

# The Sound of an Honest Signal: The Role of the *FUT2* Gene in Female Voice, Health, Fertility, and Fecundity

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## ABSTRACT

Humans prefer the voices of females at high fertility compared to those at low fertility, suggesting the voice is an indicator of fertility within the menstrual cycle. While the acoustic mechanism of these changes has been elusive, most researchers agree that cyclic hormones are underlying any changes that occur. One factor that impacts vocal production is the quality and quantity of mucus in the vocal tract. The current paper reviews the function of a gene, *FUT2*, which impacts the production of mucins by epithelial and secretor cells in both the vocal and reproductive tract. We explore the possibility that estrogen is a transcription factor for this gene and that genotypes containing at least one allele of the *FUT2* gene (known as secretors) have direct health and fertility advantages. Further, breastfed infants of secretors and infants who are themselves secretors are afforded additional health and cognitive advantages. Therefore, we argue that the female voice could be considered an honest indicator of a female's health, genes, fertility, and fecundity. Further, *FUT2* secretors may advertise this signal more than non-secretors.

## KEYWORDS

*FUT2*, Fertility, Ovulation Cues, Honest Signaling, Voice, Mucosa

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## INTRODUCTION

The female voice has been suggested as an honest signal of health and fertility status (Pipitone & Gallup, 2008). Otte (1974) defined signaling as the observable communicative behaviors, physiology, or morphological characteristics that are preserved through natural selection. Honest signals are characteristics that accurately transmit important information about an individual's genetic quality, health, and fertility status. While the voice can convey age, social status, health status, and

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is preferred when females are at high fertility, evidence that the voice conveys meaningful genetic benefits has yet to be articulated.

The first step to investigating the link behind biological advantages of the voice is to examine its associated physiological structures and secretions. The primary structure involved in voice production, the larynx, is also a target for circulating sex hormones, indicating that the same hormones directly impacting fertility and fecundity likely also impact the voice (Abitbol et al., 1989; 1999; Caruso et al., 2000; for review see Kumar et al., 2016). The impact of these hormones on the larynx facilitates the sexually dimorphic nature of the voice. Male and female voices sound similar up until puberty. Increased testosterone among males at puberty causes fundamental frequency (perceived as voice pitch) to lower dramatically. Among females, puberty doesn't produce drastic changes to the larynx or fundamental frequency (Vorperian et al., 2019), but instead the structures become vulnerable to the effects of fluctuating estrogen and progesterone levels (Brunings et al., 2013). These hormonal changes have been reported to impact listener perception of female voices. Previous research has shown that recordings of females at high fertility are preferred by listeners (Bryant & Haselton, 2009; Pipitone & Gallup, 2008; Shoup-Knox & Pipitone, 2015; Puts et al., 2013). High fertility voices even produce differential physiological (Shoup-Knox & Pipitone, 2015) and hormonal (Ostrander et al., 2018) changes among both male and female listeners compared to recordings of the same females at low fertility. Puts and colleagues (2013) directly linked this preference to speakers' hormone status, showing that voices rated as most attractive were recorded from females with high estrogen, but low progesterone. This hormonal state matches that of the ovulatory phase of the menstrual cycle. Interestingly, research has not consistently demonstrated any acoustic fluctuations that account for listener preference, or that correlate with hormonal status (Puts et al., 2013; Bryant & Haselton, 2009; Pavela Banai, 2017; Fischer et al., 2011; Karthikeyan & Locke, 2015; Celik et al., 2013; Shoup-Knox et al., 2019). Collectively, these findings suggest that the voice varies across the menstrual cycle in ways that elude typical acoustic measures, but clearly impact listener responses.

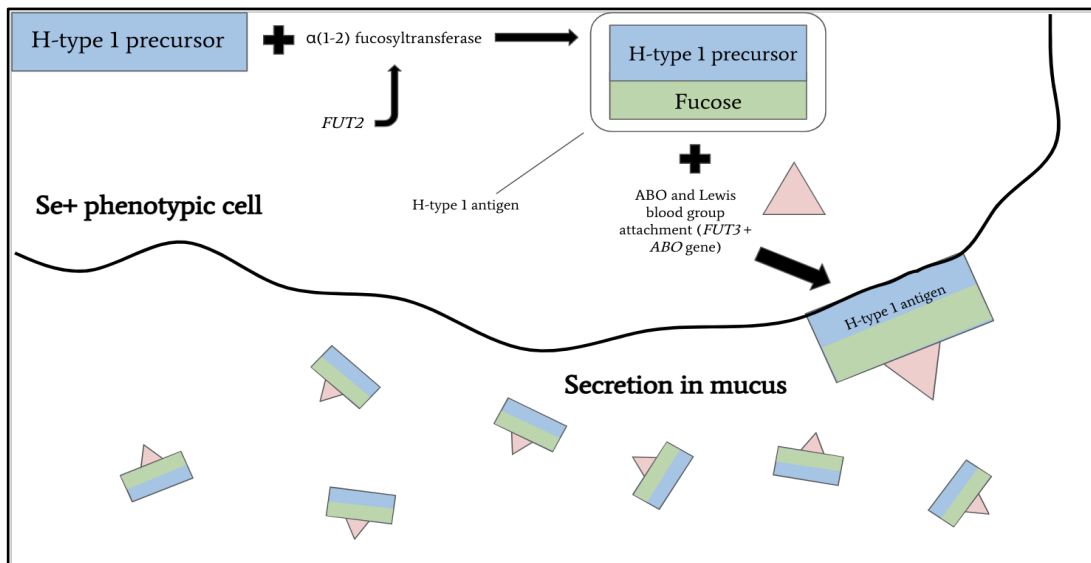
Vocal production occurs when vocal folds oscillate. A mucous membrane produced by epithelial cells covers the muscles and ligaments of the vocal folds (Zamponi et al., 2021). This mucosal layer is essential to producing vocal fold oscillations, and its viscosity impacts vocal frequency (Chan & Titze, 1999). Even slight changes in the hydration of this mucosal surface from oral breathing can produce perceptible increases in vocal effort (Sivasankar & Fisher, 2002). Dehydration also reduces vocal stability, as measured by increased jitter, shimmer, and amplitude perturbation quotient (Zou et al., 2019) Loss of mucosa or damage to this membrane layer can lead to a variety of dysphonias and voice impairments. In fact, bioengineered mucosa has recently been introduced as a treatment to restore vocal communication (Ling et al., 2015).

It is possible that hormones impact the voice partly via their effect on mucosal production. Mucosal surfaces throughout the vocal tract are responsive to hormone fluctuations (Brodnitz, 1971). Estrogen increases the size and mucosal output of secretory cells in the larynx (Kumar et al., 2016). Later in the cycle, and during pregnancy, progesterone is responsible for a decrease in mucosal production, resulting in higher viscosity and dryness in the vocal folds (Chan & Titze, 1999).

Extreme cases produce premenstrual vocal syndrome, characterized by a decreased range of vocal pitch and increased vocal fatigue (Abitbol et al., 1999). The high levels of progesterone experienced during pregnancy amplify these outcomes, and, when coupled with blood vessel dilation that often occurs, the mucosa can become congested resulting in inflammation. Further evidence from menopause shows that the drop in estrogens and excess of androgens leads to a drop in voice pitch, vocal huskiness, and vocal fatigue (Kumar et al., 2016). These hormonally-driven mucosal changes suggest that voice quality could be a *within* female indicator of hormonal and reproductive status. Additionally, it may be the case that differences in mucosal production produce differences in voice quality and cycle-dependent variation *between* women. Therefore, it is important to understand the factors contributing to mucosal production that vary between women as well as in response to hormonal fluctuations within women.

### MUCOSAL PRODUCTION IN THE VOCAL AND REPRODUCTIVE TRACT

Mucosal production occurs when endothelial and secretory cells present carbohydrate chain structures, such as glycolipids and glycoproteins, on their surface. The quality and quantity of mucus secreted from some locations depends on an enzyme adding an external sugar to these transmembrane carbohydrates. This process is called fucosylation and the necessary enzyme is  $\alpha(1,2)$ -fucosyltransferase (see Figure 1). Fucosylation facilitates the secretion of antigens, which build mucosal surfaces. The gene that codes for  $\alpha(1,2)$ -fucosyltransferase is *FUT2*. Having at least one functional *FUT2* allele grants an individual 'secretor status' (Se+), in which secretion of antigens at various epithelial sites is enhanced (see Figure 1). In general, the secretor phenotype is expressed in approximately 80% of the population, but the phenotype ratio differs based on the ethnic population being studied (Kaur et al., 2022).



**Figure 1.** Among secretors (Se+), the *FUT2* gene encodes  $\alpha(1,2)$ -fucosyltransferase, an enzyme that catalyzes the transfer and binding of a fucose sugar to the H-type 1 precursor via an  $\alpha(1,2)$  linkage. The binding of the fucose to the precursor is what forms the H-type 1 antigen. The H antigen provides the foundation upon which Lewis and ABO antigens are attached. To summarize, *FUT2* expression in non-red blood cells promotes formation of antigen-containing compounds which, once secreted out of the cells, is what alters mucosal and epithelial composition. The secretion of this compound containing the blood group antigens into mucus and other bodily secretions is the basis of what it means to be granted 'secretor status'.

Interestingly, fucosyltransferase activity fluctuates across the estrus cycle in mammals. A study by White and Kimber (1994) measured enzyme activity in response to estrogen and progesterone treatment in mice. Animals receiving estradiol alone had significantly higher fucosyltransferase activity than any other group. In naturally cycling animals, enzyme activity was nearly five times higher during estrus (White & Kimber, 1994), demonstrating the direct relationship between fucosylation rates, estrogen levels, and fertility status. A similar mechanism appears to exist in humans. A study of human bronchial epithelial cells showed increased fucosyltransferase mRNA and mucins in response to estradiol (Tam et al., 2014). These studies strongly implicate estrogen as an *FUT2* gene transcription factor. Sites where *FUT2* is expressed include epithelium of the intestines, bladder, and kidney, as well as sites throughout the vocal tract (trachea, salivary glands) and in the female reproductive tract (for review see Cooling, 2015). In the reproductive tract specifically, this enhanced mucosal production affords secretors multiple health and fertility advantages.

### **FUT2 IMPACTS WOMEN'S REPRODUCTIVE HEALTH**

Fucosylated endocervical mucins have protective anti-bacterial and anti-fungal properties that reduce the binding of pathogens to the vaginal epithelial cells

(Domino et al., 2009). For example, *Candida albicans* is a common species of yeast found in human mucosal surfaces, but an overgrowth can result in a vaginal infection (Hurd et al., 2005). Domino et al. (2009) found that *C. albicans* bind more readily to vaginal epithelial cells of mice lacking the *FUT2* gene, increasing their susceptibility to vaginal candidiasis compared to wildtype mice (Domino et al., 2009). This is one of many pathologies implicated by *FUT2* gene status, suggesting that it plays a strong role in the health and immunity of the reproductive tract in females.

Endocervical mucus also plays an important role in the likelihood of conception. Similar to the vocal tract, fluctuations in the quantity and quality of the endocervical mucus are hormonally dependent. The rise of estrogen during the ovulatory phase decreases endocervical mucosa viscosity, yet increases volume of the cervical mucus by nearly 20-fold (Grande et al., 2015). These changes facilitate sperm motility throughout the female reproductive tract upon insemination (Domino et al., 2009). During the luteal phase, the cervical mucus has less water content and is more viscous, making sperm motility more challenging (Nakano et al., 2015). It has been suggested that this increased viscosity provides an effective barrier to both sperm cells and pathogens during the luteal phase (Wira et al., 2015).

Should fertilization occur, the *FUT2* gene continues to impact fertility during the implantation phase of conception. One of the fucosylated products, the H-type 1 antigen, is synthesized after an  $\alpha(1,2)$ -fucosyltransferase creates a link between a type 1 precursor and a fucose sugar (see Figure 1) (Le Pendu, 2004). The H-type 1 antigen is important for adhesion processes in mammals, including sperm and egg interactions and embryo adhesion (Kimber, 1990; Wassarman, 1992). The production of this antigen creates the foundation for another fucose addition, which generates the  $Le^b$  antigen (Le Pendu, 2004). This specific Lewis antigen is found in high concentrations on the oocyte zona pellucida, which is made up of glycoproteins that act as receptors for sperm adhesion. Once fertilization has occurred, the  $Le^b$  antigen further promotes embryo adhesion and recognition by inhibiting enzymes ( $\beta$ -galactosidases) that would otherwise interfere with recognition mechanisms required for embryo attachment (Marionneau et al., 2001). Embryo implantation is further enhanced by clotting factors such as Von Willebrand Factor and Clotting Factor VIII (Domino, 2003). Interestingly, secretor status of the *FUT2* gene predisposes an individual to have higher levels of these clotting factors.

### **FUT2 CONTRIBUTES TO OFFSPRING IMMUNE SYSTEM FUNCTIONING**

Following birth, the *FUT2* gene continues to impact both mother and offspring. Not only does breast milk contain glycoproteins, glycopeptides, and glycolipids, but it also contains various forms of oligosaccharides (Kobata, 2010). Human milk oligosaccharides (HMOs) are a class of glycans that require fucosylation. Non-secretor mothers produce breast milk lacking important oligosaccharides, all of which require fucosyltransferase for addition of the Fuc( $\alpha$ 1-2)Gal group to the oligosaccharide structure (Kobata et al., 1969). Interestingly, human milk has the highest concentration and diversity of fucosylated oligosaccharides compared to any other species (Tao et al., 2011). If breastfeeding occurs, these oligosaccharides

benefit the offspring by inhibiting pathogens from attaching to the surface of the epithelial cells within the intestines. This function potentially reduces bacterial and viral infections among breastfed babies (Newburg et al., 2005; Newburg & Chaturvedi, 1997; Cravioto et al., 1991). HMO presence can protect against diarrhea, *E. coli*, diseases carried by birds, and much more (Newburg et al., 2005, Cravioto et al., 1991). Research has linked many of these HMO-driven pathologies to infants' gut microbiome.

Secretor status allows mothers to pass on and enhance beneficial microbiota to their offspring. In a study of the microbiota in breast milk, it was found that secretors produced milk higher in *Bifidobacteria*, *Lactobacillus*, *Enterococcus* and *Streptococcus* strains (Cabrera-Rubio et al., 2019). These bacteria are passed directly to offspring during breastfeeding. Fucosylated HMOs also independently promote the growth of commensal strains of gut bacteria. The addition of the fucose sugar on the surface of HMO glycans acts as nutrients to bacteria such as *Bifidobacteria* (Bevins & Salzman, 2011). These commensal strains enhance absorption of nutrients within the epithelial cells of the intestines (Saturio et al., 2021), acting as a prebiotic for the infant (for review see Smilowitz et al., 2014). In the competition for real-estate within the gut, enhancing the quantity and diversity of commensal strains simultaneously reduces the ability for pathogenic strains to flourish. Indeed, *Bifidobacterium* is found in significantly higher levels and found earlier among infants who were breastfed by secretor compared to non-secretor mothers (Lewis et al., 2015). Secretor mothers also have more substantial and versatile immune systems than non-secretors (Blackwell, 1989), so they have a higher variety of protective H antigens to pass on to their infant during the breastfeeding period (Milani et al., 2017). It has been argued that fucosylated mucins and HMOs play a primary role in programming infant gut microbiota throughout the first two years of life (Kononova, 2017).

The gut microbiome of infants is also directly impacted by their own *FUT2* gene variants. Within the first month of life, secretor infants were found to have better *Bifidobacterium* and *Bacteroides* diversity and abundance compared to non-secretors (Wacklin et al., 2011). Non-secretors, however, show higher levels of intestinal inflammation than secretors (Ye & Yu, 2021), which could lead to chronic illness and autoimmune disorders. A study of neonatal necrotizing enterocolitis (NEC), a disorder related to changes in the gut microbiome (Elgin et al., 2016), showed that the proportion of non-secretors was higher among NEC patients than in the general population (Ye & Yu, 2021). Additionally, the gut microbiome also plays an important role in mental health. Research has shown that lower *Bifidobacterium* levels are associated with more severe autism disorder symptoms (De Angelis et al., 2013), aggressive and depressed thoughts (Steenbergen et al., 2015), and anxiety (Savignac et al., 2015).

Finally, *FUT* gene variants can impact infant health via their connection to the Lewis blood groups. *FUT2* synthesizes the  $Le^b$  antigen, while *FUT1* is responsible for the  $Le^a$  antigen. Both can act as binding sites for certain pathogens, however the H antigens produced when *FUT2* is expressed may protect infants from an array of pathogens. For example, *S. aureus*, the most dangerous strain of staphylococcal bacteria, binds to the  $Le^a$  antigen. Interestingly, both *S. aureus* and  $Le^a$  were found

to be disproportionately high in victims of sudden infant death syndrome (Saadi et al., 2009).

The health and reproductive benefits conferred by secretor phenotype begs the question of whether this gene is being positively selected. Varying *FUT2* nucleotide diversities across different countries paired with polymorphisms in the promoter region suggests that natural selection has, indeed, been active in the gene's growth and maintenance in populations (Koda et al., 2001; Fumagalli et al., 2008). The type of mutation that results in homozygous null *FUT2* alleles depends on the ethnicity of the individual (Koda et al., 2001) and may be higher among populations where susceptibility to pathogens that target the null phenotype is lower. Thus, it has been hypothesized that the magnitude of advantage of either the null or the functional allele depends on the selective pressure of the various environmental pathogens (Koda et al., 2001; Fumagalli et al., 2008).

### CONCLUSION

The *FUT2* gene is responsible for producing an enzyme that has critical impacts on health, fertility, and fecundity. This enzyme is necessary for building antigen-rich mucosal surfaces (see Figure 1) on endothelial cells in the vocal tract, throughout the gut, and in the reproductive tract. Within the vocal and endocervical tracts mucin production is enhanced by the presence of estrogen (White & Kimber, 1994; Grande et al., 2015; Tam et al., 2014). Among women, we would expect mucosal variation to impact the voice in response to fluctuating sex steroid hormones across the menstrual cycle as well as across the entire reproductive lifespan. We theorize that changes in the mucosal lining of the vocal folds directly contribute to hormonally-dependent changes in voice quality and may account for preferences for fertile female voices. Listeners may be more likely to detect this variation within individual speakers, because in addition to variation in circulating hormone levels, the *FUT2* allele status and resulting mucosa production varies across speakers. The quantity and quality of the mucosal lining may contribute to speaker-specific changes in voice quality via measurable acoustics changes that may be unique to that individual. Importantly, it could be the case that the enhanced mucosal production among secretor-status speakers elicits greater variation in their vocal quality across hormonal states. This variation could result in more perceptible vocal fertility cues.

In addition to the benefits to the voice, *FUT2*-derived mucosal surfaces in the reproductive tract serve as a pathogen barrier, assists with sperm-egg adhesion, and facilitate successful zygote implantation. Female secretors also enjoy advantages associated with offspring gut health and survivability, which are each enhanced by the presence of *FUT2* alleles in the offspring. Thus, any mucin-related changes to vocal quality could be an indicator of a female's likelihood of conception, successful gestation, and offspring health. Variation in the *FUT2* allele status directly affects secretion of these mucins, potentially amplifying secretors' vocal cues to their reproductive status. Therefore, we suggest that the female voice is an honest signal of health, reproductive ability, and genetic quality in environments where *FUT2* alleles confer an advantage.

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