

# The Earliest Illustration of Cutis Laxa Macroscopic Pattern in Jan van Eyck's *Lucca Madonna*

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**KEY WORDS:** cutis laxa, Jan van Eyck, *Lucca Madonna*

IMAJ 2020; 22: 127–129

Identification of diseases and abnormal conditions are of interest to those who study the history of medicine and art as well as the life of the painters. We were attracted to skin changes in paintings of the baby found in Jan van Eyck's *Lucca Madonna* [1], alternatively named *Lucca Virgin* [2], *Madonna and Child*, *Suckling Madonna*.

Jan van Eyck was one of the founders of the Early Netherlandish painting style and was a significant artist of Early Northern Renaissance art. He lived and worked from the late 14th to the middle of the 15th centuries in the region of the Old Netherlands, now territories of three European countries: Belgium, Holland, and France.

### CANVAS TITLE

The word, Lucca, the name of a city located about 70 miles northwest Florence and 10 miles northeast of Pisa, became part of the title probably in the early 19th century, when *Lucca Madonna* was a part of the private collection of Charles Louis, Duke of Lucca (1824–1847). Masterpieces were named to honor the owner, sometimes by adding the city of residence as part of the name. It was a usual practice during this period to differentiate works of art. Residents of the Italian city of Lucca were members of the Arnolfini families, merchants who lived in Bruges and who patronized van Eyck. Family members were possibly models for at least two van Eyck paintings [3].

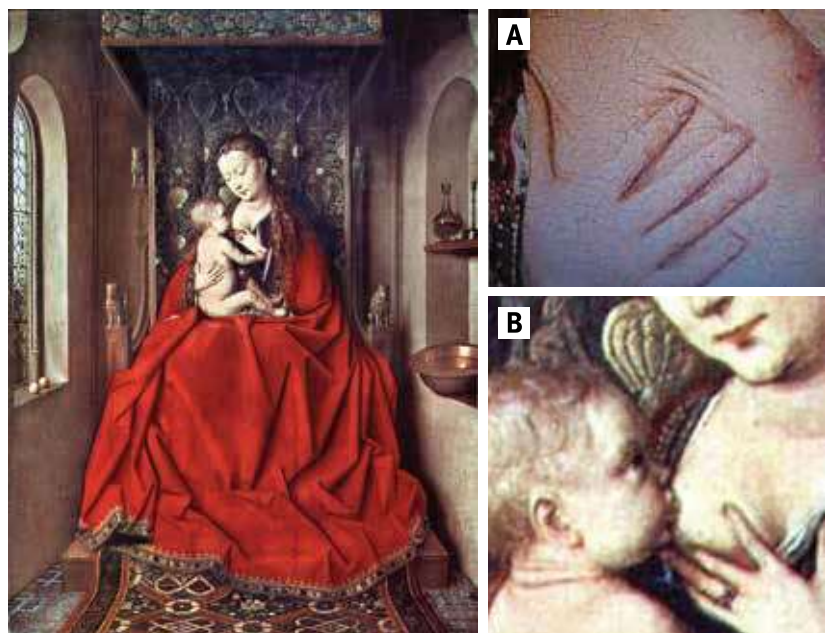
*Lucca Madonna* was probably created over several years, most likely between 1435 and 1437, when van Eyck lived with his family in Bruges and served as a court painter to Philip the Good, Duke of Burgundy. During that time, he combined painting with several diplomatic missions to European countries and probably to the Holy Land.

Paintings of landscapes and of lactating women were important themes. Nursing and breast feeding was considered by art critics to exemplify domestic religious imagery. With regard to *Lucca Madonna*, Harbison [3] noted, "One would say that the

sitting is domestic." The moment of physical saturation and spiritual contact is shown by the posture of the mother and baby, the head tilt, facial expressions, and visual touch [Figures 1 and 1B]. The baby's right hand sits comfortably and confidently on the mother's left hand, which supports the breast for easier sucking [Figure 1B]. The mother's right hand is holding the infant's body, particularly its dorsal part. Multiple magnification using the zoom-in option of Google Arts & Culture [1] reveals the baby's skin wrinkles with folds of the first (all mother fingers), second (fingers 1,2,5),

**Figure 1.** The earliest illustration of the cutis laxa macroscopic pattern in Jan van Eyck artwork *Lucca Madonna*. This image of *Lucca Madonna* depicts a legendary popular scene of a baby breastfeeding by the Virgin Mary (*Lucca Madonna*, Oakwood, 49.6 × 65.7, by Jan van Eyck, 1437. Städel Museum, Frankfurt am Main, Germany)

- [A]** Wrinkles with folds of baby's skin in points of contact with mother's fingers
- [B]** Mother's skin is free of changes where the points of her fingers touch



and third (fingers 1,2) order in points of her hand in contact with the child's back [Figure 1A].

The folds of baby skin are a sign of a dermal elasticity defect known as cutis laxa. Sometimes folds are spontaneous and at other times they may be induced by a light touch [4,5]. The literal translation of the Latin name cutis laxa is lax or loose skin. The disorder was described by Graft in 1836. Thirteen forms of inherited cutis laxa differ by clinical manifestation and molecular defect [6].

The baby depicted in this painting is probably 8 to 9 months old. It is the neonatal or infancy period when congenital variant, diagnosed for a first time about one century ago, manifests clinically. Two forms of congenital cutis laxa inheritance are recognized: autosomal dominant and autosomal recessive.

The opinions of art historians about the domestic imagery in *Lucca Madonna* is supplemented with the assessment of the mother's body language in relation to her child. "The intimacy of the relation between mother and child is delicately expressed by the position of their hands. .... The intense feeling of the mother offering her breast to her child appears to reflect the artist's real-life experience" [2]. According to the same expert, the mother's representation reflects the artist's feelings as a father and husband, "The serenity and happiness which radiate from the work may indicate in fact, that Jan painted it for his personal pleasure. .... The sublimation of the maternal gesture seems to express the painter's own experience as a father in 1434–35" [2].

Identification of the mother in the painting as van Eyck's wife was suggested due to matching *Lucca Madonna* with a canvas entitled *Jan's wife, Margaret*. This portrait was completed in 1439, the year of her 33 birthday. Four or five years earlier (1434–1435), she gave birth to two children. Van Eyck was about 49 years old at the time. The date of the painting's completion corresponds with van Eyck's motto "als ich can" (as I can), confirming artist's authorship. These words are painted in canvas borders. This painting is one of about

10 surviving van Eyck pieces in which the painter used Latin, Greek, and Hebrew alphabets, particularly for the inscription, which is written in Netherlandish, French, Greek, and Latin.

Matching two works—*Lucca Madonna* and *Jan's wife, Margaret*—art historians concluded, "The Virgin clearly bears the traits of Margaret van Eyck" [2]. Information about the identities of the two images may help to understand the origin of child's cutis laxa.

Van Eyck was not the only artist who portrayed his family members as participants and models, especially if the topic of the painting was Biblical scenes. Other artists followed similar practices for their relatives, friends, and even themselves. Sandro Botticelli portrayed himself and representatives of the Medici family as kings and their proponents in "Adoration of the Magi, 1475". Russian master Alexander Ivanov placed the self-portrait and the image of the writer Nicolay Gogol among the people who meet the Messiah in his painting "The Apparition of Christ to the People (The Apparition of the Messiah), 1837–1857".

The two portraits of Margaret may remind the viewer of a baby's cutis laxa nature. Additional information for such perception supports van Eyck's *A Man with a Red Turban*, which was painted in 1433. According many art historians it is a painter's self-portrait. In fact, "both tradition and the best critics have called this fascinating picture a self-portrait of van Eyck" [2]. At the time this portrait was completed, the painter was 43 years old. He had married Margaret about one year earlier. The families of the newlyweds were not related.

The parent's skin condition may be important for understanding the heredity nature of their child's cutis laxa. Facial features include a noticeable characteristic for loose skin. Sagging and dropping skin of cheeks, chin, eyelids, neck, and nasolabial folds are common observable characteristics [7]. A viewer would be hard pressed to find cutis laxa-related skin changes in the painter's self-portrait or in two paintings with Margaret. Absent in the painter's and

his wife's images are also appearances of premature aging, sometimes manifesting by lax skin.

An additional argument in favor of the absence of the mother's cutis laxa in *Lucca Madonna* is the lack of her breast skin reaction to contact with fingers. No skin folds are seen where her fingers touch her breast [Figure 1B], unlike the skin of the baby's back. Lack of specific cutaneous manifestations in the portraits of Margaret and Jan and their non-consanguineous marriage suggest the absence of autosomal dominant inheritance of the baby's cutis laxa.

Skin changes in another hereditary form of cutis laxa—autosomal recessive—are associated with the pathology of the nervous system, internal organs, and skeleton. Each of the conditions worsen the prognosis. The birth of two of the artist's children, possibly daughters, born in 1434 and 1435, respectively, is documented by a gift given to the Duke of Burgundy. The same force helped Helen (Lievein) van Eyck, the 15–16 year old daughter of the deceased master, earn the required fee to enter a convent as a nun. Jan, Margaret, Helen, Jan's brothers and father are registered as the van Eyck family [8], with more than 136 million families, including Elizabeth II, Queen of the United Kingdom, and Nicolas II, Tsar of Russia. To the best of our knowledge, neither this registry, nor any other source, mention the fate of any other Jan and Margaret van Eyck child.

#### SKIN CHANGES OF BREASTFED BABIES CORRESPOND TO CUTIS LAXA

Damaged skin loses its elasticity. Important clinical sign of the disorder are skin folds, which are spontaneous or induced by light touch.

Cutis laxa in 8- to 9-month-old babies is congenital. Documents and analyses of paintings by van Eyck suggest the absence of the autosomal dominant nature of the baby's cutis laxa. Modern textbooks show illustrations of many skin diseases. *Lucca Madonna* reproduces possibly for the first time the macroscopic pattern of cutis laxa about four centuries prior to the entity recognition and dermatology commencement. *Lucca Madonna* may be included in

discussions of potential medical conditions found in van Eyck's artworks, along with *The Virgin and Child with Canon van der Paele, 1443–1436* in which temporal arteritis and polymyalgia rheumatica seem to be noticeable [9,10].

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**Capsule**

**Spinal subpial delivery of AAV9 enables widespread gene silencing and blocks motoneuron degeneration in ALS**

Gene silencing with virally delivered shRNA represents a promising approach for treatment of inherited neurodegenerative disorders. In the present study **Bravo-Hernandez** and colleagues developed a subpial technique, which in adult animals successfully delivers adeno-associated virus (AAV) throughout the cervical, thoracic and lumbar spinal cord, as well as brain motor centers. One-time injection at cervical and lumbar levels just before disease onset in mice expressing a familial amyotrophic lateral sclerosis (ALS)-causing mutant *SOD1* produces long-term suppression of motoneuron disease, including near-complete preservation of spinal

$\alpha$ -motoneurons and muscle innervation. Treatment after disease onset potentially blocks progression of disease and further  $\alpha$ -motoneuron degeneration. A single subpial AAV9 injection in adult pigs or non-human primates using a newly designed device produces homogeneous delivery throughout the cervical spinal cord white and gray matter and brain motor centers. Thus, spinal subpial delivery in adult animals is highly effective for AAV-mediated gene delivery throughout the spinal cord and supraspinal motor centers.

*Nature Medicine* 2020; 26: 118  
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**Capsule**

**HBO1 is required for the maintenance of leukemia stem cells**

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by transcriptional dysregulation that results in a block in differentiation and increased malignant self-renewal. Various epigenetic therapies aimed at reversing these hallmarks of AML have progressed into clinical trials, but most show only modest efficacy owing to an inability to effectively eradicate leukemia stem cells (LSCs). To specifically identify novel dependencies in LSCs, **MacPherson** and co-authors screened a bespoke library of small hairpin RNAs that target chromatin regulators in a unique ex vivo mouse model of LSCs. The authors identified the MYST acetyltransferase HBO1 (also known as KAT7 or MYST2) and several known members of the HBO1 protein complex as critical regulators of LSC maintenance. Using CRISPR domain screening and quantitative mass spectrometry, the authors identified the

histone acetyltransferase domain of HBO1 as being essential in the acetylation of histone H3 at K14. H3 acetylated at K14 (H3K14ac) facilitates the processivity of RNA polymerase II to maintain the high expression of key genes (including *Hoxa9* and *Hoxa10*) that help to sustain the functional properties of LSCs. To leverage this dependency therapeutically, the group developed a highly potent small-molecule inhibitor of HBO1 and demonstrated its mode of activity as a competitive analogue of acetyl-CoA. Inhibition of HBO1 phenocopied the genetic data and showed efficacy in a broad range of human cell lines and primary AML cells from patients. These biological, structural and chemical insights into a therapeutic target in AML will enable the clinical translation of these findings.

*Nature* 2020; 577: 266  
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**“Achievement is largely the product of steadily raising one’s level of aspiration and expectation”**

Jack Nicklaus (Born 1940), American golfer