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Preferential Maternal Transmission of *STX16-GNAS* Mutations Responsible for Autosomal Dominant Pseudohypoparathyroidism Type Ib (PHP1B): Another Example of Transmission Ratio Distortion

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Abstract

Preferential transmission of a genetic mutation to the next generation, referred to as transmission ratio distortion (TRD), is well established for several dominant disorders, but underlying mechanisms remain undefined. Recently, TRD was reported for patients affected by pseudohypoparathyroidism type Ia or pseudopseudohypoparathyroidism. To determine whether TRD is observed also for autosomal dominant pseudohypoparathyroidism type Ib (AD-PHP1B), we analyzed kindreds with the frequent 3-kb *STX16* deletion or other *STX16/GNAS* mutations. If inherited from a female, these genetic defects lead to loss-of-methylation at exon A/B alone or at all three differentially methylated regions (DMR), resulting in parathyroid hormone (PTH)-resistant hypocalcemia and hyperphosphatemia and possibly resistance to other hormones. In total, we investigated 212 children born to 80 females who are unaffected carriers of a *STX16/GNAS* mutation ($n = 47$) or affected by PHP1B ($n = 33$). Of these offspring, 134 (63.2%) had inherited the genetic defect ($p = .00012$). TRD was indistinguishable for mothers with a *STX16/GNAS* mutation on their paternal (unaffected carriers) or maternal allele (affected). The mechanisms favoring transmission of the mutant allele remain undefined but are likely to include abnormalities in oocyte maturation. Search for mutations in available descendants of males revealed marginally significant evidence for TRD ($p = .038$), but these analyses are less reliable because many more offspring of males than females with a *STX16/GNAS* mutation were lost to follow-up (31 of 98 versus 6 of 218). This difference in follow-up is probably related to the fact that inheritance of a mutation from a male does not have clinical implications, whereas inheritance from an affected or unaffected female results in PHP1B. Lastly, affected PHP1B females had fewer descendants than unaffected carriers, but it remains unclear whether abnormal oocyte development

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Disclosures

None of the authors has potential conflicts of interest.

or impaired actions of reproductive hormones are responsible. Our findings highlight previously not recognized aspects of AD-PHP1B that are likely to have implications for genetic testing and counseling.

Keywords

PHP1A; TRANSMISSION RATIO DISTORTION; PARATHYROID HORMONE; EPIGENETICS

Introduction

The term pseudohypoparathyroidism type Ia (PHP1A) refers to a rare genetic disorder characterized by hypocalcemia and hyperphosphatemia due to parathyroid hormone (PTH) resistance restricted to the proximal renal tubules that is caused by inactivating maternal mutations involving *GNAS* exons 1–13 encoding the alpha-subunit of the stimulatory G protein (Gsα).[1-4] Besides elevated PTH levels, affected individuals often develop resistance to other hormones, such as thyroid-stimulating hormone, that mediate their actions through Gsα-coupled receptors. In addition to hormonal resistance, PHP1A patients present with developmental abnormalities, now referred to as Albright's hereditary osteodystrophy (AHO), that include short metacarpals and/or -tarsals, early onset obesity, adult short stature, and variable neurodevelopmental deficiencies. Mutations involving the paternal *GNAS* exons encoding Gsα lead to some but not all AHO features, and these do not cause hormonal resistance; this disorder is therefore referred to as pseudopseudohypoparathyroidism (PPHP).[2-4]

Pseudohypoparathyroidism type Ib (PHP1B) can follow an autosomal dominant trait, but most cases are sporadic.[2-4] PHP1B, which appears to be as rare as PHP1A,[5,6] is characterized primarily by PTH-resistant hypocalcemia and hyperphosphatemia or less frequently by resistance to other hormones; shortening of metacarpals and/or -tarsals is typically less frequent and less pronounced.[7-10] The autosomal dominant form of PHP1B (AD-PHP1B) is caused in most cases by a maternal 3-kb deletion in *STX16*, which is associated with complete loss of methylation (LOM) at *GNAS* exon A/B.[1-3] Other genetic alterations on the maternal allele lead to indistinguishable epigenetic *GNAS* changes, including 4.4-kb, 24.6-kb, or 87.5-kb *STX16* deletions,[11-13] a large 18.9-kb deletion involving *GNAS* exon NESP and the region centromeric thereof,[14] duplications or triplications involving portions of the *GNAS* locus,[15,16] and an inversion of approximately 1.8 million base pairs comprising exon A/B and all 13 exons encoding Gsα.[17] Several different genetic alterations can thus lead to indistinguishable epigenetic *GNAS* changes.

Other causes of AD-PHP1B, observed only in single families, include four distinct deletions removing *GNAS* exons NESP and/or AS exons 3 and 4; these forms of the disorder are associated with changes at all three differentially methylated regions (DMR) on the maternal *GNAS* allele.[18-20] Furthermore, PHP1B occurs most frequently as a sporadic disorder and all patients affected by this latter disease variant (sporPHP1B) show either complete or in some cases partial LOM of the maternal *GNAS* methylation imprints and typically complete gain of methylation (GOM) at *GNAS* exon NESP.[9,20] No genetic mutations have yet

been identified as causes of sporPHP1B, with the exception of paternal uniparental disomy involving the long arm of chromosome 20 (patUPD20q) that accounts for approximal 10% of the sporadic cases.[21-25]

A recent retrospective analysis revealed evidence for transmission ratio distortion (TRD) for inactivating mutations involving the maternal *GNAS* exons 1–13.[26] In that report, females affected by PHP1A or PPHP, ie, patients with AHO features in the presence or absence of hormonal resistance, showed a significantly higher likelihood of passing the underlying genetic mutation to their children. In contrast, males affected by PHP1A/PPHP passed the mutant allele to about half of their offspring as expected for a Mendelian disorder. Furthermore, PHP1A patients with *GNAS* mutations that are predicted to reduce, but not abolish, Gsα function had a comparable number of affected and unaffected children, whereas mothers with severe Gsα mutations had considerably more affected than unaffected offspring.[26] Observations similar to those for PHP1A/PPHP females had been previously made for several other genetic disorders, including the long QT syndrome,[27,28] but the underlying mechanism(s) that causes TRD in these families remains unknown.

To expand the findings in PHP1A/PPHP to a disease variant in which genetic mutations lead to epigenetic *GNAS* defects, we analyzed numerous families in which the affected members have PHP1B due to LOM at the maternal *GNAS* exon A/B alone or at all three differentially methylated regions (DMR) within this complex locus. For the majority of these kindreds, a maternal 3-kb *STX16* deletion was identified in genomic DNA of the affected family members and the unaffected carriers. Other genetic defects that occurred in only single families included a 4-kb *STX16* deletion, a large inversion involving the region telomeric of *GNAS* exon XL, as well as four different deletions within *GNAS*. Our analyses showed that mothers who are affected or unaffected carriers of the genetic mutation had passed the mutant allele almost twice as frequently to their offspring as the normal allele.

Materials and Methods

AD-PHP1B kindreds

We had previously reported numerous AD-PHP1B families in which the genetic defect causes LOM at the maternal *GNAS* exon A/B alone[11,17,29-38] or at all three maternal DMRs.[18-20] Since discovery of the first disease-causing genetic *STX16* mutation, we evaluated, for several of these families, additional new members for the presence or absence of the genetic defect (Fig. 1, Supplemental Table S1). For all previously not reported family members, we collected clinical information and/or laboratory results, if available, and we searched for the family-specific genetic defect. Importantly, we determined whether some children had not been captured in these families and whether children, who could not be investigated, were descendants of males or females with the genetic defect.

In addition to the AD-PHP1B families investigated by us, review of the literature revealed several publications describing families with AD-PHP1B due to the 3-kb *STX16* deletion.[39-41] If we were able to confirm by directly contacting the authors of these studies that all offspring had been captured for each of these families, the reported findings were included in our analysis (Fig. 1, Supplemental Table S1).

Informed consent for this study, which was approved by the Institutional Review Board of the Massachusetts General Hospital, had been obtained from all investigated subjects or their parents.

Search for the genetic defects leading to AD-PHP1B and methylation-sensitive multiplex ligation-dependent probe amplification (MS-MLPA)

Genomic DNA for evaluation of new members in AD-PHP1B families was extracted from peripheral blood leukocytes or buccal swabs. The presence or absence of the 3-kb or the 4.4-kb *STX16* deletion was determined as previously described.[11,31,34] *GNAS* methylation changes were assessed by MS-MLPA using kit ME031 GNAS (MRC-Holland, Amsterdam, The Netherlands; https://www.mlpa.com/), as reported.[20]

Statistical analyses

The chi-square test was used to evaluate differences between two groups. All p values <.05 were considered significant when performed two-sided.

Results

A recent study had revealed that females affected by PHP1A or PPHP are more likely to transmit the allele with disease-causing *GNAS* mutation instead of the normal allele to their children, particularly if the genetic defect was predicted to severely reduce or abolish Gsα function.[26] We now sought to determine whether a similar TRD can be observed also for mutations that reduce Gsα function through LOM at *GNAS* exon A/B alone or LOM at all three maternal DMRs. We therefore investigated first all available members of kindred F that had facilitated the initial identification of genetic locus for AD-PHP1B and the subsequent discovery of the 3-kb *STX16* deletion on the maternal allele as the most frequent cause of this disorder.[29,31] The updated pedigree shows that the 10 females, who are either affected themselves or who are carriers of the *STX16* deletion, have 19 affected children (6 males, 13 females) and 9 unaffected offspring (67.9% versus 32.1%) (Supplemental Fig. S1). This suggested that TRD is observed not only for the offspring of females affected by either PHP1A or PPHP[26] but also for women carrying the 3-kb *STX16* deletion that causes LOM at *GNAS* exon A/B when located on the maternal allele.

To expand these initial observations, we analyzed numerous additional AD-PHP1B families and combined the findings with those observed in kindred F (Fig. 1, Supplemental Table S1). In the majority of these unrelated families (n = 40), we had identified the 3-kb *STX16* deletion.[31-41] The 4.4-kb *STX16* deletion,[11] the large *GNAS* inversion,[17] as well as four different deletions within the *GNAS* locus were found only in single families.[18-20] In total, 80 females were studied, who are either unaffected carriers (n = 47) or affected by PHP1B (n = 33). These women had given birth to a total of 212 children (53.3% boys, 46.7% girls; p = 34). Of these offspring, 134 (55.2% boys, 44.8% girls; p = .23) had inherited the mutant *STX16/GNAS* allele, whereas 78 (50.0% boys, 50.0% girls) had inherited the wild-type allele; the likelihood of passing the mutant allele to the offspring was therefore strongly favored (p = .00012; chi-square test) (Fig. 2). Similar to the findings in PHP1A/PPHP

females,[26] the odds of transmitting the mutant, not the wild-type, *STX16/GNAS* allele to the next generation is therefore approximately 2:1.

We next determined whether mothers with the *STX16/GNAS* mutation on their paternal (unaffected carrier) or their maternal allele (affected by PHP1B) show differences with regard to the number of affected offspring (Fig. 3). The unaffected carrier females ($n = 47$) have in total 147 children (73 boys, 74 girls) and of whom 93 are affected (48 boys, 45 girls) and 54 are unaffected (25 boys, 29 girls). Thus, 63.3% of the children of unaffected carrier females had inherited the mutant *STX16/GNAS* allele, whereas 36.7% of the offspring had inherited the wild-type allele (affected versus unaffected children $p = .0013$). Virtually identical results were obtained when excluding for the analysis families with <3 affected individuals or when excluding the data for the four families with LOM of all maternal DMRs (Supplemental Table S1).

The affected PHP1B females ($n = 33$) have a total of 65 children (40 boys, 25 girls; $p = .063$) of whom 41 (63.1%) are affected by PHP1B (26 boys, 15 girls; $p = .086$). In contrast only 24 offspring (36.9%) are unaffected (14 boys, 10 girls; $p = .41$). These data indicate that the percentage of boys and girls born to affected and carrier females is indistinguishable and that the overall likelihood of passing the mutant *STX16/GNAS* allele to offspring is similar for females with the genetic defect on their maternal or paternal allele. Six of the known offspring of females had been lost to follow-up, but these children were included in the analysis of fertility. Subgroup analysis revealed that unaffected female carriers ($n = 47$) have 151 children (3.2 offspring/female), whereas females affected by PHP1B ($n = 33$) have 67 children (2.0 offspring/female) ($p = .00015$) (Fig. 4). Thus, in comparison to unaffected carriers, affected females had significantly fewer children.

Fewer data were available to explore the impact of paternally inherited *STX16/GNAS* mutations. In fact, information was available for only 67 offspring of 27 males who had inherited the mutant allele maternally (males affected by PHP1B, $n = 13$) or paternally (unaffected male carriers, $n = 14$). Thus, males with a genetic defect in *STX16/GNAS* represented only 25.2% of the total investigated cohort with a defined mutation. Likewise, these males had only 24.0% of the total number of the investigated children. The smaller number of male carriers and males affected by PHP1B was surprising given the even distribution of boys and girls born to females with *STX16/GNAS* mutations, who are either unaffected carriers or affected by PTH1B.

We therefore determined the number of offspring of affected or unaffected males with a *STX16/GNAS* mutation and how many of these children had not been investigated genetically. This analysis revealed that 31 of 98 descendants of these males had received no follow-up, which is in contrast to only 6 of 218 known offspring of females with a *STX16/GNAS* mutation who had been lost to follow-up. The transmission frequency of the mutant allele by males is therefore less reliable. Nonetheless, 14 unaffected male carriers had passed the mutant allele to 25 of their 43 offspring ($p = .29$), whereas 17 of 24 offspring had received the genetic defect from 13 affected males ($p = .041$); however, the frequency of transmission of the mutant allele by males seems less reliable because their children are

more frequently lost to follow-up. The difference in the number of children of males who are unaffected carriers versus those affected by PHP1B was marginally significant ($p = .033$).

Discussion

Based on the presented findings, female carriers of *STX16/GNAS* mutations that cause LOM at *GNAS* exon A/B alone or at all three maternal DMRs are more likely to have children affected by AD-PHP1B. This TRD was equally evident for unaffected and affected female carriers of the disease-causing mutations, ie, for mothers who have the genetic mutation on their paternal allele and thus show no epigenetic defect and no laboratory abnormalities themselves, and for mothers who carry the defect on their maternal allele and thus show LOM at *GNAS* exon A/B resulting in PTH-resistant hypocalcemia and hyperphosphatemia. These findings in our AD-PHP1B cohorts are consistent with those recently reported for offspring of females affected by either PHP1A or PPHP.[26] Furthermore, analysis of AD-PHP1B kindreds with a *STX16/GNAS* mutation that had been reported previously by others appear to be similar to our findings.[12,14,42-46] However, not all family members had been captured for some of these publications and not all individuals had been tested for the genetic defect and/or for laboratory abnormalities, thus making these analyses less reliable.

In contrast to our findings in females with a *STX16/GNAS* mutation, descendants of affected or carrier males revealed no evidence for TRD. However, overall many fewer descendants of males affected by PHP1B and particularly of unaffected males with a *STX16/GNAS* mutation were captured. This is most likely related to the fact that inheritance of the genetic defect from an affected or an unaffected male does not lead to LOM at *GNAS* thus causing no PTH-resistant hypocalcemia; consequently, there is no immediate medical need for genetic testing. In fact, only daughters who inherited a mutation from an affected or unaffected father with a *STX16/GNAS* mutation can have children affected by PHP1B if these offspring inherited the genetic defect. This emphasizes the need for genetic counseling and testing of all descendants of female and male carriers of a *STX16/GNAS* mutation.

Several different mechanisms have been postulated for TRD in the previously reported disorders,[27,28,47] including abnormalities in meiotic drive with possible preferential segregation of the wild-type allele to the polar body, errors in resetting genetic imprints during oocyte development, or early embryonic defects. Furthermore, increased early embryo lethality could contribute to TRD, which would imply that it is disadvantageous for the maternal wild-type *STX16/GNAS* allele to be present in a zygote that had developed from a diploid oocyte with reduced Gαs expression (Fig. 5). Chromosome segregation during meiosis is generally assumed to follow Mendelian law, but non-random segregation can occur in oocytes due to asymmetrical meiotic division, functional asymmetry of the meiotic spindle poles, or functional heterozygosity at a locus that mediates attachment of a chromosome to the spindle.[48] It is, however, unclear how an allele with a *STX16/GNAS* mutation is more likely to remain in the cytoplasm of the secondary oocyte during the first meiotic division.

There was no difference in the number of boys and girls born to mothers who are either affected themselves or are unaffected carriers of one of the different *STX16/GNAS* mutations. This suggested that the methylation defect at *GNAS* exon A/B and the resulting reduction in Gsα expression caused by maternally inherited *STX16/GNAS* mutations has no sex-specific impact on the offspring. Because of the even distribution of male and female descendants born to affected or carrier mothers, it was surprising that approximately three times fewer males with the genetic defect had been captured for analysis in our studies. We therefore determined whether fewer descendants of males with a *STX16/GNAS* mutation had been studied genetically. In fact, 31.6% (31 of 98 children) of the offspring of affected or carrier males had been lost to follow-up, which is probably related to the fact that all descendants of males with the genetic defect are unaffected, thus providing no immediate benefit from genetic testing. The search for the presence or absence of a *STX16/GNAS* mutation would benefit only subsequent generations and only if daughters of a male carrier happen to pass the mutation to their children.

Interestingly, females affected by PHP1B had approximately one-third fewer children than females who are carriers of a *STX16/GNAS* mutation ($p = .00015$; Fig. 4). Consistent with an essential role of Gsα during oocyte maturation, Xie and colleagues showed that Cre-mediated ablation of *Gnas* exon 1 under the control of the oocyte-specific Zp3 promoter results in complete female infertility due to premature resumption of meiosis and poor oocyte quality.[49] It is likely that the DMR at *GNAS* exon A/B (and the secondary DMRs at exons XL and AS) is not remethylated during oocyte maturation because of the genetic mutation thus allowing little or no Gsα transcription from the mutant *STX16/GNAS* allele, particularly after the first meiotic division. It is therefore plausible that the mutant oocytes resume meiosis too early and that oocyte quality is impaired; this should, however, be the case for females with a maternal or paternal *STX16/GNAS* mutation. Thus, PHP1B females may have as yet not recognized endocrine abnormalities that impair function of luteinizing hormone and/or follicle-stimulating hormone. Post-fertilization defects as a cause of fewer children seem less likely because zygotes derived from affected and unaffected females with a *STX16/GNAS* mutation are expected to show identical epigenetic *GNAS* modifications.

Collection bias may have limited our findings and resulting conclusions. However, the majority of the presented data were extracted from our own constantly updated database and the few findings previously published by others were verified by directly contacting the authors. This makes it unlikely that numerous family members had not been captured for analysis, at least for the descendants of females. It is furthermore unlikely that the birth of the first affected child would have led to the parental decision not to have additional children because PHP1B is typically not associated with readily detectable AHO stigmata and because symptoms from hypocalcemia usually do not occur until the second decade of life. This conclusion is supported by the finding that several females who are either unaffected carriers or affected by PHP1B had additional children even if the first child was diagnosed with the disorder through genetic testing early in life. Furthermore, TRD was readily apparent even when excluding affected or unaffected females who have fewer than three children.

In summary, females with a *STX16/GNAS* mutation on their maternal or paternal allele have considerably more affected than unaffected children, and females affected by PHP1B have fewer children. Based on our data, TRD is unlikely for the descendants of affected and unaffected males who are all healthy, even if they inherit the disease-causing mutation. However, these children are frequently lost to follow-up, even though genetic testing could reveal carrier females, who should undergo counseling to allow early diagnosis, if the genetic defect is passed on to the next generation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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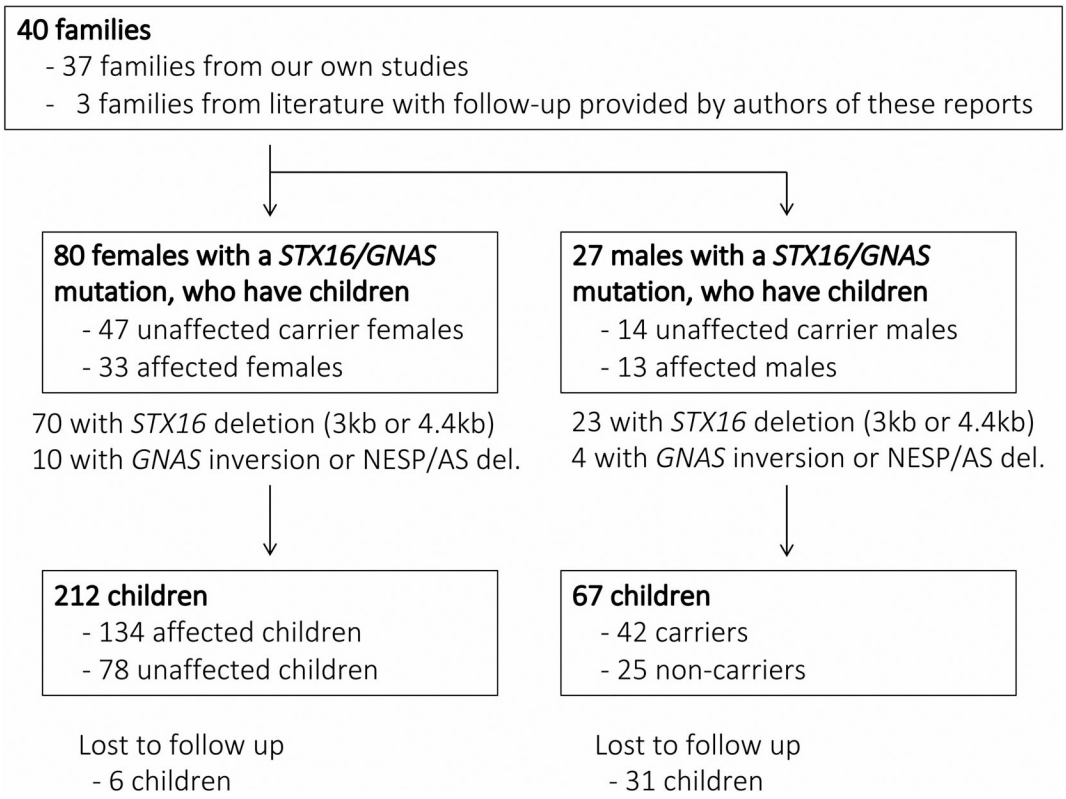

Fig 1.

Flow chart of our study material. Shown are the investigated AD-PHP1B kindreds, number of male and female carriers of a mutant *STX16/GNAS* allele, the number of affected and unaffected children, and the number of offspring of male and female carriers who were lost to follow-up.

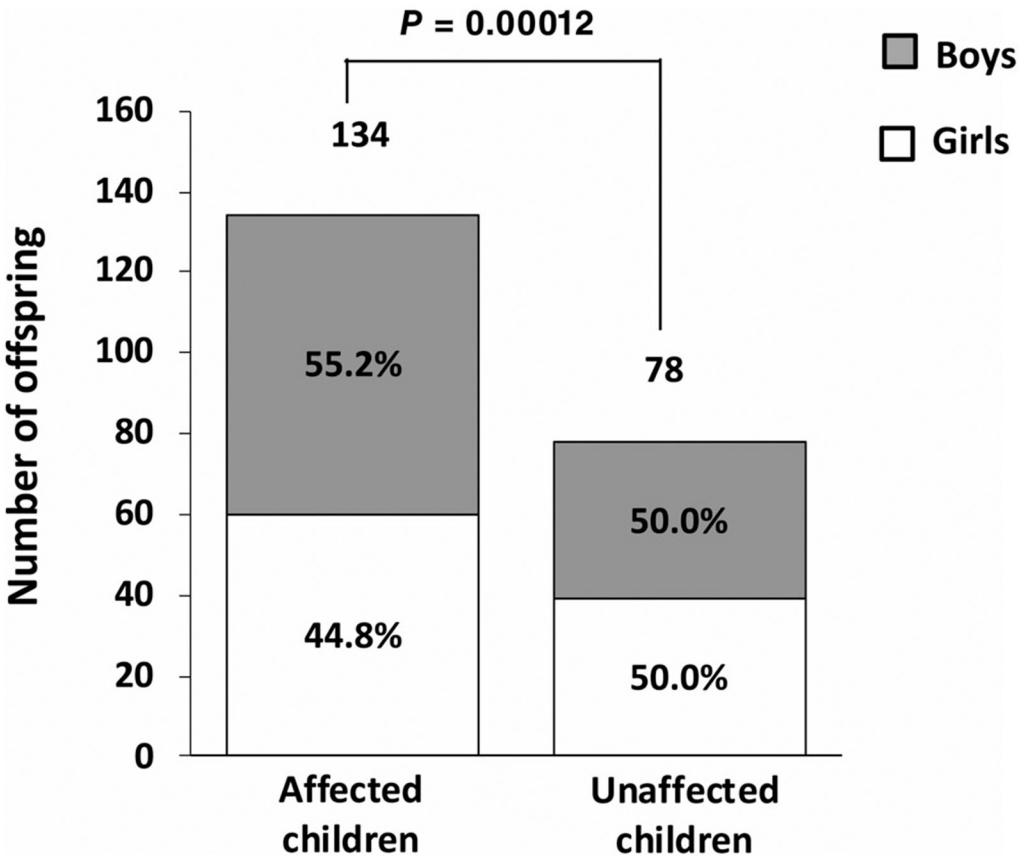

Fig 2.

Female carriers of a *STX16/GNAS* mutation are more likely to have affected children. In total, 80 females with the mutant *STX16/GNAS* allele had given birth to a total of 212 children. Of those, 134 children had inherited the mutant allele, whereas 78 children had inherited the wild-type allele ($p = .00012$; chi-square test). This indicated a significantly higher likelihood of transmitting the mutant rather than the wild-type allele to the next generation.

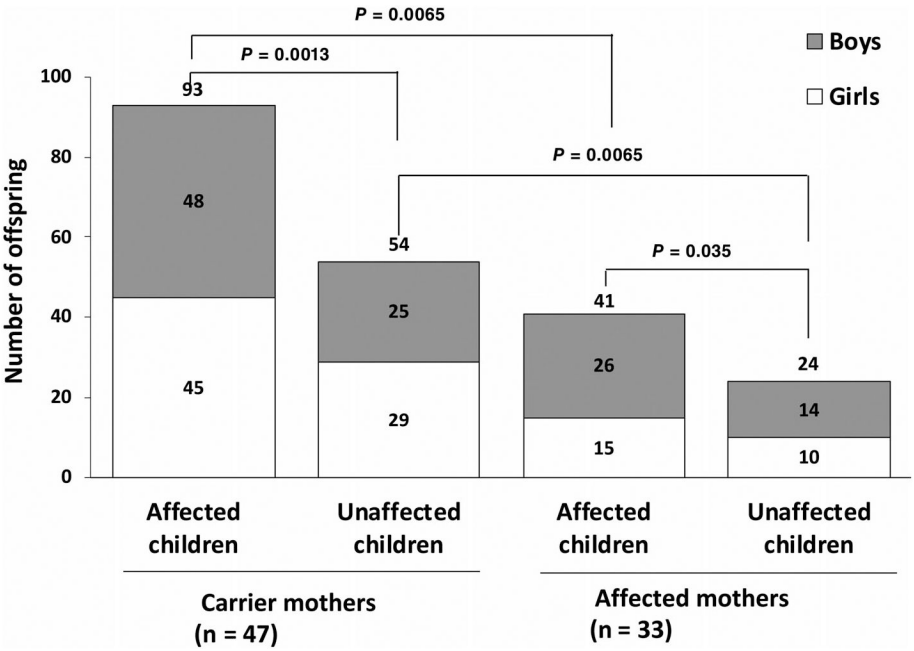

Fig 3.

Mothers with a *STX16/GNAS* mutation have more affected offspring regardless whether they are unaffected carriers or are affected themselves. The unaffected carrier females (n = 47) have a total of 147 children (73 boys, 74 girls) of whom 93 (63.3%) are affected (48 boys, 45 girls) and 54 (36.7%) are unaffected (25 boys, 29 girls) (p = .0013). The affected PHP1B females (n = 33) have a total of 65 children (40 boys, 25 girls) of whom 41 (63.1%) are affected by PHP1B (26 boys, 15 girls). In contrast, only 24 offspring (36.9%) are unaffected (14 boys, 10 girls) (p = .035). These data indicate that the percentage of boys and girls born to affected and carrier females is indistinguishable and that the overall likelihood of passing the mutant *STX16/GNAS* allele to offspring is similar for females with the genetic defect on their maternal or paternal allele. Chi-square test for statistical analyses.

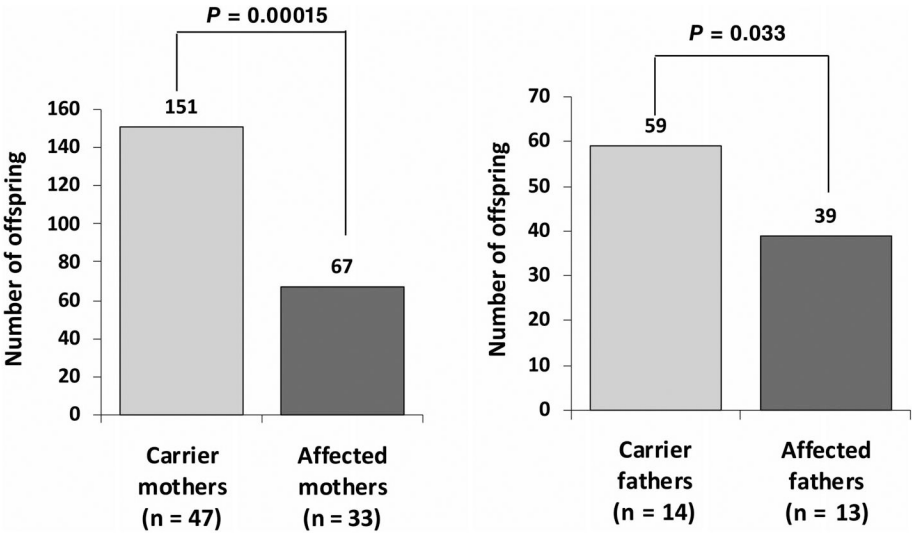

Fig 4.

Females affected by PHP1B due to a *STX16/GNAS* mutation have fewer children than unaffected carriers. These graphs include children lost to follow-up for whom genetic analyses could not be performed. Carrier mothers have 151 children. In contrast, affected mothers have 67 children ($p = .00015$). Affected mothers thus showed a 37% reduction in fertility compared with carrier mothers. On the other hand, carrier fathers have 59 children and affected fathers have 39 children ($p = .033$). Chi-square test for statistical analyses.

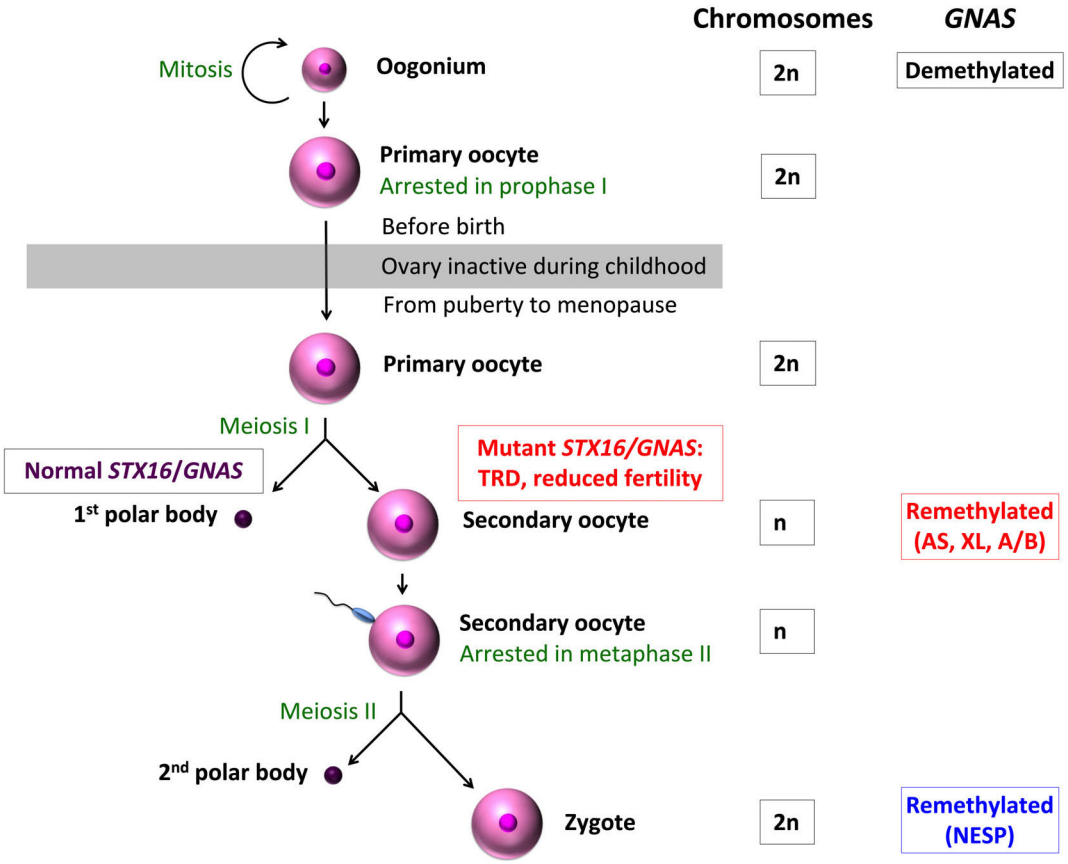

Fig 5.

GNAS methylation predicted based on findings during murine oogenesis. Hypothesis regarding the sequence of events leading to transmission ratio distortion (TRD). After demethylation in murine oogonia, the differentially methylated regions at the maternal *GNAS* exons A/B, XL, and AS are remethylated by meiosis I; remethylation at paternal exon NESP occurs after fertilization. Preferential segregation of the wild-type allele to the polar body occurs during meiosis I due to asymmetrical meiotic division. This leads to TRD in offspring of females with a *STX16/GNAS* mutation and implies that a zygote with the mutant allele has a developmental advantage.