Syndromic Craniosynostosis: A Review

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Abstract

Craniosynostosisis a defect of the skull caused by premature fusion of one or more cranial sutures. It may be isolated finding or part of a syndrome and affects 1 in every 2,500 live births. Usually multiple sutures are involved and correspond in at least 20% of the cases. Syndromic craniosynostosis can be associated with various dysmorphic features involving the face, skeleton and nervous system. More than 180 syndromes have been reported with craniosynostosis.

The aim of this review is to present the clinical and genetic characteristics of the most common types of syndromiccraniosynostosis.

Introduction

Abnormal skull shapes were described by both Hippocrates and Galen. In 1851, Virchow was the first to associate these alterations to premature fusion of cranial sutures.[1]

Craniosynostosis is a congenital skeletal disorder caused by the premature fusion of one or more cranial sutures,[2-4] causing restriction in skull and skull base growth which produced shape deformities with associated midface hypoplasia, facial asymmetry and dysmorphisms.[3,5] This condition is divided into syndromic and non-syndromic forms, depending on the presence or absence of other associated findings.[2]

Patients with syndromic craniosynostosis can have an increased risk of increased intracranial pressure, ventricular expansion, hydrocephalus, expanded subarachnoid space, cerebellar tonsillar herniation, visual impairment, deafness and cognitive deficits compared with patients with sporadic single suture synostoses.[3,5]

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The clinical diagnosis of thesyndromic craniosynostosisis based on physical and radiological findings for craniofacial and limb/digital features, as well as other infrequent associations.[2] The prevalence is estimated to be 1 in every 2,500 live births, and a non-syndromic form accounts for more than half of the cases.[2,6] On the other hand, there are greater than 180 syndromes associated with craniosynostosis,[3] some of them shown in (Table 1).

Craniosynostosis can occur primarily and secondarily. The primary form is due to premature fusion of one or more of the sutures in a developmental error during embryogenesis whereas secondary craniosynostosis is due to mechanical causes such as intrauterine compression of the fetal skull, the effect of teratogens and metabolic causes.[5] The sagittal suture is the most commonly affected (40–55%), followed by the coronal (20–25%), metopic (5–15%), and lambdoid (<5%) sutures.[6]

Entity	Gene	Locus
Apert syndrome	*FGFR2*	10q26.13
Crouzon syndrome	*FGFR2*	10q26.13
Crouzon syndrome with acanthosis nigricans	*FGFR3*	4p16.3
Pfeiffer syndrome	*FGFR1*	8p11.23
	FGFR2	10q26.13
Muenke syndrome	*FGFR3*	4p16.3
Saethre–Chotzen syndrome	*TWIST1*	7p21.1
Carpenter syndrome	*RAB23*	6p12.1-p11.2

Table 1. Common forms of syndromic craniosynostosis.[2]

Apert syndrome (OMIM #101200) was first reported by Wheaton in 1894,[7] and the French paediatrician, Eugene Apert, who published a series of nine cases in 1906, in a condition that named acrocephalosyndactyly.[1,8] This syndrome is caused by a genetic mutation in the fibroblast growth factor receptor 2 gene (*FGFR2*). It is characterized by acrocephaly due to premature fusion of the bilateral coronal suture with various other sutures usually involved and severe syndactily in both hands and feet. Syndactily is a characteristic feature of Apert syndrome that permits distinction from the other *FGFR2*-related syndromes,[6,8] which also includes Pfeiffer, Crouzon, Beare–Stevenson, and Jackson–Weiss syndromes.[10] Also is characterized by wide and flatened forehead, flat occiputus, midface hypoplasia with narrow pharynx can result in airway compromise, proptosis, ocular hypertelorism, low set ears, symphalangism, radio-humeral fusion and varying degrees of neurocognitive impairment requiring special education. Up to 75% of patients also have an associated cleft palate or bifid uvula, also orthodontic and other dental problems.[6,8]

Apert syndrome is an infrequent disorder, with prevalence of 1 in 65,000 live births.[1,8] Although presents an autosomal dominant inheritance pattern, most cases are sporadic, with equal numbers of affected males and females, and accounts for about 4.5% of all cases of craniosynostosis.[9] Approximately 98% of all cases are due to gain-of-function *FGFR2*.[6] This gene encodes a belongs to a family of four fibroblast growth factor receptors, which contain an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain with tyrosine kinase activity.[10] Genetic mutations discovered in 1995 by Wilkie et al. identified two adjacentmissense mutations located in the linker between the IgII and IgIII domains, either p.Ser252Trp (66%) or p.Pro253Arg (32%) in the highly conserved region linking Ig-like domains II and III of *FGFR2*.[6,8,10]

The p.Pro253Arg mutation is associated with more severe syndactily when compared withp.Ser252Trp which is strongly associated with cleft palate. These mutations lead to loss of ligand specificity of receptor, causing abnormalities in extracellular matrix composition and premature calvarial ossification.[7] Another distinct pathological basis has also been identified, signaling through keratinocyte growth-factor receptor has been shown to be responsible for syndactili in this entity.[10]

Subsequently, has identified two other de novo insertion mutations in *FGFR2*. These four mutations transmitted in the paternal chromosome, thus the theory of advanced paternal age being a risk factor.[1,7] The significant phenotypic variability observed in Apert syndrome is thought to be due to genetic and environmental factors.[1] Carries a high mortality rate, about 10% especially during early infancy and surviving infants need multidisciplinary medical and surgical care.[9]

Crouzon syndrome (OMIM #123500) is the most frequent syndromic craniosynostosis occurring without syndactyly. It was first described by a French neurologist, Louis Edouard Octave Crouzon, in a mother and daughter in 1912.[11-15] Half of the cases of this congenital condition are sporadic, and the other half have an autosomal dominant inheritance pattern with complete penetrance and variable expression. There's no racial or gender predilection.[15]

Crouzon syndrome has abnormalities of branchial arch formation with the triad of skull, face, and eye abnormalities.[15] It is characterized by synostosis of coronal, (but often pan-synostosis) that can produce brachycephaly, scaphocephaly, trigonocephaly and in severe disease, cloverleaf skull deformity. Typical symptoms are ocular proptosisdue to shallow orbits, other ocular anomalies include hypertelorism, strabismus, ametropia, hypermetropia, reduced monocular visual acuity and blindness, midface hypoplasia, parrot-beaked nose, and oral manifestations as underdeveloped maxilla, relative mandibular prognathism,short upper lip,[11-13,15] ectopic eruption, crowding of maxillary and mandibular teeth along with class III malocclusion.[11,12,14] It may also present conductive hearing impairment and stenosis or atresia of the auditory canals.[15] Subtle anomalies of other structures, including the limbs and vertebrae also have been described.[14] The incidence of increased intracranial pressure in untreated cases of Crouzon syndrome has been reported as 62.5%. Possible consequences include visual loss that can extend to blindness as well as impaired neuro-cognitive development.[14] Moreover; the

proptotic eye is vulnerable to traumatic injury, corneal abrasion, and exposure keratitis.[13]

Prevalence of this condition is 1 in 60,000 live births. Is associated with mutations in exons IIIA and IIIC in *FGFR2* gene in 95% of cases.[12,15,16] In contrast to Apert syndrome, the spectrum of *FGFR2* mutations that cause Crouzon syndrome is broader.[8]

Crouzon syndrome with acanthosis nigricans is also called Crouzon-dermo-skeletal syndrome (OMIM #612247) represents a clinically and genetically distinct entity with an autosomal dominant inheritance pattern, with variable expressivity and a female predominance of 2.4:1,[16] and the severity is the same in affected males and females.[17] It Affects 1 in 25,000 live births,[18] accounting for 1% to 2% of all craniosynostosis syndromes,[16,17] and all ethnicities are affected.[17] These include choanal atresia and/or stenosis and hydrocephalus often with a Chiari I malformation. It is due to a characteristic mutation in the fibroblast growth factor receptor 3 gene (*FGFR3*), a change in a GCG sequence by a GAG sequence in nucleotide 1172.[16] The Ala391Glu mutation in the transmembrane domain of FGFR3.[17,18] The mutation is supposed to activate constitutively the tyrosine kinase activity of the receptor independently from its ligands.[17]

Pfeiffer syndrome (OMIM #101600) is a rare autosomal dominant entity resulting from heterozygous mutations in the fibroblast growth factor receptors types 1 (*FGFR-1)* and *FGFR-2* mutations.[19-21] It was first described in 1964, and has an estimated incidence of 1 in 100,000 live births.[6,19,22,23] It is characterized by bicoronal craniosynostosis, prominent forehead, midface hypoplasia with shallow orbits, hypertelorism, convex nasal ridge, depressed nasal bridge, broad and deviated thumbs and great toes, brachydactyly and a variable degree of syndactily in hands and feet can be accompanied in some patients.[6,19,22,24-26] Other manifestations including delayed neuropsychological development, hydrocephalus, Chiari malformation, choanal stenosis, visceral anomalies and ankylosed elbows.[6,21,26]

Differentiation between Pfeiffer syndrome and Crouzon syndrome rely on the presence or absence of hands and feet anomalies.[6]

It Is divided into three subtypes according to the clinical severity and prognostic significance (Table 2), described by Cohen in 1993.[2,19,26] It

was suggested that *FGFR1* mutations often result in less severe craniofacial involvement.[24] A specific mutation, p.Pro252Arg, in the *FGFR1* gene can be identified in Pfeiffer syndrome type 1.[27] However, The majority of cases are caused by gain of function mutations in a wide spectrum of mutations in *FGFR2*.[24]

Type	Form	Findings
1	Mildest (classic) phenotype	Brachycephaly
	Normal intelligence	Midface hypoplasia
		Hypertelorism
		Proptosis
		Brachydactyly
		Syndactyly
		Broad thumbs/great toes
2	Severe phenotype	Cloverleaf skull
3	Intermediate phenotype	Very short skull base
		Severe proptosis
		Without the cloverleaf skull

All types demonstrate craniofacial anomalies and limb deformities as the findings described in type 1.

Table 2. Classification of Pfeiffer syndrome.[6,23]

Jackson-Weiss syndrome (OMIM #123150) is an autosomal dominant disorder with high penetrance and variable expressivity due to mutations in the *FGFR1* and *FGFR2* genes. The features are similar to Pfeiffer syndrome except that the thumbs are typically normal.[3]

Muenke syndrome (OMIM #602849) is an autosomal dominant disorder with reduced penetrance and variable expressivity, characterized by unilateral or bilateral coronal synostosis, midface hypoplasia, palpebral ptosis, downslanting palpebral fissures, high and/or arched palate, sensorineural hearing loss, developmental delay, seizures and abnormalities of the hands and feet such as brachydactyly and clinodactyly and radiographic changes such as cone-shaped epiphyses, thimble-like phalanges, carpal and tarsal fusions, broad thumbs and halluces.[28-32]

It was described by Maximilian Muenke in 1997 and is caused by a heterozygous missense and gain-of-function mutations c.749C>G p.Pro250Arg in the *FGFR3* gene.[29] This is one of the most common transversions in humans with an estimated mutation rate of 8×10^{-6}.[28,30] The majority of patients arise as novo mutational events and it has been associated with advanced paternal age.[28] Constitutes the most common syndromic form of craniosynostosis, with an estimated incidence of 1 in 30,000 live births,[28-31] and represents 8 % of all patients with craniosynostosis.[30,31]

Equal representation in the two sexes, however, sex-related expressivity is more severe phenotype observed in females.[28]

Saethre-Chotzen syndrome (OMIM #101400) acrocephalosyndactyly type III,[33] is an autosomal dominant entity with high penetrance and variable expressivity.[34] Characterized by unilateral or bilateral coronal synostosis and simple in complete syndactyly of the index and middle fingers, the third and fourth toes as well as broad/duplicated/laterally deviated of the hallux.[35]

Typically in ear has a small pinna with prominent superior crus.[34] In addition to the turribrachycephaly, a low frontal hairline may be appreciated, facial asymmetry, strabismus, palpebral ptosis, downward slanting palpebral fissures, depressed nasal bridge, narrow and/or cleft palate, bifid uvula and congenital heart malformations.[34-36]

It was first described in 1931 bySaethre and Chotzen a Norwegian neurology and psychiatry and German psychiatrist, respectively.[33,34,37] It has an estimated incidence of 1 in 25,000 to 50,000 live births.[34] Loss of *TWIST1* function is thought to be responsible for the premature suture fusion.[35] The molecular diagnosis has allowed acknowledging the great interfamilial and intrafamilial variability of the clinical phenotype associated with > 100 mutations that involving intragenic mutations, micro deletions, or translocations within the already mentioned *TWIST1*gene.[37]

Carpenter syndrome (OMIM # 201000) acrocephalo polysyndactyly type II, is a rare autosomal recessive with marked intrafamilial variability.[38] It was first described in 1909 by George Carpenter,[3,39] andhas an incidence of 1 in a million live births.[40] This pleiotropic disorder is characterized by sagittal, lambdoid, and coronal synostosis (acrocephaly), unusual facies, midfacial hypoplasia,[3,39] flat nasal bridge, broad cheeks, malformed and unevenly set ears, and late eruption of small and widely spaced teeth.[40] Other features include brachydactyly, broad or bifid thumbs, absent or small middle phalanges, postaxial polysyndactyly of the hands and preaxial polysyndactyly in the toes. In addition to increased birth weight, later obesity, congenital heart defect, umbilical hernia, cryptorchidism or hypoplastic testes, talipes, bowed femora and tibiae, intellectual disability, and central nervous system malformations.[38-42]

Is caused by mutations in the *RAB23* gene, which encodes a small GT Pase of the Ras super family which that regulates vesicular transport and acts as an essential negative regulator of the Sonic hedgehog signaling pathway.[39,41] No genotype-phenotype correlations are so far reported.[42]

Conclusions

The different clinical findings and the molecular studies can guide the differential diagnosis of different types of syndromic craniosynostosis. This review emphasizes the need of an integrated medical and surgical approach and providing an adequate genetic counseling.

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Declaration of Interest

References

1. Breik O, Mahindu A, Moore MH, Molloy CJ, Santoreneos S, David DJ.Central nervous system and cervical spine abnormalities in Apert syndrome. Childs Nerv Syst 2016;32(5):833-8.
2. Ohishi A, Nishimura G, Kato F, Ono H, Maruwaka K, Ago M, Suzumura H, Hirose E, Uchida Y, Fukami M, Ogata T. Mutation analysis of *FGFR1-3* in 11 Japanese patients with syndromic craniosynostoses. Am J Med Genet Part A 2016;9999A:1–6.
3. Wang JC, Nagy L, Demke JC. Syndromic Craniosynostosis. Facial Plast Surg Clin North Am 2016;24(4):531-543.
4. Cornelissen M, Ottelander Bd, Rizopoulos D, van der Hulst R, Mink van der Molen A, van der Horst C, Delye H, van Veelen ML, Bonsel G, Mathijssen I. Increase of prevalence of craniosynostosis. J Craniomaxillofac Surg 2016;44(9):1273-9.
5. Kim HJ, Roh HG, Lee IW. Craniosynostosis: Updates in Radiologic Diagnosis. J Korean Neuro surg Soc 2016;59(3):219-26.
6. Ko JM. Genetic Syndromes Associated with Craniosynostosis. J Korean Neurosurg Soc 2016;59(3):187-91.

7. Fadda MT, Ierardo G, Ladniak B, Di Giorgio G, Caporlingua A, Raponi I, Silvestri A; Group of Apert syndrome, Policlinico Umberto I, "Sapienza" University of Rome, Italy.Treatment timing and multidisciplinary approach in Apert syndrome. Ann Stomatol (Roma) 2015;6(2):58-63.

8. Breik O, Mahindu A, Moore MH, Molloy CJ, Santoreneos S, David DJ. Apert syndrome: Surgical outcomes and perspectives. J Craniomaxillofac Surg 2016;44(9):1238-45.

9. Sobaih BH, Al Ali AA.A third report of Apert syndrome in association with diaphragmatic hernia. Clin Dysmorphol 2015;24(3):106-8.

10. Fernandes MB, Maximino LP, Perosa GB, Abramides DV, Passos-Bueno MR, Yacubian-Fernandes A. Apert and Crouzon syndromes-Cognitive development, brain abnormalities, and molecular aspects. Am J Med Genet A 2016;170(6):1532-7.

11. Rahimov C, Asadov R, Hajiyeva G, Verdiyev N, Novruzov Z, Farzaliyev I.Crouzon syndrome: Virtual planning of surgical treatment by application of internal distractors. Ann Maxillofac Surg 2016;6(1):135-40.

12. Kumar DS, Murugesan D, Murugan K, Subramanian D, Maheshwari SU. Crouzon Syndrome: Report in a Family. J Clin Diagn Res 2016;10(1):ZJ02-3.

13. Forte AJ, Steinbacher DM, Persing JA, Brooks ED, Andrew TW, Alonso N. Orbital Dysmorphology in Untreated Children with Crouzon and Apert Syndromes. Plast Reconstr Surg 2015;136(5):1054-62.

14. Abu-Sittah GS, Jeelani O, Dunaway D, Hayward R. Raised intracranial pressure in Crouzon syndrome: incidence, causes, and management. J Neurosurg Pediatr 2016;17(4):469-75.

15. Giordano BP, Tuli SS, Ryan SF, Stern M, Tuli SY. Crouzon Syndrome: Visual Diagnosis.J Pediatr Health Care 2016;30(3):270-3.

16. Herman TE, Sargar K, Siegel MJ. Crouzono-dermo-skeletal syndrome, Crouzon syndrome with acanthosis nigricans syndrome. J Perinatol 2014;34(2):164-5.

17. Di Rocco F, Collet C, Legeai-Mallet L, Arnaud E, Le Merrer M, Hadj-Rabia S, Renier D. Crouzon syndrome with acanthosis nigricans: a case-based update. Childs Nerv Syst 2011;27(3):349-54.

18. Chen F, Sarabipour S, Hristova K. Multiple consequences of a single amino acid pathogenic RTK mutation: the A391E mutation in FGFR3. PLoS One 2013;8(2):e56521.

19. Ketwaroo PD, Robson CD, Estroff JA. Prenatal Imaging of Craniosynostosis Syndromes. Semin Ultrasound CT MR 2015;36(6):453-64.

20. Barber SR, Remenschneider AK, Kozin ED, Cunnane ME, Nahed BV, Leslie-Mazwi T, Quesnel AM. Cochlear Implantation in a Patient With Pfeiffer Syndrome and Temporal Bone Vascular Anomalies. Otol Neurotol 2016;37(3):241-3.

21. Colomb C, Hippard HK, Canadas K, Watcha M.A Delayed Finding of a Tracheal Cartilaginous Sleeve in a Patient with Pfeiffer Syndrome Type 2 and a Complex Airway History. A Case Rep 2015;5(3):36-9.

22. Sharma N, Greenwell T, Hammerton M, David DJ, Selva D, Anderson PJ. The ophthalmic sequelae of Pfeiffer syndrome and the long-term visual outcomes after craniofacial surgery. J AAPOS 2016;20(4):315-9.

23. Nieuwenhuyzen-De Boer GM, Hoogeboom AJ, Smit LS, Heydanus R, Eggink AJ. Pfeiffer syndrome: the importance of prenatal diagnosis. Eur J Obstet Gynecol Reprod Biol 2014;181:339-40.

24. Flöttmann R, Knaus A, Zemojtel T, Robinson PN, Mundlos S, Horn D, Spielmann M. FGFR2 mutation in a patient without typical features of Pfeiffer syndrome--The emerging role of combined NGS and phenotype based strategies. Eur J Med Genet 2015;58(8):376-80.

25. Al-Adba B, Tse SM.Radiographic manifestations in Pfeiffer syndrome. Arthritis Rheumatol 2015;67(8):2282.

26. Bessenyei B, Tihanyi M, Hartwig M, Szakszon K, Oláh É. Variable expressivity of pfeiffer syndrome in a family with FGFR1 p.Pro252Arg mutation. Am J Med Genet A 2014;164A(12):3176-9.

27. Bessenyei B, Nagy A, Szakszon K, Mokánszki A, Balogh E, Ujfalusi A, Tihanyi M, Novák L, Bognár L, Oláh É. Clinical and genetic characteristics of craniosynostosis in Hungary. Am J Med Genet A 2015;167A(12):2985-91.

28. González-Del Angel A, Estandía-Ortega B, Alcántara-Ortigoza MA, Martínez-Cruz V, Gutiérrez-Tinajero DJ, Rasmussen A, Gómez-González CS. Expansion of the variable expression of Muenke syndrome: hydrocephalus without craniosynostosis. Am J Med Genet Part A 9999A:1–8.

29. Samra F, Bauder AR, Swanson JW, Whitaker LA, Bartlett SP, Taylor JA. Assessing the midface in Muenke syndrome: A cephalometric analysis and review of the literature. J Plast Reconstr Aesthet Surg 2016;69(9):1285-90.

30. Kruszka P, Addissie YA, Yarnell CM, Hadley DW, Guillen Sacoto MJ, Platte P, Paelecke Y, Collmann H, Snow N, Schweitzer T, Boyadjiev SA, Aravidis C, Hall SE, Mulliken JB, Roscioli T, Muenke M.Muenke syndrome: An international multicenter natural history study. Am J Med Genet A. 2016;170A(4):918-29.

31. Yarnell CM, Addissie YA, Hadley DW, Guillen Sacoto MJ, Agochukwu NB, Hart RA, Wiggs EA, Platte P, Paelecke Y, Collmann H, Schweitzer T, Kruszka P, Muenke M. Executive Function and Adaptive Behavior in Muenke Syndrome. J Pediatr 2015;167(2):428-34.

32. Aravidis C, Konialis CP, Pangalos CG, Kosmaidou Z.A familial case of Muenke syndrome. Diverse expressivity of the FGFR3 Pro252Arg mutation--case report and review of the literature. J Matern Fetal Neonatal Med 2014;27(14):1502-6.

33. Zeidman LA. Dr. Haakon Sæthre: a Norwegian neuroscientist and his resistance against Nazi Germany.J Hist Neurosci. 2013;22(2):160-73.

34. Buchanan EP, Xue AS, Hollier LH Jr. Craniofacial syndromes. Plast Reconstr Surg 2014;134(1):128e-153e.

35. Tahiri Y, Bastidas N, McDonald-McGinn DM, Birgfeld C, Zackai EH, Taylor J, Bartlett SP. New pattern of sutural synostosis associated with TWIST gene mutation and Saethre-Chotzensyndrome: peace sign synostosis. J Craniofac Surg 2015;26(5):1564-7.

36. Sharma A, Patel N, Arora S, Ramachandran R.Child with Saethre-Chotzen syndrome: anesthetic management and literature review. Acta Anaesthesiol Belg 2014;65(4):179-82.

37. di Rocco F, Benoit A, Vigneron J, Segura PB, Klein O, Collet C, Arnaud E. Y-craniosynostosis by premature fusion of the metopic and coronal sutures: a new nosological entity or a variety of Saethre-Chotzen syndrome? Birth Defects Res A Clin Mol Teratol 2015;103(4):306-10.

38. Alessandri JL, Dagoneau N, Laville JM, Baruteau J, Hébert JC, Cormier-Daire V. RAB23 mutation in a large family from Comoros Islands with Carpenter syndrome. Am J Med Genet A 2010;152A(4):982-6.

39. Haye D, Collet C, Sembely-Taveau C, Haddad G, Denis C, Soulé N, Suc AL, Listrat A, Toutain A.Prenatal findings in carpenter syndrome and a novel mutation in RAB23. Am J Med Genet A 2014;164A(11):2926-30.

40. Ben-Salem S, Begum MA, Ali BR, Al-Gazali L. Novel aberrant splice site mutation in RAB23 leads to an eight nucleotide deletion in the mRNA and is responsible for Carpenter syndrome in a consanguineous Emirati family. MolSyndromol 2013;3(6):255-61.

41. Twigg SR, Lloyd D, Jenkins D, Elçioglu NE, Cooper CD, Al-Sannaa N, Annagür A, Gillessen-Kaesbach G, Hüning I, Knight SJ, Goodship JA, Keavney BD, Beales PL, Gileadi O, McGowan SJ, Wilkie AO. Mutations in multidomain protein MEGF8 identify a Carpenter syndrome subtype associated with defective lateralization. Am J Hum Genet 2012;91(5):897-905.

42. Jenkins D, Baynam G, De Catte L, Elcioglu N, Gabbett MT, Hudgins L, Hurst JA, Jehee FS, Oley C, Wilkie AO. Carpenter syndrome: extended RAB23 mutation spectrum and analysis of nonsense-mediated mRNA decay. Hum Mutat 2011;32(4):E2069-78.