *ZMPSTE24* gene have been identified in cases of restrictive dermopathy, but the pathogenetic mechanism resulting in the high rate of premature rupture of fetal membranes and preterm birth in these cases is largely unknown.

Conversely, mutations in the *FBN1*, *FBNL5*, *TGFBR1* and *TGFBR2* genes do not appear to be significant contributors to risk of PPROM. Of equal interest are certain other genes that are not implicated in prematurity, in particular *ELN*. Elastic fibers are found in the cervix and there is some debate about their presence in the fetal membrane and their contribution to the integrity of these structures [7,8]. Hieber et al. [7] detected tropoelastin in the fetal membranes, whereas Malak and Bell [8] could not identify elastin, but instead reported fibrillin-containing microfibrils. As noted above, fetuses affected with mutations in *FBN1* gene are not evidently

at risk of preterm birth from PPRM, but the exact role that defects in molecules that provide elastic properties to tissues have on PPRM is not known.

Among the deficiencies in the existing literature on collagen and related extracellular matrix disorders is the absence of information on the specific mutations that are associated with preterm birth. This is due, in part, because the diagnosis of the disorders is frequently made on a clinical basis and specific mutations are not identified. Thus, it is not possible to define genotype-phenotype relationships, or specify the genes that are most responsible for preterm birth when a syndrome is caused by mutations in more than one gene (e.g., Ehlers-Danlos syndrome types I and II and osteogenesis imperfecta type II). This is unfortunate since the knowledge of the relative contribution of each causative gene and the nature of the mutation would inform the search for genetic variants that increase risk of non-syndromic preterm delivery.

In addition, there is little information on the physical or structural abnormalities in the fetal membranes when a fetus is affected by Ehlers-Danlos syndrome, osteogenesis imperfecta or restrictive dermopathy. Consequently, we cannot construct a more refined pathophysiological mechanism other for PPRM risk in the different disease contexts. For example, it would be of interest to know how defects in type I collagen, as opposed to type V collagen influence the histological organization and physical properties of the fetal membranes.

Instances where cervical incompetence has complicated pregnancies in women with Ehlers-Danlos syndrome [41,128] and Marfan syndrome [109,110,129,130] have been reported. In a case-control study, Warren et al. [131] reported that 27.2% of women with cervical insufficiency had at least one first-degree female relative with cervical insufficiency. The authors also found polymorphisms in the *COL1A1* and *TGFB1* genes to be associated with cervical insufficiency.

The candidate genes for preterm birth gleaned from our analyses of the collagen and related disorders literature does not preclude the involvement of other genes and pathways. Indeed, genetic variations in the *SERPINH1* gene, a molecular chaperone essential for fibrillar collagen synthesis and polymorphisms in matrix metalloproteinase genes which include enzymes that degrade fibrillar collagens, type IV collagen and other matrix molecules have been associated with preterm birth due to PPRM as suggested from our previously published work [1, 132-136]. The variants identified to date in these genes that are associated with preterm birth may interact with those in the candidate genes identified in this review to compound the risk of prematurity. Additionally, environmental factors that trigger matrix turnover, including those than engender inflammation, are likely to collaborate to increase the likelihood of structural changes in the fetal membranes and cervix, precipitating preterm birth.

In summary, based on the review of the incidence of preterm birth, it can be argued that there is a significant fetal contribution to PPRM when the fetus carries mutations in genes encoding fibrillar collagens and other genes linked to classical types of Ehlers-Danlos syndrome, osteogenesis imperfecta type II and restrictive dermopathy (e.g., *COL1A1*, *COL1A2*, *COL5A1*, *COL5A2*, *CRTAP*, *LPRE1*, *ZMPSTE24*). These observations reveal the importance of the extracellular matrix in the maintenance of the integrity of the fetal membranes and reveal the propensity of those membranes with an abnormal fibrillar collagen to rupture prematurely. The recent discovery of significant natural variation in human collagen genes across ethnically diverse populations, including more than 200 novel single nucleotide polymorphisms, indicates that a comprehensive resequencing program of the genes listed above may reveal new candidate variants that predispose the pregnancies to preterm delivery as a result of PPRM [137]. Variants in these genes with different ancestral frequencies may also help explain disparities in preterm birth among populations (e.g., *COL1A1*: rs1800215, rs1057297, rs1800215;

COL1A2: rs17122498, rs1793947; *COL3A1*: rs35830636). These variations may result in a phenotype that selectively affects fetal membrane structure and function, perhaps only in the context of certain environmental factors like infection/inflammation, while not resulting in gross pathology in other connective tissues. This notion is supported by the observations of Hermanns-Lê and colleagues, which suggest a link between PPRM and Ehlers-Danlos-like histological changes in the dermis, in keeping with the idea that genetic variation which does not cause an overt clinical syndrome exists in the population and could contribute to preterm birth [48].

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References

1. Parry S, Strauss JF 3rd. Premature rupture of the fetal membranes. *N Engl J Med* 1998;338:663–670. [PubMed: 9486996]
2. Oxlund H, Helmig R, Halaburt JT, Uldbjerg N. Biomechanical analysis of human chorioamniotic membranes. *Eur J Obstet Gynecol Reprod Biol* 1990;34:247–255. [PubMed: 2311812]
3. Helmig R, Oxlund H, Petersen LK, Uldbjerg N. Different biomechanical properties of human fetal membranes obtained before and after delivery. *Eur J Obstet Gynecol Reprod Biol* 1993;48:183–189. [PubMed: 8335136]
4. Wang H, Parry S, Macones G, Sammel MD, Kuivaniemi H, Tromp G, Argyropoulos G, Halder I, Shriver MD, Romero R, Strauss JF 3rd. A functional SNP in the promoter of the *SERPINH1* gene increases risk of preterm premature rupture of membranes in African Americans. *Proc Natl Acad Sci U S A* 2006;103:13463–13467. [PubMed: 16938879]
5. Moore RM, Mansour JM, Redline RW, Mercer BM, Moore JJ. The physiology of fetal membrane rupture: Insight gained from the determination of physical properties. *Placenta* 2006;27:1037–1051. [PubMed: 16516962]
6. Malak TM, Ockelford CD, Bell SC, Dalglish R, Bright N, Macvicar J. Confocal immunofluorescence localization of collagen types I, III, IV, V and VI and their ultrastructural organization in term human fetal membranes. *Placenta* 1993;14:385–406. [PubMed: 8248033]
7. Hieber AD, Corcino D, Motosue J, Sandberg LB, Roos PJ, Yu SY, Csiszar K, Kagan HM, Boyd CD, Bryant-Greenwood GD. Detection of elastin in the human fetal membranes: Proposed molecular basis for elasticity. *Placenta* 1997;18:301–312. [PubMed: 9179924]
8. Malak TM, Bell SC. Distribution of fibrillin-containing microfibrils and elastin in human fetal membranes: A novel molecular basis for membrane elasticity. *Am J Obstet Gynecol* 1994;171:195–205. [PubMed: 8030699]
9. Heaps, BR.; House, M.; Socrate, S.; Leppert, P.; Strauss, JF, III. Matrix biology and preterm birth. In: Petraglia, F.; Strauss, JF., III; Gabbe, SG.; Weiss, G., editors. *Preterm Birth*. Oxford, England: Informa Press; 2007. p. 70-93.
10. Barabas AP. Ehlers-Danlos syndrome: Associated with prematurity and premature rupture of foetal membranes; possible increase in incidence. *Br Med J* 1966;2:682–684. [PubMed: 5912902]
11. Lind J, Wallenburg HC. Pregnancy and the Ehlers-Danlos syndrome: A retrospective study in a Dutch population. *Acta Obstet Gynecol Scand* 2002;81:293–300. [PubMed: 11952457]
12. Witt DR, Hayden MR, Holbrook KA, Dale BA, Baldwin VJ, Taylor GP. Restrictive dermopathy: A newly recognized autosomal recessive skin dysplasia. *Am J Med Genet* 1986;24:631–648. [PubMed: 2426945]
13. Mau U, Kendziorra H, Kaiser P, Enders H. Restrictive dermopathy: Report and review. *Am J Med Genet* 1997;71:179–185. [PubMed: 9217218]

14. Wesche WA, Cutlan RT, Khare V, Chesney T, Shanklin D. Restrictive dermopathy: Report of a case and review of the literature. *J Cutan Pathol* 2001;28:211–218. [PubMed: 11426829]
15. Dolan CR, Smith LT, Sybert VP. Prenatal detection of epidermolysis bullosa letalis with pyloric atresia in a fetus by abnormal ultrasound and elevated alpha-fetoprotein. *Am J Med Genet* 1993;47:395–400. [PubMed: 7510931]
16. Shaw DW, Fine JD, Piacquadio DJ, Greenberg MJ, Wang-Rodriguez J, Eichenfield LF. Gastric outlet obstruction and epidermolysis bullosa. *J Am Acad Dermatol* 1997;36:304–310. [PubMed: 9039206]
17. De Jenlis Sicot B, Deruelle P, Kacet N, Vaillant C, Subtil D. Prenatal findings in epidermolysis bullosa with pyloric atresia in a family not known to be at risk. *Ultrasound Obstet Gynecol* 2005;25:607–609. [PubMed: 15912478]
18. Lind J, Wallenburg HC. The Marfan syndrome and pregnancy: A retrospective study in a Dutch population. *Eur J Obstet Gynecol Reprod Biol* 2001;98:28–35. [PubMed: 11516796]
19. Rossiter JP, Repke JT, Morales AJ, Murphy EA, Pyeritz RE. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. *Am J Obstet Gynecol* 1995;173:1599–1606. [PubMed: 7503207]
20. Badauy CM, Gomes SS, Sant'Ana Filho M, Chies JA. Ehlers-Danlos syndrome (EDS) type IV: Review of the literature. *Clin Oral Investig* 2007;11:183–187.
21. Parapia LA, Jackson C. Ehlers-Danlos syndrome--a historical review. *Br J Haematol* 2008;141:32–35. [PubMed: 18324963]
22. Karrer S, Landthaler M, Schmalz G. Ehlers-Danlos type VIII. Review of the literature. *Clin Oral Investig* 2000;4:66–69.
23. De Coster PJ, Cornelissen M, De Paepe A, Martens LC, Vral A. Abnormal dentin structure in two novel gene mutations [COL1A1, Arg134Cys] and [ADAMTS2, Trp795-to-ter] causing rare type I collagen disorders. *Arch Oral Biol* 2007;52:101–109. [PubMed: 17118335]
24. Pyeritz RE. Ehlers-Danlos syndrome. *N Engl J Med* 2000;342:730–732. [PubMed: 10706904]
25. Germain DP. Ehlers-Danlos syndrome type IV. *Orphanet J Rare Dis* 2007;2:32. [PubMed: 17640391]
26. Ainsworth SR, Aulicino PL. A survey of patients with Ehlers-Danlos syndrome. *Clin Orthop Relat Res* 1993;286:250–256. [PubMed: 8425354]
27. Sorokin Y, Johnson MP, Rogowski N, Richardson DA, Evans MI. Obstetric and gynecologic dysfunction in the Ehlers-Danlos syndrome. *J Reprod Med* 1994;39:281–284. [PubMed: 8040845]
28. Yen JL, Lin SP, Chen MR, Niu DM. Clinical features of Ehlers-Danlos syndrome. *J Formos Med Assoc* 2006;105:475–480. [PubMed: 16801035]
29. Volkov N, Nisenblat V, Ohel G, Gonen R. Ehlers-Danlos syndrome: Insights on obstetric aspects. *Obstet Gynecol Surv* 2007;62:51–57. [PubMed: 17176488]
30. Snyder RR, Gilstrap LC, Hauth JC. Ehlers-Danlos syndrome and pregnancy. *Obstet Gynecol* 1983;61:649–650. [PubMed: 6601251]
31. Ploeckinger B, Ulm MR, Chalubinski K. Ehlers-Danlos syndrome type II in pregnancy. *Am J Perinatol* 1997;14:99–101. [PubMed: 9259907]
32. Munz W, Schlembach D, Beinder E, Fischer T. Ehlers-Danlos syndrome type I in pregnancy: A case report. *Eur J Obstet Gynecol Reprod Biol* 2001;99:126–128. [PubMed: 11604202]
33. Roop KA, Brost BC. Abnormal presentation in labor and fetal growth of affected infants with type III Ehlers-Danlos syndrome. *Am J Obstet Gynecol* 1999;181:752–753. [PubMed: 10486495]
34. Morales-Rosello J, Hernandez-Yago J, Pope M. Type III Ehlers-Danlos syndrome and pregnancy. *Arch Gynecol Obstet* 1997;261:39–43. [PubMed: 9451523]
35. Jaleel S, Olah K. Ehlers-Danlos syndrome in pregnancy. *J Obstet Gynaecol* 2007;27:420–421. [PubMed: 17654199]
36. Golfier F, Peyrol S, Attia-Sobol J, Marret H, Raudrant D, Plauchu H. Hypermobility type of Ehlers-Danlos syndrome: Influence of pregnancies. *Clin Genet* 2001;60:240–241. [PubMed: 11595028]
37. Bruno PA, Napolitano V, Votino F, Di Mauro P, Nappi C. Pregnancy and delivery in Ehlers-Danlos syndrome type V. *Clin Exp Obstet Gynecol* 1997;24:152–153. [PubMed: 9478303]
38. Kiilholma P, Gronroos M, Nanto V, Paul R. Pregnancy and delivery in Ehlers-Danlos syndrome. Role of copper and zinc. *Acta Obstet Gynecol Scand* 1984;63:437–439. [PubMed: 6496046]

39. Smith SA, Powell LC, Essin EM. Ehlers-Danlos syndrome and pregnancy. Report of a case *Obstet Gynecol* 1968;32:331–335.
40. Kulkarni S, LaGrenade L. Ehlers-Danlos syndrome in pregnancy. *West Indian Med J* 1992;41:86–87. [PubMed: 1523842]
41. De Vos M, Nuytinck L, Verellen C, De Paepe A. Preterm premature rupture of membranes in a patient with the hypermobility type of the Ehlers-Danlos syndrome. A case report. *Fetal Diagn Ther* 1999;14:244–247. [PubMed: 10420050]
42. Fujimoto A, Wilcox WR, Cohn DH. Clinical, morphological, and biochemical phenotype of a new case of Ehlers-Danlos syndrome type VIIIC. *Am J Med Genet* 1997;68:25–28. [PubMed: 8986271]
43. Lurie S, Manor M, Hagay ZJ. The threat of type IV Ehlers-Danlos syndrome on maternal well-being during pregnancy: Early delivery may make the difference. *J Obstet Gynaecol* 1998;18:245–248. [PubMed: 15512069]
44. Young ID, Lindenbaum RH, Thompson EM, Pembrey ME. Amniotic bands in connective tissue disorders. *Arch Dis Child* 1985;60:1061–1063. [PubMed: 3840971]
45. Taylor DJ, Wilcox I, Russell JK. Ehlers-Danlos syndrome during pregnancy: A case report and review of the literature. *Obstet Gynecol Surv* 1981;36:277–281. [PubMed: 6972498]
46. Atalla A, Page I. Ehlers-Danlos syndrome type III in pregnancy. *Obstet Gynecol* 1988;71:508–509. [PubMed: 3347446]
47. Wood J. Case study: Pregnancy and Ehlers-Danlos syndrome type IV. *Midwives Chron* 1993;106:446–448. [PubMed: 8277897]
48. Hermanns-Le T, Pierard G, Quatresooz P. Ehlers-Danlos-like dermal abnormalities in women with recurrent preterm premature rupture of fetal membranes. *Am J Dermatopathol* 2005;27:407–410. [PubMed: 16148410]
49. Malfait F, De Paepe A. Molecular genetics in classic Ehlers-Danlos syndrome. *Am J Med Genet C Semin Med Genet* 2005;139C:17–23. [PubMed: 16278879]
50. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med* 2000;342:673–680. [PubMed: 10706896]
51. Brusin JH. Osteogenesis imperfecta. *Radiol Technol* 2008;79:535–48. [PubMed: 18650529] quiz 549-51
52. Glorieux FH. Osteogenesis imperfecta. *Best Pract Res Clin Rheumatol* 2008;22:85–100. [PubMed: 18328983]
53. Baldridge D, Schwarze U, Morello R, Lenington J, Bertin TK, Pace JM, Pepin MG, Weis M, Eyre DR, Walsh J, Lambert D, Green A, Robinson H, Michelson M, Houge G, Lindman C, Martin J, Ward J, Lemyre E, Mitchell JJ, Krakow D, Rimo DL, Cohn DH, Byers PH, Lee B. CRTAP and LEPRE1 mutations in recessive osteogenesis imperfecta. *Hum Mutat*. 2008
54. Morello R, Bertin TK, Chen Y, Hicks J, Tonachini L, Monticone M, Castagnola P, Rauch F, Glorieux FH, Vranka J, Bachinger HP, Pace JM, Schwarze U, Byers PH, Weis M, Fernandes RJ, Eyre DR, Yao Z, Boyce BF, Lee B. CRTAP is required for prolyl 3- hydroxylation and mutations cause recessive osteogenesis imperfecta. *Cell* 2006;127:291–304. [PubMed: 17055431]
55. Martin E, Shapiro JR. Osteogenesis imperfecta: Epidemiology and pathophysiology. *Curr Osteoporos Rep* 2007;5:91–97. [PubMed: 17925189]
56. Barnes AM, Chang W, Morello R, Cabral WA, Weis M, Eyre DR, Leikin S, Makareeva E, Kuznetsova N, Uveges TE, Ashok A, Flor AW, Mulvihill JJ, Wilson PL, Sundaram UT, Lee B, Marini JC. Deficiency of cartilage-associated protein in recessive lethal osteogenesis imperfecta. *N Engl J Med* 2006;355:2757–2764. [PubMed: 17192541]
57. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *J Med Genet* 1979;16:101–116. [PubMed: 458828]
58. Rauch F, Glorieux FH. Osteogenesis imperfecta. *Lancet* 2004;363:1377–1385. [PubMed: 15110498]
59. Cheung MS, Glorieux FH. Osteogenesis Imperfecta: Update on presentation and management. *Rev Endocr Metab Disord* 2008;9:153–160. [PubMed: 18404382]
60. Taksande A, Vilhekar K, Khangare S. Osteogenesis Imperfecta Type II with Congenital Heart Disease. *Iran J Pediatr* 2008;18(2):175–178.

61. Marini JC, Forlino A, Cabral WA, Barnes AM, San Antonio JD, Milgrom S, Hyland JC, Korkko J, Prockop DJ, De Paepe A, Coucke P, Symoens S, Glorieux FH, Roughley PJ, Lund AM, Kuurila-Svahn K, Hartikka H, Cohn DH, Krakow D, Mottes M, Schwarze U, Chen D, Yang K, Kuslich C, Troendle J, Dagleish R, Byers PH. Consortium for osteogenesis imperfecta mutations in the helical domain of type I collagen: Regions rich in lethal mutations align with collagen binding sites for integrins and proteoglycans. *Hum Mutat* 2007;28:209–221. [PubMed: 17078022]
62. Key TC, Horger EO 3rd. Osteogenesis imperfecta as a complication of pregnancy. *Obstet Gynecol* 1978;51:67–71. [PubMed: 619339]
63. Byrne BM, Morrison JJ. Prenatal diagnosis of lethal fetal malformation in Irish obstetric practice. *Ir Med J* 1999;92:271–273. [PubMed: 10360111]
64. Teng SW, Guo WY, Sheu MH, Wang PH. Initial experience using magnetic resonance imaging in prenatal diagnosis of osteogenesis imperfecta type II: A case report. *Clin Imaging* 2003;27:55–58. [PubMed: 12504324]
65. Cho E, Dayan SS, Marx GF. Anaesthesia in a parturient with osteogenesis imperfecta. *Br J Anaesth* 1992;68:422–423. [PubMed: 1642923]
66. Brady AF, Patton MA. Osteogenesis imperfecta with arthrogryposis multiplex congenita (Bruck syndrome)--evidence for possible autosomal recessive inheritance. *Clin Dysmorphol* 1997;6:329–336. [PubMed: 9354841]
67. Chen CP, Su YN, Lin SP, Lin ML, Wang W. Favourable outcome in a pregnancy with concomitant maternal and fetal osteogenesis imperfecta associated with a novel COL1A2 mutation. *Prenat Diagn* 2006;26:188–190. [PubMed: 16470573]
68. Parasuraman R, Taylor MJ, Liversedge H, Gilg J. Pregnancy management in type III maternal osteogenesis imperfecta. *J Obstet Gynaecol* 2007;27:619–621. [PubMed: 17896267]
69. Anderer G, Hellmeyer L, Hadji P. Clinical management of a pregnant patient with type I osteogenesis imperfecta using quantitative ultrasonometry--a case report. *Ultraschall Med* 2008;29:201–204. [PubMed: 17315113]
70. Chan B, Zacharin M. Maternal and infant outcome after pamidronate treatment of polyostotic fibrous dysplasia and osteogenesis imperfecta before conception: A report of four cases. *J Clin Endocrinol Metab* 2006;91:2017–2020. [PubMed: 16551739]
71. Datta V, Sinha A, Saili A, Nangia S. Bruck syndrome. *Indian J Pediatr* 2005;72:441–442. [PubMed: 15973030]
72. Cole WG, Patterson E, Bonadio J, Campbell PE, Fortune DW. The clinicopathological features of three babies with osteogenesis imperfecta resulting from the substitution of glycine by valine in the pro alpha 1 (I) chain of type I procollagen. *J Med Genet* 1992;29:112–118. [PubMed: 1613761]
73. Rodriguez JI, Perera A, Regadera J, Collado F, Contreras F. Lethal osteogenesis imperfecta. Anatomopathologic (optical and structural) study of 8 autopsy cases. *An Esp Pediatr* 1982;17:18–33. [PubMed: 7137723]
74. Fine JD. Epidermolysis bullosa: A genetic disease of altered cell adhesion and wound healing, and the possible clinical utility of topically applied thymosin beta4. *Ann N Y Acad Sci* 2007;1112:396–406. [PubMed: 17468231]
75. Fine JD, Eady RA, Bauer EA, Bauer JW, Bruckner-Tuderman L, Heagerty A, Hintner H, Hovnanian A, Jonkman MF, Leigh I, McGrath JA, Mellerio JE, Murrell DF, Shimizu H, Uitto J, Vahlquist A, Woodley D, Zambruno G. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. *J Am Acad Dermatol* 2008;58:931–950. [PubMed: 18374450]
76. Uitto J. Epidermolysis bullosa: Prospects for cell-based therapies. *J Invest Dermatol* 2008;128:2140–2142. [PubMed: 18695685]
77. Buscher U, Wessel J, Anton-Lamprecht I, Dudenhausen JW. Pregnancy and delivery in a patient with mutilating dystrophic epidermolysis bullosa (Hallopeau-Siemens type). *Obstet Gynecol* 1997;89:817–820. [PubMed: 9166333]
78. Price T, Katz VL. Obstetrical concerns of epidermolysis bullosa. *Obstet Gynecol Surv* 1988;43:445–449. [PubMed: 3047604]

79. Baloch MS, Fitzwilliams B, Mellerio J, Lakasing L, Bewley S, O'Sullivan G. Anaesthetic management of two different modes of delivery in patients with dystrophic epidermolysis bullosa. *Int J Obstet Anesth* 2008;17:153–158. [PubMed: 18308542]
80. Broster T, Placek R, Eggers GW Jr. Epidermolysis bullosa: Anesthetic management for cesarean section. *Anesth Analg* 1987;66:341–343. [PubMed: 3565798]
81. Fine JD, Eady RA, Levy ML, Hejtmancik JF, Courtney KB, Carpenter RJ, Holbrook KA, Hawkins HK. Prenatal diagnosis of dominant and recessive dystrophic epidermolysis bullosa: Application and limitations in the use of KF-1 and LH 7:2 monoclonal antibodies and immunofluorescence mapping technique. *J Invest Dermatol* 1988;91:465–471. [PubMed: 3049834]
82. Berryhill RE, Benumof JL, Saidman LJ, Smith PC, Plumer MH. Anesthetic management of emergency cesarean section in a patient with epidermolysis bullosa dystrophica polydysplastica. *Anesth Analg* 1978;57:281–283. [PubMed: 565172]
83. Bianca S, Reale A, Ettore G. Pregnancy and cesarean delivery in a patient with dystrophic epidermolysis bullosa. *Eur J Obstet Gynecol Reprod Biol* 2003;110:235–236. [PubMed: 12969591]
84. Goldstein AM, Davenport T, Sheridan RL. Junctional epidermolysis bullosa: Diagnosis and management of a patient with the Herlitz variant. *J Pediatr Surg* 1998;33:756–758. [PubMed: 9607491]
85. Takizawa Y, Pulkkinen L, Shimizu H, Lin L, Hagiwara S, Nishikawa T, Uitto J. Maternal uniparental meroisodisomy in the LAMB3 region of chromosome 1 results in lethal junctional epidermolysis bullosa. *J Invest Dermatol* 1998;110:828–831. [PubMed: 9579554]
86. Azarian M, Dreux S, Vuillard E, Meneguzzi G, Haber S, Guimiot F, Muller F. Prenatal diagnosis of inherited epidermolysis bullosa in a patient with no family history: A case report and literature review. *Prenat Diagn* 2006;26:57–59. [PubMed: 16378325]
87. Nazzaro V, Nicolini U, De Luca L, Berti E, Caputo R. Prenatal diagnosis of junctional epidermolysis bullosa associated with pyloric atresia. *J Med Genet* 1990;27:244–248. [PubMed: 2182874]
88. Marras A, Dessi C, Macciotta A. Epidermolysis bullosa and amniotic bands. *Am J Med Genet* 1984;19:815–817. [PubMed: 6517104]
89. Aubard Y, Genet C, Bedane C, Gilbert B. Prenatal diagnosis of hereditary bullous epidermolysis. A case report *J Gynecol Obstet Biol Reprod (Paris)* 1996;25:588–593.
90. Puvabanditsin S, Garrow E, Kim DU, Tirakitsoontorn P, Luan J. Junctional epidermolysis bullosa associated with congenital localized absence of skin, and pyloric atresia in two newborn siblings. *J Am Acad Dermatol* 2001;44:330–335. [PubMed: 11174408]
91. Peltier FA, Tschen EH, Raimer SS, Kuo TT. Epidermolysis bullosa letalis associated with congenital pyloric atresia. *Arch Dermatol* 1981;117:728–731. [PubMed: 7316533]
92. Fox AT, Alderdice F, Atherton DJ. Are children with recessive dystrophic epidermolysis bullosa of low birthweight? *Pediatr Dermatol* 2003;20:303–306. [PubMed: 12869148]
93. Nijsten TE, De Moor A, Colpaert CG, Robert K, Mahieu LM, Lambert J. Restrictive dermopathy: A case report and a critical review of all hypotheses of its origin. *Pediatr Dermatol* 2002;19:67–72. [PubMed: 11860576]
94. van der Stege JG, van Straaten HL, van der Wal AC, van Eyck J. Restrictive dermopathy and associated prenatal ultrasound findings: Case report. *Ultrasound Obstet Gynecol* 1997;10:140–141. [PubMed: 9286026]
95. Sander CS, Salman N, van Geel M, Broers JL, Al-Rahmani A, Chedid F, Hausser I, Oji V, Al Nuaimi K, Berger TG, Verstraeten VL. A newly identified splice site mutation in ZMPSTE24 causes restrictive dermopathy in the Middle East. *Br J Dermatol* 2008;159:961–967. [PubMed: 18671782]
96. Thill M, Nguyen TD, Wehnert M, Fischer D, Hausser I, Braun S, Jackisch C. Restrictive dermopathy: A rare laminopathy. *Arch Gynecol Obstet* 2008;278:201–208. [PubMed: 18470519]
97. Smitt JH, van Asperen CJ, Niessen CM, Beemer FA, van Essen AJ, Hulsman RF, Oranje AP, Steijlen PM, Wesby-van Swaay E, Tamminga P, Breslau-Siderius EJ. Restrictive dermopathy. Report of 12 cases. Dutch Task Force on Genodermatology. *Arch Dermatol* 1998;134:577–579. [PubMed: 9606327]
98. Kim YN, Jeong DH, Jeong SJ, Sung MS, Kang MS, Kim KT. Complete chorioamniotic membrane separation with fetal restrictive dermopathy in two consecutive pregnancies. *Prenat Diagn* 2007;27:352–355. [PubMed: 17286315]

99. Navarro CL, Cadinanos J, De Sandre-Giovannoli A, Bernard R, Courrier S, Boccaccio I, Boyer A, Kleijer WJ, Wagner A, Giuliano F, Beemer FA, Freije JM, Cau P, Hennekam RC, Lopez-Otin C, Badens C, Levy N. Loss of ZMPSTE24 (FACE-1) causes autosomal recessive restrictive dermopathy and accumulation of Lamin A precursors. *Hum Mol Genet* 2005;14:1503–1513. [PubMed: 15843403]
100. Moulson CL, Go G, Gardner JM, van der Wal AC, Smitt JH, van Hagen JM, Miner JH. Homozygous and compound heterozygous mutations in ZMPSTE24 cause the laminopathy restrictive dermopathy. *J Invest Dermatol* 2005;125:913–919. [PubMed: 16297189]
101. Bergo MO, Gavino B, Ross J, Schmidt WK, Hong C, Kendall LV, Mohr A, Meta M, Genant H, Jiang Y, Wisner ER, Van Bruggen N, Carano RA, Michaelis S, Griffey SM, Young SG. Zmpste24 deficiency in mice causes spontaneous bone fractures, muscle weakness, and a prelamin A processing defect. *Proc Natl Acad Sci U S A* 2002;99:13049–13054. [PubMed: 12235369]
102. Pendas AM, Zhou Z, Cadinanos J, Freije JM, Wang J, Hultenby K, Astudillo A, Wernerson A, Rodriguez F, Tryggvason K, Lopez-Otin C. Defective prelamin A processing and muscular and adipocyte alterations in Zmpste24 metalloproteinase-deficient mice. *Nat Genet* 2002;31:94–99. [PubMed: 11923874]
103. Pyeritz RE. The Marfan syndrome. *Annu Rev Med* 2000;51:481–510. [PubMed: 10774478]
104. Dietz HC, Cutting GR, Pyeritz RE, Maslen CL, Sakai LY, Corson GM, Puffenberger EG, Hamosh A, Nanthakumar EJ, Currstin SM. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature* 1991;352:337–339. [PubMed: 1852208]
105. Pearson GD, Devereux R, Loeys B, Maslen C, Milewicz D, Pyeritz R, Ramirez F, Rifkin D, Sakai L, Svensson L, Wessels A, Van Eyk J, Dietz HC. National Heart, Lung, and Blood Institute and National Marfan Foundation Working Group. Report of the National Heart, Lung, and Blood Institute and National Marfan Foundation Working Group on research in Marfan syndrome and related disorders. *Circulation* 2008;118:785–791. [PubMed: 18695204]
106. Lipscomb KJ, Smith JC, Clarke B, Donnai P, Harris R. Outcome of pregnancy in women with Marfan's syndrome. *Br J Obstet Gynaecol* 1997;104:201–206. [PubMed: 9070139]
107. Pyeritz RE. Maternal and fetal complications of pregnancy in the Marfan syndrome. *Am J Med* 1981;71:784–790. [PubMed: 7304650]
108. Liang ST. Marfan syndrome, recurrent preterm labour and grandmultiparity. *Aust N Z J Obstet Gynaecol* 1985;25:288–289. [PubMed: 3869451]
109. Meijboom LJ, Drenthen W, Pieper PG, Groenink M, van der Post JA, Timmermans J, Voors AA, Roos-Hesselink JW, van Veldhuisen DJ, Mulder BJ. ZAHARA investigators. Obstetric complications in Marfan syndrome. *Int J Cardiol* 2006;110:53–59. [PubMed: 16236373]
110. Rahman J, Rahman FZ, Rahman W, al-Suleiman SA, Rahman MS. Obstetric and gynecologic complications in women with Marfan syndrome. *J Reprod Med* 2003;48:723–728. [PubMed: 14562639]
111. Beighton P. The dominant and recessive forms of cutis laxa. *J Med Genet* 1972;9:216–221. [PubMed: 5046633]
112. Byers PH, Siegel RC, Holbrook KA, Narayanan AS, Bornstein P, Hall JG. X-linked cutis laxa: Defective cross-link formation in collagen due to decreased lysyl oxidase activity. *N Engl J Med* 1980;303:61–65. [PubMed: 6104292]
113. Hamalainen ER, Jones TA, Sheer D, Taskinen K, Pihlajaniemi T, Kivirikko KI. Molecular cloning of human lysyl oxidase and assignment of the gene to chromosome 5q23.3-31.2. *Genomics* 1991;11:508–516. [PubMed: 1685472]
114. Loeys B, Van Maldergem L, Mortier G, Coucke P, Gerniers S, Naeyaert JM, De Paepe A. Homozygosity for a missense mutation in fibulin-5 (FBLN5) results in a severe form of cutis laxa. *Hum Mol Genet* 2002;11:2113–2118. [PubMed: 12189163]
115. Szabo Z, Crepeau MW, Mitchell AL, Stephan MJ, Puntel RA, Yin Loke K, Kirk RC, Urban Z. Aortic aneurysmal disease and cutis laxa caused by defects in the elastin gene. *J Med Genet* 2006;43:255–258. [PubMed: 16085695]
116. Markova D, Zou Y, Ringpfeil F, Sasaki T, Kostka G, Timpl R, Uitto J, Chu ML. Genetic heterogeneity of cutis laxa: A heterozygous tandem duplication within the fibulin-5 (FBLN5) gene. *Am J Hum Genet* 2003;72:998–1004. [PubMed: 12618961]

117. Graul-Neumann LM, Hausser I, Essayie M, Rauch A, Kraus C. Highly variable cutis laxa resulting from a dominant splicing mutation of the elastin gene. *Am J Med Genet A* 2008;146A:977–983. [PubMed: 18348261]
118. Rodriguez-Revenga L, Iranzo P, Badenas C, Puig S, Carrio A, Mila M. A novel elastin gene mutation resulting in an autosomal dominant form of cutis laxa. *Arch Dermatol* 2004;140:1135–1139. [PubMed: 15381555]
119. Hu Q, Loeys BL, Coucke PJ, De Paepe A, Mecham RP, Choi J, Davis EC, Urban Z. Fibulin-5 mutations: Mechanisms of impaired elastic fiber formation in recessive cutis laxa. *Hum Mol Genet* 2006;15:3379–3386. [PubMed: 17035250]
120. Patton MA, Tolmie J, Ruthnum P, Bamforth S, Baraitser M, Pembrey M. Congenital cutis laxa with retardation of growth and development. *J Med Genet* 1987;24:556–561. [PubMed: 3669050]
121. Nanda A, Lionel J, Al-Tawari AA, Anim JT. What syndrome is this? Autosomal recessive type II cutis laxa. *Pediatr Dermatol* 2004;21:167–170. [PubMed: 15078361]
122. Marchase P, Holbrook K, Pinnell SR. A familial cutis laxa syndrome with ultrastructural abnormalities of collagen and elastin. *J Invest Dermatol* 1980;75:399–403. [PubMed: 7430706]
123. Dogra N, Kalsotra P, Dogra D. Congenital generalized cutis laxa in two sisters. *Indian J Dermatol Venereol Leprol* 2004;70:108–109. [PubMed: 17642578]
124. Andiran N, Sarikayalar F, Saraclar M, Caglar M. Autosomal recessive form of congenital cutis laxa: More than the clinical appearance. *Pediatr Dermatol* 2002;19:412–414. [PubMed: 12383097]
125. Khakoo A, Thomas R, Trompeter R, Duffy P, Price R, Pope FM. Congenital cutis laxa and lysyl oxidase deficiency. *Clin Genet* 1997;51:109–114. [PubMed: 9111998]
126. Koklu E, Gunes T, Ozturk MA, Akcokus M, Buyukkayhan D, Kurtoglu S. Cutis laxa associated with central hypothyroidism owing to isolated thyrotropin deficiency in a newborn. *Pediatr Dermatol* 2007;24:525–528. [PubMed: 17958802]
127. Gupta N, Phadke SR. Cutis laxa type II and wrinkly skin syndrome: Distinct phenotypes. *Pediatr Dermatol* 2006;23:225–230. [PubMed: 16780467]
128. Leduc L, Wasserstrum N. Successful treatment with the Smith-Hodge pessary of cervical incompetence due to defective connective tissue in Ehlers-Danlos syndrome. *Am J Perinatol* 1992;9:25–27. [PubMed: 1550628]
129. Tzialidou I, Oehler K, Scharf A, Staboulidou I, Westhoff-Bleck M, Hillemanns P, Gunter HH. Marfan syndrome in pregnancy: Presentation of four cases and discussion. *Z Geburtshilfe Neonatol* 2007;211:36–41. [PubMed: 17327991]
130. Paternoster DM, Santarossa C, Vettore N, Dalla Pria S, Grella P. Obstetric complications in Marfan's syndrome pregnancy. *Minerva Ginecol* 1998;50:441–443. [PubMed: 9866956]
131. Warren JE, Silver RM, Dalton J, Nelson LT, Branch DW, Porter TF. Collagen 1Alpha1 and transforming growth factor-beta polymorphisms in women with cervical insufficiency. *Obstet Gynecol* 2007;110:619–624. [PubMed: 17766609]
132. Fujimoto T, Parry S, Urbanek M, Sammel M, Macones G, Kuivaniemi H, Romero R, Strauss JF 3rd. A single nucleotide polymorphism in the matrix metalloproteinase-1 (MMP-1) promoter influences amnion cell MMP-1 expression and risk for preterm premature rupture of the fetal membranes. *J Biol Chem* 2002;277:6296–6302. [PubMed: 11741975]
133. Ferrand PE, Parry S, Sammel M, Macones GA, Kuivaniemi H, Romero R, Strauss JF 3rd. A polymorphism in the matrix metalloproteinase-9 promoter is associated with increased risk of preterm premature rupture of membranes in African Americans. *Mol Hum Reprod* 2002;8:494–501. [PubMed: 11994547]
134. Wang H, Parry S, Macones G, Sammel MD, Ferrand PE, Kuivaniemi H, Tromp G, Halder I, Shriver MD, Romero R, Strauss JF 3rd. Functionally significant SNP MMP8 promoter haplotypes and preterm premature rupture of membranes (PPROM). *Hum Mol Genet* 2004;13:2659–2669. [PubMed: 15367487]
135. Wang H, Sammel MD, Tromp G, Gotsch F, Halder I, Shriver MD, Romero R, Strauss JF 3rd. A 12-bp deletion in the 5'-flanking region of the SERPINH1 gene affects promoter activity and protects against preterm premature rupture of membranes in African Americans. *Hum Mutat* 2008;29:332. [PubMed: 18205191]

136. Wang H, Ogawa M, Wood JR, Bartolomei MS, Sammel MD, Kusanovic JP, Walsh SW, Romero R, Strauss JF 3rd. Genetic and epigenetic mechanisms combine to control MMP1 expression and its association with preterm premature rupture of membranes. *Hum Mol Genet* 2008;17:1087–1096. [PubMed: 18178580]
137. Chan TF, Poon A, Basu A, Addleman NR, Chen J, Phong A, Byers PH, Klein TE, Kwok PY. Natural variation in four human collagen genes across an ethnically diverse population. *Genomics* 2008;91:307–314. [PubMed: 18272325]

Table 1
Ehlers-Danlos syndrome subtypes, pregnancy outcome and gene mutations.

Case/Population description	Disorder in mother	Age at Delivery (in weeks)	Clinical condition	Condition diagnosed in infant	Reference
32 yrs, white	Type III EDS	40			29
33 yrs	Type III EDS	26	PPROM	EDS	41
26 yrs, hispanic	Healthy	30	PPROM	Type VIIC EDS	42
33 yrs	Type IV EDS	32	PPROM	Type IV EDS	43
	Type IV EDS	39			30
32 yrs	Type II (mitis) EDS	39		Not known	45
	Type II EDS	41			31
27 yrs, white	Type I EDS	38			32
28 yrs, white	Type III EDS	42		Type III EDS	33
31 yrs, white	Type III EDS	40			33
23 yrs, white	Type III EDS	38			34
39 women	Type III EDS				34 (Review)
38 yrs	Type III EDS	38			35
46 Dutch women	EDS (different types)		Preterm - 22%; PPROM - 35%; Preterm - 12.5%	EDS Not affected	11
33 Dutch women	Healthy		Preterm - 40%; PPROM in 50%	EDS	11
98 men & women	EDS (different types)		PPROM - 26-75 %	EDS (types I - IV)	26
43 women	6 had EDS. 36 did not		Recurrent PPROM		27
42 women	Healthy women				48
33 women	Type III EDS	38	Delivery by CS		36
21 yrs	Type III EDS	38	Delivery by CS		36
22 yrs	EDS type V	39	Delivery by CS		37
27 yrs	Type IV EDS	30	PPROM	Type IV EDS	44
28 yrs	Type IV EDS	33	PPROM	Type IV EDS	44
26 yrs	Type III EDS	35	Delivery by CS		46
29 yrs	Type II (mitis) EDS	26			38
	Type II (mitis) EDS	40			38

Case/Population description	Disorder in mother	Age at Delivery (in weeks)	Clinical condition	Condition diagnosed in infant	Reference
17 yrs, white	EDS	39			39
18 men & women		32 - 35	Preterm - 77.7% (PPROM -72.2%	Affected with EDS	10
16 men & women	EDS (types I - IV)		PROM - 19% Preterm - 19%	EDS (types I - IV)	28
17-year-old, black	EDS type I	38	Delivery by CS		40
24-year-old	EDS type IV	36	Delivery by CS	EDS type IV	47
EDS subtype	Designation	Gene mutations			
Classical	EDS I and II	COL5A1, COL5A2, COL1A1 (rare)			
Hypermobility	EDS III	TNXB			
Vascular	EDS IV	COL3A1			
Kyphoscoliosis	EDS VI	PLOD1			
Arthrochalasia	EDS VIIA and VIIB	COL1A1, COL1A2			
Dermatosparaxis	EDS VIIC	ADAMTS2			
EDS = Ehlers Danlos syndrome					

Table 2
Osteogenesis imperfecta subtypes, pregnancy outcome and gene mutations.

Case/Population description	Disorder in mother	Age at Delivery (in weeks)	Clinical condition	Condition diagnosed in infant	Reference
20 yrs	Healthy	34	Preterm	OI type II	60
			Preterm - 19/21	OI type II	57
			Preterm - 4/8	OI type II	73
22 yrs, black	OI tarda	39		Not affected with OI	62
15 women	OI of varying severity		Preterm - 1/15	6/16 infants were affected with OI	62 (Review)
			Preterm - 1 out the 6 affected infants	6 were affected with OI	62 (Review)
25-year-old	Healthy	28	PPROM	OI type IIC	72
33-year-old	Healthy	30	PPROM	OI type IIA	72
27-year-old	Healthy	40		OI type IIA	72
40-year-old	Healthy	38		OI	44
35-year-old		38		OI	63
20-year-old		38	PROM	OI	65
20-year-old	OI Type III	33		OI	68
35-year-old	OI Type I	33		Not affected with OI	69
28-year-old	OI Type IV	34		Not affected with OI	70
28-year-old	OI Type I	37		OI type I	67
35-year-old		37		OI type II	64
		34		Anthrogryposis multiplex congenita and OI	71
26-year-old		40		Anthrogryposis multiplex congenita and OI	66
(same mother)		40		Affected with OI	66

OI subtype	Clinical severity	Gene mutations
I	Mild non-deforming OI	<i>COL1A1, COL1A2</i>

Case/Population description	Disorder in mother	Age at Delivery (in weeks)	Clinical condition	Condition diagnosed in infant	Reference
II	Perinatal lethal	<i>COL1A1, COL1A2, ?CRTAP</i>			
III	Severely deforming	<i>COL1A1, COL1A2</i>			
IV	Moderately deforming	<i>COL1A1, COL1A2</i>			
V	Moderately deforming	Unknown			
VI	Moderately to severely deforming	Unknown			
VII	Moderately deforming	<i>CRTAP</i>			
VIII		<i>LEPRE1</i>			
OI = Osteogenesis Imperfecta					

Table 3
Epidermolysis bullosa subtypes, pregnancy outcome and gene mutations.

Case/Population description	Disorder in mother	Gestation age at Delivery (in weeks)	Clinical condition	Condition diagnosed in infant	Reference
24-year-old	DEB	36	PPROM	No sign of DEB	83
(same mother)	DEB of the Hallopeau-Siemens type	28	Preterm	JEB and pyloric atresia	16
27 yrs (consanguineous couple)	DEB of the Hallopeau-Siemens type	40		No sign of DEB	77
22-year-old, white	DEB of the Hallopeau-Siemens type	40		No sign of DEB	77
29 yrs, Indian	JEB hereditaria letalis	41.5	Premature	DEB of the Hallopeau-Siemens type	89
(same mother)	Healthy	35	Delivery by CS	Not affected with EB	78/
34-year-old	Healthy	32	Delivery by CS	EB simplex and pyloric atresia	90
Black	Healthy	35	Delivery by CS	JEB and pyloric atresia	90
18-year-old	Healthy	40	Preterm	JEB and pyloric atresia	17
Japanese	Healthy	23	Preterm	JEB	84
29-year-old	DEB	40	Preterm	EB and pyloric atresia	15
33-year-old	DEB	40	Delivery by CS	JEB	85
35-year-old	DEB	39	Delivery by CS		79
30-year-old	EB	34	Delivery by CS		82
17-year-old	DEB	38	Delivery by CS	Not affected with EB	80
24-year-old		40	Delivery by CS	Not affected with EB	
25-year-old		37	Pregnancy was terminated	JEB and pyloric atresia	86
(same mother)		34	Preterm	JEB and pyloric atresia	87
22-year-old	DEB	38		JEB and pyloric atresia	87
24-year-old		40		Not affected with EB	81
		40		ED and Amniotic bands	88
		35	Preterm	JEB and pyloric atresia	88
		40		ED and Amniotic bands	88
		32	Preterm	EB letalis and pyloric atresia	91

Case/Population description	Disorder in mother	Gestation age at Delivery (in weeks)	Clinical condition	Condition diagnosed in infant	Reference
ED subtype	Designation	Gene mutations			
Intraepidermal	EBS	<i>PKP1, DSP, KRT5, KRT14, PLEC1, ITGA6, ITGB4</i>			
Junctional	JEB	<i>LAMA3, LAMB3, LAMC2, COL17A1, ITGA6, ITGB4</i>			
Dermolytic	DEB	<i>COL7A1</i>			
Mixed	Kindler syndrome	<i>KIND1</i>			

EB = Epidermolysis bullosa; EBS = Epidermolysis bullosa simplex; DEB = Dystrophic epidermolysis bullosa; JEB = Junctional epidermolysis bullosa

Table 4
Restrictive dermopathy, pregnancy outcome and gene mutations.

Case/Population description	Disorder in mother	Age at Delivery (in weeks)	Clinical condition	Condition diagnosed in infant	Reference
36 yrs, white (same mother)	Healthy	32	PPROM at 30 weeks	RD	12
22 yrs; African origin	Healthy	32	PPROM	RD	12
24-year-old, white	Healthy	34	PPROM	RD	14
27-year-old, white	Healthy	32	PPROM	RD	93
		31	PPROM	RD	13
		28-34	Preterm - 100% (31/31). 16 cases with information on spontaneous membrane rupture all showed PPRM	RD	13(Review)
25-year-old		31	PPROM	RD	94
		31		RD	95
		33		RD	95
21-year-old		29	PPROM	RD	96
		PPROM - 24/30	All affected with RD		96 (Review)
30-year-old (same mother)	Chorioamniotic membrane separation	32	PPROM	RD	98
	Chorioamniotic membrane separation	30	PPROM	RD	98

Disorder	Gene mutation
Restrictive dermopathy	<i>ZMPSTE24</i>
RD = Restrictive dermopathy	