Neurochirurgie 65 (2019) 196–201

Disponible en ligne sur ScienceDirect www.sciencedirect.com

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Craniosynostosis: State of the Art 2019

Genetic bases of craniosynostoses: An update

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ARTICLE INFO

Article history:
Received 28 June 2019
Received in revised form
27 September 2019
Accepted 2 October 2019
Available online 9 October 2019

Keywords:
Craniosynostosis
Genes
Syndromes

ABSTRACT

Craniosynostosis (CS) is defined as the premature fusion of cranial sutures, leading to an abnormal skull shape. The overall incidence is between 1: 2,000 and 1: 3,000 live births. Genetic causes are found in 20% of cases. CS can be isolated (non-syndromic CS/NSCS) or they can be part of multiple congenital abnormalities syndromes (syndromic CS/SCS). A few SCS, such as Crouzon, Pfeiffer, Apert and Saethre-Chotzen syndromes, are very well known and their molecular bases have been clarified in the 90s and early 2000s, thus showing the major role of the FGF receptors and *TWIST* signaling pathways in the etiology of these conditions. The recent availability of powerful molecular tools for genetic diagnosis, such as whole exome or whole genome sequencing, has led to the characterization of the molecular bases of an increasing number of CS, thus emphasizing the significant genetic heterogeneity of these conditions, and blurring the limit between SCS and NSCS. The genetic characterization of patients affected by CS leads to appropriate genetic counseling and provides relevant information concerning comorbidity and prognosis. Nevertheless, this can also lead to the detection of susceptibility factors with low penetrance whose interpretation in genetic counseling is difficult and it raises the question of its cost-effectiveness for health systems. These aspects suggest the need of a patient-tailored clear rationale for performing genetic tests. In this study, we reviewed the main molecular etiologies reported in the last 15 years of either SCS or NSCS, and we propose a systematic multidisciplinary approach as well as a diagnostic flowchart for the genetic evaluation of these patients.

1. Introduction

Craniosynostosis (CS) is defined as the premature fusion of one or more cranial sutures leading to an abnormal skull shape.

During infancy and childhood, the calvaria expands to accommodate the growing brain. This growth occurs predominantly at the junctions of undifferentiated mesenchyme, named sutures, which lie between cranial bones. The paired frontal and parietal bones are separated in the midline by the metopic and sagittal sutures, respectively; coronal sutures separate frontal and parietal bones; parietal bones are separated from the occipital bone by lambdoid sutures.

Following Virchow's law [1], a premature fusion of a cranial suture is associated with restricted bone perpendicular growth and compensatory parallel growth resulting, ultimately, in an abnormal skull shape.

Among rare diseases (defined as affecting less than 1 in 2,000 live births), CS are relatively common, their incidence being estimated between 1: 2,000; 1: 3,000 [2].

Differential diagnosis includes positional plagiocephaly which is characterized by a deformation of skull bones in the absence of abnormal fusion of the sutures [1].

CS are heterogeneous conditions from a clinical and etiological point of view and their classification, diagnosis and treatment represent a challenge for physicians.

Various classifications have been proposed, based on different approaches. Firstly, CS can be classified on the basis of the resulting head-shape (e.g.: scaphocephaly for the premature fusion of sagittal suture; brachycephaly, when coronal sutures are involved; trigonocephaly when metopic suture is involved; plagiocephaly, when lambdoid suture is involved; oxycephaly/turricephaly when

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https://doi.org/10.1016/j.neuchi.2019.10.003
0028-3770/

multiple sutures such as sagittal, coronal and lambdoid, are involved, sometimes leading to a cloverleaf appearance) as well as the affected cranial suture (sagittal in about 50% of cases, metopic in about 25%, coronal in about 20%, and lambdoid in < 5% of cases) [3–5].

Furthermore, they can be classified on the basis of the possible association with other malformations, syndromic forms (SCS) being rarer (25–30%) than non-syndromic CS (NSCS) (70–75%) [6]. In this respect, a few papers suggest a progressively increasing incidence of NSCS, which currently remains unexplained [3,7,8]. It is well-known that developmental delay can be observed in SCS, but increasing evidence suggests that neurodevelopmental problems can be observed also in a subset of patients presenting "NSCS", regardless the type of surgery performed, thus suggesting that a clear difference between SCS and NSCS is not always possible [6].

A further classification is based on the etiology: primary CS are due to intrinsic genetic causes acting alone or in combination with environmental factors, while secondary CS are caused by systemic disorders affecting also the developing suture. Systemic diseases possibly associated with CS include skeletal dysplasias such as acrodysostosis [OMIM: # 101800], hypophosphatasia [OMIM: # 146300], hypophosphatemic rickets [OMIM: # 307800]; inherited metabolic diseases with skeletal involvement such as mucopolysaccharidoses; ciliopathies, such as Sensenbrenner syndrome [OMIM: # 218330].

In this respect, CS have been included in the last nosology of skeletal disorders (group 33), a classification based on a combination of radiological and molecular criteria [9].

Various etiologies have been reported for CS. Prenatal exposure to some teratogens, such as valproic acid (affecting mainly metopic suture), retinoic acid, hydantoin, and fluconazole, can cause CS [10]. A genetic cause is found overall in 20% of cases and significant heterogeneity is observed: on one hand, one clinical picture can be caused by different genetic abnormalities and, on the other hand, one gene can cause different clinical pictures, thus making differential diagnosis difficult.

Currently chromosomal imbalance represents about 20% of the observed genetic causes. The main chromosomal abnormalities causing CS have already been extensively reviewed [11]. A chromosomal imbalance should be considered in patients presenting with SCS, especially involving metopic or sagittal sutures, and developmental delay.

The clinical phenotypes and genetic bases of various Mendelian SCS are very well known. Mutations in the FGF/TWIST pathways cause the majority of these conditions, with *FGFR1* causing Pfeiffer syndrome type 1; *FGFR2* causing Crouzon, Apert, Pfeiffer (type 2 and 3), autosomal dominant Antley-Bixler, and Beare-Stevenson cutis gyrata syndromes; *FGFR3* causing Muenke and Crouzon with acanthosis nigricans syndromes; *TWIST1* causing Saethre-Chotzen syndrome/Craniosynostosis type 1 [12] [OMIM: # 101400].

Mutations in these genes are currently found in three-quarters of all genetically diagnosed cases [6]. Concerning the remaining quarter, in the last 15 years, the availability of next generation sequencing has led to the identification of the genetic bases of an increasing number of SCS as well as NSCS and a better characterization of the associated clinical phenotypes [6,13] (Fig. 1). This study aims to review the main molecular etiologies reported in the last 15 years of either SCS or NSCS.

2. *MSX2* (MSX homeobox 2) [OMIM: # 12301] [14]

This homeobox gene codes for a transcription factor with a major role in survival and apoptosis of neural crest-derived cells required for craniofacial morphogenesis.

MSX2 mutations cause Craniosynostosis 2/Boston type, an autosomal dominant condition characterized by variable intra-familial expressivity. The main clinical features include frontal bossing, turricephaly, trigonocephaly, brachycephaly and cloverleaf skull in the most severely affected patients. The craniosynostosis is generally "non-syndromic"; brachydactyly can be observed and intelligence is usually normal.

3. *ERF* (ETS2 repressor factor) [OMIM: # 611888] [15,16]

ETS2 is a transcription factor and proto-oncogene involved in development, apoptosis, and telomerase regulation. *ERF encodes* for an inhibitory ETS transcription factor which directly binds to ERK1/2.

Mutations in *ERF* where initially found in patients with a Crouzon-like appearance, showing midface-hypoplasia and eye proptosis (CS 4/Crouzon-like CS, OMIM: # 611888) with possible multisuture involvement. Associated features include relatively frequent learning difficulties and behavioral problems as well as non-specific brain abnormalities, such as Chiari type 1 and dilated ventricles. Subsequently, it has been shown that mutations in *ERF* can cause also NSCS. CS4 is inherited with an autosomal dominant pattern.

4. *TCF12* (transcription factor 12) [OMIM: # 600480] [17,18]

TCF12 is a member of the helix-loop-helix family; it forms heterodimers with TWIST1 and acts as a SMAD cofactor, thus playing a major role in coronal suture development [6]. Mutations in *TCF12* cause Craniosynostosis 3 (OMIM: # 615314), an autosomal dominant disorder. Skull involvement can be isolated (NSCS) or associated with mild dysmorphic features such as eyelids ptosis, minor ear anomalies (prominent ear crus), malocclusion, brachydactyly, toe syndactyly, clinodactyly, camptodactyly) and the possible presence of developmental delay and/or learning difficulties. Hence, this condition has to be considered particularly in the differential diagnosis of either Saethre–Chotzen [18] or Muenke syndromes. Incomplete penetrance (up to 50%) has been reported [17].

5. *SMAD6* (SMAD family member 6) [OMIM: # 602931] [19]

SMAD proteins are signal transducers and transcriptional modulators that mediate multiple signaling pathways. SMAD6 acts in the negative regulation of the BMP and TGF-beta/activin-signaling pathways. Mutations in *SMAD6* have been reported in CS (SCS and NSCS) characterized by the involvement of metopic and sagittal sutures (NSCS) and the possible presence of developmental delay (SCS), with a low penetrance (Craniosynostosis 7).

6. *ZIC1* (Zic family member 1) [OMIM: # 600470] [20]

This gene encodes a member of the ZIC family, which acts as a transcriptional activator playing a significant role in the early stages of central nervous system development, dorsal spinal cord development and maturation of the cerebellum.

Mutations in *ZIC1* gene cause Craniosynostosis 6. This condition is characterized by coronal CS (mostly bilateral) which can be isolated (NSCS) or associated with dysmorphic features such as brachycephaly, eyelid ptosis, and strabismus. Skeletal involvement includes scoliosis, delayed closure of anterior fontanelle, and skull defects. Non-specific brain anomalies have been reported in some patients including dilated ventricles, corpus callosum abnormalities, pons hypoplasia, and cerebellar anomalies (such as atrophy and Dandy–Walker malformation). A variable neurological

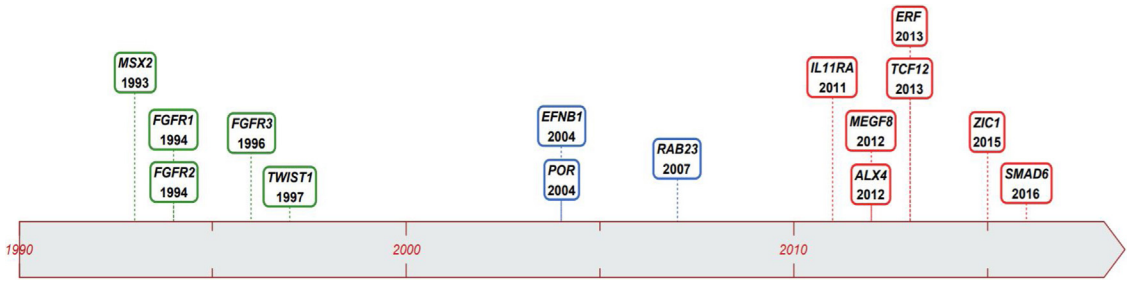

Fig. 1. Main craniosynostosis causing genes discovered in the last 25 years.

involvement is frequently associated, ranging from absence of speech and autistic spectrum disorders to mild learning difficulties.

7. *IL11RA* (interleukin 11 receptor subunit alpha) [OMIM: # 60039] [21,22]

This gene encodes the IL-11 receptor, which is a member of the hematopoietic cytokine receptor family implicated in a protein complex which is essential for the normal development of craniofacial bones and teeth. *IL11RA* mutations cause Craniosynostosis with dental anomalies/Kreiborg-Pakistani syndrome characterized by variable CS (mainly metopic and/or coronal, but also sagittal and/or lambdoid), midface hypoplasia, eye proptosis, prognathism; dental anomalies (ectopic or supernumerary teeth, delayed eruption) have been reported but they are not invariably present. Some patients have a facial appearance reminiscent of Crouzon syndrome. A few patients have been described with minor limb anomalies (clinodactyly, cutaneous syndactyly). The inheritance pattern is autosomal recessive.

8. *ALX4* (ALX homeobox 4) [OMIM: # 605420] [23]

This gene encodes a paired-like homeodomain transcription factor expressed in the mesenchyme of developing bones, limbs, hair, teeth, and mammary tissue. This factor plays a crucial role in craniofacial, skin and hair follicle development.

A cohort study of 203 patients of Yagnik et al. in 2012 [23] identified 2 missense gain-of-function mutations in *ALX4* (Craniosynostosis 5). These variants were also present in an unaffected parent of each family, thus suggesting incomplete penetrance (Table 1). *ALX4* variants are considered to be susceptibility factors to NSC.

9. *EFNB1* (ephrin-B1) [OMIM: # 300035] [24,25]

The ephrin-B1 protein is characterized by various domains: EPH, interacting with Eph receptor tyrosine kinases; a single pass transmembrane (TM) sequence; and an intracellular PDZ (protein interaction) domain, involved in cell recognition.

Mutations in *EFNB1* cause Craniofrontonasal syndrome, characterized by an X-linked inheritance pattern, with a high penetrance. Heterozygous females are generally more severely affected than hemizygous males; this apparent paradox is due to a cellular interference mechanism due to the random X-inactivation in females. The prevalence of this condition has been estimated to be < 1/100 000. Females have severe hypertelorism, unicoronal or bicoronal synostosis, bifid nasal tip, characteristic longitudinal nail splits and, at lower frequency, sloping shoulders, asymmetric nipples, bifid digits and agenesis of the corpus callosum.

10. *EFNA4* (ephrin-A4) [OMIM: # 601380] [26,27]

This gene encodes another member of the ephrin family. Like EFNB1, EFNA4 is a receptor protein-tyrosine kinase which is implicated in the development especially of the central nervous system. Unlike EFNB1, it is anchored to the cell membrane by a glycosylphosphatidylinositol linkage.

Merrill et al. in 2006 [26] identified by WES heterozygous variants in the *EFNA4* gene in 3 patients out of 81 presenting with unicoronal NSCS; penetrance was incomplete. In 2018, Lee et al. [27] had also found a pathogenic variant in this gene in one patient with coronal NSCS.

11. *RAB23* (member RAS oncogene family) [OMIM: # 606144] [28]

Rab proteins are small GTPases belonging to the Ras superfamily involved in the regulation of intracellular membrane trafficking. The *RAB23* gene encodes an essential negative regulator of the Sonic hedgehog signaling pathway.

Mutations in this gene cause type 1 Carpenter syndrome, an autosomal recessive SCS. Clinical phenotype includes CS with multisuture involvement (trigonocephaly, scaphocephaly), limb anomalies (brachydactyly, preaxial polydactyly, syndactyly of hands and foot, coxa valga, coxa vara, genu valgum), obesity, dental abnormalities such as hypodontia, precocious puberty, congenital heart defects, hydronephrosis and the possible presence of developmental delay of variable severity.

12. *MEGF8* (multiple EGF like domain 8) [OMIM: # 604267] [29]

The protein encoded by this gene is a single-pass type I membrane protein of unknown function that contains several EGF-like domains, Kelch repeats, and PSI domains. *MEGF8* mutations cause autosomal recessive type 2 Carpenter syndrome.

Clinical phenotype includes metopic CS (usually less severe than type 1 Carpenter syndrome), dysmorphic facial features (a paradoxical hypertelorism, a large nose, up-slanted palpebral fissures, epicanthal folds, ear anomalies); limbs abnormalities (brachydactylies, preaxial polydactyly, finger and toe syndactyly), lateralization defects, congenital heart disease, cryptorchidism, umbilical hernia, obesity and the possible presence of variable neurodevelopmental delay [29]. Inheritance pattern is autosomal recessive.

13. Discussion

The availability of powerful molecular tools for genetic diagnosis, such as whole exome or whole genome sequencing, has led in the last 15 years to the characterization of the molecular bases of an increasing number of CS [30], thus emphasizing the

Table 1
Main features reported in association with genetic anomalies of craniosynostosis-causing genes.

Gene	*MSX2*	*ERF*	*TCF12*	*SMAD6*	*ZIC1*	*IL11RA*	*ALX4*	*EFNB1*	*EFNA4*	*RAB23*	*MEGF8*
Location	5q35.2	19q13.2	15q21.3	15q22.31	3q24	9p13.3	11p11.2	Xq13.1	1q21.3	6p12.1-p11.2	19q13.12
Inheritance pattern	AD	AD	AD	AD	AD	AR	AD	XLD	AD	AR	AR
Suture Involved											
Metopic	++	-	-	++	-	++	+	-	-	++	++
Coronal	++	++	+++	-	+++	++	-	++	++	++	+
Sagittal	-	++	+	++	-	+	+	-	-	++	+
Lambdoid	-	+	-	-	+	+	-	-	-	+	-
Multisuture	++	++	-	-	-	++	-	-	-	+++	-
Possible systemic involvement	±	+ Crouzon-like	+ Saethre-Chotzen–like	-	±	+ Crouzon-like	-	+ (more severe in females)	-	+	+
Facial dysmorphic features											
Limb anomalies	B	B, C, large thumb	B, C, S	-		C, S	-	B, C	-	B, PP, fingers/toes S	B, PP, fingers/toes S
CNS malformations	-	CT1, EPPG, VD	VD, Cca	-	Cerebellar anomalies, Cca, VD, PH	-	-	Cca	-	-	-
Cognitive involvement	Normal IQ	Normal IQ Possible LD/BD	Possible DD/LD	Possible DD	Mild to severe DD, autistic features	Possible DD	-	Possible DD	Normal IQ	Possible DD	Possible DD
Other	VI, Sz	-	-	-	Strabismus, SNHL, SD, DFC, scoliosis	Teeth anomalies	-	Possible DH	-	Mixed HL, OA, CHD, UGM	Situs anomalies, CHD

AD: autosomal dominant. AR: autosomal recessive. B: brachydactyly. BD: behavioral difficulties. C: clinodactyly. CCa: Corpus callosum agenesis. CHD: congenital heart disease. CNS: Central Nervous System. CT1: Chiari type 1. DD: developmental delay. DFC: delayed fontanel closure. DH: diaphragmatic hernia. EPPG: ectopic posterior pituitary gland. HL: hearing loss. IQ: intelligence Quotient. LD: learning difficulties. OA: optic atrophy. PH: pons hypoplasia. PP: preaxial polydactyly. S: syndactyly. SD: skull defects. SN: sensory-neural. Sz: Seizures. UGM: urogenital malformations. VD: Ventricular Dilatation. VI: visual impairment. XLD: X-linked dominant.

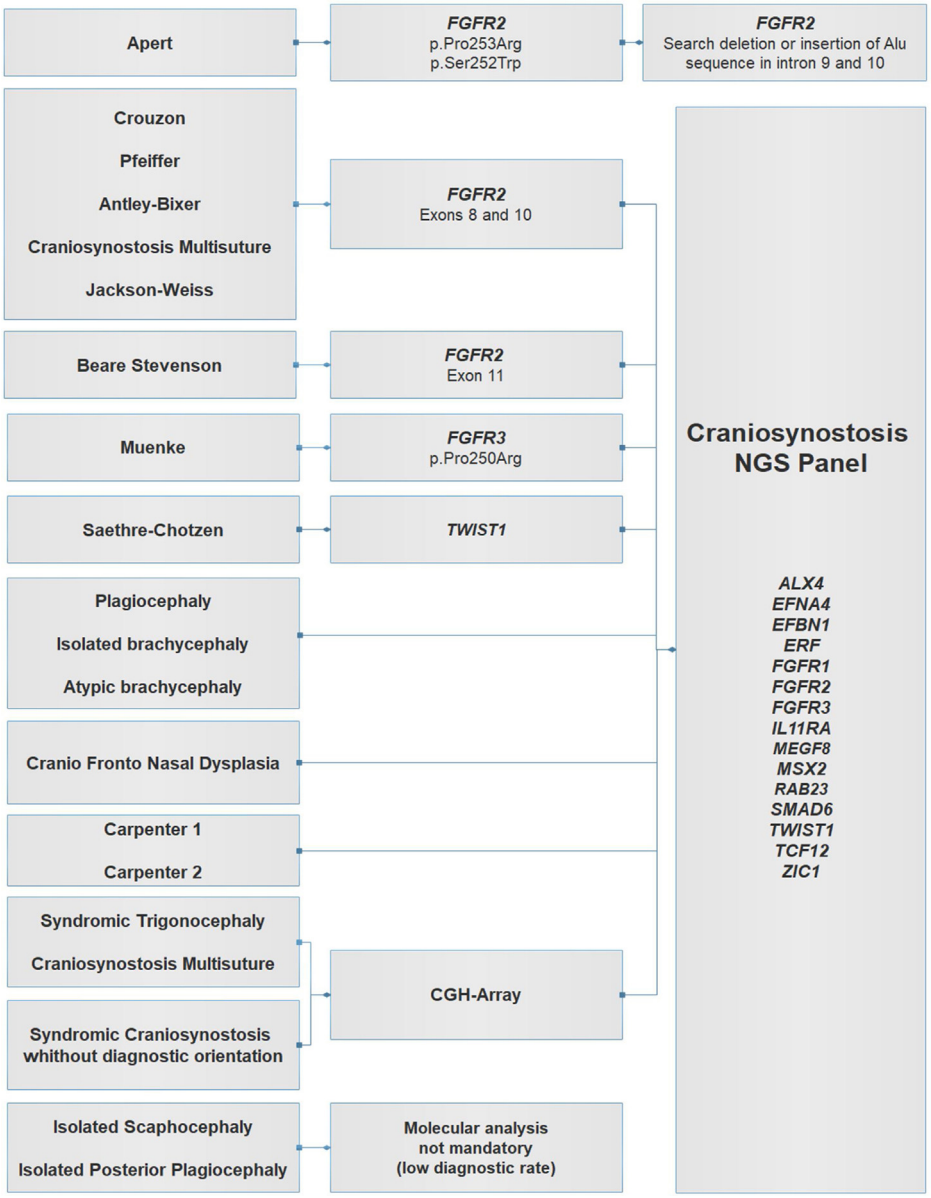

Fig. 2. Flowchart for genetic evaluation of patients affected by craniosynostosis. NGS: Next generation sequencing. Note: Concerning patients with isolated trigonocephaly, a genetic evaluation is indicated in the presence of a positive family history.

significant genetic heterogeneity of these conditions (Table 1) and blurring the limit between SCS and NSCS [6]. Currently, the diagnostic rate in SCS and NSCS is about 20–30%, depending on the type of suture involved (≈60% for bicoronal, ≈30% for coronal synostosis/brachycephaly; ≈10% for sagittal synostosis/scaphocephaly; ≈6–10% for metopic synostosis/trigonocephaly; unknown for lambdoid synostosis) [6,31].

An early diagnosis of secondary CS is crucial for an appropriate management of the associated complications of the underlying disease (for example, the multisystemic involvement of ciliopathies or mucopolysaccharidoses), thus improving the final prognosis for the child.

Concerning primary CS, even if SCS can be clinically recognized on the basis of the suture involved and the associated signs (i.e. Craniofrontonasal dysplasia, Carpenter syndrome), the differential diagnosis of NSCS is difficult. The molecular characterization of these conditions leads to appropriate genetic counseling, provides relevant information concerning co-morbidity and prognosis and, sometimes, leads to a “reverse” characterization of the phenotypic spectrum associated with gene mutations. Nevertheless, a systematic genetic evaluation of NSCS patients can also lead to the detection of susceptibility factors with low penetrance whose interpretation in genetic counseling is difficult and it raises the question of its cost-effectiveness for health systems. These aspects emphasize the need of a clear rationale for performing genetic tests.

In France, patients with CS, either syndromic or non-syndromic, should be addressed to appropriate Referral Centers for rare diseases. A multidisciplinary evaluation by experimented teams, including neurosurgeons, clinical geneticists, molecular geneticists, genetic counsellor and psychologists, should be systematically warranted in order to select medically appropriate and patient-tailored indications for performing genetic tests [32]. We propose a diagnostic flowchart for CS molecular assessment (Fig. 2). The results of the genetic tests should also be discussed in multidisciplinary meetings, including clinical and molecular geneticists, genetic counselors as well as the referral neurosurgeon, in order to evaluate the pathogenicity and the clinical significance of gene variants.

In conclusion, we review in this study the main molecular etiologies of either SCS or NSCS reported in the last 15 years, and we propose a systematic multidisciplinary approach and a diagnostic flowchart for the genetic assessment of these patients.

Funding

No funding was received for this study.

Disclosure of interest

The authors declare that they have no competing interest.

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