A genetically transmitted, benign habit - A case report and review .

Abstract

Habits are defined as acquired, repetitive, involuntary and body focused, stereotyped motor acts .Tics have the same attributes, but are characterised by muscle spasm additionally .So far, the emphasis in the literature is that the habits are acquired. There is no reference in the literature as to the habits being transmitted genetically. Whereas in the case of tics, some like, Tourette Syndrome (TS) , are accepted to have genetic basis Habits are harmless. But some are self - destructive Out of the group of the four destructive habits, like trichotillomania (TTM), bruxism, scabiomania or skin pulling (SP),and onychophagia, TTM , along with chronic persistent motor tics, persistent vocal tics and combined motor and vocal tics like TS , are grouped together, as habit disorders by the American Psychiatry Association (APA) Statistical Manual of Mental Disorders classification , 4th edition (DMS 4) . Virginia Commission recommends inclusion of SP also under habit disorders. Other authors include all the four destructive habits under the habit disorders. It is also accepted that habits are related to behavioural patterns and that the behavioural patterns are genetically determined. Thus an indirect link is established between the habits and heredity, through behaviours. The author presents in this article, a benign , 'nose rubbing habit' being transmitted through 6 generations in a family tree. Unique to the pattern of inheritance, 100 % desendents in some generations (generations 1,2 and 3) with involvement of both males and females, without any skip generations, is seen .Very early onset is recorded at the age as low as 2 years and as high as 6 years belonging to the in the 6th generation. This is the first of it's kind reported in literature that a benign habit is shown to run in a family, across 6 generations. This is contrary to the popular belief, that habits are always acquired. If it is so, what is it that irrefutably transmitted through 6 generations in this case ? Mitochondrial gene (mtDNA) transmission, involving recombinant maternal and paternal mtDNA, is suggested , by inference and after eliminating the other Mendalean and non Mendalean types of inheritance. Of course, the main intended focus of the article is to highlight the transmission of a habit- trait (?) genetically. As a possible explanation of this observed phenomena only, the tentative inheritance pattern is suggested. The matter is open for discussion by the concerned fraternity.

Key words : Habits, Tics, Habit disorders, mitochondrial inheritance, Tourette syndrome.

INTRODUCTION :

Can a habit be transmitted genetically ?

At the very outset, the question appears superfluous, if not rediculous .Such cynicism, stems from the well entrenched notion in the literature, that the habits are acquired .Even the online Webster's dictionary assumes so, when it defines habit. (vide infra) At least, there is consensus that the habits are related to behavioural patterns. To cite a few such opinions, " the habit is an automatic and rigid pattern of behavior."(behavioural economic.com) "Habits are self-sustaining patterns of sensorimotor behaviour".[1] The connection between the behaviour and genetics is established in the recent literature , as seen by umpteen number of articles published in this regard. As early as the nineteenth century, Francis Galton, (a cousin of Charles Darwin) , systematically studied behavior and heredity. [2] it is held " that the behavior is determined by a combination of inherited traits, experience, and the environment" . One more step forward is the view that "Some behaviors , called innate, comes

from our genes, but other behaviors are learned, either from interacting with the world or by being taught".[3]The dawn of a new branch of science- the " Behavioral genetics examines the role of genetic and environmental influences on behavior.[4] It is now generally believed, that the human behavior is determined by complex interactions of both nature and nurture." [5] How genetics does affect the behaviour is summed up in the statement that "Behavior can influence genetic expression in humans and animals by activating or deactivating genes.[6] [7] [8] This interrelationship between the behaviour and genetics is not necessarily be rigid and universal is suggested by the view that "the relationship between the genes and behavior can change over time as one has new experiences. In some situations, genes play a larger role in determining one's behavior; in other situations, environment plays a larger role in influencing your behavior.[9] If the fact, that the habits are but manifestation of certain behavioural patterns, and the behavioural patterns have genetic basis, the possibility of acquiring at least, some habits by genetic inheritance, becomes more obvious . With this background, this article presents a family lineage , in which a benign, nose rubbing habit, is traced through six generations. Such continuous unbroken chain of transmission over generations can't be coincidental, as the author asserts. A possible type of inheritance is suggested by a process of inference and elimination of different types of inheritance .But the primary aim of this article is to objectively break the myth, that the habits are acquired only , notwithstanding the fact, that it would be an uphill task

Habits vs Tics :

Merriam-Webster's online dictionary defines habits as:
" an acquired mode of behavior that has become nearly or completely involuntary. "A habit is defined as a way of behaving that is repeated so often it no longer involves conscious thought". The other definitions explicitly implicating their genetic basis are broached above. They are characterized by being repetitive and involuntary and some are motor acts, habitually repeated. "A motor habit is a habit which involves movement." (Psychology dictionary) . For example, rubbing of the nose . Habit is more of a behavior or practice . Biologic and environmental factors are considered responsible for habit formation .

Some habits are destructive while others are harmless. The former constitute a separate group , named, " **Habit disorders"** . Some of the recognised examples of the either type are listed below.

Harmless, nondestructive habits :
Nose picking
Nose rubbing
Nose pinching
Ear pulling
Shoulders shrugging and Eye brows raising , etc.
destructive, impulsive habits :
(Termed as Habit Disorders)
Trichotillomania, (hair pulling)
Bruxism, (teeth grinding)
Onychophagia,(nail biting)
Scabiomania (skin pricking)
There seems to be a consensus among researchers that TD and TS share enough common aspects to be considered on a continuum of severity.

A tic is an involuntary , repetitive contraction of certain muscles A tic is an uncontrolled sudden, repetitive movement(motor tics) or sound (vocal), that can be difficult to control. Tics can be either simple or complex . **Simple tic** involves a single muscle or a discrete group of muscles A **complex tic** involves different muscle groups. simple tic is purposeless, such as an eye blink, any other muscle twitch, a grunt, or a production of a **noise**. A complex tic may appear as purposeful , like scratching of nose. While habits are normal, a tic might be a symptom of a health problem. Tics that persist beyond 12 months, are diagnosed as "**Persistent Tic Disorder** " . They are associated with comorbidities like ADHA, OCD and anxiety. **Vocal tics** are repeated noises . **Simple vocal tics** consist of repeated clearing of the nose or grunting. **Complex vocal tics** are characterised by imitating the actual words of others, persistently. Persistent imitation of words may be a sign of **Tourette syndrome** (TS) or **Autism**. Combined vocal and motor tic (TS) may be inherited buy the pattern of inheritance is not clear. Habit disorders are typified by repetitive body focused behaviours and include trichotillomania, skin picking, nail biting .

Childhood habits and ticks :

Tics are common in children. They are usually benign. Any of the motor habits/tics or vocal tics (but not both) described, may be involved. They may last for less than one year or in any case not beyond adolescent period. They are typically transient tic disorders (renamed as provisional tic disorder) .The American Academy of Child and Adolescent Psychiatry states that tics affect up to 10 percent of children during their early school years. Over years, they outgrow their habits/ tics. It is also true that TS , a pathological entity also begins in childhood , a fact that should not be lost sight of.

Habits and Tics, do they represent a spectrum ?

Both , habits and tics have more in common than in what they differ. for instance , both are repetitive and involuntary and some are persistent. Only the presence (tic) or absence (habit) of muscle spasm makes the difference . The Virginia Commission on youth behaviour includes both the Tic disorders (TD) and body focused habit disorders like nail biting, skin pulling (SP) and trichotillomania (TTM) under a single umbrella" , "the habit disorders" . "The Commission foresees a common entity ,from which both tics and habits. might diverge" .The APA (American Psychiatric Association) has included the habit disorder TTM, along with tic disorders like , Transient motor Tic disorder, Chronic motor tic disorder, Chronic coal tic disorder and Tourette syndrome (TS) in the DMS 4 (Statistical Manual of Mental Disorders classification , 4th edition).but left out SP, under the habit subgroup. of the classification. But Virginia Commission found justification to include SP at part with TTM to continue to include SP as a constituent of the Habit disorder .That makes the so called distinction between the tics and habits , superfluous., at least as far as destructive habits are concerned . That leaves apart , the other non destructive habits. It has already been shown that both habits (irrespective, whether, destructive or otherwise) and tics share common characteristics in being, involuntary, repetitive , rhythmical and apparently purposeless movements that are faithfully reproduced true to their types. They only differing the terminal event i.e. the tic ends in a muscle spasm but the habit terminates in the motor act. In this deference also there is some similarity that both involve a coordinated action of a muscle group or groups. Both the injurious as well as other non injurious habits are related to behaviour and are stated to be ' body focused acts' .Further it is reported in literature that child hood onset favours the entity to be called as tic rather than a habit. The author conclusively has shown that the children in the age group of 2 to years belonging to either sex, exhibited the inherited habit of nose rubbing , a family trait shown to have been transmitted in six generations ! The author is of the opinion, that, save for the traditional

and time honoured separation of the two entities, no harm would befall if considered as variants of a single motor act, basing on the points of similarities adduced.

Discussion :

Types of habits involving nose :-

Nose meddling is of common occurrence , the significance of which may vary depending on the circumstances. For instance, it may be a sign of greetings (as is done mutually , nose to nose, between friend/relatives of men in Emeritus, Saudi, Qatar, and in Eskimos) as a part of ritual (In praying posture, face and nose touching the ground) or as a habit , exhibited more are less unconsciously. The Last type is the subject matter of the present article. Among the habits involving the nose, are-

1. Nose picking or Rhinotillexis : It is an(an act of putting finger in nostril to extract dried mucus. It a benign habit exhibited by many people in general population. It is one of the child hood habit which almost all children overcome. It is followed by Swallowing the extracted mucus (**mucophagy**) . When it becomes an obsession (OCD), it is called **Rhinotillexomania .**

2.**Nose pinching :**
same as , like one is tempted to pinch the nose of a cute child ! with a difference here that the & pincher and the pinched and are one and the same !
3) **Nose rubbing** : This is the least focused benign habit in literature, which indicates that this habit is not as frequently observed in population in general, as are nose picking and nose pinching .Nevertheless one comes across a person exhibiting this disorder. This puts the habit at a different footing than other benign habits. The presentation of such habit in a family tree through six generations as described in this article assumes special importance. Vigorous rubbing of the nose clockwise or anticlockwise, or vertically (called nose salaam) or horizontally or a combination of any of the above. This last habit is seen as a hereditary transmitted trait in a family tree and is being discussed in present article. "nose scratching " is an entity , distinct from nose rubbing It must be conceded that this entity is not existing when literature is scanned but it is no less common than “ear pulling “ .in this habit, only the finger nails are at work, and is easily identifiable by anybody. itchy nose (due to any cause whatsoever) invites scratching of nose and in the absence of identifiable scratching , itchy nose could not exist. The habit on which the present article concentrates is nose rubbing as a chronic , complex, persistent , benign , inherited habit .Nose meddling is interpreted as a sign of nervousness and anxiety by psychologists whereas it is viewed as a deception by the Behavior experts. Others feel that they are simply " body focused act .

The genealogy of the family transmitting the " nose rubbing habit " :
Genealogy is the study of families, family history, and the tracing of their lineages. It helps in constructing the pedigree chart or family tree with respect to a trait / disease that is transmitted genetically .
A case of "Nose rubbing habit" being transmitted , genetically over 5 generations reported in this article. The ery mention of a habit being transmitted genetically may raise some eye brows but the facts in the foregoing section might set the disbelief if any ,to rest. **The case came to light when interacting with the first degree relatives(Siblings and first cousins) of the 4th generation a family genealogy.** On further investigation and analysis , the second degree(parents and their siblings) and third degree relatives (grand parents and their siblings) are found to be involved .So parents of the 3rd

degree are the source of the transmitted trait. If the 3rd degree relatives are taken as the first affected generation? 2nd and 3rd degree relations constitute 2nd and third generations. The children of the 3rd degree relation constitute the 4th generation. Involvement of parents of 3rd degree is inferred from involvement of 3rd degree relatives themselves . so , in all , the trait is traceable over 5 generations. Another interesting feature of the transmitted trait is that a daughter aged 6 years and a son of 2 years of age , of a first cousin (uncle's son) of the index 3rd degree members , are affected. This has two implications. Firstly exhibiting the same act at an early age of 2 years rules out the chances of the habit being acquired and secondly, the onset in early childhood onset qualifies the habit to be considered as a tic , going by the current notion. of such being the roots of the trait , it can never be considered as acquired . But as seen at the outset, the Webster dictionary defines a habit as being " acquired ". Similar is the view of almost all scientific community and even intelligentsia . Any evidence contrary to such notions shall be deemed " unique" . Further, a search of the literature did not disclose any habit being transmitted genetically. The same is not true in case of "tics" as there is some agreement as to genetic transmission of Tourette syndrome (TS) which is characterised by the presence of both motor and vocal tics). It is also seen above that the distinction between a habit and a tic is made superfluous by including both under one condition, " the habit disorders by the Virginia commission on youth as broached earlier. so what is reported herewith may be taken as habit / tic of a habit disorder

More details of the family tree of the affected family. ;

The status of the great grand father's of the index group is not known. But their two sons are affected. Hence it is speculated that either of the great grand father or great grand mother (or both)might be the source of the transmitted trait. If the two brothers of the third degree relatives of the index group of the degree (first generation) are designated. By say, letters X and Y, It is seen that the dependents of X carried forward the gene but not the descendants of Y. Y had a son and a daughter who are not affected and so are the grad children of Y. in short the whole lineage of Y is not affected except for Y himself , whereas the all the four sons and 3 daughters of X (2nd generation or 2nd degree relatives of the index group) are affected in varying degrees . Neither X nor Y had consenguous marriage. Let the 4 sons of X be designated by letters S1 , S2, S3 , S4 and daughters as D1, D2 and D3..

S1 has one son and 3 daughters – all are affected. The son has one un affected son and an affected daughter (grand children of S1). The status of the other grand sons/ grand daughters of S1 are not known.

S2 has one son and 3 daughters , none of them are affected. It might be of interest that S2 had the mildest expression of the trait. His grand children are also not affected (?)

S3 has 2 daughters and one son , of which both daughters but not the son are affected. The status of grad children of S3 are not known.

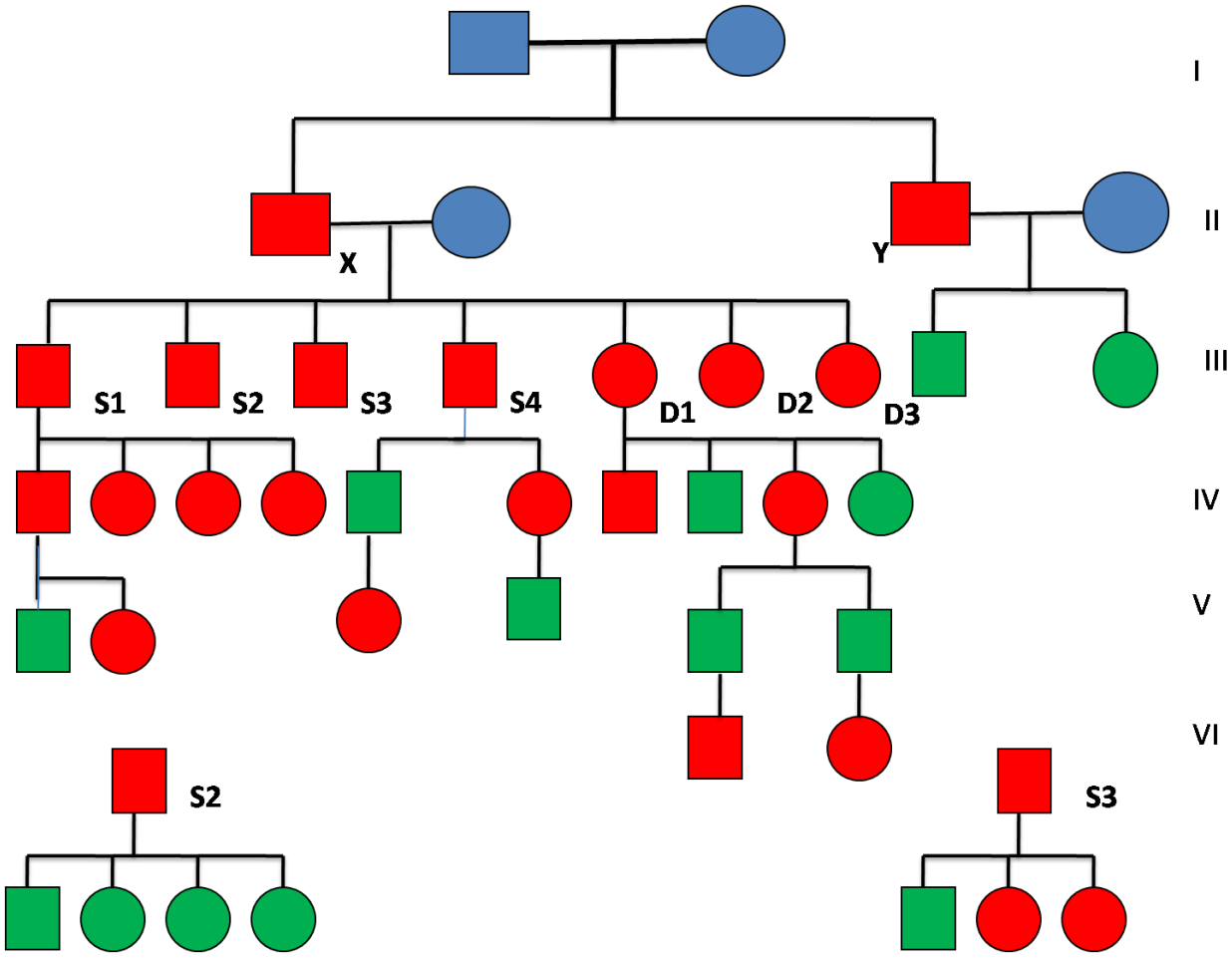
S4 has one non affected son who in turn had an affected 2 year daughter. S4 also has an affected daughter whose 10 year old son is affected.

D1 has 2 sons and 2 daughters of which eldest son and one daughter are affected. The affected daughter's 2 sons are not affected but her first son's daughter (6 Years)and the other son' son (4 yers) are affected (the grand children of the affected daughter of D1) . This represents the involvement of 5th generation affected excluding the source and 6th generation through which the trait is transmitted.

D2 - status of children not known.

D3- status of children not known.

The pedigree chart :



Pedigree chart. Blue: Status not known, Red: Affected, Green: Unaffected

X and Y represent the affected males of the second generation. Square – Males , Circle- females . All the spouses of the affected are normal.

Pedigree chart: Blue: Status not known, Red: Affected, Green: Unaffected

Review of possible types of inheritance :

Mandela type of inheritance is excluded for reasons given against each type , in the following table.

Mendalean type …….. **Reason for exclusion**

1. A D. in the second generation all 7 are affected where as only 50% arexpected
2. A R. No skipped generation.. Some members , affected in each generation.
3. SEX Linked recessive. … Daughters are also affected , Whereas they should be carriers only.
4. Sex linked dominant … No father to son transmission possible. Not so in gen 1, 2 &,3
5. Y linked. .. Male to Male transmission can occur but not male to female . But this is seen in gene 2 &3

Non Mendalean type inheritance ;

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1. **Genetics imprinting :**

Maternal gene imprinting : Maternal gene is silenced. Half her progeny only , irrespective of gender are effected. Paternal gene Imprinting : Paternal gene is silenced .Only half of his progeny is affected irrespective of gender.

Objection : The imprinted gene passes unaffected through mitotic division. In generation 2 and 3 there is 100% inheritance of the affected gene , which is against the inheritance pattern of gene imprinting either maternal or paternal gene imprinting.

Polygenic inheritance or quantitative inheritance, refers to a single inherited phenotypic trait that is controlled by two or more different genes. Each of the genes that contributes to a polygenic trait, has an equal influence and each of the alleles has an additive effect on the phenotype outcome. occur on a continuous gradient, with many variations of quantifiable increments.
The distribution of phenotypes fits into a normal distribution (bell shaped distribution , with minimal phenotypes represented at the extremes and maximal at the center) of probabilities. with mostly the offspring displays an intermediate or a mixture of phenotypes of the two parents. Examples of this type of inheritance are skin colour and height etc. The offspring can inherit a mixture of different skin shades or highs presented by each parent.
Difference between Mendalean and polygenic inheritance :
Polygenetic traits are determined by a number of different genes that interact between them. Whereas in Mendelian Genetics, monogenic traits are determined by the different alleles of a single gene.
In Mendelian Genetics, one allele dominates or masks another.
polygenic traits exhibitincomplete dominance so the phenotype displayed in offspring is a mixture of the phenotypes displayed in the parents.

Multifactorial inheritance :

It is a polygenic inheritance with an added dimension of the influence of environmental factors. Both polygenic and multifactorial inheritance are often used synonymously and interchangeably .

Objection :

If multifactorial inheritance is indeed the case, then the chance of the patient contracting the disease is reduced only if cousins and more distant relatives have the disease.[10

Epigenetics refers to modification of genetic information not encoded in the DNA sequence of genomes. Epigenetics marks can change a gene expression pattern without a change in primary nucleotide sequence - without changing an A, C, G or T. Changes in gene expression often correspond with epigenetic changes such as methylation of DNA, changes in chromatin conformation (methylation, acetylation), and expression of non-coding RNAs.

Behavioral epigenetics is defined as the study of how epigenetic alterations induced by experience and environmental stress may affect animal(and human) behavior. If it is accepted that habit is a pattern of behaviour, as suggested above, there may be a possibility transmission genetically of the behavioural pattern , epigenetic ally. For instance, even in mono-zygotic twins, though they inherit the same genes, their behaviours can be entirely different. This difference in behaviour is sought to be explained by epigenetic behavioural inheritance.

Transgenerational stress inheritance : is the transmission of adverse effects of stress-exposure in parents to their offspring through epigenetic mechanisms.[1] The effects are mediated by HPA axis (Hypothalamic -pituitary axis , by releasing stress hormones . If the habit is considered as stress related behavioural act, this type of transmission becomes feasible. But it is difficult to prove this possible transmission.

Mitochondrial inheritance : This is the speculated type of inheritance where 100% progeny including sons and daughters is possible , as seen in generations 2 & 3, With some limitations as seen below. It also explains the father to son transmission as seen in generation 2 and 3 . Recent knowledge of paternal contribution and Recombinant DNA from both father and mother could explain this anomaly also. Further, the degree of severity among those affected and non-expression of the trait in some siblings of the same generation can also be explained by the mtDNA inheritance. **is discussed more in detail below.**

The mitochondrial Inheritance : (Cytoplasmic or maternal inheritance)

The mt DNA is the Genetic material present in mitochondria, which is transmitted exclusively by the mothers only .The mtDNA is passed unchanged from a mother to her offspring, [12] Mothers inherit from their own mothers, which is the basis for the conceptualization of the "Mitochondrial eve" Many studies hold that paternal mtDNA is never transmitted to offspring.[.On the other hand, In the nuclear DNA inheritance, one copy is contributed by each of the two parents. This inheritance obeys Mendel's laws. Needless to say, that the mitochondrial Inheritance does not obey the Mendealean laws as the contribution is from the mother only.
The mtDNA type of inheritance ,satisfies the occurrence of the trait in all the males and females in a generation, as seen in generation 2 , in the present case. But it can't explain the father to son transmission as seen in generation 2 and 3 . Recent knowledge of paternal contribution of mt DNA and recombinant DNA resulting from the mix up of mtDNA transmitted by both the parents could explain the father to son transmission. Further, the varying degree of severity as seen among those affected and non-expression of the trait in some siblings of the same generation , could also be explained by the concept of " threshold level of transmitted mtDNA" that the offspring inherits.
Paternal transmission of mtDNA and Recombinant mtDNA :

Maternal transmission of mtDNA :

Evidence in favour :

1) The inheritance of mitochondrial and chloroplast genes differs from that of nuclear genes in showing vegetative segregation, uniparental inheritance, intra- cellular selecThe inheritance of mitochondrial and chloroplast genes differs from that of nuclear genes in showing vegetative segregation, uniparental inheritance, intra- cellular selection, and reduced recombination . [10]
2) Giles RE, et al (1980) by his studies conclusively proved that the mt DNA transmission is a maternal. [13]

Reasons for predominant maternal transmission of mtDNA :

1.There are 100 000 mitochondria in the human egg and only 100 in the sperm (Satoh and Kuroiwa, 1991).[14] The probability of paternal mitochondrial transmission is considered rare.

2. The tailpiece or the mitochondrial sheath is destroyed during fertilization of the egg , precluding the paternal transmission.

Evidence in favour of paternal mtDNA transmission ;

1. few studies indicate that very rarely a small portion of a person's mitochondria can be inherited from the father. A 28 years male patients case was cited.(Schwartz and Vising's) [15]

2.Paternal transmission of mitochondrial DNA is (fortunately) rare.
(Johns DR. Ann Neurol. 2003.) [16]

3. Mitochondrial DNA can be inherited from fathers, not just mothers (TG McWilliams · 2019] [17]

4. A 2005 study by HJ; Kong QP; Parson W , et al produced more evidence in favour of paternal transmission mission.20) [18]

Evidence for Biparental transmission of mtDNA.

1.Direct evidence of recombination. Schwartz and Vissing (2002) presented the case of a 28-year-old man who had both maternal and paternally derived mtDNA .

2.Comprehensive exploration of mtDNA segregation in some families shows biparental mtDNA transmission" . (S Luo · 2018) [19]

Evidence for recombinant bi-parental mtDNA mtDNA :

1. Kraytsberg et al (2004) {20] have taken the observation of Schwartz and Vissing in their case(cited above), one step further, and claim to show that there has been recombination between the maternal and paternal mtDNA in this individual .

2.DNAE D Ladoukakis & A Eyre-Walker (2004) reviewed the direct evidence in favour of recombinant mtDNA resulting from the mixup of maternal and paternal mtDNA.(21)

3. The mixing of maternal and paternal mtDNA was thought to have been found humans in

human beings in 2028 [22]

Explanation of variable degree of severity of expression of the habit in the genealogy . :

It is seen that in the above genealogy, the extent of severity of expression as revealed by the frequency with which the habit is exhibited varied from mild through moderate to severe. This is explained by the homoplasmy plasma and heteroplasmy exhibited by each of them.
Typically, individuals and
all mitochondrial genomes are approximately genetically identical, they harbor only one mtDNA genotype ,that of the mother. This is called homoplasmy. In many wild-type and mutant maternal alleles coexist, and this is known as heteroplasmy. The extent of heteroplasmy may determine the degree of severity of expressed trait.
In humans, since mtDNA is transmitted to subsequent generations exclusively through the maternal lineage (2), a clinically asymptomatic woman with low levels of a deleterious heteroplasmic mtDNA mutation may pass her trait -causing mutation to all of her offspring . The

severity of clinical symptoms in affected children is often associated with the level of mtDNA heteroplasmy (i.e., the percentage of the deleterious mutation) .

The Reason why a few siblings are unaffected by the trait. :

This is explained by what is called " threshold effect " It means that the trait is seen unless a critical copies of the mutated gene are inherent ed. Conversely, subthreshold inheritance of the mutated genes may not express the trait. This could be the reason of siblings and first cousins not affected in the family tree cited in this article.

Explanation of the non expression of the habit in some members of the genealogy :

The possible explanations listed and no hazard of guessing as to the actual cause, operating in this reference family tree could be made by the author.

1) Variable expression of the gene.
2) Incomplete penetrate of the gene.
3) Gene silencing or imprinting .
4) Sub-optimal " **threshold effect** " described above.

Conclusion :

A benign habit , the nose rubbing, is traced to have been inherited over six generations of a family tree. It made its presence in all generations and in most among any given generation. .Such observed pattern can't be coincidental , and is believed by the author to be undoubtedly a genetically inherited trait. Incidentally, the habits are considered to be 'acquired' and it is the first report to suggest a genetic background . The Inheritance patterns of both Mendalean and non-Mendalean types are briefly reviewed The possibility of the trait being inherited epigenetically , though considered possible, proving the same is difficult. The possibility of mitochondrial inheritance is discussed , at length, In particular, the recambinant DNA from boy the mother and father is inferred from the pattern of inheritance as deduced from the pedigree chart .

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