Received: 31 August 2022 | Revised: 13 November 2022 | Accepted: 17 November 2022

DOI: 10.1002/ajmg.a.63063

AMERICAN JOURNAL OF medical genetics PART A WILEY

REVIEW ARTICLE

Inversions on human chromosomes

Klara Kosuthova | Roman Solc

Department of Anthropology and Human Genetics, Faculty of Science, Charles University, Prague, Czech Republic

Correspondence
Roman Solct, Department of Anthropology and Human Genetics, Faculty of Science, Charles University, Vinicna 7, Prague, 128 00, Czech Republic.
Email: roman.solc@natur.cuni.cz

Funding information
Charles University, Grant/Award Number: PROGRES Q43

Abstract

Human chromosome inversions are types of balanced structural variations, making them difficult to analyze. Thanks to PEM (paired-end sequencing and mapping), there has been tremendous progress in studying inversions. Inversions play an important role as an evolutionary factor, contributing to the formation of gonosomes, speciation of chimpanzees and humans, and inv17q21.3 or inv8p23.1 exhibit the features of natural selection. Both inversions have been related to pathogenic phenotype by directly affecting a gene structure (e.g., inv5p15.1q14.1), regulating gene expression (e.g., inv7q21.3q35) and by predisposing to other secondary arrangements (e.g., inv7q11.23). A polymorphism of human inversions is documented by the InvFEST database (a database that stores information about clinical predictions, validations, frequency of inversions, etc.), but only a small fraction of these inversions is validated, and a detailed analysis is complicated by the frequent location of breakpoints within regions of repetitive sequences.

KEYWORDS
cytogenetics, disease, evolution, human chromosome, inversion, polymorphism

1 | INTRODUCTION

Inversions belong to the classic structural chromosomal rearrangements of the human genome together with deletions, insertions, translocations and duplications. Inversions are balanced rearrangements characterized by a change in the direction, but not the amount, of the cell's genetic information. They can be paracentric or pericentric, which means that they include the centromeric region and thus affect both chromosomal arms. Inversions, paracentric and pericentric, were found on all 22 autosomes (Thomas et al., 2008).

In 1921, Alfred Sturtevant published an article dealing with the chromosomal rearrangements of *Drosophila*, in which he concluded that one of the serious consequences of inversions occurring in the heterozygous state is the suppression of recombination (Sturtevant, 1921). This is (believe to be) the first documented reference to inversions in history.

The second half of the 20th century is characterized by the huge onset of new molecular methods that contributed to the development of our knowledge about structural variations of the genome, including inversions. As is the case with many other types of genetic variants, only a small fraction of inversions appear to result in a pathogenic effect manifesting itself phenotypically. Even the chromosomal change is often undetectable by common cytogenetic methods, because a large part of it is cryptic (Kirkpatrick, 2010).

Inversions are a permanent part of the human genome in the form of polymorphisms. They play an important role in our efforts to understand evolution and adaptation processes and they can be the causes of various serious diseases. Thus, the study of inversions is important for the understanding of various processes. Despite the facts, the research of inversions lags behind the research of other chromosomal aberrations, and the object of interest is not often a human. Therefore, the aim of this article is to summarize the current knowledge of the issue with a focus on the speciation effect of inversions, association with clinical manifestations and polymorphism of inversions in the human population.

2 | EVOLUTION AND INVERSIONS

One of the functional consequences of inversions is their proven influence on evolution. A classic example is their ability to suppress

the course of recombination in the heterozygous state by losing the resulting unbalanced gametes. Evidence supporting the involvement of inversions in adaptation processes is geographically conditioned variation in the frequencies of their alleles (Kirkpatrick, 2010).

2.1 | Evolution of sex chromosomes

The X and Y sex chromosomes are thought to have evolved from autosomes (Rice, 1996). Inversions played a significant role in this development, as a series of inversions on the Y chromosome gradually reduced the size of the pseudoautosomal recombinant region of the X and Y chromosomes, allowing their gradual differentiation. This differentiation of the X and Y chromosomes took place in four phases, evidenced by the four evolutionary layers occurring on the X chromosome (Lahn & Page, 1999). The Y chromosome, incapable of recombination, subsequently lost genes and degenerated during its evolution, while the X chromosome was still capable of recombination in the female organism and thus retained most of its genes (Charlesworth & Charlesworth, 2000).

2.2 | The role of inversions in primate evolution

The fourth and final inversion event on the Y chromosome occurred relatively recently and occurs in primate evolution only (Lahn & Page, 1999). Humans and chimpanzees evolved from a common ancestor. This cladogenesis occurred about 6 million years ago (Takahata & Satta, 1997) and divergent evolution caused 1.24% variability in their DNA sequences (Navarro & Barton, 2003a). Chimpanzee and human genomes have diverged and lost their homology due to differences in nucleotide sequence, gene expression, but mainly due to chromosomal rearrangements (Marqués-Bonet et al., 2004).

The property of inversions to function as a reproductive barrier between newly formed species has been known for quite long time and is based on the idea of reduced fertility in heterozygotes containing inversions. However, the low fitness of heterozygotes caused by the presence of inversions does not explain speciation sufficiently because spreading of such inversions is limited to low-density populations (Hey, 2003). The speciation effect of inversions is better explained by Rieseberg's theory, which describes the suppressive effect of inversions on recombination in heterozygotes in inverted sections and sections close to them (Rieseberg, 2001). This theory describes the condition of two closely related populations where alleles incompatible with genes in the other population occur in both. Incompatible alleles create a genetic barrier to the exchange of closely linked genes (Barton & Bengtsson, 1986). Thus, if an inversion occurs in one population as opposed to another, and both the inverted and noninverted chromosomes carry an incompatible allele within the range of the inversion, the genetic barrier caused by these alleles also includes the entire region of tight linkage to the alleles, which is the region in which the inversion suppresses recombination in heterozygotes. This indicated genetic barrier is stable because chromosomes cannot replace each other due to the presence of incompatible alleles. Inversion causes the accumulation of additional alleles favorable to only one of the two populations. The essence of the whole model is the fact that inversions increase the probability of a stable configuration of incompatible alleles (Noor et al., 2001). Inversions are especially important as a speciation factor in the case of high gene flow between populations, because they create areas with significantly reduced gene flow, where incompatible alleles arise and persist, which cannot be suppressed in both populations by occurrence of other genetic variants (Navarro & Barton, 2003b). According to this model, genes near genetic barriers should accumulate changes at a higher rate than genes far from the genetic barrier. Humans and chimpanzees differ in 10 major rearrangements: pericentric inversions on chromosomes 1, 4, 5, 9, 12, 15, 16, 17, 18 and the fusion of two acrocentric chromosomes into the current human chromosome 2 (Yunis & Prakash, 1982). The protein evolution occurred about 2.2 times faster on these chromosomes than on chromosomes in which human and chimpanzee do not differ in any way (Navarro & Barton, 2003b). Several scientific works support the claim that rearranged chromosomal regions have a higher degree of expression difference between humans and chimpanzees (Ebersberger et al., 2002; Yi et al., 2002).

Although comparative genomic techniques confirm the frequent occurrence of chromosomal variations (Korbel et al., 2007; Tuzun et al., 2005), difficulties in proving the centrality of the suppressive influence of chromosomal variations in speciation have caused conflicting views on this influence. The notion of chromosomal evolution was rejected in most scientific circles and an allopatric explanation of speciation processes was preferred (Faria & Navarro, 2010). Contrary to the initial research, recent experiments not only found no significant link between chromosomal and molecular evolution (Zhang et al., 2004), but some of them even found the opposite trend (Szamalek et al., 2007). The same authors published works that support (Marqués-Bonet et al., 2004) and refute (Marqués-Bonet et al., 2007) the fundamental speciation effect of inversions. A low level of recombination within the inverted regions may eventually result in the loss of the much emphasized divergence compared to collinear chromosomes. Yet the authors themselves emphasize that their scenario is not dynamic, as they used only a limited amount of inversion-fixed incompatibilities (Feder & Nosil, 2009).

Even when differences are detected within chromosomal variations, it is difficult to confirm their connection with speciation, and not being able to detect differences is not a clear marker either. Not every chromosomal variation that differentiates two species must have played a role in speciation (Noor & Bennett, 2009). In addition, the interpretation of the results is complicated by the fact that distant species show a higher degree of diversity in sections of chromosomal variation than close species (Marqués-Bonet & Navarro, 2005).

Chromosomal speciation had a strategic role in the development of some species, for example, in *Drosophila*, but its role in primate speciation is negligible. The concept of chromosomal speciation, not only in humans and chimpanzees, but in general, should be viewed as a set of evolutionary processes in which chromosomal rearrangements contributed to the emergence of reproductive isolation (Faria & Navarro, 2010).

2.3 | Human inversions and natural selection

In contrast to data on the position of inversions in primate speciation, information on the role of inversions in the formation of the human population is only partial. The reason behind this is primarily the lack of suitable techniques that would secure data on whether and what advantage or disadvantage is possessed by individual inversions. In this sense, perhaps the most studied chromosomal locus is 17q21.31, which exists in two haplotypes: as a direct haplotype H1 and as an inverted haplotype H2. Recombination does not occur between these haplotypes in a section of about 2 Mb and this results in their population linkage disequilibrium (Stefansson et al., 2005). The inverted H2 haplotype occurs in the European population with a relatively high frequency reaching up to 30% (Steinberg et al., 2012). Which is in contrast to the African (6%) and Asian (<1%) populations. The reason may be that the H2 lineage undergoes positive selection, as demonstrated in Icelandic women, where H2 carriers had more children than women without H2 (Stefansson et al., 2005). However, the same haplotype is associated with disease-causing microdeletions in the European population (Koolen et al., 2006). Thus, one identical haplotype is associated with dangerous microdeletions, but at the same time brings an advantage to female carriers. In addition, it protects its carriers, albeit partially, from neurodegenerative diseases (Webb et al., 2008). Accordingly, some authors believe that the high frequencies of H2 in the European population are the result of a founder effect and not selection mechanisms (Zody et al., 2008). Another hypothesis states that H1 first appeared in Africa and the other complex haplotypes containing duplications appeared and spread among non-African populations only later (Steinberg et al., 2012). The 15 Mb nonpathogenic paracentric inversion of chromosome 21, which occurs in carriers in the Czech population with a frequency of 1 of 660, is also assumed to have spread due to the founder effect (Drabova et al., 2014).

The 8p23.1 inversion (8p23-inv) is a 4.5 Mb inversion and thus ranks among the largest polymorphic human inversions ever (Giglio et al., 2001). Several sites within the inversion have been described as putative targets of natural selection (Deng et al., 2008), including sites associated with cardiovascular and autoimmune diseases, although no clear evidence of positive selection has been found (Salm et al., 2012).

The allele carrying the inversion at 16p11 is variously population-stratified, from 10% in East Africa to 49% in Northern Europe, suggesting the likely existence of selective mechanisms after human migration from Africa (Gonzalez et al., 2014).

HsInv0030, a 17,120 bp long inversion that occurs on chromosome 16 is ancestral and it is associated with the deletion of exon 6 in the *CTRB2* gene, which encodes the precursor of chemotrypsinogen B. The frequency of haplotypes varied by population type, and this was most likely the result of adaptation to different dietary habits of populations (Pang et al., 2013). However, it is often difficult to distinguish whether the different frequencies of inversions between different populations and continents are the result of natural selection, or whether this stratification is caused by demography. Demographic reasons are the presumed cause of the increase in the occurrence of the HsInv0059 inversion in the Asian population, on the contrary, for HsInv0006 (frequency 90% in Africa, 33%–43% on other continents) the influence of natural selection is more likely (Vicente-Salvador et al., 2017).

3 | INVERSIONS ASSOCIATED WITH CLINICAL MANIFESTATIONS

3.1 | Inversions as simple pathogenic variants with phenotypic expression

From a medical point of view, the greatest attention is paid to inversions manifested by pathogenic changes in phenotype (Table 1). Unlike commonly occurring polymorphic inversions, which do not have health consequences for their carriers, the inversions described in the following section are associated with clinical manifestations.

There are two common mechanisms of such diseases. One of them is the direct interruption of the gene section, for example, an inversion

TABLE 1 Inversions as simple pathogenic variants with phenotypic expression

Localization of inversion	Affected genes	Phenotypic expression	Source
5p15.1q14.1	*AP3B1*	Hermansky–Pudlak syndrome	Jones et al. (2013)
X	*XIAP, TMEM47*	Immunodeficiency, mental retardation	Utami et al. (2014)
Xq21.1q22.3	*POU3F4*	Deafness	Anger et al. (2014)
7q21.3q35	*DLX5, DLX6*	Deafness, craniofacial defects	Brown et al. (2010)
7q22.1;q36.3	*SHH*	Disorders of the holoprosencephalic spectrum, syndactyly, synpolydactyly	Lettice et al. (2011)
2p25q31	*ZNF804A*	Schizophrenia, bipolar disorder	Blake et al. (2014)
21p12; q22	-	Repeated miscarriages in an inversion carrier	Tayebi and Khodaei (2011)
Xq28	*F8*	Hemophilia type A	Turner et al. (2006)
Xq	*IDS, IDS2*	Hunter syndrome	Bondeson et al. (1995)
2p	*MSH2*	Lynch syndrome	Rhees et al. (2014)
2p	*EML4, ALK*	Nonsmall cell lung cancer	Soda et al. (2007)
16p13.3q24.3	*CBFA2T3, GLIS52*	Acute megakaryoblastic leukemia	Gruber et al. (2012)

on chromosome 5 can affect the *AP3B1* gene encoding the β3A subunit of the protein complex, which is important for the transport of cargo proteins to lysosomes, but if an inversion is present, this gene is disrupted, and this is manifested phenotypically as the autosomal recessive disorder Hermansky–Pudlak syndrome (Jones et al., 2013). Similarly, the inversion on the X chromosome, which disrupted the *XIAP* and *TMEM47* genes encoding proteins from the PMP22/EMP/Claudin family, that are expressed in human tissues, including the brain, is associated with the manifestation of immunodeficiency and mental retardation in the observed patients (Utami et al., 2014).

The second most frequent mechanism of disease manifestation due to the occurrence of inversion is a change in gene expression. Dysregulation of the *POU3F4* gene on the X chromosome was caused by an upstream inversion that separated the gene from regulatory elements, resulting in the patient's hearing loss (Anger et al., 2014). The same situation can also be observed on chromosome 7, where the resulting paracentric inversion inv(7)(q21.3q35) changed the expression of the *DLX5* and *DLX6* genes by separating these genes from their regulatory elements, which phenotypically resulted in hearing loss and craniofacial defects (Brown et al., 2010). A de novo inversion of the long arm of chromosome 7 separated the sonic hedgehog gene from enhancers that control expression in the forebrain (Lettice et al., 2011). The carrier of this inversion showed symptoms of a disorder of the holoprosencephalic spectrum, severe syndactyly of the upper limb and synpolydactyly of the lower limb. In addition to the above, a submicroscopic inversion occurring on chromosome 2 that shortens the transcription factor *ZNF804A*, which is associated with schizophrenia and bipolar disorder, can be mentioned as another interesting clinical manifestation causing inversion (Blake et al., 2014).

Along with the development of a disease due to the interaction of the inversion and the gene, offspring of inversion carriers may develop an unbalanced genome incompatible with life. Such manifestation was reported in case of a mother with inv(21)(p12; q22) who had recurrent miscarriages (Tayebi & Khodaei, 2011).

All the above mentioned pathogenic variants occurred de novo in the patients, or only familial occurrence was recorded and thus they are not polymorphic inversions. These variants appear rarely and the diseases associated with them are mostly rare, therefore the study of these inversions has only clinical significance for individual patients. However, some inversions have been repeatedly reported to be associated with worldwide diseases. Such inversions include the inversion int22h, which occurs in chromosome region Xq28 and is caused by the recombination of repetitions in intron 22 of the *F8* gene encoding coagulation factor VIII and one of two blocks of repetitions located at the distal end of the short arm of the X chromosome (Turner et al., 2006). According to the type of recombination a distinction is made between type 1 inversion, the so-called distal inversion, which is the cause of hemophilia in 37% of patients, and type 2 inversion, the so-called proximal, which disrupts the *F8* gene in 7% of patients. Patients with hemophilia A carrying the inversion are having a higher risk of developing a factor VIII inhibitor (Antonarakis et al., 1995).

In the metabolic disorder mucopolysaccharidosis of the second type—Hunter's syndrome, in about 13% of patients, the cause is an inversion, which occurs by recombination between the X-linked gene *IDS*, which codes for the enzyme idunorate 2-sulfatase, and between the adjacent pseudogene *IDS2* (Bondeson et al., 1995; Puig et al., 2015). Cases where inversions were the cause of tumors are also described, for example, a 10 Mb inversion on exons 1–7 of the *MSH2* gene is the presumed cause of Lynch syndrome in the observed individuals (Rhees et al., 2014), or a small inversion on the short arm of the second chromosome, the consequence of which is the fusion of the *EML4* gene with the *ALK* gene, which causes the emergence of nonsmall cell lung cancer in 6.7% of patients (Soda et al., 2007). Fusion of two genes also occurs in some cases of acute megakaryoblastic leukemia, when an inversion-induced fusion occurs between the gene for the nuclear corepressor *CBFA2T3* and the gene for the transcription factor *GLIS52* (Gruber et al., 2012).

3.2 | Polymorphic inversions as a cause of phenotype change and the development of diseases

Despite the lack of information about most polymorphic inversions in the human genome, some inverted gene segments were associated with the development of a phenotypic manifestation, often pathogenic or, on the contrary, acting protectively against the development of diseases (Table 2). In fact, most of the known polymorphic inversions on human chromosomes were discovered by studying various diseases. Thus, 6 large inversion polymorphisms (including 3 new ones: 1.2 Mbp inversion at 15q24, 1.5 Mbp inversion at 17q12 and 1.9 Mbp inversion at 3q29) were revealed, occurring with different frequencies in three populations: Nigerian, European and Asian (Antonacci et al., 2009). In the case of inversion at 17q12, its association with RCAD syndrome (renal cysts and diabetes syndrome) was confirmed, inversions at 15q24 and 3q29 were associated with microdeletion syndromes (Antonacci et al., 2009).

The most studied example of the association of a polymorphic inversion with a disease is the 900 kb segment located on 17q21.31, where the HsInv0573 inversion occurs, which includes the *MAPT* gene occurring in two haplotypes in the population (Stefansson et al., 2005). The homology of the noninverted haplotype H1 and the inverted haplotype H2 is 99.52%, the deviations being caused by the occurrence of microdeletions on H1 and duplications that border the breakpoints and were localized to a larger extent on H2 (Zody et al., 2008). Haplotype H1 has been shown to be associated with various tauopathies (Pittman et al., 2006), including progressive supranuclear palsy (Baker et al., 1999), frontotemporal dementia (Verpillat et al., 2002), corticobasal degeneration (Webb et al., 2008), Alzheimer's (Myers et al., 2005) and Parkinson's disease (Skipper et al., 2004). Thus, haplotype H2 provides its carriers with some kind of protection against these neurodegenerative diseases (Webb et al., 2008), and women with haplotype H2 have also been reported to have a higher number of children (Stefansson et al., 2005). The disadvantage is that this haplotype is being associated with microdeletion syndromes (Koolen et al., 2006).

A 4.5 Mb inversion HsInv0501, which occurs on chromosomal segment 8p23.1, has been described to have similar protective significance as the H2 haplotype of the *MAPT* gene. The inverted allele

TABLE 2 Polymorphic inversions as a cause of phenotype change and disease development

Localization of inversion	Size of inversion	Possible impact on the carrier	Source
17q12	1.5 Mb	Renal cysts and diabetes syndrome	Antonacci et al. (2009)
3q29	1.9 Mb	Microdeletion syndrome	
15q24	1.2 Mb		
15q13.3	2 Mb	Mental retardation, epilepsy, schizophrenia, autism	
17q21.31	900 kb	Microdeletion syndrome Protection against neurodegenerative diseases, higher birth rate	Koolen et al. (2006) Webb et al. (2008) Stefansson et al. (2005)
8p23.1	4.5 Mb	Risk of developing autoimmune and cardiovascular diseases Protection against lupus erythematosus and Rheumatoid arthritis	Namjou et al. (2014) Salm et al. (2012)
16p11.2	0.45 Mb	Protection against co-occurrence of asthma and obesity	Gonzalez et al. (2014)

protects against the development of systemic lupus erythematosus (Namjou et al., 2014) and it also provides the same protection against the development of rheumatoid arthritis (Salm et al., 2012). At the same time, inv8p23.1 is being associated with the risk of offspring with an unbalanced genome (Hollox et al., 2008), and also poses potential risk loci associated with autoimmune and cardiovascular disease phenotypes (Salm et al., 2012).

Five independent studies have confirmed that the inversion at 16p11.2 with a range of 0.45 Mb or the entire haplotype of this chromosomal segment protects its bearer not only from the development of asthma, but especially from the co-occurrence of asthma and obesity in the monitored individuals (Gonzalez et al., 2014).

The pathogenic influence of some inversions, specifically their connection with the development of psoriasis, a chronic inflammatory skin disease affecting 2%–3% of the world's population, was attempted to be shown by Ma et al. (2014). However, the results are questionable. Only two candidate inversions were confirmed to have a link between psoriasis and inverted segments in the secondary data set, and the locations of these inversions do not overlap with any of the known inversions listed in the InvFEST (the database that stores and merges inversion predictions from healthy individuals, information of validations and genotyping assays, frequency in different populations, association with genes, and the evolutionary history of the inversions) (Puig et al., 2015). Conflicting results were also obtained in the study of inv(9)(p11q12) (incidence in the general population 1–3%), where one paper linked this inversion with cases of infertility (Ceylan et al., 2008), but another rejected this connection (Dana & Stoian, 2012).

3.3 | Inversions as a predisposition to other genomic rearrangements

Some inversions do not have a direct pathogenic consequence, but their occurrence in the human genome means a higher risk of the occurrence of other structural rearrangements, and this can ultimately manifest again in a pathological phenotype (Table 3). An indicator of an inversion of this type is its increased frequency in the parents of the affected individual compared to the general population. A good example is Williams–Beuren syndrome, a disease characterized by developmental disorders caused by a large deletion of up to 1.5 Mb involving 17 genes on 7q11.23, in which an inversion was discovered in 33% of families with a proband (Osborne et al., 2001). The size of this inversion varies between 1.79 and 2.56 Mb (Bayés et al., 2003). The increased risk of the syndrome becomes even more prominent when comparing inversion frequencies in parents of Williams–Beuren syndrome patients with a control parental cohort, where the inversion rate was only 5.8% (Hobart et al., 2010).

The HsInv0389 inversion inverts up to two genes, namely *FLNA* and *EMD*, and its occurrence is associated with a deletion that causes Emery–Dreifuss muscular dystrophy (Aguado et al., 2014). Other examples of inversions that predispose to the occurrence of deletions include inversions identified in parents of patients with Angelman (Gimelli et al., 2003) or Sotos syndrome (Visser et al., 2005). The same association was discovered in a microdeletion syndrome at 17q21.31 (Koolen et al., 2006). Haploinsufficiency of one of the deleted genes is considered to be the cause of the mentioned diseases, because the amount of the product of the second copy of the gene on the patient's undamaged chromosome is not sufficient for the normal function of the organism. In several cases, however, the specific affected gene has not yet been identified, because the deletion affects large sections involving several genes (see, e.g., Williams–Beuren syndrome). Moreover, haploinsufficiency does not explain the emergence of X-linked diseases such as muscular dystrophy Emery–Dreifuss (Small et al., 1997). Likewise, the cause of Angelman syndrome is not haploinsufficiency, but loss of function of the paternally imprinted *UBE3A* gene at 15q11.2–q13, which can be caused by a pathogenic variant (e.g., 5–7 Mb deletion) of the maternal allele, paternal uniparental disomy or an imprinting defect (Buiting et al., 2016).

Inversions can also be a predisposition to more complex genomic rearrangements than just deletions. The maternal gene region 8p23.1 carrying a 4.5 Mb inversion predisposes the offspring to various

TABLE 3 Inversion as a predisposition to other genomic rearrangements

Localization of inversion	Size of inversion	Secondary rearrangement	Phenotypic expression	Source
7q11.23	1.79–2.56 Mb	Deletion	Williams–Beuren syndrome	Hobart et al. (2010)
Xq28	48 kb		Emery–Dreifuss muscular dystrophy	Aguado et al. (2014)
15q11-q13	4 Mb		Angelman syndrome	Gimelli et al. (2003)
5q35	1.9 Mb		Sotos syndrome	Visser et al. (2005)
17q21.31	970 kb		Microdeletion syndrome	Koolen et al. (2006)
3q29	1.9 Mb			Antonacci et al. (2009)
15q13.3	1.8 Mb			
15q24	1.2 Mb			
8p23.1	4.5 Mb	Deletion, duplication t(4;8) (p16;p23)	Mental retardation, facial dysmorphia, agenesis of the corpus callosum, congenital heart defects Wolf–Hirschhorn syndrome	Hollox et al. (2008) Guo et al. (1995) Giglio et al. (2002)
Yp11.2	4 Mb	Translocation PRKX/PRKY	Sex reversal, male infertility	Jobling et al. (1998)
4p16	6 Mb	t(4;8)(p16;p23)	Wolf–Hirschhorn syndrome	Giglio et al. (2002)

intrachromosomal (classical inverted duplications and deletions) and interchromosomal (dicentric chromosome) rearrangements, which are the result of ectopic meiotic recombination (Hollox et al., 2008). Such large chromosomal imbalances manifest themselves in the phenotype of patients with severe disorders occurring at different frequencies, including severe mental retardation, facial dysmorphia, agenesis of the corpus callosum, and congenital heart defects (Guo et al., 1995).

Another example of a complex chromosomal rearrangement, the emergence of which is conditioned by the presence of an inversion, is the more frequent generation of the unbalanced translocation t(4; 8)(p16; p23) in mothers who carry the inversion at 8p23.1. and at the same time on chromosome 4 manifesting as Wolf–Hirschhorn syndrome (Giglio et al., 2002). Reciprocal translocation of genes *PRKX* to Xp and *PRKY* to Yp causing the so-called sex reversal is also more frequent on the Y chromosome, which contains a 4 Mb inversion (Jobling et al., 1998).

Even if the frequency of the aforesaid inversions in the population is relatively high, their final impact on the emergence of other structural rearrangements with a pathogenic manifestation is low, since the above-mentioned diseases occur relatively rarely. For example, the 15q11–q13 inversion is present on 4.5% of chromosomes in the general population, but the incidence of the deletion associated with Angelman syndrome is less than 1%, so the penetrance of the inversion, given the risk of BP2/BP3 gene deletion in the offspring of mothers with this inversion, it is only 0.1–0.2% (Gimelli et al., 2003). Moreover, a deletion (or another inversion-associated rearrangement) is not always the cause of the disease in patients. In such cases the presence of an inversion in parents is completely irrelevant. Some scientific works, in contrast to the original studies, did not even confirm the connection of the inversion with another genomic rearrangement causes pathological manifestation, as in the case of Williams–Beuren syndrome (Frohnauer et al., 2010). However, there may be individual variability in recombination due to which there is a change in susceptibility to further structural rearrangements (Gimelli et al., 2003).

Further studies are needed to better clarify the role of inversions as predispositions to other rearrangements in the genome, however, it can be argued that a carrier of an inversion has a relatively high chance of having an affected child compared to a noncarrier.

3.4 | Effect of inversions on genes and their expression

Inversions that directly affect the genes can have different consequences for the bearer, the severity of which varies from mild to drastic. To make a diagnosis, it is important to determine this influence. If the exact breakpoints of the inversion are known, it is relatively easy to prove whether the given inversion disrupts the gene. On the other hand, proving the effect of the inversion on gene regulation is more difficult. Approximately 12% of the inversions found in the InvFEST database disrupt at least one gene, the HsInv0030 and HsInv0159 inversions are validated to disrupt two genes, and a further 30 inversions are suspected to disrupt two genes (Martinez-Fundichely et al., 2014). An example of a disease that developed due to an inversion of a disrupted gene is Hunter syndrome (mucopolysaccharidosis type 2), which is caused by an inversion of the gene for idunorate 2-sulfatase on the X chromosome (Bondeson et al., 1995; Puig et al., 2015).

The inversion may not have any effect on gene expression. This can be observed for example in three cases of genes located at breakpoints, where the gene exon sequences were identical to the short inversion repeats (HsInv0124, HsInv0344, and HsInv0393) and there was no change in the mRNA sequence (Aguado et al., 2014). A similar case was found at 16q23.1 where a 16.6 kb inversion caused the chymotrypsinogen B precursor genes *CTRB1* and *CTRB2* (both up to 97% sequence homologous) to exchange exon 1 (Pang et al., 2013).

Inversions can disrupt a gene in such a way that parts of it come long distances apart. The HsInv1051 inversion moved the first two

exons of the 87.8 kb long *CCDC144B* gene to a distance of 200 kb, while the HsInv0340 inversion shortened the long noncoding RNA LINC00395 by a similar mechanism (Aguado et al., 2014). The *ZNF257* gene can be disrupted by the occurrence of the HsInv0379 inversion (Martinez-Fundichely et al., 2014), the *VIPR2* gene was disrupted by the HsInv0626 inversion in 1% of healthy individuals (Beri et al., 2013). Unfortunately, for most of these inversions, there are no detailed studies examining their effect on gene expression. A possible hypothesis is the relocation of the gene to the heterochromatin region. But a similar phenomenon has not been reported in the human genome in contrast to studies in *Drosophila* (Vogel et al., 2009).

The effect of inversions on gene expression was studied mainly in the case of frequent polymorphic inversions with the results showing, for example, association between inv8p23 and the abundance of *BLK*, *PPP1R3B*, *XKR6*, *FAM167A*, and *CTSB* genes mRNA (Salm et al., 2012). Other examples include the 16p11.2 inversion that affects the expression of the mitochondrial energy balance regulator *TUFM* gene, obesity candidate genes *APOB48R* and *SH2B1* and asthma candidate *IL27* (Gonzalez et al., 2014). However, all these studies focused only on determining gene expression in selected tissues. For instance, in case of inversion at 17q21.31 increased expression of genes *LRRC37A4*, *PLEKH1M*, *MAPT* and decreased expression of genes *MGC57346*, *LRRC37A*, *CRHR1* were found in haplotype H1 in human brain tissue or whole blood (De Jong et al., 2012). Another limitation that prevents the generalization of the results of these studies is the fact that they focused only on genes within the inversion and no research was conducted on the effect of inversions on larger sequence distances, even though the inversion at 16p11 was demonstrably affected by genes not located directly in the inverted region, but with inversion neighbors only (Gonzalez et al., 2014). This indicates, that the influence of inversions can extend to greater distances than originally assumed. In addition, some of the observed differences in gene expression were found within only one population, as was the case with the finding of variation in *BLK* gene expression in European but not Asian and African populations (Salm et al., 2012). In other genes, for example, for the *PPP1R3B* gene on 8p23 (Salm et al., 2012), the association was clear in different populations, for example, increased expression of the Tau transcript due to an inversion affecting the *MAPT* gene in the H1 haplotype, which was found across the board independently of the studied population (Myers et al., 2007).

Most expression differences show that heterozygotes for the inversion have intermediate levels of expression compared to homozygotes, but this does not rule out the existence of exceptions, for example, the *NEIL2* gene on 8p23.1 contradicts this additive model (Bosch et al., 2009). Differences in expression between the standard and inverted allele in cases of polymorphic inversions at 8p23.1, 17q21.31 and 16p11.2 could be caused by the separation of the coding region of the gene from its regulatory elements, or due to the presence of functional single-nucleotide polymorphisms maintained by the inversion (De Jong et al., 2012), but it is clear from the above study results that the effect of inversions on gene expression cannot be clearly predicted and that it is a rather complex issue.

Some papers also describe differential expression in genes occurring in multiple-copy genes in the region of short repeats near the inversion breakpoints. Such genes include the brain-expressed *LRRC37A* gene and the blood-expressed *LRRC37A4* gene, which are located at inversion breakpoints on 17q21.31 (De Jong et al., 2012) and the *EIF3C*, *SULT1A1*, and *SULT1A4* genes on 16p11.2 (Gonzalez et al., 2014). Multiple copies of a gene complicate the analysis of the effect of inversion on expression, since changes in expression can be caused by inaccurate determination of the expression of individual genes, in other words, by inaccurate binding of the used probe. In the study dealing with the inversion at 17q21.31 and gene *LRRC37A*, the probe also bound to the genes *LRRC37A2*, *LRRC37A3* and *LRRC37A4* (De Jong et al., 2012). The different level of gene expression at 17q21.31 may have another explanation, namely that the two different haplotypes H1 and H2 differ in the number of gene copies located at the chromosome breakpoints and the expression changes may be caused by this different number (De Jong et al., 2012).

Some inversions that change gene expression are also associated with clinical manifestations, and the change in gene expression can therefore be a mechanism that causes a phenotypic change. A typical example is the change in BLK gene expression, which increases the risk of systemic lupus erythematosus and rheumatoid arthritis in a carrier of an 8p23.1 inversion (Salm et al., 2012). Overproduction of the Tau protein encoded by the *MAPT* gene, which occurs in the event of an inversion at 17q21.31 in H1, is in turn the cause of some neurodegenerative diseases (Webb et al., 2008). On the contrary, the inversion of 16p11 mediating a change in the expression of the *TUFM* gene, which encodes a mitochondrial protein regulator of energy balance and an inhibitor of type 1 interferon, has a protective function against the development of asthma and obesity (Gonzalez et al., 2014).

For a better understanding of the impact of inversions on the expression of selected genes, it is necessary to perform a genome-wide analysis of expression changes and at the same time a comprehensive screening of inversions in various types of tissues.

4 | POLYMORPHISMS OF INVERSIONS

The competition of two different chromosomal forms results either in their coexistence as stable polymorphisms or in the complete exclusion of one of them. The distribution and frequency of inversions in different populations are further influenced by various evolutionary forces such as genetic drift, selection or migration of individuals. Polymorphic inversions can originate from a single ancient ancestor or arise repeatedly. Repeated occurrence was confirmed for inv(2)(p11.2q13) (Fickelscher et al., 2007). On the contrary, a strong influence of the founder effect was found for 8p23 (Salm et al., 2012) and with the same applies for most polymorphic inversions (Thomas et al., 2008).

The size of human polymorphic inversions varies from a few tens to hundreds of kilobases, in most cases, to exceptionally large inversions, for example, an 800 kb inversion at 7p22, a 1.1 Mb inversion at 16p12, or to exceptionally larger ones up to 1.2 Mb inversion on chromosome 10 (Bansal et al., 2007). Differences in inversion frequencies may not only be between populations. Intercontinental frequency

differences have been observed for HsInv0068, which occurs in up to 92% of Americans, but is not present at all in the Asian population (Vicente-Salvador et al., 2017). The most studied human polymorphic inversions are inversions on 8p23.1 and 17q21.31, the pathogenic impact of which was described in more detail in section 4.2. of this work. The inverted H2 at inv17q21.31 is distributed in human population as follows: up to 25% in Europeans, 5% in Central Asians, and 0% in all other populations (Evans et al., 2004), and inv8p23.1 occurs at a frequency of 79% in the Algerian population, 63% in Italians and 25% in Manchus, while these data correlate with patterns of human migration from Africa (Salm et al., 2012).

4.1 | Inversions observable by cytogenetic methods

The use of cytogenetic methods for detecting inversions has a long history and apart from the discovery of inversions associated with clinical manifestations led to the discovery of inversions that have no effect on the phenotype of their carrier. Classical staining revealed inversions in heterochromatin regions on autosomes 1, 9, and 16, on the long arm of the Y gonosome and revealed euchromatin pericentric inversions on chromosomes 2, 3, 5, and 10 (Gardner & Sutherland, 1996). The frequent occurrence of the mentioned inversions can be explained by recombination between homologous regions in the breakpoint regions. The inversions then show heterogeneity in the breakpoints, as was demonstrated for inv(2)(p11q13) (Fickelscher et al., 2007). Other polymorphic inversions have been proven to have a common origin, for example, inv(10)(p11.2q21.2) probably spread from a single founder in a northern European population (Gilling et al., 2006) and although this 12 Mb large inversion occurs at a frequency of 0.11% in the Swedish population, it is not associated with any typical phenotypic expression (Entesarian et al., 2009).

Inversions are the most frequently detected aberration of the constitutional karyotype in cytogenetic laboratories (Schmidt et al., 2005). However, cytogenetic techniques have a limited discriminating ability, and only new methods were able to reveal the true variability of inversions in the human genome.

4.2 | Occurrence of inversions in the human genome according to the InvFEST database

Using modern techniques, it was found that the occurrence of inversions and structural variations in general is much more frequent than previously thought. One study revealed up to 1695 regions of structural variation (Kidd et al., 2008), another 217 inversions, most of which were newly discovered beyond the resolution of previously used methods (Tuzun et al., 2005). By comparing the human genome and the chimpanzee genome, three new polymorphic inversions were found (730 kb inv7p22, 13 kb inv7q11 and 11,065 bp inv16q24), which was up to 13% increased of the found inversions and this supports the hypothesis of high variability of human genome inversions (Feuk et al., 2005). A more recent work confirmed 22 polymorphic inversions out of 90 predicted with sizes ranging from 83 bp to 16.5 kb and allele frequencies of 0.01 to 0.80 (Vicente-Salvador et al., 2017). The first population study mapping the entire spectrum of structural variations of the diseased human genome was conducted in 2017 on 689 individuals suffering from autism or other developmental disorders. In this extensive study, more than 11,000 different structural variations were discovered, 16.8% of which were complex or balanced, of which up to 42.6% were polymorphic and 84.4% contained an inversion (Collins et al., 2017).

Inversions in the InvFEST database have different labels. A validated inversion has at least one experimentally confirmed breaking point, a predicted inversion has not been experimentally verified, but is predicted using modern methods. An unreliable inversion has not been confirmed by experiment either. Moreover, the predictions do not meet the reliability criteria, more than 90% of the predicted breaking points are located in the area of repetitive sequences, the false inversion was experimentally shown to be invalid or the assumptions that supported it were incorrect (Martinez-Fundichely et al., 2014).

Inversion in the human genome can be located in the intergenic, intronic, or gene region. An intergenic inversion does not damage the gene sequence, but can involve entire genes. An intronic inversion is entirely within an intronic region and a gene inversion disrupts the gene sequence either at one end of a gene or inverts one or more exons within a gene.

5 | CLINICAL EVALUATION AND REPORTING

Clinical evaluation and reporting of inversion found in the human genome follow standardized guidelines (e.g., Silva et al., 2019). Inversions normally considered benign are not clinically reported and are only registreted internally, for example, for research purposes. Other inversions are reported with a note that this information may be essential for the patient or relatives planning reproduction, to find relatives at risk, and so on. In the case of an affected patient, the parents are also examined to clarify the question of whether the inversion is inherited or created de novo. In the case of de novo inversions, the balance of the rearrangement is verified (e.g., using aCGH). If it is verified, the genes near the break area that could be interrupted or affected by the positional effect are examined and the break points are mapped.

6 | CONCLUSION

The presented evidence provides proof of the complexity of inversions in the human genome. Inversions play an important role not only in the current modern gene pool, but according to several sources they are an important evolutionary factor. Inversions play an important role in gnosomes' appearance. Some authors believe that they

also performed an important role in the speciation of chimpanzees and humans. However, it is necessary to approach this information with caution, since most of the works only dealt with the evolutionary effects of individual inversions. Nonetheless, some inversions can cooperate and influence each other in the course of evolution.

The effect of natural selection on inversions is yet to be determinated. Natural selection effect was investigated on the most researched polymorphic inversion 17q21.31. The analysis found a simultaneous negative and positive influence of this inversion on its carrier. Demographic reasons are another factor that complicates determining the effect of natural selection on inversions.

Rarely occurring inversions can disrupt the gene region (e.g., inversion on chromosome 5 and the *AP3B1* gene) or change gene regulation (inversion of the X chromosome and the *POU3F4* gene), which results in negative changes in the phenotype. A significant association was demonstrated in the case of the mutational influence of the Xq28 inversion on the development of hemophilia type A. A number of other inversions were in turn indicated as the cause of the development of tumors. Polymorphic inversions, for example, 17q21.31 or 8p23.1 have also been proven to be the cause of various pathogenesis.

The complexity of the study of inversions best documents their effect on the emergence of other structural rearrangements. Most often, the presence of selected inversions is a predisposition for the occurrence of a deletion, for example, in the case of Williams–Beuren syndrome. Other inversions, for example, inv8p23.1 increase the risk of complex genomic rearrangements. A change in gene expression can be caused by a simple disruption of the gene, as in the case of Hunter's syndrome and an inversion on the X chromosome. However, the inversion may not have any effect on gene expression, alternatively altered mRNA levels occur only in certain types of tissues.

The occurrence of polymorphic inversions in human populations was initially studied by classical cytogenetic methods and was mainly aimed at morbid phenotypes. The use of modern procedures enabled discovery of the real variability in the occurrence of inversions. Such findings constitute a possible basis for future studies. Many questions remain unanswered and call for further research. The goal of future research projects may be to ascertain the exact mechanism of the occurrence of inversions, to characterize the breakpoints, to study the mutual influence of different inversions or to create means for the study of inversions in whole-genome population studies.

AUTHOR CONTRIBUTIONS

RS designed the study. KK reviewed the literature. RS and KK analyzed the information obtained and wrote a manuscript.

ACKNOWLEDGMENT

Both authors declare no conflict of interest. The article was supported by Charles University (PROGRES Q43).

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Roman Solc https://orcid.org/0000-0003-2322-6689

REFERENCES

Aguado, C., Gayá-Vidal, M., Villatoro, S., Oliva, M., Izquierdo, D., Giner-Delgado, C., Montalvo, V., García-González, V., Martínez-Fundichely, A., Capilla, L., Ruiz-Herrera, A., Estivill, X., Puig, M., & Cáceres, M. (2014). Validation and genotyping of multiple human polymorphic inversions mediated by inverted repeats reveals a high degree of recurrence. *PLoS Genetics*, *10*, e1004208.

Anger, G. J., Crocker, S., McKenzie, K., Brown, K. K., Morton, C. C., Harrison, K., & MacKenzieet, J. J. (2014). X-linked deafness-2 (DFNX2) phenotype associated with a paracentric inversion upstream of POU3F4. *American Journal of Audiology*, *23*, 1–6.

Antonacci, F., Kidd, J. M., Marques-Bonet, T., Ventura, M., Siswara, P., Jiang, Z., & Eichler, E. E. (2009). Characterization of six human disease-associated inversion polymorphisms. *Human Molecular Genetics*, *18*, 2555–2566.

Antonarakis, S. E., Rossiter, J. P., Young, M., Horst, J., de Moerloose, P., Sommer, S. S., Ketterling, R. P., Kazazian, H. H., Jr., Négrier, C., Vinciguerra, C., Gitschier, J., Goossens, M., Girodon, E., Ghanem, N., Plassa, F., Lavergne, J. M., Vidaud, M., Costa, J. M., Laurian, Y., … Inaba, H. (1995). Factor VIII gene inversions in severe hemophilia A: Results of an international consortium study. *Blood*, *86*, 2206–2212.

Baker, M., Litvan, I., Houlden, H., Adamson, J., Dickson, D., Perez-Tur, J., Hardy, J., Lynch, T., Bigio, E., & Hutton, M. (1999). Association of an extended haplotype in the tau gene with progressive supranuclear palsy. *Human Molecular Genetics*, *8*, 711–715.

Bansal, V., Bashir, A., & Bafna, V. (2007). Evidence for large inversion polymorphisms in the human genome from HapMap data. *Genome Research*, *17*, 219–230.

Barton, N., & Bengtsson, B. O. (1986). The barrier to genetic exchange between hybridizing populations. *Heredity*, *56*, 357–376.

Bayés, M., Magano, L. F., Rivera, N., Flores, R., & Pérez Jurado, L. A. (2003). Mutational mechanisms of Williams–Beuren syndrome deletions. *American Journal of Human Genetics*, *73*, 131–151.

Beri, S., Bonaglia, M. C., & Giorda, R. (2013). Low-copy repeats at the human VIPR2 gene predispose to recurrent and nonrecurrent rearrangements. *European Journal of Human Genetics*, *21*, 757–761.

Blake, J., Riddell, A., Theiss, S., Gonzalez, A. P., Haase, B., Jauch, A., Janssen, J. W., Ibberson, D., Pavlinic, D., Moog, U., Benes, V., & Runz, H. (2014). Sequencing of a patient with balanced chromosome abnormalities and neurodevelopmental disease identifies disruption of multiple high risk loci by structural variation. *PLoS One*, *9*, e90894.

Bondeson, M. L., Dahl, N., Malmgren, H., Kleijer, W. J., Tönnesen, T., Carlberg, B. M., & Pettersson, U. (1995). Inversion of the IDS gene resulting from recombination with IDS-related sequences is a common cause of the Hunter syndrome. *Human Molecular Genetics*, *4*, 615–621.

Bosch, N., Morell, M., Ponsa, I., Mercader, J. M., Armengol, L., & Estivill, X. (2009). Nucleotide, cytogenetic and expression impact of the human chromosome 8p23.1 inversion polymorphism. *PLoS One*, *4*, e8269.

Brown, K. K., Reiss, J. A., Crow, K., Ferguson, H. L., Kelly, C., Fritzsch, B., & Morton, C. C. (2010). Deletion of an enhancer near DLX5 and DLX6 in a family with hearing loss, craniofacial defects, and an inv(7)(q21.3q35). *Human Genetics*, *127*, 19–31.

Buiting, K., Williams, C., & Horsthemke, B. (2016). Angelman syndrome—Insights into a rare neurogenetic disorder. *Nature Reviews Neurology*, *12*, 584–593.

Ceylan, G., Ceylan, C., & Yuce, H. A. (2008). A rare seen case with homozygosity for pericentric inversion of chromosome 9 and primary infertility. *The American Journal of Case Report*, *9*, 385–388.

Charlesworth, B., & Charlesworth, D. (2000). The degeneration of Y chromosomes. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *355*, 1563–1572.

Collins, R. L., Brand, H., Redin, C. E., Hanscom, C., Antolik, C., Stone, M. R., Glessner, J. T., Mason, T., Pregno, G., Dorrani, N., Mandrile, G., Giachino, D., Perrin, D., Walsh, C., Cipicchio, M., Costello, M., Stortchevoi, A., An, J. Y., Currall, B. B., … Talkowski, M. E. (2017). Defining the diverse spectrum of inversions, complex structural variation, and chromothripsis in the morbid human genome. *Genome Biology*, *18*, 36.

Dana, M., & Stoian, V. (2012). Association of Pericentric Inversion of chromosome 9 and infertility in Romanian population. *Maedica*, *7*, 25–29.

De Jong, S., Chepelev, I., Janson, E., Strengman, E., van den Berg, L. H., Veldink, J. H., & Ophoff, R. A. (2012). Common inversion polymorphism at 17q21.31 affects expression of multiple genes in tissuespecific manner. *BMC Genomics*, *13*, 458.

Deng, L., Zhang, Y., Kang, J., Liu, T., Zhao, H., Gao, Y., Li, C., Pan, H., Tang, X., Wang, D., Niu, T., Yang, H., & Zeng, C. (2008). An unusual haplotype structure on human chromosome 8p23 derived from the inversion polymorphism. *Human Mutation*, *29*, 1209–1216.

Drabova, J., Hancarova, M., Novotna, D., Havlovicova, M., Sedlacek, Z., Trkova, M., & Hejtmankova, M. (2014). A 15 mb large paracentric chromosome 21 inversion identified in Czech population through a pair of flanking duplications. *Molecular Cytogenetics*, *7*, 51.

Ebersberger, I., Metzler, D., Schwarz, C., & Paabo, S. (2002). Genomewide comparison of DNA sequences between humans and chimpanzees. *The American Journal of Genetics*, *70*, 1490–1497.

Entesarian, M., Carlsson, B., Mansouri, M. R., Stattin, E. L., Holmberg, E., Golovleva, I., Stefansson, H., Klar, J., & Dahl, N. (2009). A chromosome 10 variant with a 12 mb inversion [inv(10)(q11.22q21.1)] identical by descent and frequent in the Swedish population. *American Journal of Medical Genetics*, *149A*, 380–386.

Evans, W., Fung, H. C., Myers, A., Vrieze, F. W.-D., Singleton, A., Hardy, J., Steele, J., Eerola, J., Tienari, P., Pittman, A., & Silva, R. D. (2004). The tau H2 haplotype is almost exclusively Caucasian in origin. *Neuroscience Letters*, *369*, 183–185.

Faria, R., & Navarro, A. (2010). Chromosomal speciation revisited: Rearranging theory with pieces of evidence. *Trends in Ecology & Evolution*, *25*, 660–669.

Feder, J. L., & Nosil, P. (2009). Chromosomal inversions and species differences: When are genes affecting adaptive divergence and reproductive isolation expected to reside within inversions? *Evolution*, *63*, 3061–3075.

Feuk, L., MacDonald, J. R., Tang, T., Carson, A. R., Li, M., Rao, G., Khaja, R., & Scherer, S. W. (2005). Discovery of human inversion polymorphisms by comparative analysis of human and chimpanzee DNA sequence assemblies. *PLoS Genetics*, *1*, e56.

Fickelscher, I., Liehr, T., Watts, K., Bryant, V., Barber, J. C. K., Thomas, N. S., Heidemann, S., Siebert, R., Hertz, J. M., & Tümer, Z. (2007). The variant inv(2)(p11.2q13) is a genuinely recurrent rearrangement but displays some breakpoint heterogeneity. *American Journal of Medical Genetics*, *81*, 847–856.

Frohnauer, J., Caliebe, A., Gesk, S., Siebert, R., Partsch, C.-J., Pankau, R., & Jenderny, J. (2010). No significantly increased frequency of the inversion polymorphism at the WBS-critical region 7q11.23 in German parents of patients with Williams–Beuren syndrome as compared to a population control. *Molecular Cytogenetics*, *3*, 21.

Gardner, R. J. M., & Sutherland, G. T. (1996). *Chromosome abnormalities and genetic counselling* (2nd ed., pp. 115–182). Oxford University Press ISBN 0-19-510615-6.

Giglio, S., Broman, K. W., Matsumoto, N., Calvari, V., Gimelli, G., Neumann, T., Ohashi, H., Voullaire, L., Larizza, D., Giorda, R., Weber, J. L., Ledbetter, D. H., & Zuffardi, O. (2001). Olfactory receptor-gene clusters, genomic-inversion polymorphisms, and common chromosome rearrangements. *The American Journal of Human Genetics*, *68*, 874–883.

Giglio, S., Calvari, V., Gregato, G., Zuffardi, O., Gimelli, G., Camanini, S., Giorda, R., Ragusa, A., Guerneri, S., Selicorni, A., Stumm, M., Tonnies, H., Ventura, M., Rocchi, M., Zollino, M., Neri, G., Barber, J., & Wieczorek, D. (2002). Heterozygous submicroscopic inversions involving olfactory receptor-gene clusters mediate the recurrent t(4; 8)(p16; p23) translocation. *American Journal of Human Genetics*, *71*, 276–285.

Gilling, M., Dullinger, J. S., Gesk, S., Metzke-Heidemann, S., Siebert, R., Meyer, T., Brondum-Nielsen, K., Tommerup, N., Ropers, H.-H., Tümer, Z., Kalscheuer, V. M., & Thomas, N. S. (2006). Breakpoint cloning and haplotype analysis indicate a single origin of the common inv(10)(p11.2q21.2) among Northern Europeans. *American Journal of Human Genetics*, *78*, 878–883.

Gimelli, G., Pujana, M. A., Patricelli, M. G., Russo, S., Giardino, D., Larizza, L., Cheung, J., Armengol, L., Schinzel, A., Estivill, X., & Zuffardi, O. (2003). Genomic inversions of human chromosome 15q11-q13 in mothers of Angelman syndrome patients with class II (BP2/3) deletions. *Human Molecular Genetics*, *12*, 849–858.

Gonzalez, J. R., Cáceres, A., Esko, T., Cuscó, I., Puig, M., Esnaola, M., Reina, J., Siroux, V., Bouzigon, E., Nadif, R., Reinmaa, E., Milani, L., Bustamante, M., Jarvis, D., Antó, J. M., Sunyer, J., Demenais, F., Kogevinas, M., Metspalu, A., … Pérez-Jurado, L. A. (2014). A common 16p11.2 inversion underlies the joint susceptibility to asthma and obesity. *The American Journal of Human Genetics*, *94*, 361–372.

Gruber, T. A., Larson Gedman, A., Zhang, J., Koss, C. S., Marada, S., Ta, H. Q., Chen, S.-C., Su, X., Ogden, S. K., Dang, J., Wu, G., Gupta, V., Andersson, A. K., Pounds, S., Shi, L., Easton, J., Barbato, M. I., Mulder, H. L., Manne, J., … Downing, J. R. (2012). An inv(16)(p13.3q24.3)-encoded CBFA2T3-GLIS2 fusion protein defines an aggressive subtype of pediatric acute megakaryoblastic leukemia. *Cancer Cell*, *22*, 683–697.

Guo, W. J., Callif-Daley, F., Zapata, M. C., & Miller, M. E. (1995). Clinical and cytogenetic findings in seven cases of inverted duplication of 8p with evidence of a telomeric deletion using fluorescence in situ hybridization. *American Journal of Medical Genetics*, *58*, 230–236.

Hey, J. (2003). Speciation and inversions: Chimps and humans. *BioEssays*, *25*, 825–828.

Hobart, H. H., Morris, C. A., Mervis, C. B., Kistler, D. J., Pani, A. M., Rios, C. M., Kimberley, K. W., Bray-Ward, P., & Gregg, R. G. (2010). Inversion of the Williams syndrome region is a common polymorphism found more frequently in parents of children with Williams syndrome. *American Journal of Medical Geneics Part C—Seminars in Medical Genetics*, *154C*, 220–228.

Hollox, E. J., Barber, J. C., Brookes, A. J., & Armour, J. A. (2008). Defensins and the dynamic genome: What we can learn from structural variation at human chromosome band 8p23.1. *Genome Research*, *18*, 1686–1697.

Jobling, M. A., Williams, G., Schiebel, K., Pandya, A., McElreavey, K., Salas, L., Rapppold, G. A., Affara, N. A., & Tyler-Smith, C. (1998). A selective difference between human Y-chromosomal DNA haplotypes. *Current Biology*, *8*, 1391–1394.

Jones, M. L., Murden, S. L., Brooks, C., Maloney, V., Manning, R. A., Gilmour, K. C., Bharadwaj, V., de la Fuente, J., Chakravorty, S., & Mumford, A. D. (2013). Disruption of AP3B1 by a chromosome 5 inversion: A new disease mechanism in Hermansky–Pudlak syndrome type 2. *BMC Medical Genetics*, *14*, 42.

Kidd, J. M., Cooper, G. M., Donahue, W. F., Hayden, H. S., Sampas, N., Graves, T., Hansen, N., Teague, B., Alkan, C., Antonacci, F., Haugen, E., Zerr, T., Yamada, N. A., Tsang, P., Newman, T. L., Tüzün, E., Cheng, Z., Ebling, H. M., Tusneem, N., … Eichler, E. E. (2008). Mapping and sequencing of structural variation from eight human genomes. *Nature*, *453*, 56–64.

Kirkpatrick, M. (2010). How and why chromosome inversions evolve. *PLoS Biology*, *8*, 1–5.

Koolen, D. A., Vissers, L. E. L. M., Pfundt, R., de Leeuw, N., Knight, S. J., Regan, R., Kooy, R. F., Reyniers, E., Romano, C., Fichera, M., Schinzel, A., Baumer, A., Anderlid, B. M., Schoumans, J., Knoers, N. V., van Kessel, A. G., Sistermans, E. A., Veltman, J. A., Brunner, H. G., & de

Vries, B. B. (2006). A new chromosome 17q21.31 microdeletion syndrome associated with a common inversion polymorphism. *Nature Genetics*, *38*, 999–1001.

Korbel, J. O., Urban, A. E., Affourtit, J. P., Godwin, B., Grubert, F., Simons, J. F., Kim, P. M., Palejev, D., Carriero, N. J., Lei, D., Taillon, B. E., Zhoutao, C., Tanzer, A., Saunders, A. C. E., Chi, J., Yang, F., Carter, N. P., Hurles, M. E., Weissman, S. M., & Harkins, T. T. (2007). Paired-end mapping reveals extensive structural variation in the human genome. *Science*, *318*, 420–426.

Lahn, B. T., & Page, D. C. (1999). Four evolutionary strata on the human X chromosome. *Science*, *286*, 964–967.

Lettice, L. A., Daniels, S., Sweeney, E., Venkataraman, S., Devenney, P. S., Gautier, P., Morrison, H., Fantes, J., Hill, R. E., & FitzPatrick, D. R. (2011). Enhancer-adoption as a mechanism of human developmental disease. *Human Mutation*, *32*, 1492–1499.

Ma, J., Xiong, M., You, M., & Lozano, G. (2014). Genome-wide association tests of inversions with application to psoriasis. *Human Genetics*, *133*, 967–974.

Marqués-Bonet, T., Cáceres, M., Bertranpetit, J., Preuss, T. M., Thomas, J. W., & Navarro, A. (2004). Chromosomal rearrangements and the genomic distribution of gene-expression divergence in humans and chimpanzees. *Trends in Genetics*, *20*, 524–529.

Marqués-Bonet, T., & Navarro, A. (2005). Chromosomal rearrangements are associated to higher rates of molecular evolution in mammals. *Gene*, *353*, 147–154.

Marqués-Bonet, T., Sánchez-Ruiz, J., Armengol, L., Khaja, R., Bertranpetit, J., Lopez-Bigas, N., Rocchi, M., Gazave, E., & Navarro, A. (2007). On the association between chromosomal rearrangements and genic evolution in humans and chimpanzees. *Genome Biology*, *8*, R230.

Martinez-Fundichely, A., Casillas, S., Egea, R., Ràmia, M., Barbadilla, A., Pantano, L., Puig, M., & Cáceres, M. (2014). InvFEST, a database integrating information of polymorphic inversions in the human genome. *Nucleic Acids Research*, *42*, D1027–D1032.

Myers, A. J., Gibbs, J. R., Webster, J. A., Rohrer, K., Zhao, A., Marlowe, L., Kaleem, M., Leung, D., Bryden, L., Nath, P., Zismann, V. L., Joshipura, K., Huentelman, M. J., Hu-Lince, D., Coon, K. D., Craig, D. W., Pearson, J. V., Holmans, P., Heward, C. B., … Hardy, J. (2007). A survey of genetic human cortical gene expression. *Nature Genetics*, *39*, 1494–1499.

Myers, A. J., Kaleem, M., Marlowe, L., Fung, H. C., Duckworth, J., Leung, D., Hardy, J., Pittman, A. M., Lees, A. J., de Silva, R., Gibson, A., & Morris, C. M. (2005). The H1c haplotype at the MAPT locus is associated with Alzheimer's disease. *Human Molecular Genetics*, *14*, 2399–2404.

Namjou, B., Ni, Y., Harley, I. T. W., Chepelev, I., Cobb, B., Kottyan, L. C., Gaffney, P. M., Guthridge, J. M., Kaufman, K., & Harley, J. B. (2014). The effect of inversion at 8p23 on BLK association with lupus in Caucasian population. *PLoS One*, *9*, e115614.

Navarro, A., & Barton, N. H. (2003a). Accumulating postzygotic isolation genes in parapatry: A new twist on chromosomal speciation. *Evolution*, *57*, 447–459.

Navarro, A., & Barton, N. H. (2003b). Chromosomal speciation and molecular divergence—Accelerated evolution in rearranged chromosomes. *Science*, *300*, 321–324.

Noor, M. A., & Bennett, S. M. (2009). Islands of speciation or mirages in the desert? Examining the role of restricted recombination in maintaining species. *Heredity*, *103*, 439–444.

Noor, M. A. F., Grams, K. L., Bertucci, L. A., & Reiland, J. (2001). Chromosomal inversions and the reproductive isolation of species. *Proceedings of the National Academy of Sciences of the United States of America*, *98*, 12084–12088.

Osborne, L. R., Li, M., Pober, B., Chitayat, D., Bodurtha, J., Mandel, A., Costa, T., Grebe, T., Cox, S., Tsui, L. C., & Scherer, S. W. (2001). A 1.5 million-base pair inversion polymorphism in families with Williams–Beuren syndrome. *Nature Genetics*, *29*, 321–325.

Pang, A. W. C., Migita, O., Macdonald, J. R., Feuk, L., & Scherer, S. W. (2013). Mechanisms of formation of structural variation in a fully sequenced human genome. *Human Mutation*, *34*, 345–354.

Pittman, A. M., Fung, H. C., & de Silva, R. (2006). Untangling the tau gene association with neurodegenerative disorders. *Human Molecular Genetics*, *15*, R188–R195.

Puig, M., Casillas, S., Villatoro, S., & Cáceres, M. (2015). Human inversions and their functional consequences. *Briefings in Functional Genomics*, *14*, 369–379.

Rhees, J., Arnold, M., & Boland, C. R. (2014). Inversion of exons 1–7 of the MSH2 gene is a frequent cause of unexplained Lynch syndrome in one local population. *Familial Cancer*, *13*, 219–225.

Rice, W. R. (1996). Evolution of the Y sex chromosome in animals. *Bioscience*, *46*, 331–343.

Rieseberg, L. H. (2001). Chromosomal rearrangements and speciation. *Trends in Ecology & Evolution*, *16*, 351–358.

Salm, M. P. A., Horswell, S. D., Hutchison, C. E., Speedy, H. E., Yang, X., Liang, L., Schadt, E. E., Cookson, W. O., Wierzbicki, A. S., Naoumova, R. P., & Shoulders, C. C. (2012). The origin, global distribution, and functional impact of the human 8p23 inversion polymorphism. *Genome Research*, *22*, 1144–1153.

Schmidt, S., Claussen, U., Liehr, T., & Weise, A. (2005). Evolution versus constitution: Differences in chromosomal inversion. *Human Genetics*, *117*, 213–219.

Silva, M., de Leeuw, N., Mann, K., Schuring-Blom, H., Morgan, S., Giardino, D., Rack, K., & Hastings, R. (2019). European guidelines for constitutional cytogenomic analysis. *European Journal of Human Genetics*, *27*, 1–16.

Skipper, L., Wilkes, K., Toft, M., Baker, M., Lincoln, S., Hulihan, M., Ross, O. A., Hutton, M., Aasly, J., & Farrer, M. (2004). Linkage disequilibrium and association of MAPT H1 in Parkinson disease. *American Journal of Human Genetics*, *75*, 669–677.

Small, K., Iber, J., & Warren, S. T. (1997). Emerin deletion reveals a common X-chromosome inversion mediated by inverted repeats. *Nature Genetics*, *16*, 96–99.

Soda, M., Choi, Y. L., Enomoto, M., Takada, S., Yamashita, Y., Ishikawa, S., Fujiwara, S., Watanabe, H., Kurashina, K., Hatanaka, H., Bando, M., Ohno, S., Ishikawa, Y., Aburatani, H., Niki, T., Sohara, Y., Sugiyama, Y., & Mano, H. (2007). Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature*, *448*, 561–566.

Stefansson, H., Helgason, A., Thorleifsson, G., Steinthorsdottir, V., Masson, G., Barnard, J., Baker, A., Jonasdottir, A., Ingason, A., Gudnadottir, V. G., Desnica, N., Hicks, A., Gylfason, A., Gudbjartsson, D. F., Jonsdottir, G. M., Sainz, J., Agnarsson, K., Birgisdottir, B., Ghosh, S., … Stefansson, K. (2005). A common inversion under selection in Europeans. *Nature Genetics*, *37*, 129–137.

Steinberg, K. M., Antonacci, F., Sudmant, P. H., Kidd, J. M., Campbell, C. D., Vives, L., Malig, M., Scheinfeldt, L., Beggs, W., Ibrahim, M., Lema, G., Nyambo, T. B., Omar, S. A., Bodo, J. M., Froment, A., Donnelly, M. P., Kidd, K. K., Tishkoff, S. A., & Eichler, E. E. (2012). Structural diversity and African origin of the 17q21.31 inversion polymorphism. *Nature Genetics*, *44*, 872–880.

Sturtevant, A. H. (1921). A case of rearrangement of genes in Drosophila. *Proceedings of the National Academy of Sciences of the United States of America*, *7*, 235–237.

Szamalek, J. M., Cooper, D. N., Hoegel, J., Hameister, H., & Kehrer-Sawatzki, H. (2007). Chromosomal speciation of humans and chimpanzees revisited: Studies of DNA divergence within inverted regions. *Cytogenetic and Genome Research*, *116*, 53–60.

Takahata, N., & Satta, Y. (1997). Evolution of the primate lineage leading to modern humans: Phylogenetic and demographic inferences from DNA sequences. *Proceedings of the National Academy of Sciences of the United States of America*, *94*, 4811–4815.

Tayebi, N., & Khodaei, H. (2011). A rare case of pericentric inversion, Inv (21) (p12; q22) in repeated pregnancy loss: A case report. *Oman Medical Journal*, *26*, 441–443.

Thomas, N. S., Bryant, V., Maloney, V., Cockwell, A. E., & Jacobs, P. A. (2008). Investigation of the origins of human autosomal inversions. *Human Genetics*, *123*, 607–616.

Turner, D. J., Shendure, J., Porreca, G., Church, G., Green, P., Tyler-Smith, C., & Hurles, M. E. (2006). Assaying chromosomal inversions by single-molecule haplotyping. *Nature Methods*, *2006*(3), 439–445.

Tuzun, E., Sharp, A. J., Bailey, J. A., Kaul, R., Morrison, V. A., Pertz, L. M., Haugen, E., Hayden, H., Albertson, D., Pinkel, D., Olson, M. V., & Eichler, E. E. (2005). Fine-scale structural variation of the human genome. *Nature Genetics*, *37*, 727–732.

Utami, K. H., Hillmer, A. M., Aksoy, I., Chew, E. G., Teo, A. S., Zhang, Z., Lee, C. W., Chen, P. J., Seng, C. C., Ariyaratne, P. N., Rouam, S. L., Soo, L. S., Yousoof, S., Prokudin, I., Peters, G., Collins, F., Wilson, M., Kakakios, A., Haddad, G., … Cacheux, V. (2014). Detection of chromosomal breakpoints in patients with developmental delay and speech disorders. *PLoS One*, *9*, e90852.

Verpillat, P., Camuzat, A., Hannequin, D., Thomas-Anterion, C., Puel, M., Belliard, S., Dubois, B., Didic, M., Michel, B. F., Lacomblez, L., Moreaud, O., Sellal, F., Golfier, V., Campion, D., Clerget-Darpoux, F., & Brice, A. (2002). Association between the extended tau haplotype and frontotemporal dementia. *Archives of Neurology*, *59*, 935–939.

Vicente-Salvador, D., Puig, M., Gayá-Vidal, M., Pacheco, S., Giner-Delgado, C., Noguera, I., Izquierdo, D., Martínez-Fundichely, A., Ruiz-Herrera, A., Aguado, C., Lucas-Lledó, J. I., Cáceres, M., & Estivill, X. (2017). Detailed analysis of inversions predicted between two human genomes: Errors, real polymorphisms, and their origin and population distribution. *Human Molecular Genetics*, *26*, 567–581.

Visser, R., Shimokawa, O., Harada, N., Kinoshita, A., Niikawa, N., Ohta, T., & Matsumoto, N. (2005). Identification of a 3.0-kb major recombination hotspot in patients with Sotos syndrome who carry a common 1.9-Mb microdeletion. *American Journal of Human Genetics*, *76*, 52–67.

Vogel, M. J., Pagie, L., Talhout, W., Nieuwland, M., Kerkhoven, R. M., & van Steensel, B. (2009). High-resolution mapping of heterochromatin redistribution in a Drosophila position-effect variegation model. *Epigenetics & Chromatin*, *2*, 1.

Webb, A., Miller, B., Bonasera, S., Boxer, A., Karydas, A., & Wilhelmsen, K. C. (2008). Role of the tau gene region chromosome inversion in progressive supranuclear palsy, corticobasal degeneration, and related disorders. *Archives of Neurology*, *65*, 1473–1478.

Yi, S., Ellsworth, D. L., & Li, W. H. (2002). Slow molecular clocks in Old World monkeys, apes, and humans. *Molecular Biology and Evolution*, *19*, 2191–2198.

Yunis, J. J., & Prakash, O. (1982). The origin of man: A pictorial legacy. *Science*, *215*, 1525–1530.

Zhang, J., Wang, X., & Podlaha, O. (2004). Testing the chromosomal speciation hypothesis for humans and chimpanzees. *Genome Research*, *14*, 845–851.

Zody, M. C., Jiang, Z., Fung, H. C., Antonacci, F., Hillier, L. W., Cardone, M. F., Graves, T. A., Kidd, J. M., Cheng, Z., Abouelleil, A., Chen, L., Wallis, J., Glasscock, J., Wilson, R. K., Reily, A. D., Duckworth, J., Ventura, M., Hardy, J., Warren, W. C., & Eichler, E. E. (2008). Evolutionary toggling of the MAPT 17q21.31 inversion region. *Nature Genetics*, *40*, 1076–1083.

How to cite this article: Kosuthova, K., & Solc, R. (2023). Inversions on human chromosomes. *American Journal of Medical Genetics Part A*, *191*A:672–683. https://doi.org/10.1002/ajmg.a.63063