

## Biomolecular Analysis of Juvenile Nasopharyngeal Angiofibroma

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### Abstract

Juvenile nasopharyngeal angiofibroma (JNA), a rare type of tumor that occurs most frequently in adolescent males, is difficult to treat. The relationship between JNA and certain biomolecules has been the subject of a great deal of research conducted over a long period. This review summarizes the research on the etiopathogenesis of JNA.

**Keywords:** Nasopharyngeal angiofibroma; Juvenile; Biomolecule; Cancer; Genetic

### Introduction

Juvenile nasopharyngeal angiofibroma (JNA) is a benign tumor of the nasopharynx, which accounts for 0.5% of all head and neck tumors. Although it can occur in all age groups, it is most common in adolescents and young adults between 14 and 25 years of age. It is also more common in males than in females [1].

Although JNA is histologically benign, it shows locally invasive behavior and is treated surgically. However, recurrence rates are high, at up to 42% [2]. The most common complication of surgery is bleeding. Therefore, studies on JNA have focused on the difficulty of surgical treatment and high relapse rate. Primary or adjuvant therapy targeting biomolecules secreted from tumor tissue in large quantities (molecular-targeted therapy) can help to reduce the rates of complications, can be used primarily in the treatment, can render otherwise inoperative tumors amenable to surgical intervention, and can be used in palliative treatment.

### Literature Review

The pathogenesis of JNA is still unknown. There have been a number of studies regarding tumor formation and growth in JNA, and regarding its prognostic. These studies took into consideration the male predominance of the tumor, its vascular nature, and its common onset in adolescence. The roles of growth factors, hormone receptors, tumor suppressor genes, oncogenes, and cytokines in the etiopathogenesis of JNA have all been evaluated (Table 1) [2-42].

JNA-related molecular studies have focused on sex hormone receptors, with investigations being done of androgen receptors (AR), estrogen receptors (ER), and progesterone receptors (PR) [6,10,14,18-24,39,40]. These studies indicated that AR is frequently expressed at high levels in cases of JNA [18-22]. However, some studies indicated that ER and PR expression levels are high, while those of AR are low, in JNA [24,39,40]. Kumagami et al. conducted two studies on this subject [39,40]. In both of them, ER was over-secreted by JNA tissue.

Excessive release of growth factors is seen frequently in the development of JNA. Therefore, vascular endothelial growth factor (VEGF), nerve growth factor (NGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF) were assessed in many studies [2,5,6,10,12,14-16,23,25-27]. The levels of TGF- $\beta$ 1 [10,25,27,29], basic fibroblast growth factor (bFGF) [6,15,25,26], NGF (2), and VEGF [5,6,10,12,14,16,23,25] were found to be elevated in JNA. The most notable of which are TGF- $\beta$ 1 and VEGF. Dillard et al. evaluated only TGF- $\beta$ 1 in one study. They reported over-expression of TGF- $\beta$ 1. Saylam et al. reported that both VEGF and TGF- $\beta$ 1 were over-expressed.

The roles of tumor suppressor genes, oncogenes, and cancer

protooncogenes, including p53, c-Myc, H-Ras, Ki-Ras, c-Kit, p130Cas, Friend leukemia integration-1 (FLI-1), endoglin, podoplanin, stromelysin-3 (ST3), tenascin-C (TNC), syndecan-2, proliferating cell nuclear antigen (PCNA), Bcl-2, Ki-67, S-100, c-Fos, GSTM1 gene, AURKA, MDM2, Her-2/neu, and Hif-1 [2,5-7,9-13,15-17,25,27,28,32-35], in the etiology of JNA have been investigated. Among these, c-Myc [6,7,28], c-Kit (2,6,7), FLI-1 [5], endoglin [5,11], TNC [9], PCNA [10,12], Ki-67 [16], GSTM1 [17,33], AURKA and MDM2 (34) were shown to be associated with JNA. Among these, GSTM1-null genotype gene seems important. Expression of GSTM1 mRNA (which encodes glutathione S-transferase M1, a protein involved in detoxification) should be normally in all human beings. When this is not expressed there is an increased risk of developing some malignancies [17,42]. Two studies performed on GSTM1-null genotype [17,33]. In both studies, the GSTM1-null genotype was associated with the formation of JNA.

### Discussion

Some authors have suggested that cellular structural proteins are involved in the etiopathogenesis of JNA. For example, E-cadherin, N-cadherin,  $\alpha$ -catenin,  $\beta$ -catenin,  $\gamma$ -catenin, bone morphogenic protein 4 (BMP4), MNF116, CAM5.2, desmin, vimentin, calponin [2,13,14,30,31,41] have all been studied, and both  $\beta$ -catenin [2,14,30,31,41] and vimentin [13] were shown to be associated with JNA.

In addition, the roles of Toll-like receptors (TLR 3, TLR 7, TLR 9), cell-surface antigens (CD31, CD34, CD68, CD99), matrix metalloproteinases (MMP-1, MMP-2, MMP-9, MMP-14), and certain cytokines (IL-6, IL-17) were investigated [6,8,12,13,16,36-38]. Of these, TLR 3 [8], CD34 [12], MMP 9 [36,37], IL-6, and IL-17 [6,38] were shown to be associated with JNA.

There have also been investigations regarding the associations between biomolecules and the prognosis of JNA, with ER, MMP-9, and IL-17 all being shown to be associated with poor prognosis [23,37,38].

Carlos et al. postulated that human herpes virus-8 (HHV-8) and Epstein-Barr virus (EBV) may play roles in the etiology of JNA, but their results indicated no such associations of these viruses with the pathogenesis of JNA [4].

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Received November 01, 2017; Accepted November 16, 2017; Published November 20, 2017

Citation: Mazlumoglu MR (2017) Biomolecular Analysis of Juvenile Nasopharyngeal Angiofibroma. J Mol Genet Med 11: 304 doi:10.4172/1747-0862.1000304

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Study	Marker	Associated with JNA (Over-expressed or up-regulated, gene mutation, gene nullity)
Zhang et al. [2]	$\beta$ -catenin, c-Kit (CD117), p130Cas, TGF- <i>B</i> 3, BMP 4, NGF, IGF-1R	$\beta$ -catenin (nuclear), c-Kit (CD117) (cytoplasmic), NGF (cytoplasmic)
Carlos et al. [4]	HHV-8, EBV	-
Nonogaki et al. [5]	FLI-1, endoglin (CD105), podoplanin, VEGFR3, VEGFC, GLUT-1, ST3, SPARC	FLI-1, endoglin (CD105), VEGFC
Pandey et al. [6]	c-Kit (CD117), c-Myc, VEGFA, bFGF, PDGF-A, H-Ras, AR, IL-6, p53	c-Kit (CD117), c-Myc, VEGFA, bFGF, PDGFA, H-Ras, IL-6
Renkonen et al. [7]	c-Kit (CD117), c-Myc, BMI-1	c-Kit (CD117), c-Myc, BMI-1
Renkonen et al. [8]	TLR 3, TLR 7, TLR 9	TLR 3
Renkonen et al. [9]	GLUT-1, TNC, syndecan-2	GLUT-1, TNC
Saylam et al. [10]	ER, PR, PCNA, VEGF, TGF- <i>B</i>	PCNA, VEGF, TGF- <i>B</i>
Wang et al. [11]	Endoglin (CD105)	Endoglin (CD105)
Zhang et al. [12]	VEGFR-1, VEGFR-2, PCNA, CD34	VEGFR-1, VEGFR-2, PCNA, CD34
Pauli et al. [13]	MNF116, CAM5.2, S-100, CD31, CD34, CD99, CD68, vimentin, EMA, SMA, desmin, calponin, Bcl-2, c-Kit (CD117)	Vimentin
Ponti et al. [14]	$\beta$ -catenin, E-cadherin, AR, VEGFR-2	$\beta$ -catenin, VEGFR-2
Sun et al. [15]	PCNA, VEGF, bFGF	bFGF
Brieger et al. [16]	VEGF, CD31, Ki67	VEGF, Ki67
Gautham et al. [17]	GSTM1-null genotype	GSTM1-null genotype
Brentani et al. [18]	ER, PR, AR, GR	PR, AR
Lee et al. [19]	ER, PR, AR	AR
Hwang et al. [20]	ER, PR, AR	AR
Farag et al. [21]	AR	AR
Gatalica [22]	ER, PR, AR	AR
Liu et al. [23]	AR, ER- $\alpha$ , ER- $\beta$ , PR, VEGF	AR, ER- $\alpha$ , ER- $\beta$ , VEGF
Montag et al. [24]	PR, ER- $\alpha$ , ER-ss, AR	ER-ss
Schuon et al. [25]	TGF- $\beta$ 1, bFGF, VEGFR-1, VEGFR-2, Hif-1 $\alpha$	TGF- $\beta$ 1, bFGF, VEGFR-2,
Schiff et al. [26]	bFGF	bFGF
Nagai et al. [27]	IGF-II, bFGF, VEGF, TGF- $\beta$ 1, PDGF-A, PDGF-B, c-myc, c-fos, p53	IGF-II, TGF- $\beta$ 1,
Shick et al. [28]	c-Myc	c-Myc
Dillard et al. [29]	TGF- <i>B</i> 1	TGF- <i>B</i> 1
Rippel et al. [30]	E-cadherin, N-cadherin, $\alpha$ -catenin, $\beta$ -catenin, $\gamma$ -catenin	<i>B</i> -catenin
Abraham et al. [31]	<i>B</i> -catenin	<i>B</i> -catenin
Shick et al. [32]	p53, Her-2/neu	-
Maniglia et al. [33]	GSTM1-null genotype	GSTM1-null genotype
Shick et al. [34]	AURKA gene, MDM2 gene	AURKA gene, MDM2 gene
Coutinho et al. [35]	Ki-ras, H-ras	-
Duerr et al. [36]	MMP-1, MMP-2, MMP-9, MMP-13, MMP-14, TIMP-1, TIMP-2	MMP-1, MMP-2, MMP-9,
Sun et al. [37]	MMP-9	MMP-9
Sun et al. [38]	IL-17	IL-17
Kumagami [39]	ER, AR	ER
Kumagami [40]	ER, PR, AR	ER, PR
Valanzano et al. [41]	$\beta$ -catenin	$\beta$ -catenin

TGF- $\beta$ 1: Transforming Growth Factor Beta1, BMP4: Bone Morphogenic Protein 4, NGF: Nerve Growth Factor, IGF-1R: Insuline Like Growth Factor Receptor, HHV-8: Human Herpes Virus-8, EBV: Epstein-Barr Virus, FLI-1: Friend Leukemia Integration-1, VEGFR: Vascular Endothelial Growth Factor Receptor, VEGFC: Vascular Endothelial Growth Factor Cognate Ligand, ST3: Stromelysin 3, GLUT: Glucose Transporter, SPARC: Secreted Protein Acid Rich In Cysteine, C-Myc: Avian Myelomatosis Viral Oncogene Homolog, Bfgf: Basic Fibroblast Growth Factor, PDGFA: Platelet-Derived Growth Factor, H-Ras: Harvey Rat Sarcoma Viral Oncogene Homolog, AR: Androgen Receptor, ER: Estrogen Receptor, PR: Progesterone Receptor, GR: Glucocorticoid Receptor, IL-6: Interleukin 6, BMI-1: Polycomb Complex Protein, TLR: Toll-Like Receptor, TNC: Tenascin-C, PCNA: Proliferating Cell Nuclear Antigen, Fit-1: Fms-Like Tyrosine Kinase-1, Flk-1: Fetal Liver Kinase-1, GSTM1: Glutathione S Transferase M1, TGF-*B*1: Transforming Growth Factor Beta 1, Hif-1 $\alpha$ : Hypoxia Inducible Factor 1 $\alpha$ , MMPs: Matrix Metalloproteinases.

**Table 1:** Biomolecular studies of juvenile nasopharyngeal angiofibroma.

## Conclusion

A number of studies have indicated associations between certain biomolecules and JNA. However, molecular targeting has not yet been applied during clinical treatment. Nevertheless, these studies are promising in terms of the future development of possible alternative methods to surgical treatment. Also, the studies about JNA were summarized in this review. These studies were presented in the form of a table. This presentation can help authors who plan to study on JNA.

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