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# Pallister-Hall Syndrome: A Rare Developmental Phenomenon

Tierney McGonegal

Johnson & Wales University - Providence, TMcGonegal01@wildcats.jwu.edu

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# Pallister-Hall Syndrome

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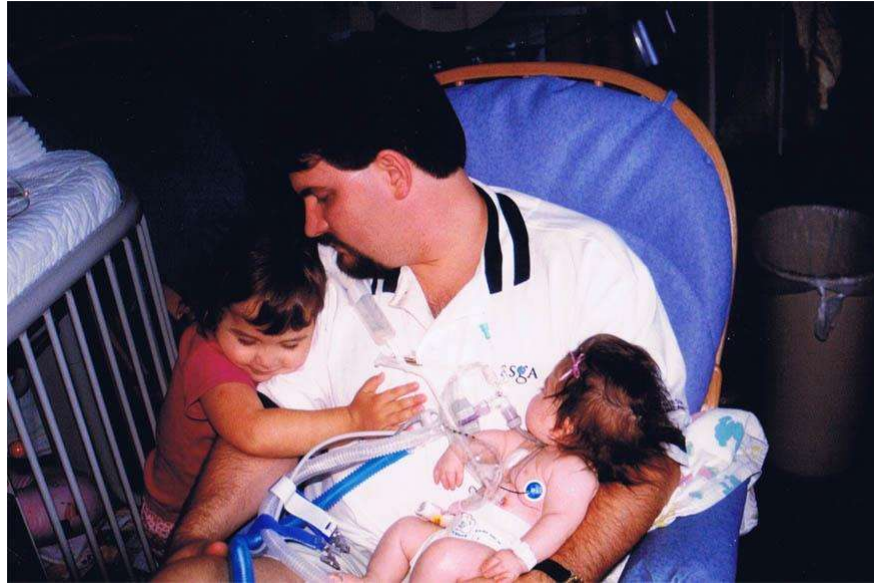
A RARE DEVELOPMENTAL PHENOMENON

Tierney McGonegal

JOHNSON & WALES UNIVERSITY | 8 ABBOTT PARK PLACE, PROVIDENCE

When I was three years old my family was blessed with another child. I remember painting the room across the hall from mine a soft purple and putting glow-in-the-dark stars on the ceiling with my parents, anxiously awaiting the arrival of my baby sister. On February 16<sup>th</sup> of 2000 she was born. It was quickly evident that something was very wrong. Many somethings. The National Organization for Rare Disorders (NORD) reported that in 2016 only 100 patients had been reported to have Pallister-Hall Syndrome. My sister was one of them. Pallister-Hall Syndrome disrupts the formation of organs and tissues during embryonic development (U.S. Library of National Medicine, *Pallister-Hall Syndrome*). As an incredibly rare disorder, very little is known about the origin and pathological properties. Judith Hall and Philip Pallister were the first to *describe* the condition in 1980 (NORD).

The most common clinical symptoms of Pallister-Hall Syndrome (further on referred to as PHS) are polydactyly and syndactyly (distinguishable in Picture 1) - the presence of extra fingers or toes and the fusion of them through the bones – and a hypothalamic hamartoma (NORD). It is important to note that the hypothalamic hamartoma is not a tumor but a malformation in the brain. This section of the brain grows with, or slightly slower, than the rate of surrounding tissue. It can be as large as four centimeters in the longest dimension. While these hamartomas may be large in size there is no correlation between its size and presence and severity of other symptoms (Biesecker). There are two types of polydactyly to look for in diagnosis. Postaxial polydactyly is the presence of an extra digit on the ulnar or fibular side of the hand and is more common. Mesoaxial, also known as central or insertional, polydactyly is the presence of a sixth digit formed off of the metacarpal or metatarsal bones. It is also important to note that in clinical diagnosis that there is a higher frequency of postaxial polydactyly in those of central African decent and that this should not be used as a key symptom (Biesecker).



Picture 1: Syndactyly and Polydactyly in patient with Pallister-Hall Syndrome

As a pan ethnic disorder (Biesecker), ethnicity cannot be used to determine risk in pregnancies and growing families. There are two ways to contract the syndrome. The first way is through hereditary information passed on from both parents. In this form PHS is expressed as autosomal dominant characteristics, meaning that only one affected allele is needed for the mutation to be expressed, not two (Biesecker). If a patient were to be diagnosed with hereditarily-passed PHS, one of their parents would have also had to express the trait. The origin of PHS can be traced to the *GLI3* gene. This gene is located at 7p14.1. (NIH, *Pallister-Hall Syndrome*). *GLI3* provides instructions on how to create the *GLI3* protein that regulates gene expression, by either inducing or repressing targeted genes. As a gene that controls whether or not certain pathways are turned on or off, it has a more than significant importance in shaping organs and tissues prior to birth (NIH, *Pallister-Hall Syndrome*).

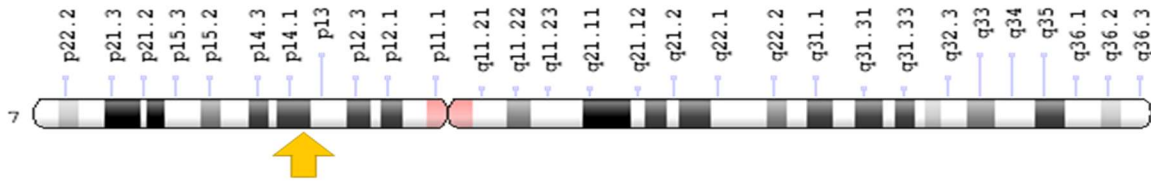


Figure 1: Location of the GLI3 gene on the 7<sup>th</sup> chromosome from NIH, *GLI3* gene

It has been reported that the mutations responsible for PHS typically result in an abnormally short GLI3 protein. While the normal GLI3 protein can turn induce or repress certain genes, this short version can only repress (NIH, *Pallister-Hall Syndrome*). So far, this is the only gene known to cause PHS, but it is not a one to one ratio. Only 95% on patients with PHS have been identified to have the GLI3 mutation (NORD). The other type of inheritance of the syndrome is through a sporadic variant. One in four patients with PHS develop it through this new mutation and often express more severe and even lethal symptoms than those who inherit it through their parents (Biesecker). While only the handful of those who develop PHS experience the lethal phenotype, the possibility of death leads PHS to be placed in the ‘CAVE’ category of disorders- the cerebroacrovisceral early lethality group (Biesecker). As PHS symptoms vary drastically in affected patients it is very difficult to pinpoint the actual frequency of PHS in populations. As hypothalamic hamartomas can be asymptomatic and polydactyly is not all too rare, misdiagnoses are very likely on the mild end of the spectrum.

The GLI3 protein produced is a bifunctional zinc finger transcription factor (*GLI3 mutations in syndromic...*) that serves as both an activator and as a repressor (*UniProtKB*). When the protein are fully functional it aide in assembling the transcriptional activation complexes involved in targeting other genes. The GLI3 protein recognize 5’-GACCACCC-3’ in

their promoter regions. GLI3 protein has been determined to bind to a location on the PAF complex (known as CDC 73). These two work together to aid in RNA polymerase II-mediated transcription. Areas within the C-terminus have been shown to function with histone acetyltransferase CBP, TAF31, and Mediator component Med12 (*GLI proteins bind promoters...*). In one study (*GLI3 mutations in syndromic...*), certain nonsense mutations resulted in the loss of C-terminal domains, resulting in Postaxial Polydactyly and Greig-Cephalopolysyndactyly syndrome. This results from the sudden lack of ability to function with histone acetyltransferase CBP, TAF31, and Mediator component Med12 (*GLI proteins bind promoters...*). It is mostly splicing and nonsense mutations of the middle third of the gene that tend to result in PHS (McKusick).

Arguably the most important role of GLI3 proteins is their interaction with the Sonic Hedgehog Pathway (referred to as Shh). This pathway is essential in proper cell differentiation, proliferation, and tissue polarity. Some of the tissues specifically influenced are those of the lung, spleen, colon, placenta, uterus, and testes (*UniProtKB*). Many cancers have been linked back to the Shh pathway including lung, pancreas, prostate, breast, medulloblastoma, basal cell carcinoma, and malignant gliomas. This pathway is upstream of GLI zinc finger transcription factors. Various GLI proteins are turned on through Shh ligand mechanisms- both independent and dependent (Rimkus et al.).

This is done through interaction of GLI3FL (full length form) and SUFU. The two form a neutral complex within the cytoplasm of the cell. This complex turns GLI3FL to GLI3 which then disassociates from SUFU, allowing it to move into the nucleus and repress Shh targeted genes. This only occurs in the absence of Shh signaling. When signals are present the two dissociate from each other and the targeted genes are not repressed. This halts creation of

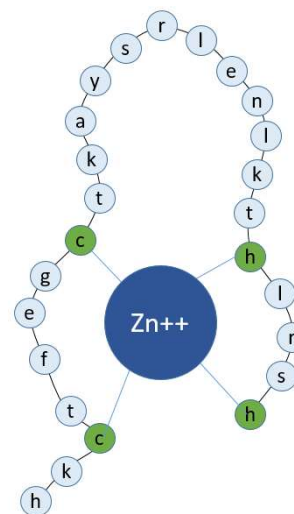
GLI3R. The now available GLI3FL is moved into the nucleus where it is phosphorylated, destabilized, and turned into the transcriptional activator form (GLI3A) (*UniProtKB*). Various cells respond to Shh differently depending on the type of cell, time exposed, and the amount of exposure received. The latter two are determined by multiple feedback loops. Germline mutations (covered later) that work with Shh have been linked to various developmental disorders and somatic mutations have been linked to multiple forms of cancer (Varjosalo, M. & Taipale, J.).

Zinc finger transcription factors are proteins that regulate transcription and are composed of *zinc fingers*- the GLI3 protein is one of these. As stated earlier this protein can function as either as a repressor or an activator in its fully functioning form. One important lesson in biology, whether it be biochemistry or physiology, is that the shape of the protein dictates function. This is due to the chemical interactions between various molecules and the specificity required for two things to work together. Zinc fingers give GLI3 their shape. There are five located in the beginning of the second third of the 1580 amino acids (Figure 2). While there are five zinc finger locations there are only two binding areas, highlighted in dark teal. These binding sites are composed of two cysteines and two histidines. The different amount of finger areas to binding sites results in a complex shape, meaning a complex protein. An example of how one zinc finger forms around one  $\text{Zn}^{2+}$  ion is shown in Figure 3.

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1 meaqhsstt tekkevnsi vkcsrttdvs ekavasstts nedespqgty hrerrnaitm
61 qpqnvgglsk vseeptsssd eraslikkei hgsplhvae svpyrgtvfa mdrngymep
121 hyhphlflpa fhppvpidar hhegryhydp spiplhmts alssstypd lpfirisphr
181 npaaasespf sphpyinpy mdyirslhss psismisatr glsptdapha gvspaeeyhq
241 malltgqrsf yadiipsaat agtgaihmei lhamdstrfs sprlsarpsr krtlsispls
301 dhsfdlqtmf rtspsnslvti lnnssrsssa sgsgyhlsas aispalsfty ssapvslhmf
361 qqilsrqgsl gsafghsppl ihpaptfptq rpiqgiptvl npvqvssgss essqnkptse
421 savstgdpd hnkrskikpd edlpspgarg qgeqpegttl vkeegdkdes kqepviyett
481 nchwecare fdtqeqivhh inndhihgek kervcrwidc sreokpfkaq ymlvvhmrrh
541 tgekphtctf eggtkaysrl enktllrsf tgekpvyfch eglnkafnsa sdraklgrrt
601 snekpyvch lpgcttkytd psalrkhyk wqgeahvtk kqrgdihprp ppprdsgshs
661 qsrspgrptq galgeqqdls nttskreecf qvktvkaekp mtsqpspggg sscssqqspi
721 snysnsglel pltdggsigd lsaidetpim dstistatta lalqarrnpa gtwkmevhkl
781 erlkqvnqmf prlnpilppk apavspign gtqsnntcsl ggpmtllpgr sdlsqvdvtm
841 lnmInrrdsf astissayls srsssgispc fssrrsseas qaegrpqnvs vadsydpist
901 dasrrsseas qsdglpslls ltpaqgyrlk akyaaatggp pptplpnmer mslktrllal
961 gdalepgval ppvhaprrcs dggahgygrr hlqphdalgh gvrrasdpvr tgseglalpr
1021 vprfsslssc nppamatsae krsllvlnyt rpeggqsrnf hsspcpsit envtlesltm
1081 dadanlnedf flpddvvqyl nsqngagyec hfpsalpdss kvphgggdfd apglpdsahg
1141 qqfhaleqpc pegsktdlpi qwnevssgsa dlsssklkcg prpavqtra fgfcngmvvh
1201 pgnplrsqpa ggyqtlgens npyggpehlm lhnspgsgts gnafheqpc apqygnclnr
1261 qpvaagaldg acgagiqask lkstpmqgsg gqlnfglpva pnesagsmvr gmqnqdpvqg
1321 gylahqlldg smqhpqagrp gqqlmgqisa tshiniyqgp esclpgahgm gsqpslslavv
1381 rgyqpcasfg gsrrqamprd slalqsgqls dtsqtervng ikmemkgqph plcsnlqns
1441 gqfydqtvgf sqqdtkagsf sisdascllq gtsaknsell spgangvtst vdsldshdle
1501 gvqiddfadi ddgdhsslms galpsliqn lshsssrllt praslfpfal smsttnmaig
1561 dmsllttsla eeskflavmq

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Figures 2 & 3: (2) 1,500 amino acid sequence with five zinc finger regions and two zinc finger binding domains highlighted. (3) 3<sup>rd</sup> zinc finger region and their binding with a  $Zn^{2+}$  through cysteines and histidines

While the National Institute of Health only published through Genetics Home Reference that an abnormally short *GLI3* gene can result in PHS, OMIM confirms on “*Oncogene GLI3*” that the truncation more often than not occurs in the middle third of the gene- where zinc finger binding occurs. OMIM also reports that patients with mutations in the first third and last third of the gene were patients with Greig Cephalopolysyndactyly Syndrome. Not only does this support the hypothesis that Greig Cephalopolysyndactyly Syndrome and PHS have identifiably different pathologies, but also suggests that the five zinger fingers are what are most vital in the process of normal activation and repression. Shape dictates function, and in this case it becomes readily apparent that varying the folding pattern prevents targeted genes from recognizing and reacting to the protein.

It is an incorrect assumption that PHS is strictly a severe condition and that Greig Cephalopolysyndactyly syndrome is a mild one. This disorder, which also affects the *GLI3* gene, is sometimes confused with PHS due to their “mild” similarities. The assumption is inaccurate as not all individuals affected by PHS display severe and lethal symptoms- most cases are mild (Biesecker). This can lead patients with PHS to be misdiagnosed as having Greig Cephalopolysyndactyly. Mild PHS is also commonly misdiagnosed as isolated postaxial polydactyly type A. PHS can also cause severe pituitary insufficiency through the hypothalamic hamartoma, causing possible patients to die as neonates, resulting in a miscarriage (Biesecker). PHS can still be misdiagnosed as Ellis Van Creveld syndrome, craniopharyngioma, Bardet-Biedl syndrome, oral-face-digital syndrome type 6, Holzgreve-Wagner Rehder syndrome, Smith-Lemli-Opitz syndrome, and congenital hypothalamic hamartoma syndrome (Orpha).



Picture 2: Pallister-Hall Syndrome is in the ‘CAVE’ category of disorders- the cerebroacrovisceral early lethality group

Neonates are typically miscarried due to the body's 'knowledge' that something has gone awry but sometimes pregnancies with fatal complications are brought to term. The two complications thought to be directly linked to early fatality are pan hypopituitarism caused by hypothalamic or pituitary dysplasia and laryngotracheal cleft, particularly posterior clefts (Biesecker). Bifid epiglottis tends to be asymptomatic. This anterior-posterior midline cleft within the epiglottis is incredibly useful in clinical diagnoses as it is very rare as an isolated malformation (Biesecker). Past infancy PHS is treatable, but not curable. Endocrine abnormalities rise as a result of the hypothalamic hamartoma. The two main manifestations, aside from the fatal pan hypopituitarism, are isolated growth hormone deficiency and isolated precocious puberty. It has been recorded that de novo forms of PHS can also spur cortisol deficiency, which seems to be uncommon in patients with familial PHS (Biesecker).

For those who have symptomatic hypothalamic hamartomas, gelastic epilepsy is expected to be a complication. This neurological partial seizure manifests itself as repetitive spasms of diaphragm and chest, mimicking laughter (Biesecker). This problem is often not discovered until patients are old enough to convey that something is wrong. The remainder of observed symptoms in literature may not all be tied to PHS, but are common in some patients. Some mild observations include upturned nostrils, a flat bridge of the nose, and a visible vertical groove in the patient's upper lip (midline) (NORD). Low-set posteriorly rotated ears have also been common (OrphaNet). These facial symptoms can be seen in Picture 3. Natal teeth, buccal frenula (movement-reducing mucous membrane tissue in the mouth), short limbs, dislocated hips, agenesis or dysplasia of kidneys, and congenital heart defects have all been observed in patients as well (NORD). With the wide range and severity of possible symptoms it is assumed that possible patients are OK until proven otherwise (OrphaNet).



Picture 3: Upturned nostrils, flat bridge of nose, vertical groove in upper lip, and low-set posteriorly rotated ears in patient with Pallister-Hall Syndrome

For those plagued with PHS in its non-fatal form life goes on. There are many steps taken to ensure PHS stays in check throughout the remainder of development and adolescence. The most common symptom, polydactyly, is often fixed quickly during infancy by removing the extra digit surgically (NORD). Hormonal replacement therapy is the best course of action for those who experience hypopituitarism. This type of therapy typically relieves all symptoms (NORD). Those who experience gelastic seizures as a result of the hypothalamic hamartoma can take anticonvulsant medication to reduce the effects (NORD). As the hamartoma is a malformation and not a tumor, it is not suggested to remove it. Removing the malformation is expected to result in furthered pituitary insufficiency (Biesecker). As patients grow it is important to have yearly developmental assessments and evaluations to keep an eye out for precocious puberty (Biesecker). Perhaps the most difficult part of living with PHS is the toll it

takes on patients and their families. Those who are affected and their families are encouraged to meet with a Genetics Counselor (NORD).

Determining whether one has PHS can be done two ways- clinically and through genetic testing. Many clinical tests can be done, including a brain MRI, X-rays of both hands and feet, a renal ultrasound, and a laryngoscopy (OrphaNet). As polydactyly and the hamartoma are the most common symptoms the basic clinical diagnosis requires the presence of both (Biesecker). The hypothalamic hamartoma is shown in MRIs as a midline mass isointense to surrounding gray matter (OrphaNet). If both landmark symptoms are present genetic testing is completed. Single-gene testing is comprised of both analysis of the *GLI3* gene and duplication analysis, though duplication is rare in PHS. Some laboratories may sequence just the exons (expressed regions of the gene) to begin testing. The exons examined are between codons 667 and 1161. Multi-gene testing may be completed instead to test other genes that may be responsible, if other diagnoses may be possible. If these genetic tests come back inconclusive, more genetic testing is available, including whole-exome sequencing, whole mitochondrial sequencing, and whole-genome sequencing (Biesecker).

After my sister was born with Pallister-Hall Syndrome both of my parents were clinically tested for syndactyly and the hypothalamic hamartoma. Both tests came back negative. In 2000, much less was known than is today, and it was concluded that my mother had come into contact with *something* during a fragile stage in her pregnancy. In personal communication with Julie Sapp, a researcher at NIH, in December, it was determined that that conclusion is inaccurate. If that were the case, there would be many more occurrences of Pallister-Hall Syndrome. It is most likely that my sister experienced a *de novo* variant. Her symptoms were so severe that doctors were astounded she came to term, which reflects well with the literature on *de novo* variants. The

lack of certainty in just how rare the disease is due to misdiagnoses, miscarriages, common postaxial polydactyly, and asymptomatic hypothalamic hamartomas, creates a lot of questions in affected families. In speaking with Sapp, while not likely at all, it is *theoretically* possible that Pallister-Hall Syndrome runs in my family (refer to Figure 2 and 3). The one other explanation is that of germline mosaicism. There has been only one case that mosaicism was identified in (Sapp), but it is possible. Germline mosaicism is a phenomenon in which a mutation occurs either in a germ cell or in a somatic cell prior to division into germinal cells (Zlotogora). In this event, the affected parent either expresses no symptoms at all (if the mutation is just in germinal cells) or very few, if at all, symptoms (if in early in a somatic cell) but the affected offspring displays all symptoms. Despite the clinical tests coming back negative 17 years ago, Sapp has suggested genetic testing for my parents for more definite and conclusive answers. While much has been learned over the past two decades about Pallister-Hall Syndrome, there is still so much more to learn.

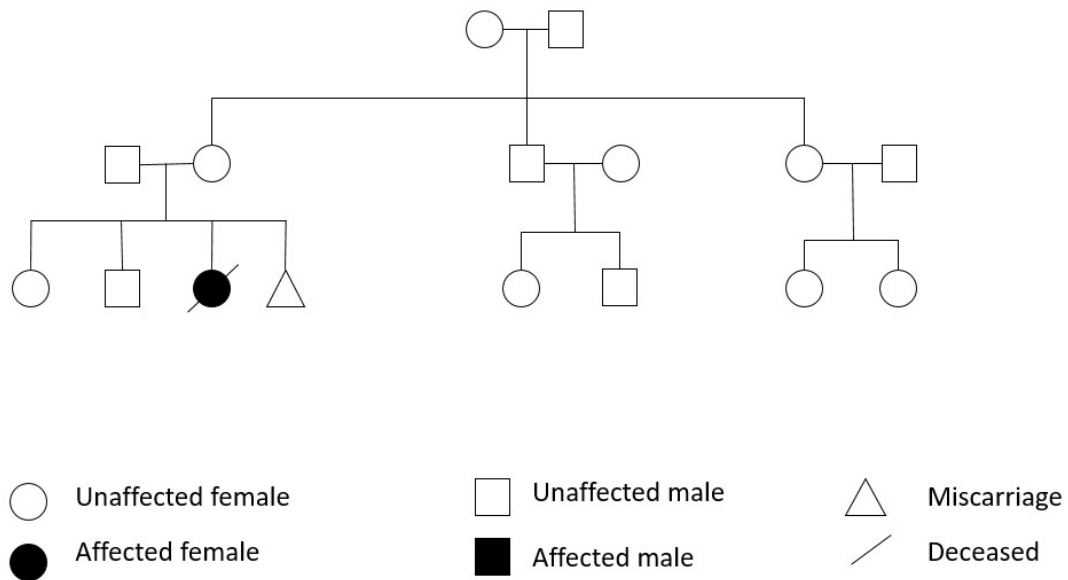


Figure 2: Pedigree of likely de novo inheritance of Pallister-Hall Syndrome

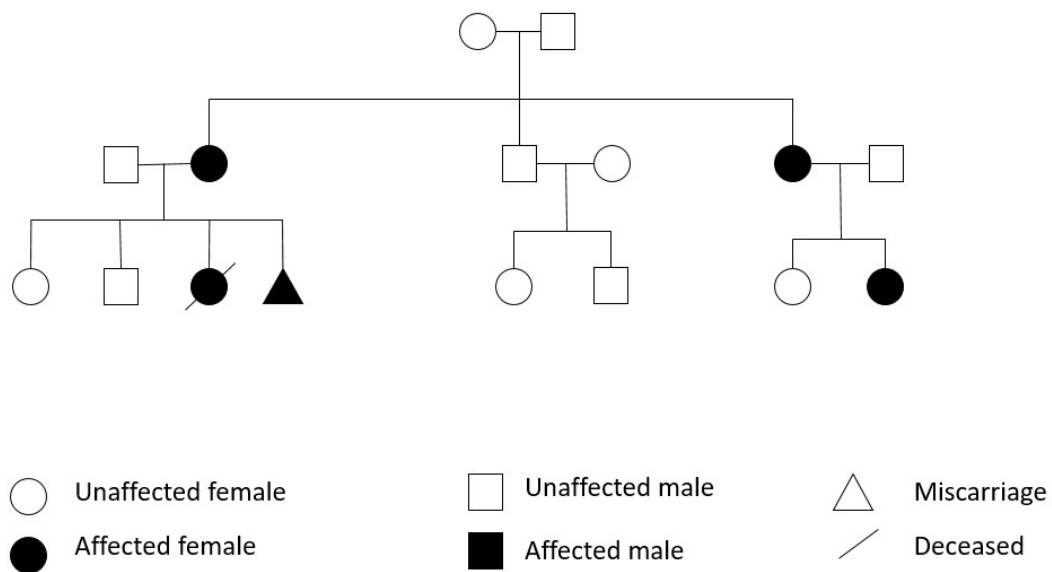


Figure 3: Pedigree of possible autosomal dominant inheritance of Pallister-Hall Syndrome

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