Genetic Origins of Dizygotic Twinning

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Abstract

Spontaneous dizygotic twinning is known to have a genetic component, with higher frequencies of DZ twinning found in certain families. However, it is not certain which genetic factors contribute to an increased risk of dizygotic twinning. One well-known hypothesis is that mutations in the follicle-stimulating hormone (FSH) are a genetic cause of familial patterns of dizygotic twinning. However, some studies appear to disprove the notion that mutations in the FSH receptor contribute to increased risk of dizygotic twinning, raising questions as to the role of FSH in dizygotic twinning. At the same time, location-specific studies have found further information as to possible genetic roots of dizygotic twinning. In sub-Saharan Africans, dizygotic twinning is associated with Pentraxin 3, a gene that is linked to both female fertility and immunity to infection. In Iceland – another location known for a high frequency of dizygotic twinning – twinning was associated with alleles for certain fertility traits, including higher serum FSH levels, earlier age at first lifetime, and other genetic variants. Last, a genome-wide linkage scan revealed further genetic components identified as contributing to dizygotic twinning, as well as indications that FSH receptors may, in fact, have a role in DZ twinning as well.

Twins are no longer the sensation they used to be. In fact, one in 30 Americans have a twin sister or brother (Hoekstra, Zhao, Lambalk, Willemsen, Martin, & Montgomery, 2008). While the rates differ across the world, with the highest rates reported in Nigeria and the lowest in Hawaii and Japan (Hoekstra et al., 2008), a deeper look into the topic is required to understand the factors that play a role in this process.

There are two forms of twinning, monozygotic (MZ) twinning and dizygotic (DZ) twinning. MZ twinning occurs when a fertilized embryo splits in half, giving rise to two genetically identical fetuses of the same sex (Hoekstra et al., 2008). DZ twinning, on the other hand, occurs when multiple ovulation causes two oocytes to be fertilized separately by two sperm, thereby forming two embryos. Since the oocytes are released individually, each twin shares the same amount of genetic similarity as any siblings would (Hoekstra et al., 2008). Typically, the human female produces only one oocyte per month. Therefore, when multiple ovulation occurs, as seen in DZ twinning, it prompts many questions regarding the causes of this phenomenon (Lambalk, 2001).

Another reason for investigating the causes of DZ twinning is its recently-increased rates. Although DZ twinning has always been more common than MZ twinning, the rates have multiplied dramatically in the past three decades. Currently, DZ twinning is at an all-time high, occurring in a whopping 1%-4% of women around the world (Mbarek, Steinberg, Nyholt, Gordon, Miller, McRae, ... Magnusson, 2016). The rapid increase in the DZ twinning rate has prompted increased investigation about the etiology of this phenomenon, as researchers attempt to identify the cause of this change. Some have pointed toward the increased use of fertility treatments, including in-vitro fertilization, ovulation induction, intra-uterine insemination, and others, and stated that these likely play a role in the increased rates of same-sex twinning. However, research demonstrates that the increase in DZ twinning is primarily due to natural conception and not conception stimulated by fertility treatments (Hoekstra et al., 2008). This refutes the notion that fertility treatments have caused the increase in DZ twinning, and points toward genetic factors as a possible cause of this phenomenon.

Currently, research has identified several predictors of DZ twinning. For one, studies have shown that maternal age plays an important role in a woman’s fertility. More specifically, an increase in age is associated with DZ twinning. Another factor that contributes to DZ twinning is parity, or the number of children born to a mother prior to a certain pregnancy. A mother who has had several children prior to a pregnancy is more likely to give birth to DZ twins than a mother experiencing her first pregnancy (Hoekstra et al., 2008). Other factors such as body characteristics are significant as well. Women who are taller, have a higher BMI, or are overweight are more susceptible to conceiving DZ twins than shorter, thinner women. (Mbarek et al., 2016). Interestingly, those who take oral contraceptives and/or use folic acid are also more likely to give birth to DZ twins (Hoekstra et al., 2008). While many mistakenly believe that smoking is associated with infertility, it is in fact linked to higher rates of DZ twinning when the woman smokes prior to conception (Mbarek et al., 2016). These factors, while important to consider, do not explain much about the etiology of DZ twinning. Moreover, they do not explain whether DZ twinning is rooted in genetic factors. Therefore, it is important to consider research that specifically focuses on the genetic causes of DZ twinning.

**Genetic Factors in DZ Twinning**

The current literature demonstrates that DZ twinning has many genetic links. In one study that utilized laboratory mice as subjects, DZ twinning was associated with certain genetic backgrounds. This indicates that there are genetic determinants in the phenomenon of DZ twinning, and that DZ twinning may run in families (Mbarek et al., 2016). There is evidence that DZ twinning has genetic linkages in humans as well; research shows that women with mothers or sisters who have DZ twins are twice as likely to have DZ twins themselves compared to others (Montgomery et al., 2001). Another indication of the genetic roots of DZ twinning is the presence of multiple ovulation; this causes researchers to believe that DZ twinning is associated with genetic predisposition for higher fertility due to the presence of multiple ovulation (Mbarek et al., 2016). Yet another indication of genetic contributors to DZ twinning is the association of certain genetic diseases with DZ twinning. For example, one study conducted over 20 years ago found that female carriers of Fragile X syndrome were more likely to have DZ twins (Hoekstra et al., 2008). However, there was no explanation of why Fragile X syndrome might be associated with DZ twinning.

Unfortunately, although research clearly establishes that DZ twinning is rooted in genetic factors, efforts to identify the genomes associated with DZ twinning have been largely unsuccessful. Research has repeatedly focused on identifying the exact genomes that are at the root of DZ twinning, but few have been effective, causing the specific contributors to DZ twinning to remain largely elusive. For this reason, the study of genetic roots of DZ twinning is especially necessary (Mbarek et al., 2016).

**The Well-Known Hypothesis: Mutations in the FSH Receptor**

One of the earliest hypotheses of DZ twinning is related to the FSH receptor. The hypothesis states that a mutation in the FSH receptor causes it to be overly sensitive, which in turn results increases the responsiveness of the ovary. Once the ovary is more responsive, multiple ovulations are more likely to occur. This hypothesis was proposed by Al-Hendy and colleagues after studying the case of a 26-year-old mother of DZ twins. They found that their subject also had a mutation on the FSH receptor, leading them to conclude that FSH receptor mutations lead to DZ twinning (Lambalk, 2001). The hypothesis further states that Gain-of-function mutations, which are located in the follicle-stimulating hormone receptor (FSHR), could cause mothers to be more likely to give birth to DZ twins (Montgomery et al., 2016).

For a long while, the FSH receptor hypothesis was the primary genetic theory for the etiology of DZ twinning. However, recent research has found little support for that hypothesis, as no mutations of the FSH receptor gene have been found. For example, one study found that there was indeed a mutation on the FSH receptor in mothers of DZ twins. However, the presence of the mutation made women *less* sensitive to FSH rather than increasing their sensitivity to the hormone, as Al-Hendy and colleagues had first theorized. This was because the mutation required women with FSH receptor mutations, as compared to those without mutations, to produce greater FSH levels to yield the same number of follicles. This finding directly contradicts the FSH receptor hypothesis; while it states that the FSH receptor mutation makes the receptor *more* sensitive to FSH, producing *more* follicles, research shows that the mutation causes the receptor to be *less* sensitive to FSH, and that it does not easily produce more follicles than the receptor of typical women (Lambalk, 2001).

Another study further disputes the FSH receptor mutation hypothesis. Montgomery et al. (2001) conducted a study with 21 unrelated mothers of DZ twins. Contrary to Al-Hendy and colleagues’ hypothesis, no mutations in the FSH receptor gene were found at all. Moreover, Montgomery et al. (2001) conducted a genome scan in 383 mothers of DZ twins. As with their first study, results found no linkage to the region containing the FSH receptor. These findings raise questions as to the accuracy of the FSH receptor mutation hypothesis. It appears that even if FSH receptor mutations are common in mothers of DZ twins – which they may not be, according to the findings of Montgomery et al. (2001) – they are not likely to play a key role in DZ twinning (Lambalk, 2001).

**Alternative Genetic Theories of DZ Twinning**

Apart from the FSH receptor mutation theory, there are other theories that explain the genetic connection to DZ twinning. These include theories that focus on FSH levels, those that look at genomes, and those that target linkage peaks on certain chromosomes. These theories, unlike that of Al-Hendy and colleagues, have been supported by research.

**FSH Theories.** One theory related to FSH levels proposes that increased concentrations are related to increased likelihood of twinning. The thought is that higher FSH levels cause multiple follicle growth (Mbarek et al., 2016). Indeed, studies have found raised FSH concentrations in the follicular phase for mothers of DZ twins (Lambalk, 2001; Mbarek et al., 2016).In one study, 2,411 men and 15,586 women in Iceland had their FSH levels tested. Results indicated that the majority of mothers of DZ twins – although not fathers, and not all mothers – had higher-than-typical FSH levels (Mbarket et al., 2016). These results indicate that even if FSH receptors aren’t involved, = higher FSH levels likely contribute to DZ twinning.

**FSHB and SMAD3 Variation.** Despite the many theories that focus on FSH receptors and levels, there has been an increased effort to identify the genomes, rather than the receptors, that are responsible for DZ twinning. In one study, Mbarek et al. (2016) conducted a genome-wide association of mothers of DZ twins to identify the genomes associated with DZ twinning. Participants were from the Netherlands, Australia, Minnesota, and Iceland. Apart from the case studies, which were mothers of DZ twins, control subjects were utilized in the study as well. The findings revealed that a certain sequence variation of the genomes FSHB and SMAD3 loci increase the likelihood of DZ twinning. Yet another genome, SNP rs12064466, was found in only the Netherlands, Australia, and Minnesota groups, but not in the Iceland group (Mbarek et al., 2016).

The sequence variation of *FSHB* is especially interesting given the genome’s association with several aspects of reproduction. *FSHB* has been shown to be related to higher FSH levels, and research shows that the genome can be used in clinical assisted pregnancy. Moreover, *FSHB* is associated with a variety of reproduction-related factors, including early breast development, menarche menopause, and higher lifetime parity. The other genome variation that was found across groups was *SMAD3*, but this has no reported connection to FSH levels (Mbarek et al., 2016).

There has been some evidence that Mbarek et al.’s (2016) findings may not be generalizable. Specifically, Painter et al.’s (2010) study of mothers of DZ twins did not find any linkages with the *FSHB* gene, although they had been expecting to. This is interesting considering that Painter et al. (2010) utilized participants from similar geographic locations as Mbarek et al. (2016). It is possible that the reason for the difference in findings across the two studies is that Painter et al. (2010) utilized families rather than random participants, as Mbarek et al.’s (2016) study did.

**PTX3, GDF9, and BMP15 Variation.** Another genome-related theory of DZ twinning focuses on variations in the *PTX3* genome. Support for this theory was found by Sirugo et al. (2012), who conducted a study on mothers of DZ twins in Gambia, Africa. The Sub-Saharan region of Africa is known to have the highest incidence of twinning, with women having three-to-four times the rate of DZ twinning as European women. In Gambia, over 75% of the twins are dizygotic. For this reason, Sirugo et al. (2012) hypothesized that there was likely to be a genome that caused these higher rates of DZ twinning in the area.

Indeed, the study found a variation in Pentraxin 3 (*PTX3)*, a gene that is linked to female fertility. Interestingly, *PTX3* is also linked to immunity to infection, as it mediates the innate immune response. The role of *PTX3* in DZ twinning is likely because its expression and secretion in the peri-ovulatory cumulus oophorus facilitates fertilization. *PTX3* is a downstream target of *GDF9*, a genome that, when mutated, is linked to DZ twinning as well. However, *PTX3* is also directly related to DZ twinning rather than only via *GDF9* (Sirugo et al., 2012).

Indeed, *GDF9* is another genome that has been implicated as being significant to DZ twinning in previous studies as well, and is understood to encode a protein in the oocyte (Sirugo et al., 2012; Painter et al., 2010). *GDF9,* along with the genome *BMP15,* is essential in ensuring fertility. Mutations of *BMP15* have caused ovarian dysgenesis, and even rarer mutations in both *BMP15* and *GDF9* are linked to premature ovarian failure (POF) (Hoekstra et al., 2008). Both *BMP15* and *GDF9* have been implicated in DZ twinning, which indicates the likelihood of POF among mothers of DZ twins. Indeed, mothers of DZ twins tend to reach menopause earlier than other women, suggesting that mutations in *BMP15* and *GDF9* could have a dual function in some women: initiate DZ twinning, as well as cause mothers of DZ twins to have a higher incidence of POF (Hoekstra et al., 2008). Ultimately, the findings of Sirugo et al.’s (2012) study, like that of Mbarek et al. (2016), indicate that genome variations play a strong role in DZ twinning.

**Linkage Peaks on Chromosomes.** Genome variation is not the only genetic factor that has been related to DZ twinning. Rather, studies also have identified certain chromosome linkages that are associated with DZ twinning. For example, Painter et al. (2010) conducted a genome-wide linkage study with 525 Caucasian families containing mothers of DZ twins. They found high linkage peaks on several chromosomes; the highest being Chromosome 6 for the overall sample. Moreover, there were linkage peaks to Chromosome 1 and Chromosome 12 for certain cohorts, although not for all (Painter et al., 2010).

Other research studies have found additional chromosome linkages in mothers of DZ twins as well. In one study, the INHA gene located on Chromosome 2 was found to have polymorphisms in mothers of DZ twins. At the same time, although the study did not come up with other chromosome linkages related to DZ twinning, the authors suggested that there could be other mutations on Chromosome 2 that are associated with DZ twinning (Hoekstra et al., 2008). These findings indicate that chromosome linkages, like genome mutations, play an important role in DZ twinning.

**Conclusion**

The present paper reviews the genetic causes of DZ twinning, and investigates the well-known hypothesis that mutations in the FSH receptor gene cause DZ twinning. According to the literature, it appears that the FSH receptor mutation theory proposed by Al-Hendy and colleagues is largely disputed by subsequent research. Contrary to the theory, a series of studies found no evidence of a mutation that causes the receptors to be exceptionally sensitive, causing multiple ovulations. Rather, the evidence points toward alternative genetic roots of DZ twinning. These include variations in genomes, including the *FSHB, SMAD3, PTX3, BMP15,* and *GDF9* genomes. Furthermore, studies indicate that chromosome linkage peaks play a role in DZ twinning as well; specifically, in Chromosomes 1, 6, and 12. The current research, while not as comprehensive as it might be, demonstrates that there are significant genetic causes of DZ twinning.

Further research should work on confirming the genetic causes of DZ twinning, and identifying new causes. Based on the prevalence of research that have identified genomes as playing a role in DZ twinning, it is likely that there are further genomes that have not yet been discovered, but that are essential to DZ twinning as well. Currently, there is a lack of genome-wide association studies on the genetic causes of DZ twinning. There have been increased efforts to gather families in which DZ twinning is prevalent to determine genetic components of the phenomenon, but their results are still unknown (Hoekstra et al., 2008). Therefore, it is essential that future studies investigate the genomes – as well as the chromosome linkages, and other genetic factors – that might contribute to DZ twinning. Last, it is still unknown whether the genetic causes of DZ twinning are responsible for the strong increase in DZ twinning rates. Future studies may want to investigate a possible link between these two phenomena. It is hoped that with increased research, a greater amount of knowledge about DZ twinning can be available to the scientific community.

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