Congenital supernumerary teats in cows: a review associated with personal observations

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Abstract. Hyperthelia and hypermastia are two forms of supernumerary teats, when the lack of milk secretion or its presence, respectively, can be noticed. Initially assumed as a trait with a simple mechanism of inheritance, supernumerary teats is now considered a polygenic trait in various species, including cattle, with a complex mechanism of inheritance. Different chromosomal segments were identified as associated with udder morphology traits, and candidate genes were discussed in various reports to influence the presence of supernumerary teats. This paper aims to review aspects of supernumerary teats types, their comparative incidence, genetic and environmental factors of etiopathology, and to present some personal observations in some of these aspects. Our results showed an incidence of 8.67% of non-lactating supernumerary teats in a population of 300 Holstein Friesian cows, with a higher share of caudal type compared to the intercalar type. One cow was recorded with hypermastia, with a functional lactating supernumerary teat. Considering the surgical removal of supernumerary teats as a controversial method, we recommend further studies for candidate genes identification, and programs of genomic selection in order to reduce their incidence in the offspring.
Key Words: BTA, heritability, hyperthelia, hypermastia.

Introduction. Supernumerary teats (SNTs) represent a common abnormality of the mammary gland morphology in many mammalian species (Pausch et al 2012; Martin et al 2016). They should be differentiated as hyperthelia – the presence of non-secreting supernumerary teats, and hypermastia, when secreting supernumerary teats are present (Juhr 1967). A not attached extra teat to a main teat is the most common form of this abnormality in cattle, where the SNT possesses its own streak canal and sphincter (Saifzadeh et al 2005). The term "polythelia" is usually used for hyperthelia in humans, although some discussions also include it for animals (Martin et al 2016). Specifically, a supernumerary nipple or polythelia and ectopic breast tissue or polymastia are terms used for humans (Grossl 2000; Requena & Sangüeza 2017).

In cattle, but also in sheep and goats, SNTs are undesired since they are considered a reservoir of bacteria for the whole udder, a risk factor for mastitis, an impediment for suckling, milking or efficient total milk removal, an impediment for the right positioning of the milking machine. However, in one way or another, all of these are with economic relevance in farms and dairy industry (Joerg et al 2014; Palacios & Abecia 2014; Martin et al 2016; Butty et al 2016). In humans, supernumerary nipples are associated with a number of conditions, including malignancies, and pathogenies of urinary, cardiovascular, gastrointestinal, central nervous and musculoskeletal systems (Johnson et al 1986; Grossl 2000; Brown & Schwartz 2003; Byadarahally et al 2013; Krishna 2020). Requena & Sangüeza (2017) documented a neurotic behavior to be frequently associated with supernumerary nipples in humans. Casey et al (1996) reported no association of polythelia with nephrourological anomalies when three cases were studied in a family over two generations. However, the authors did not exclude the necessity of urinal system evaluation in patients with a significant familial history of polythelia.

The aim of this paper is to review some aspects of SNT types, comparative incidence in various species, genetic and environmental causes, and to present some personal observations of the incidental and clinical aspects.

Material and Method. A review based on 34 scientific papers with relevance in the debated subject was performed. Clinical investigations including observations and palpations in a population of cows were considered to complete the research.

Results and Discussion

Reports on the incidence of SNTs. Among various udder abnormalities in cows, hyperthelia and hypermastia shared frequencies of 1.5% and 0.26% in a population of cows with mixed breeds examined, after papillomatosis (8%) and atrophy (4.7%), and hypertrophy (0.7%) in the case of hypermastia (Pobrić et al 1990). Another prevalence of udder and teat affections was established by Ragab et al (2017) on cows, buffaloes, and she-camels. They reported that 3.6% of cows were with congenital anomalies, including hyperthelia, leaker, athelia, pendulous udder, hypermastia, hypoplasia of the mammary gland, hyperplasia of the teat, teat obstruction, and fistula, while 0.72% of buffaloes were diagnosed with these kind of anomalies, including only hypermastia, hyperthelia, and fistula. No congenital anomalies were reported in she-camels. Hyperthelia had the higher frequency among other congenital disorders in cows, of 2.17%, while hypermastia occupied the third position, together with athelia, both with a frequency of 0.26%. In buffaloes, the highest incidence among congenital disorders of the mammary gland was reported for hypermastia (0.59%), while hyperthelia and fistula were both reported with the same frequency of 0.07% (Ragab et al 2017).

A frequency of SNTs ranging from 15 to 31.6% was reported for Red Danish cows (Juhr 1967). Joerg et al (2014) and Pausch et al (2012) documented for SNTs a higher frequency of more than 40% in Fleckvieh breed, while other breeds, such as Brown Swiss and Holstein Friesian, were affected to a lesser degree, of 31% and 15%, respectively. A large interval of variation for polythelia in cattle of 15 to 69% was reviewed by Martin et al (2016), and a lesser one of 17% for its incidence in Turkish Saanen goats. Butty et al (2016) reported a frequency of 19.9% of SNTs in Brown Swiss cows. Brka et al (2002a) reported 44.3% affected German Simmental with SNTs, and 31.2% of German Brown Swiss. The authors also documented frequencies of 29% and 69% for Simmental, and of 55.6% in Brown Swiss, mentioning that the higher frequency found in Brown Swiss was before the re-importation of Brown Swiss genetics from the United States. Misk et al (2018), in a retrospective study conducted from 2003 to 2015 in Egypt on 282 animals, including 184 females, mature mixed breed cattle and 98 water buffaloes *(Bubalus bubalis),* found supernumerary teats in 49 animals (17.38%), with 41 cows and 8 buffaloes affected. They classified five types for this condition, with the most affected number of animals in types IV and V, in which no treatment was required due to either no connection with the udder or teat cistern was observed in type IV, or the supernumerary teats appeared as a localized elevation on the skin of the udder or on the skin of the teat, in type V. The smallest number of affected individuals was in types II and III, and half of the number of individuals for the types IV and V was recorded for type I. All three types refer to functional teats, with surgical intervention needed for the type III condition, where the extra teat was located close to the base of the original teat. Investigating the incidence of SNTs in three pure breeds of Indian buffaloes *(Bubalus bubalis)* and comparing their obtained results, Dwivedi & Prabhu (1970) reported a higher frequency of this condition in Indian cattle (14.68%) than in Indian buffaloes (2.3955%) and, unlike other findings in cattle, in buffaloes, a large percentage of the diagnosed SNTs were considered functional. Males seem to be less affected than females in cows, as Gilmore (1950) revised (14% vs 25.8%). An appropriate percentage was reported by Gifford (1934), 14.07% of bulls possessing one or more SNTs, with different patterns of distribution.

An incidence of 5.6% for supernumerary nipple and of 0.22-6% for ectopic breast tissue was documented in humans by Requena & Sangüeza (2017). Krishna (2020) reviewed a general frequency of supernumerary nipple between 0.22% and 5.6%, black neonates being more frequently affected than white neonates, males more than females, and the left side of the body compared to the right side. The predominance in black

people compared to Caucasians was also reviewed by Byadarahally et al (2013). Although various reports described either an increased frequency of supernumerary nipples in males or in females, Requena & Sangüeza (2017) earlier reviewed as Krishna (2020), with a higher male to female ratio, and a higher frequency on the left side of the trunk. Byadarahally et al (2013) documented a frequency of 2-6% in females and of 1-3% in males for supernumerary nipple. Supernumerary mammae were documented in the Rhesus monkey, and supernumerary nipples in orangutan, siamang, gibbon and chimpanzee. A higher frequency of supernumerary nipples was reported for the last specie of those four, and a special case was discussed about a female chimpanzee with symmetrical supernumerary nipples located below the normal ones, with milk obtained from all four of them (Matthews & Baxter 1948).

Causes reported in SNTs. A possible intrauterine effect of lactation was considered for cattle, since a higher incidence of SNTs has been reported in animals born from multiparous cows (of second and later parities) than from those in the first parity, when the female is pregnant and not lactating in the same time (Brka et al 2002a; Pausch et al 2012; Martin et al 2016). Also, a prenatal hormonal predisposition was documented for pigs, when the proportion of the males in the litter is related to the number of the teats (Martin et al 2016). A hypothesis of atavism for polythelia and polymastia in monkeys, cows, and other mammalian species was considered since 1889 by Sutton (Requena & Sangüeza 2017). In an interesting debate, Verhulst (1996) stated that although simian primates and humans may develop polythelia and polymastia, these conditions are further to be considered as atavism or the reappearance of an ancestral condition, since they do not respect a specific and symmetric pattern, as is observed in other animals. Other theories were reviewed by Brown & Schwartz (2003) for humans and referred to the displacement of embryologic mammary crests to form supernumerary nipples outside the milk lines, or the supernumerary nipples are modified apocrine sweat glands.

Describings on SNTs localizations. Normally, each species develops a characteristic number of mammary glands in the mammary line; for example, four in the inguinal region of cows and buffaloes, two in the inguinal region of sheep and goats, 8 to 18 on the abdominal wall of pigs, 10 distributed as four pectoral, four abdominal and two inguinal for bitches, two inguinal for mares, two pectoral for elephants, humans, and non-human primates (Myers 1919; Brown & Schwartz 2003; Byadarahally et al 2013; Palacios & Abecia 2014; Pandey et al 2018; Hardwick et al 2020; Ventrella et al 2021), 10 distributed in five pairs between the cervical and inguinal area in mice, 12 distributed in six pairs along the milk line in rats (one pair in the cervical region, two pairs in the thoracic, one in the abdominal, and two in the inguinal regions), and 8 to 10 mammary glands in rabbits, two pairs located in thoracic area, two pairs of abdominal area and one pair of inguinal (Ventrella et al 2021). According to their location on the udder, SNTs are named as intercalary, caudal, or ramal, if they are located between, at the rear, or ramified with normal teats, respectively (Butty et al 2016; Dwivedi & Prabhu 1970; Gifford 1934; Gilmore 1950; Pausch et al 2012). Gifford (1934) pointed out that SNTs located anterior to the normal have not been observed. Martin et al (2016) reviewed the most significant frequency of caudal teats in cattle, with possibilities to be functional or not when they have a separate supernumerary gland with milk emission or not. The same idea was also reviewed by Joerg et al (2014), Pausch et al (2012) and reported in his investigations by Gifford (1934). Moreover, Gifford (1934) established the ramal type as the most rare of the three types, and also established different patterns and combinations at the level of the investigated cattle population. On the other hand, caudal supernumerary teats were reported with the least frequency in Indian buffaloes, while the intercalary type was the more frequent (Dwivedi & Prabhu 1970). In this report, 70.31% of the cases of SNTs in Indian buffaloes and crossbreds were able to be milked, while the difference was for rudimentary and non-functional SNTs. In humans, supernumerary nipples are frequently located along the milk line, from the middle axilla to the medial groin, although other locations, such as the face, posterior neck, back, and lower limbs were also reported (Requena & Sangüeza 2017).

Heritability, quantitative trait loci (QTL) and genes affecting SNTs. The presence of SNTs is considered a congenital character with different patterns of inheritance. Since 1950, Gilmore reviewed recessive genes to be responsible for intercalary teats in cattle, while a different autosomal dominant gene was believed to be involved for the after teats. The reported hypothesis of quantitative inheritance without dominant genes in pigs was later completed considering a single gene dominant/recessive to be likely involved in humans, sheep, guinea pigs and mice (Brka et al 2002b; Pausch et al 2012; Martin et al 2016). In a previous article, Brka et al (2000) discussed a dominant single-gene inheritance in at least three mammalian species. A clear dominance was reviewed for sheep and guinea pigs, while for humans, in addition to the autosomal dominance as the most probable pattern of inheritance, a recessive one and even an X-linked one were also included (Brka et al 2000).

Brown & Schwartz (2003) documented an autosomal-dominant pattern with incomplete penetrance for about 6% of familial cases in humans. Requena & Sangüeza (2017) discussed supernumerary nipples as rarely associated with some syndromes in humans, such as Simpson-Golabi-Behmel (an X-linked disorder due to mutations in GCP3 gene at Xq26 or deletions in Xp22), Char's syndrome (an autosomal dominant disorder) and McKusick-Kaufman syndrome. Considering the incomplete penetrance observed for hypermastia without hyperthelia in females, but not males of humans, and diagnosed in a three-generation family, Brka et al (2000) supposed for cattle the possibility of a co-existence of a single gene with large effect and other loci with minor effect, respecting the mechanism of incomplete penetrance.

Hardwick et al (2020) documented for sheep and goats a complex polygenic inheritance for SNTs. The hypothesis of SNTs as a polygenic trait in goats was also agreed by Martin et al (2016). Although a single gene inheritance mechanism was reviewed for cattle (Brka et al 2002b), further investigations allowed either a more complex pattern of penetrance or an oligo- or polygenic inheritance to be considered in this species (Brka et al 2000, 2002a, 2002b; Pausch et al 2012; Joerg et al 2014; Martin et al 2016). The heritability (h^2) of udder conformation traits in cattle was reported to range in large limits, from 0.14 to 0.42, with various correlations established among them (Pausch et al 2016). Brka et al (2000) and Martin et al (2016) reviewed a range of h^2 from 0.09 to 0.63 for SNTs and accessory mammary tissue (hypermastia), while in 2002(a), Brka et al estimated an h^2 of 0.45 and a standard error of 0.012 in 179793 German Simmental cattle, and of 0.43 and a standard error of 0.026 in 37460 German Brown Swiss cows. An upper superior limit for h^2 in cattle was documented by Joerg et al (2014) and Pausch et al (2012) (0.15-0.6). Interestingly, Martin et al (2016) cited for h^2 a value of 0.34 for goats, a small sample of animals being investigated in 2007, and reported in their study in 2016 values of 0.4 and 0.44 for Alpine and Saanen goat females.

Various studies, some of them of genome-wide associations (GWAS – Genome-Wide Association Studies) using Single Nucleotide Polymorphisms (SNPs), led to the identification of different Quantitative Trait Loci (QTL) related with various traits of udder morphology, and subsequent candidate genes involved in mammary gland pathology (Pausch et al 2012; Joerg et al 2014; Butty et al 2016). Most of the identified genes affect the Wnt signaling pathway which includes a large family of glycoproteins involved in various aspects of cell fate regulating, their motility, polarity, neural patterning, organogenesis during embryonic development, and stem cell renewal, as recently was discovered (Komiya & Habas 2008). Various locations were described, and different autosome chromosomes, namely BTA *(Bos taurus autosome)* followed by the pair's number, were discussed together with neighboring genes and their implications in SNTs pathology. These genes and their related QTL were considered highly conserved in this pathway signaling, which, in fact, is an initiator in the embryonic mammary gland development and a major determinant for the development of SNTs in cattle (Pausch et al 2012).

In 2012, Pausch et al reviewed BTA5 region as containing a cluster of sequences similar to genes encoding Ankyrin Repeat Domain-Containing Proteins and Frizzled-Family Receptor 3 (FZD3) like. Ankyrin Repeat (AR) proteins are a group of newly

discovered proteins consisting of 30-34 amino acid residues, generally involved in mediating protein-protein interactions (Li et al 2006), and more specifically, in Wnt signaling. In the same aim, FZD3 transmembrane receptor acts as an activator of Wnt signaling (Pausch et al 2012). The regulation of Wnt signaling pathway by Ankyrin Repeat Domain-Containing the Protein-Like coding sequence of LOC78893 was also documented by Butty et al (2016) to be involved in the regulation of the Wnt signaling pathway. They also reviewed a significantly associated SNP on BTA5, namely rs383391542, located within a coding region and considered a synonymous variant of the first exon at the 5' end of the Leucine-Rich Repeat-Containing G-Protein Coupled Receptor (LGR5) and which acts as an upregulator of the Wnt signaling pathway. The LGR5 gene was considered as a candidate gene for SNTs considering the direct effect of its expression on mammary gland tissue development, its role in Wnt regulation with subsequent breast cancer in humans and supernumerary placodes and teats due to a higher expression of Wnt elements during embryonic mammogenesis and, finally, considering the fact that the synonymous mutation within the sequence of LGR5 (SNP rs 383391542) was shown to influence the gene of which is a part of as a result of mRNA folding and stability affecting, although no change in the amino acids sequences resulted (Butty et al 2016).

Another two neighboring genes were reviewed by Pausch et al (2012) to be located on BTA6, LEF1 and DKK2. The LEF1 gene or the encoding gene of the Lymphoid Enhancer Binding Factor 1 seems to be involved in underdevelopment of mammary placodes resulting in rudimentary teats and teat malformations. Inverted teats in swine were associated with the polymorphism within the coding region of LEF1 gene. Ectopic placode-like structures are formed as a result of an increased activity of the Wnt signaling pathway. This is also the result of the lack of DKK2 expression, which normally acts as an antagonist of this pathway and as a local down regulator of Wnt signaling during normal eye development. In fact, this mechanism is also for FZD3, its overexpression also leading to ectopic eye development and ectopic features of the mammary gland, as SNTs. In 2016, Pausch et al confirmed two QTL previously identified in 2014, and another in 2003. They are located on BTA6 at about 89 and 90 Mb, respectively, and were found to be associated with teat thickness and fore udder length, central ligament and udder depth. Pausch et al (2016) discussed about two candidate genes Group specific Component (GC) and Neuropeptide FF receptor 2 (NPFFR2) residing in the interval of one QTL region, the second QTL being located 6 kb down-stream of the stop codon of RASSF6 (Ras association - RalGDS/AF-6 - domain family member 6). The GC and NPFFR2 genes are known to affect mastitis susceptibility in cattle since a negative correlation between udder depth, central ligament and mastitis was debated and, therefore, an unfavorable contribution of this QTL on genetic correlation between deep udder base and udder health (Pausch et al 2016).

Exocyst Complex Component 6B (EXOC6B) is another candidate gene for teat morphology, predisposing to lactating SNTs. It is located in a QTL located on BTA11 and its product of synthesis, an exocyst component which affects the apical surface and lumen formation during mammary gland development (Pausch et al 2012). The same gene located on sheep chromosome 3 was also established as a candidate gene for milk traits in German Mutton Merino breed (Wang et al 2015). Pausch et al (2016) documented Cysteine Rich Transmembrane BMP Regulator 1 gene (CRIM1) to be closely located to a QTL on BTA11. It seems that its product contains an insulin-like growth factor-binding domain with a crucial role during mammary gland development.

In the same idea of growth-related traits association with mammary gland morphology (as discussed for GC and NPFFR2 genes), Pausch et al (2016) described a top association of rs109815800 SNP located on BTA14 for height at the sacral bone, the allele in body weight increasing being associated with udder base increasing. This SNP is located 6 kb upstream of the translation start site of PLAG1 gene (Pleomorphic Adenoma Gene 1). The authors discussed about pleiotropic effects of this SNP on animal stature and udder traits, although phenotypic variation in body size with tendency of overestimation in tall animals of udder depth (i.e. the interspace the ankle and the udder base) was rather considered than true effects of PLAG1 on mammary gland morphology (Pausch et al 2016).

On BTA17, another QTL close to TBX3, TBX5, and RBM19 genes was also documented in the aim of this paper (Pausch et al 2012, 2016; Butty et al 2016). TBX3 and TBX5 are two members of the T-Box Transcription Factor Gene family, while RBM19 gene encodes the RNA Binding Motif Protein 19 (Pausch et al 2012), whose biochemical function is to process rRNA for ribosome biogenesis, being also demonstrated as essential for preimplantation development in mouse (Zhang et al 2008). TBX3 is induced by Wnt genes but also induces other Wnt genes, the protein encoded by TBX3 being a downstream target of the canonical Wnt pathway (Butty et al 2016). Pausch et al (2012) documented the absence of teats in Japanese Black cattle when the genomic region on chromosome 17 encompassing TBX3 is affected. Moreover, Butty et al (2016) pointed out that TBX5 is located next to TBX3 gene (at 1 Mb apart on the same chromosome) and the deletion of both genes induces the Ulnar-Mammary Syndrome, a disorder in humans and mice in which both supernumerary and aplastic nipples and mammary glands, and various genital anomalies are significantly reported symptoms. On the other hand, a mutation just in TBX5 gene is responsible for the Holt-Oram Syndrome in humans, a malformation of the extremities and heart without any direct link to mammary gland development (Butty et al 2016; Pausch et al 2012).

Proteins involved in cell development and tissue growth, with a somewhat relationship with teat formation, independent of whether these are supernumerary or not, were documented by Butty et al (2016). Two neighboring genes located on BTA20 are thus involved, EMB (Embigin) and PARP8 (Poly - ADP-Ribose - Polymerase Family Member 8). The authors confirmed a previous discovery in 2014 of a chromosomal region on BTA20 reported to be linked with blind caudal SNTs, and found in their study to be associated with supernumerary mammary gland tissue. In fact, the aforementioned confirmed study of Joerg et al (2014) referred to a QTL containing five SNPs on chromosome 20, with a large heritability and dominant mode of inheritance, which is part of a polygenic inheritance influencing the occurrence of caudal SNTs without mammary gland in Holstein cattle.

Another QTL on BTA2, BTA4, BTA13, BTA19 (Pausch et al 2016) and BTA27 (Joerg et al 2014) were checked for various associations with udder conformation traits and mammary pathology. Pausch et al (2016) documented SP5 gene (Sp5 Transcription Factor) as a downstream target gene of the Wnt signaling pathway located near a QTL on BTA2, RXFP2 gene near a QTL on BTA12, and ADAM12 gene (ADAM Metallopeptidase Domain 12) on BTA26 whose protein interacts with insulin-like growth factor-binding proteins, already discussed with a major influence during mammary gland development.

Personal observations on SNTs. Our observations on a 300 Holstein Friesian cattle population revealed an incidence of 8.67% SNTs, differentiated as hyperthelia or non-secreting. A single individual, representing an incidence of 0.33% of the total of 300 females, was diagnosed with hypermastia, the fifth teat being a secreting one. These values are less than the majority reported in various cattle population and already reviewed in this paper, but this may be the consequence of the small number of individuals included in our observation. The largest share of caudal SNTs (almost 60% of the diagnosed cases) confirms various reports up to now (Gifford 1934; Pausch et al 2012; Joerg et al 2014; Martin et al 2016). Some clinical aspects of the two localizations of diagnosed SNTs are presented in Figure 1.

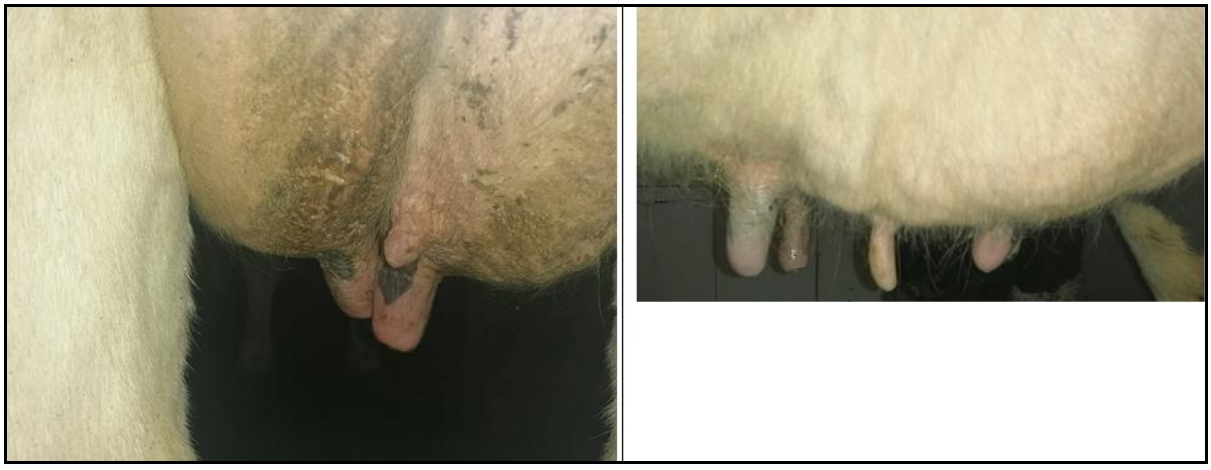

Figure 1. Clinical aspects of diagnosed SNTs; caudal SNT (left); intercalar SNT (right).

Conclusions. SNTs represent an unwanted abnormality of mammary gland with local but also economical implications. Their surgical removal may be controversial while the genomic selection represents a proper way of their incidence decreasing in the offspring. Studies of genomic association were performed and various QTL and candidate gene markers were identified in the past years by various researchers. However, SNT is considered a polygenic trait with a complex mechanism of inheritance, especially in cattle. Our investigations in a cattle population of Holstein Friesian established a lower incidence than other studies reported for this trait, but this may be in relationship with the limited number of investigated individuals. A higher incidence of caudal SNTs was confirmed in our study, if compared with intercalar SNTs. Further genomic studies are needed on genetic markers analysis to sustain the progress recorded in this area.

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