

concern regarding the detrimental effects of persistent high serum GH and IGF-I levels has been expressed in various studies. Of particular importance are the reports of an increased cancer risk (ie, breast, prostate, and colon cancer) in patients with IGF-I levels in the upper tertile to quintile, more so if accompanied by low IGFBP3 levels.²⁻⁴ Recent studies have recommended beginning GH treatment of short SGA children at an early age.²⁻⁴ Thus, GH and IGF-I levels may be elevated in many of these patients for a good part of childhood and adolescence, possibly placing them at an increased risk for complications later in their lives. The long-term deleterious effects of GH treatment in SGA children remain unknown. However, the use of an initially lower GH dose, which can then be individually adjusted and the monitoring of IGF-I and IGFBP3 during GH therapy,

in an attempt to maintain IGF-I concentrations in the upper half of the age-adjusted reference range, is strongly recommended.

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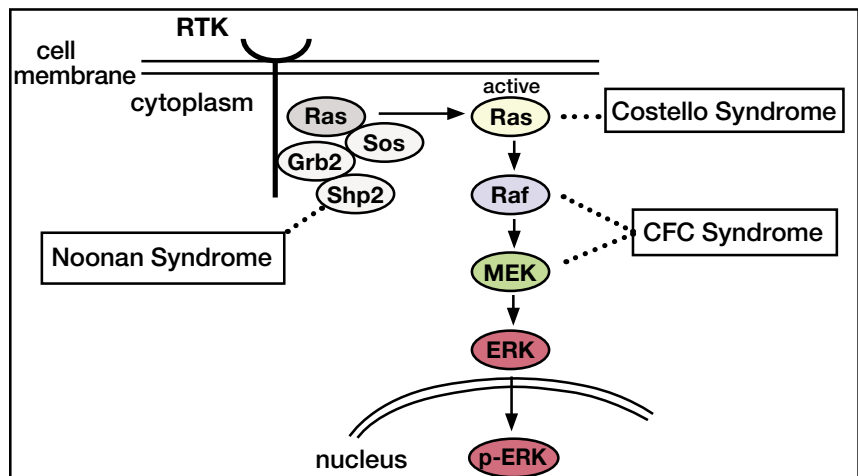
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Germline KRAS, BRAF, and MAPK Mutations in Noonan and Cardio-Facio-Cutaneous-Syndrome

The mitogen-activated protein kinase (MAPK) intracellular signal transduction system is one of several signaling systems employed by growth hormone, prolactin, epidermal growth factor, and other mitogens (Figure). The MAPK pathway is important for cell proliferation, growth, aging, and apoptosis. After a growth factor binds to its specific receptor, GRB2 (growth factor receptor-bound protein 2; chromosome 17q23-q25, OMIM 108355), a cytosolic adaptor protein with SH2 and SH3 domains, complexes with the cytoplasmic domain of the activated growth factor receptor. Subsequently, GRB2 interacts with PTPN11 (protein-tyrosine phosphatase, non-receptor type 11; chromosome 12q24.1, OMIM 176876) through SH2-SH3 bonding and then binds to the guanine nucleotide

exchange factor-SOS1 (son of sevenless drosophila, homolog 1; chromosome 2p22-p21, OMIM 182530) to mediate growth factor-induced activation of RAS (rat sarcoma viral oncogene homolog; chromosome 11p15.5, OMIM 190020). The RAS family of GTP-binding proteins includes KRAS, NRAS, and HRAS, all composed of 189 non-identical amino acids. After activation by addition of GTP, RAS initiates signal transduction through a series of 3 tyrosine-serine/threonine kinases (phosphorylases) that culminates in phosphorylation and activation of several transcription factors such as activating protein-1 (AP-1), and signal transducer and activator of transcription (STAT) 5. Intrinsic RAS GTPase assisted by GTPase activating proteins degrades RAS-linked GTP to GDP, thus decreasing RAS signaling and depressing the activity of the MAPK pathway. The intermediary kinases



Ras/Raf/MEK/ERK signal transduction pathway and associated genetic syndromes.

Noonan syndrome has also been associated with (K)RAS.

Shp2=PTPN11, MEK=MAP1K1 or MAP1K2, ERK=MAPK3 or MAPK1

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in the MAPK pathway include in sequential order:

- BRAF (V-RAF murine sarcoma viral oncogene homolog B1; chromosome 7q34, OMIM 164757) (there are additional RAF isoforms: ARAF and CRAF);
- MAP2K1 (mitogen-activated protein kinase kinase 1; chromosome 15q21, OMIM 176872) and related MAP2K2 (mitogen-activated protein kinase kinase 2; chromosome 7q32, OMIM 601263);
- MAPK3 (mitogen-activated protein kinase 3; chromosome 16p11.2, OMIM 601795) and related MAPK1 (mitogen-activated protein kinase 1; chromosome 22q11.2, OMIM 176948).

MAPK3 in turn phosphorylates AP-1, STAT-5, and other transcription factors. With somatic single point mutations at codons 12,13 or 61, RAS intrinsic GTPase activity is

diminished and the RAS proteins retain GTP, permitting them to become oncogenic by generating unbridled intracellular signaling that leads to unregulated cell proliferation and hematologic, lung, intestinal, pancreatic, thyroid, gonadal, and other neoplasms. Mutations in several of the genes involved in MAPK signaling have been identified and associated with clinical disorders.

Noonan syndrome (OMIM 163950) is an autosomal dominant disorder characterized by a "Turner-like" face, short stature, webbing of the neck, and right-sided anomalies of the heart as well as deafness, motor delay, and a clotting disorder. In approximately 45% of patients with Noonan syndrome, germline heterozygous gain-of-function missense mutations in *PTPN11* have been identified.¹ *PTPN11* (also designated SHP2) is an intracellular protein tyrosine phosphatase; adjacent to its catalytic domain are 2 tandem SRC homology 2 (SH2) domains that permit *PTPN11* to bind to other proteins with SH2 and SH3 domains and to remove phosphate groups from specific phosphotyrosine residues. Among the substrates of *PTPN11* is GRB2. Activating mutations in the SH2 or protein tyrosine phosphatase domains of *PTPN11* increase signal transduction through the MAPK pathway leading to the clinical manifestations of Noonan syndrome, although the cellular mechanism(s) by which they occur is (are) unknown at present.¹ (Heterozygous gain-of-function mutations within the protein tyrosine phosphatase domain of *PTPN11* have also been identified in the LEOPARD syndrome [OMIM 15100], an autosomal dominant disorder with café-au-lait spots and lentiginos as well as features similar to those of Noonan syndrome.)

The Costello or facio-cutaneo-skeletal syndrome (OMIM 218040) is characterized by short stature, excessive skin of the neck (webbing), fingers, palms, and soles, curly hair, perioral and perinasal papillomata, developmental delay, and increased susceptibility to neoplasia. In the majority of patients with Costello syndrome, heterozygous gain-of-function mutations in *HRAS* (V-HA-RAS-Harvey Rat Sarcoma Viral Oncogene Homolog; chromosome 11p15.5, OMIM 190020) (*v.i.*) have been found.²

The 3 articles presently reviewed document overlapping clinical manifestations and mutations in several genes within the MAPK signal transduction pathway. Schubbert et al report that the clinical manifestations of Noonan syndrome can also arise as a consequence of gain-of-function mutations in *KRAS* (V-KI-RAS2 Kirsten Rat Sarcoma 2 Viral Oncogene Homolog, chromosome 12p12.1, OMIM 190070), a gene "downstream" of *PTPN11*. They identified *de novo* germline *KRAS* mutations in 5/174 subjects with Noonan syndrome without *PTPN11* mutations. The most common mutation (present in 3 patients) was substitution of isoleucine for valine at amino acid 14 (Val14Ile); this mutation depressed intrinsic GTPase activity of *KRAS*.

The cardio-facio-cutaneous syndrome (OMIM 115150) is associated with congenital heart disease (pulmonic stenosis, atrial septal defect, hypertrophic cardiomyopathy), distinctive face (high forehead, bitemporal narrowing,

hypoplastic supraorbital ridge, depressed nasal bridge, angulated ears), cutaneous abnormalities (sparse hair, ichthyosis-like thickening), and developmental delay. Schubbert et al found a heterozygous mutation in *KRAS* in 1/12 patients with this syndrome. Niihori and colleagues also identified 2 *de novo* germline heterozygous mutations in *KRAS* in 3/43 patients with the cardio-facio-cutaneous syndrome. These investigators further demonstrated 8 heterozygous mutations in *BRAF*-encoding the serine/threonine kinase most immediately responsive to *KRAS* (Figure) in 16/40 patients with the cardio-facio-cutaneous syndrome; 6/8 mutations were localized to the catalytic domain of *BRAF*. The majority of the mutations in *KRAS* and *BRAF* increased signal transduction through the MAPK pathway. These investigators identified no mutations in *PTPN11* in any patient with the cardio-facio-cutaneous syndrome nor did they find aberrations in *KRAS* or *BRAF* in any Noonan subjects. Rodriguez-Viciana and associates found 11 heterozygous gain-of-function *BRAF* mutations in 18/23 patients with the cardio-facio-cutaneous syndrome. They also identified 2 heterozygous, activating mutations in *MAP2K1* and one such mutation in *MAP2K2* in 3/5 patients with this disorder.

Schubbert S, Zenker M, Rowe SL, et al. Germline *KRAS* mutations cause Noonan syndrome. *Nature Genet.* 2006;38:331-336.

Niihori T, Aoki Y, Narumi Y, et al. Germline *KRAS* and *BRAF* mutations in cardio-facio-cutaneous syndrome. *Nature Genet.* 2006;38:294-296.

Rodriguez-Viciana P, Tetsu O, Tidyman WE, et al. Germline mutations in genes within the MAPK pathway cause cardio-facio-cutaneous syndrome. *Science.* 2006;311:1287-1290.

First Editor's Comment: *The signal transduction pathway and associated genetic syndromes are shown in the figure. Mutations have now been found in several of the protein components of the MAPK signal transduction pathway. That Schubbert et al found 169 patients with clinical manifestations of Noonan syndrome without *PTPN11* or *KRAS* mutations demonstrates the substantial genetic heterogeneity of this disorder and leads one to anticipate the identification of gene mutations in other components of the MAPK signal transduction pathway, perhaps involving SOS, MAPK3, guanosine nucleotide exchange factors, and/or GTPase activating proteins. Indeed, neurofibromin, the neurofibromatosis type 1-associated tumor suppressor product of *NF1*, is a GTPase activating protein for RAS.*

*With the delineation of more and more specific gene mutations leading to clinically described disorders, it may well be time to redesignate such entities according to the gene mutation itself; eg, "Hyperactive RAS disease: type 1, 2 ...," "Hyperactive *PTPN11* disease: type 1,2 ...," or according to the genetic pathway involved, eg, "The MAPK syndromes." Indeed, all of the clinical disorders of this pathway share common features to a greater or lesser degree such as short stature, distinctive faces, developmental delay, congenital anomalies of the heart, and skin changes. With intimate knowledge of the basic*

abnormalities within the described syndromes, drugs might be devised that ameliorate the hyperactivity of the MAPK pathway and moderate its clinical manifestations. Prenatal diagnosis and perhaps even fetal gene therapy also loom as possible future therapeutic avenues.

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Second Editor's Comment: The reader is referred to Vol. 22, No. 2 of GGH for a review of 3 papers dealing with the increased growth hormone resistance of PTPN11 accounting for the short stature of patients with Noonan

syndrome.³ A similar resistance may also be present in other patients with syndromes with or without PTPN11 or KRAS mutations, as they all share common features and short stature. The availability of recombinant IGF-I and IGF-III/IGF BP3 may now allow treatment strategies not previously available.

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3. Growth Genet Horm. 2006;22 :23-26.

Idiopathic Short Stature: Psychosocial Development and GH Treatment

Visser-van Balen and colleagues presented a metanalysis of available research on the psychosocial functioning of medically referred children with idiopathic short stature (ISS) and the effects of growth hormone (GH) treatment. Specifically, the authors asked whether or not subgroups of medically referred children with ISS have specific risks and different outcomes when treated. Their search used the Medline and PsycInfo databases and included 11 studies that assessed psychosocial functioning. The results showed that according to parents, short children have lower social competence and more social problems than children with normal stature. The intelligence of the ISS children was within the normal range; however, they functioned on average between normal and below normal. Admittedly, the effect sizes were very small in these studies. Studies on the consequences of being short on psychosocial functioning in adulthood were inconclusive, as none of the adults in the studies had received GH. Two studies reported a relatively low percentage of marriages and relatively high percentage of unemployment and self-reported problems in social functioning among short adults. Other studies have not shown this effect. Of note, most of the studies among children only examined parental records. Studies using teachers and peers did not show lower social competence. Children's own reports regarding self esteem showed relatively few indications of psychosocial problems. The interpretation was that either these children are too young to give an adequate assessment of their own functioning, or they lack time perspective. There were no studies in which similar concepts were studied by both parents and children. The authors speculated that it was possible that medically referred children with ISS had psychosocial problems because they were short. It is also possible that children with psychosocial problems, who were also short, may be referred relatively often. Their conclusion was that medically referred children with ISS had on average more psychosocial problems than children with normal stature.

The review suggested that some risk factors for maladaptation in children with ISS include being teased, being juvenilised, being a boy, having a low intelligence,

having a younger but taller sibling, and being part of a low socioeconomic status family. Further studies on the impact of the degree of shortness did not find an effect. This may be because it was not actual height, but perceived height which was crucial in terms of psychosocial risk factors.

Finally, the effects of GH treatment on psychosocial factors were assessed in 9 studies in which the children had a mean height gain of at best 7 cm. On average, GH treatment did not improve psychosocial functioning and only a few studies showed improvement in problem behaviors. Although these pre- to post-treatment assessments with standardized questionnaires did not reveal changes in psychosocial functioning, a retrospective perception of GH treatment by parents and children was generally positive with parents reporting a positive change regarding social functioning and self-esteem of their children.

The 3 main conclusions of this review included: (1) parents of medically referred children with ISS ranked the behavior of their children on average between normal and below normal with more psychosocial problems, (2) some risk factors influencing adaptation in children with ISS have been found, and (3) GH treatment is a means to gain height, but not a means to solve psychosocial problems.

Visser-van Balen, H; Sinnema, G; Geenen, R. Growing up with idiopathic short stature: psychosocial development and hormone treatment; a critical review. Arch Dis Child. 2006;91:433-439.

First Editor's Comment: This is a very interesting metanalysis, which is probably the first of many subsequent reports to be written concerning ISS and psychosocial functioning. There are many justifiable critiques of the data presented including the lack of control groups, lack of randomization, variable ages at initiation of therapy, and variable duration of treatment. These variables suggest the need for long-term prospective studies in children with ISS for whom treatment is initiated and for whom treatment is not given. It is hoped that one of the GH registries will initiate such a study and that sufficient numbers of children can be