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Growth hormone and noonan syndrome: update in dysfunctional signaling aspects and in therapy for short stature

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Abstract

Short stature is a frequent feature of Noonan syndrome (NS), a disease caused by mutations of genes encoding components of the Ras/mitogen-activated protein kinases (MAPK) signalling pathway. To date numerous patients have been treated with growth hormone (GH) in various countries. However this treatment is still controversial, as its efficacy is a matter of debate. The final height gain of GH therapy represents 5 to 10 cm, at best, which is disappointing considering the length and burden of the treatment. The reasons explaining this lack of efficiency are poorly understood and they seemed to involve a waning effect after the first year of GH treatment or acceleration of bone maturation in patients on GH. Moreover, GH therapy raises questions about its safety, especially in subjects with NS who are at risk for cardiac defects and malignancies. Cases of severe adverse effects were described, yet too sporadically to conclude that they were certainly caused by GH therapy. Novels insights in understanding the dysfunction of GH-dependent processes in NS were recently reported and this manuscript aims at reviewing the latest advances. Clinical data suggested that growth retardation could be caused by a partial postreceptor resistance to GH, an impaired sensitivity to GH which could also explain the modest efficiency of GH therapy in NS patients. Similar observations were also obtained in a NS mouse model harboring a mutation in the gene encoding the tyrosine phosphatase Shp2. In the mouse, the mechanism of GH resistance is thought to involve upregulation by mutated Shp2 of GH-induced Ras/MAPK, a signaling pathway which seemed to play a negative regulatory role in the production of GH mediators involved in bone growth. Despite these recent finding, the underlying mechanisms of growth retardation and GH therapy in NS remain to be further explored in order to improve treatment for short stature.

Keywords: Noonan syndrome, growth hormone, PTPN11, shp2, ras/MAPK, rasopathy

Introduction

Noonan syndrome (NS) is a frequent (≈1/1500-2000 live births) autosomal dominant developmental disorder primarily characterized by short stature, typical facial features and heart defects. Patients with NS can also be affected with a variety of other symptoms including increased cancer risk, skin or bone defects, gastrointestinal issues, altered cognitive or/and psychosocial abilities etc. These manifestations are also observed, with different intensity, in related diseases including NS with multiple lentigines (also referred to as LEOPARD syndrome), Costello syndrome, cardiofaciocutaneous syndrome and neurofibromatosis-I. This family of clinically related disorders is now called the "Rasopathy" group, as they are caused by mutations in genes encoding components of the so-called Ras/mitogen-activated protein kinase (MAPK) pathway, an intracellular signaling pathway which primary function is to transduce signals from growth factor receptors to the cell nucleus. These genes include *PTPN11*, which is mutated in ≈50% of NS cases, *SOS1* (≈10%), *RAF1* (≈10%), *KRAS* (<2%), *NRAS*, *SHOC2* and *CBL*. Recently, *RIT1*, encoding a protein related to Ras, appeared as a novel NS-causing gene [1]. *HRAS, MEK1, MEK2, NF1* and *SPRED* are additionnal genes which mutations can be responsible for other Rasopathies [2-4].

As a general mechanism for pathogenicity, the mutations causing NS induce, in most cases, an activation of the enzymes encoded by these genes. Most frequently this stimulation is moderate in terms of biochemical activity measured *in vitro*. However, in the cell or *in vivo*, these mutations result almost systematically in a higher-than-normal activation of the Ras/MAPK pathway. This hyperactivation is thought to be responsible for the disease phenotype, as shown by studies in mice which began to explore the mechanisms involved in the pathogenicity of genes causing NS or other Rasopathies [5-7].

Several reviews have recently updated progress in epidemiology, etiology, diagnosis and treatment of clinical aspects of NS [2-4]. This current manuscript aims at examining in details the recent advances in understanding and treating short stature in in NS, as well as the latest progress in GH-dependent signalling pathways involved in short stature.

Short stature is one of the most frequent clinical manifestation of NS, even though adult final height may strongly vary from one patient to the other. In 2007, the U.S. Food and Drug Administration approved treatment of short stature caused by NS with recombinant growth hormone (GH) in doses up to 66 µg/kg/day. To date, numerous patients have been treated with GH in various countries. However GH treatment for NS is still

controversial. Indeed, the efficacy of GH therapy is a matter of debate, as data from the literature are sparse and difficult to compare between different reports, because of differing protocols and outcome criteria. In addition, GH treatment raises questions about its safety, especially in children who are at risk for cardiac defects and malignancies.

Other uncertainties about GH action in NS involves the mechanisms leading to short stature. Clinical data, as well as observations obtained in a NS mouse model, suggest that growth retardation could be caused by a partial postreceptor resistance to GH, an impaired sensitivity to GH which could also explain the modest efficiency of GH therapy in NS patients. Recently, insights in these different issues have been reported and this manuscript aims at reviewing the latest advances.

Characterization of short stature in NS
Spontaneous growth and adult height in patients with NS
The question of final height in patients with NS remains a pending issue. Indeed, individuals with NS seem to have delayed bone age, their onset of puberty can be postponed by up to two years, and thus their growth may occur at an older age than normal subjects [8]. Therefore final adult height in NS subjects should be measured at the end of the second decade (at least in boys) and data reported at this age are not very abundant [9]. Nevertheless, it appears that about 30-50 % of NS patients reach "normal" final adult height without treatment [10] (The height of an individual is defined as normal if it is above the 3rd percentile on the growth chart relative to her/his peers, which corresponds to a height standard deviation score (SDS) for the individual's calendar age comprised between -2 and 2).

Reports on spontaneous growth in subjects with NS have shown varying results, especially in males. Earlier reports indicated that mean final height is ≈150-152 cm in girls and ≈160-162 cm in boys [8,11]. More recently, a mean adult height for males has been measured at 167 cm [12], or at 169 cm in a German study [13], which is higher than previously observed. In contrast, a study from Brazil found a mean final height of 148.4 cm in females and 157.4 cm in males [14], which is smaller than other studies. The origin of these discrepancies is not entirely clear. It could be due to ethnic differences or to a limited number of patients measured in these studies. However, it must be noted that the Brazilian report took into account only patients with confirmed molecular diagnosis. This allowed the inclusion of individuals with subtle phenotypes, whereas other studies included patients with clinical diagnosis, among which a significant proportion did not have a molecular diagnosis.

Interestingly, Wang et al., recently suggested that NS may be an underdiagnosed cause of delayed growth in patients with idiopathic short stature. Indeed, while screening candidate genes in a cohort of children with short stature and without known genetic etiology, they identified a few individuals with *PTPN11* mutations causing NS, a disease which had not

been yet diagnosed in these subjects [15].

Influence of genotype on spontaneous growth in subjects with NS
Different groups of clinicians reported a lower prevalence of short stature in patients with *SOS1* mutations, compared with NS subjects harboring other genotypes [16-19]. In agreement, Malaquias et al., recently observed in 14 *SOS1* patients a mean height SDS of +0.4 (±0.8) compared to NS standard (which is thus composed, in majority, of subjects mutated in *PTPN11*) [14]. In this study, the authors also observed that individuals with *BRAF* mutations, similarly to those mutated in *SOS1*, have better preserved postnatal growth compared with patients harboring other genotypes [14]. In contrast, short stature seems to be more frequently associated with mutations of *RAF1* (mean height SDS of -0.5±0.9 SDS compared to NS standards) or *SHOC2* (-1.3±0.7) [14,20,21]. Nonetheless, it must be emphasized that these reports did not take into account a large number of patients, notably in the case of subjects with rare genotypes (e.g., *SHOC2* mutations). Therefore it is likely that future studies involving more individuals will certainly amend these data, at least on a quantitative point of view. Additionnally, it remains to identify the mechanisms explaining how distinct genotypes can differentially influence the spontaneous growth of children with NS.

GH therapy in NS
What is the actual gain of GH therapy on patient's height?
Thus far, data on final height after long term GH treatment are sparse and very few reports with appropriate controls on the effect of GH have been published. Most data reported in the literature have been obtained through observational studies on a limited number of patients, the majority of these investigations lacking a control group.

Despite these limitations, it is worthwhile to analyze the different reports which addressed this question [22-31]. Their data are summarized in **Table 1**. Although these studies do not all report outcomes at final height, this table suggests, as a whole, that the overall height gain under GH therapy is small, ranging from 0.8 to 1.4 in terms of height SDS increase. This represents a final height gain of 5 to 10 cm at best. At first sight, this may seem to be an outcome below expectations, considering the length, cost and burden of the treatment. However, when an increase of 5 to 10 cm in final adult height is effectively achieved, this can be considered as a reasonable result, considering that it may allow to reach normal adult height in a large subset of patients. It is also noteworthy that this range of increase in final height is similar with outcomes of GH-therapy in other non-GH deficient children. These include patients with Turner's syndrome who can usually gain a mean of 7 cm (range 5-15 cm) under GH therapy [4].

Among the data shown in **Table 1**, it is especially interesting to analyse the studies reporting GH therapy effects in patients who reached adult or near adult height. Intriguingly, these

Table 1. Results are mean values unless otherwise specified. Height SDS is reported according to general population standards.

Reference	Number of patients n (n ♀)	Baseline age year	Baseline height SDS	GH dose *mg/kg/week*	Duration of therapy year	Δheight SDS after therapy	Height gain at adult age *cm*
Kirk et al., 2001 [22]	10 (4)	12	-3.1	0.30	5.3	0.8	3.1
Mcfarlane et al., 2001 [23]	23 (7)	9.3	-2.7	0.33	3	0.8	N.A.
Ogawa et al., 2004 [24]	15 (7)	7.5	-2.8	≈ 0.17	2	0.6	N.A.
Binder et al., 2005 [25] Mut+	8 (N.A.)	7.4	-3.46	0.29	1	0.66	N.A.
Mut-	3 (N.A.)	6.3	-3.80	0.35	1	1.26	N.A.
Osio et al., 2005 [26]	18 (11)	8.7	-2.9	0.23-0.46 *range*	≈ 9.8	1.7	13(♂) 9.8(♀)
Liman et al., 2006 [27] Mut+	15 (N.A.)	10.4	-3.5	0.3 or 0.46	2	0.4	N.A.
Mut-	10 (N.A.)	10.3	-3.0	0.3 or 0.46	2	1.0	N.A.
Noordam et al., 2008 [28]*	29 (8)	11	-2.8	0.35	6.4	1.3	N.A.
Raai jmakers et al., 2008 [29]*	24 (N.A.)	10.2 *median*	-3.24 *median*	0.17-0.77 *range*	7.59 *median*	0.87 *median*	N.A.
Romano et al., 2009 [30]	65 (30)	11.6	-3.5	0.33	5.6	1.4	10.9(♂) 9.2(♀)
Lee et al., 2012 [31]	120 (30)	9.2	-2.65	0.33-0.41 *range*	4	1.33	N.A.

Baseline age: age at start of therapy
Δ height SDS after therapy: increase in height SDS after therapy
N.A., Not available; *Same research group
Mut+, patients mutated on PTPN11; Mut-, patients not mutated on PTPN11.

studies may be distinguished in two classes, depending on the extent of the increase of height SDS they report. Thus Kirk et al., observed a moderate increase in height SDS of 0.8 in 10 patients [22], which is in accordance with a rise of 0.87 in 24 patients reported by Raaijmakers et al., [29]. On the other hand, Osio et al., Noordam et al., and Romano et al., reported better outcomes of GH therapy, with increases in height SDS ranging from 1.3 to 1.7 on a total of 112 patients [26,28,30].

Various factors were proposed to explain these discrepancies between studies, in addition to the limitations described above. One of these factors is duration of therapy. For example, in the study by Kirk et al., patients were treated on average for 5.3 years, whilst reports by Osio et al., or Noordam et al., are based on subjects treated for longer duration (9.8 and 6.4 years, respectively). Nevertheless, other factors appear to be involved in these discrepancies, since patients treated for 7.6 years in the Raaijmakers' study failed to show an increase of height SDS above 0.87 (**Table 1**).

One of these factors is certainly children's age at start of therapy. Indeed, an earlier initiation of treatment is thought to result in a better outcome, as longer duration of GH therapy during the prepubertal period was found to produced greater height gains [26,30]. It is also important to consider that the link between earlier start of GH therapy and optimal height gain has been also observed in other growth-related disorders, including Turner's syndrome [4,32]. However, this view must be somewhat balanced with the fact that GH therapy has an accelerating effect on bone age, which may eventually reduce

the benefit of GH treatment, considering that patients on GH could terminate their growth earlier than in untreated individuals (Cf. 2.2.2).

An additional source of variation between the above studies could be due to different doses of GH used in these studies, even though no significant correlation of given dosage to final height has been found to date [22,26,28]. For example, Osio et al., did not observe a significant difference between two sets of nine patients receiving 0.23 or 0.46 mg of GH per kg and per week [26]. Nevertheless, additional studies are certainly required to define more accurately the role of each of these factors in the efficiency of GH therapy.

An important, yet poorly studied, aspect of GH therapy is the psychological impact of this treatment in children with NS. Besides the fact that the attitude of patients' parents is essential for treatment compliance on the long term, Westphal indicated that short stature can represent a further stigma in children who may be already perceived as different from "normal" subjects. On the other hand, daily injection of GH could increase the perception of being ill in these patients [33]. Studies are thus required to examine with attention the psychological consequences of GH therapy in NS patients, a question which interest is reinforced by the fact that NS patients may be at risk for elevated anxiety or depression [34,35].

Another significant issue of GH therapy is treatment cost. Analyses based on cases of Turner's syndrome or idiopathic short stature assessed this cost as 33,750 to 35,000 US$ per

centimeter of height gained. However, recent market entry of new competitors and/or generics is expected to decrease this cost by ≈60%, an economic progress that should indirectly contribute to the prescription of GH therapy to more NS patients [36,37].

Hypothetical mechanisms illustrating the reduced outcome of GH therapy in NS
Waning effect of GH therapy
As shown above, GH therapy in patients with NS appeared to have a limited effect on short stature, even though additional investigations are still required to define precisely the effect of GH therapy. The explanations for this lack of efficiency are unclear. An important aspect of this issue has been revealed by reports showing a waning effect of GH therapy after the first year of treatment. For example, Kirk et al., observed on a sample of 66 patients treated with GH an increase of height SDS of 0.3 during the first year of therapy, which was followed by a similar increase when considering as a whole the 5 following years [22]. Similarly, MacFarlane et al., measured, in 19 individuals treated with GH, height velocity of 8.4 cm for the 1st year of treatment, then 6.2 and 5.8 cm/year for the two following years [23]. On the same theme, Raaijmakers et al., observed increments of 0.54, 0.13 and 0.13 in height SDS for 3 successive years, respectively [29].

The mechanism of this waning effect is unknown and further investigations are necessary to address this question and define the factors influencing this effect. Recently Lee et al., reported an absence of waning effect of GH therapy [31]. The reason for this discrepancy with former studies is unclear but this latter study only included a small set of seven patients, and the dose of GH given to the patients was slightly increased each year, which might thus have compensated for the waning effect.

Acceleration of bone maturation by GH therapy
As mentioned above, subjects with NS seem to have delayed bone age, and thus their growth may occur at an older age than normal individuals [8]. Thus, Noordam et al., proposed that the lack of efficiency of GH therapy could be due, at least partially, to the accelerating effect of GH on bone maturation. Indeed, they observed that bone development was significantly faster in a group of NS patients treated with GH, compared with subjects not receiving GH. Thus, whereas patients under GH therapy may grow faster than untreated subjects, their final height might be compromised by accelerated maturation of bone which should terminate their growth earlier than in untreated individuals [38]. However, at this stage of our knowledge, the actual contribution of this hypothetical mechanism in restraining GH therapy efficiency must be further explored.

Other mechanisms
In addition to the above mechanisms, it appears to date that the limited effect of GH therapy on the growth of children with NS could be linked to the fact that patients may present mild GH resistance due to a defective postreceptor signaling. This GH insensitivity could be also the cause for short stature. Therefore this theme will be discussed in chapter 3.

Potential adverses effects of GH therapy
Besides the fact that GH therapy has a limited effect on patient's final height, this treatment raises safety questions in children affected by a syndrome with frequent cardiac defects and increased risk of malignancies.

From studies in acromegalic patients and in transgenic mice, it is known that long-standing elevated GH increases ventricular wall thickness, which can ultimately lead to long-term pathological structural and functional changes in the heart [39]. The effects of GH treatment on the heart of subjects with NS were assessed in a few prospective studies, which included children with cardiac defects (none of them with severe hypertrophic cardiomyopathy) [40-42]. These reports did not show major changes of cardiac dimensions in GH-treated individuals, compared to the group of control subjects. However the significance of these data is somewhat restricted by the reduced number of patients followed up and by the limited duration of the GH treatment in these studies (range 1-3 years), in comparison with the much longer extent of GH therapy required to improve growth in patients with NS.

Other studies reported adverse effects of GH therapy at the heart level. For example, Noordam pointed out that cardiac adverse reactions were reported in 7 subjects among 429 children with NS treated with GH. These adverse effects include 1 cyanotic episode, 3 cardiac arrhythmias, 1 angina pectoris, 1 severe left ventricular hypertrophy and 1 cardiomyopathy necessitating heart transplant. They occurred after different lengths of treatment (2-10 years) [43]. Similarly, Romano et al., identified 5 cardiac events among the combined 889 patients from studies that reported adult-height outcomes in patients with NS on GH. These cardiac events included 2 mild progressions of pulmonic stenosis, 1 hypertrophic cardiomyopathy, 1 increased biventricular hypertrophy and 1 cardiac decompensation [44].

In addition to cardiac adverse effects, the risk of promoting tumorigenesis is another important concern about GH therapy. Indeed it is well known that, as a consequence of harboring mutation of genes of the Ras/MAPK pathway, subjects with NS display spontaneously an increased risk of developing cancer, and notably juvenile hematological malignancies [3,45]. This susceptibility to cancer is certainly a consequence of the mutations causing NS which are located in genes of the Ras/MAPK pathway, a signaling module that regulates cell proliferation or survival in a variety of different tissues. Consequently, GH therapy could potentially aggravate the risk of developing cancer in subjects with NS, considering that GH can also contribute to the activation of Ras/MAPK or other proliferative signaling pathway, either directly through

its own GH receptor, or through long-term elevated IGF-1 concentration resulting from GH treatment.

Thus far the question of whether GH therapy further increases the risk of tumorigenesis in NS patients is not definitely close, even though the issue of GH safety has been studied with attention in follow-up studies [23,31]. A few reports mentioned cases of tumorigenesis (1 lymphoma and 1 skin tumor) in children treated with GH but these appeared too sporadically to conclude with confidence that they were caused by GH treatment [26,46]. Moreover, it must be taken into consideration that early cancer is more frequent in NS patients than in the general population [2,3]. Therefore, these cases of tumorigenesis can be also observed in NS subjects without GH therapy. In addition to cardiac and neoplasic adverse effects, GH therapy could potentially interfere with bone homeostasis and with carbohydrate and lipid metabolism. Supporting this view, 6 cases of scoliosis were reported in a panel of 65 patients under GH therapy [30]. Nevertheless, it is important to consider that scoliosis is not rare in NS. Therefore further studies are required to define whether GH therapy has a negative influence on the frequency of this manifestation.

The concern for putative metabolic dysregulations caused by GH is due to the well-known effect of GH as promoting a mild form of insulin resistance. Supporting this view, Osio and collaborators observed a slight temporary increase in fasting insulin levels in a small number of NS children treated with GH. However, in this set of patients, other markers of altered glucose metabolism were within the normal range [26].

Moreover, it was recently reported that patients with NS have a mean body mass index lower than normal subjects [13,14]. Although this observation requires to be confirmed in larger groups of patients, it is not totally unexpected when considering certain reports which addressed the function of Shp2 (the *PTPN11* gene product) in the mouse metabolism. For example, expression of a dominant active mutant of Shp2 (which is biochemically comparable to a mutant causing NS) in the mouse brain leads to resistance to high fat diet-induced obesity and to improved insulin sensitivity [47]. Consequently it is possible to speculate that NS patients could be somewhat protected from metabolic disorders, which could minimize the possible adverse effects of GH therapy on carbohydrate and lipid metabolism. Studies in patients and in animal models of NS are under way to investigate this intriguing question.

To conclude this chapter on adverse effects of GH therapy, it must be emphasized that, whatever the type of adverse reaction, additional studies are needed to investigate these issues, as, to date, it seems difficult to draw any definite conclusion.

Mechanism(s) explaining short stature in NS
Hypotheses drawn from clinical observation
Feeding difficulties
Various hypothesis were proposed to explain the origin of short stature in NS. Initially, as children with NS frequently display feeding difficulties during their first years of life, this was thought to explain their delay in thriving during this period. However, feeding issues are no longer considered as a major cause of growth retardation in NS, as feeding difficulties usually improve after the first year of life, whilst children remain short for their age [10].

Neurosecretory defects in GH secretion
Another possible cause for growth retardation was provided by the description of signs of neurosecretory dysfunctions at the level of GH secretion in children with NS [48]. Nevertheless, recent data showed that the majority of NS patients have normal or elevated concentrations of circulating GH, which argues against the view that short stature in NS could be primarily due to impaired GH secretion [25,27].

Defects in bone homeostasis
An emerging hypothesis regarding the cause of growth issues in NS speculates on the existence of dysfunctions at the bone level, through putative defects in the growth plate. This idea is based on the observation that orthopedic manifestations are a common feature of Rasopathies. In the case of NS, scoliosis and other spinal deformities are frequently encountered [49,50] and it was recently reported that NS children may have decreased bone mineralization [51], even though this study was performed on a limited number of patients. This hypothesis is also based on a recent report showing that *PTPN11* disruption causes severe skeletal defects in mice [52]. Nonetheless the validity of this hypothesis has not been tested yet.

Signs of GH resistance
To date, the leading hypothesis about the origin of growth impairment in NS postulates that patients present a mild resistance to GH (at least those harboring *PTPN11* mutations). This partial insensitivity to GH could be the consequence of putative postreceptor signaling defects, which seem to be partially compensated for by elevated concentrations of circulating GH. This view is based on the fact that all the genes causing NS are involved, at least in theory, in the processes of intracellular signaling activated by the GH receptor, considering that Ras/MAPK is one of the major signaling pathway stimulated by this receptor. Moreover, this hypothesis was strongly supported by recent reports showing that patients with normal or increased GH levels display lower-than-normal concentrations of insulin-like growth factor (IGF)-1, IGF-binding protein (IGFBP)-3 and acid-labile subunit (ALS) [25,27] (IGF-1 is a major mediator of GH action, as it directly promotes the growth of long bones and its production is upregulated by GH; along with IGF-1, the functional action of GH on bone growth can be assessed by assaying the circulating concentrations of IGFBP-3 and ALS, which production is also stimulated by GH).

Interestingly, these reports also suggested that the extent

of GH resistance was more pronounced in individuals with *PTPN11* mutations than in patients not mutated in this gene. Indeed, the decrease of IGF-1, IGFBP-3 and ALS levels has a tendency to be more pronounced in children harboring *PTPN11* mutations than in patients with other mutations. In agreement with this, individuals mutated in *PTPN11* appeared to respond less to GH therapy than other NS patients [25,27].

Supporting the concept of GH resistance in patients with *PTPN11* mutations, other clinicians subsequently reported that these individuals display, under GH therapy, smaller increments in IGF-1 levels or in short-term growth, compared with subjects without *PTPN11* mutations [28,53]. However, in one of these studies which also measured patients growth, long-term GH treatment was not found to make a significant difference on the growth of children harboring *PTPN11* mutations, in comparison with other NS patients [28]. Supporting this later observation, a recent study failed to find different levels of basal IGF-1 and IGFBP-3 between patients with or without *PTPN11* mutations, while this study did confirm that NS patients, harboring or not *PTPN11* mutations, have abnormally low levels of IGF-1 and IGFBP-3 in comparison with normal subjects [54]. However, a recent study measuring IGF-1 after stimulation of GH secretion did find a significant difference between 12 NS patients harboring PTPN11 mutations and 12 children with idiopathic short stature as control group. Indeed, the increase of IGF-1 following stimulation of GH secretion was significantly blunted in the first group, compared to the control group [55].

Therefore, it seems that a consensus view is established on the fact that NS patients display signs of GH resistance. In contrast, the question of whether patients with *PTPN11* mutations are less sensitive to GH than other patients is still a matter of debate. Discrepancies on this issue between the above reports could be explained by the small number of patients available in these studies and by the fact that the group of "NS subjects without *PTPN11* mutations" does not seem to represent an appropriate control group in these studies. Indeed, as seen in chapter 1.2., recent data indicate the existence of significant differences between patients in this group, considering, for example, that patients with mutations of *SOS1* or *BRAF* display a lower prevalence of short stature. Thus long term correlation between genotype and GH therapy responsiveness must be addressed in larger cohorts and by taking into account the genotype of the subjects in the control groups.

Possible mechanism for postreceptor GH resistance: Study of GH signaling in NS mouse model
As shown above, clinical data strongly suggested that defective growth in NS could be linked to postreceptor GH resistance. Considering that the mechanism of partial insensitivity to GH is unknown, it is worthwhile to explore the signaling pathways downstream of the GH receptor and possibly involved in GH resistance. Among all the genes causing NS, only the role of

PTPN11/Shp2 mutants has been adressed thus far. Shp2 is an ubiquitous protein tyrosine phosphatase which is preferentially activated by receptor tyrosine kinases, including cytokine receptors such as the GH receptor. In the following section, we will present the knowledge of Shp2 contribution to GH signaling as it is currently envisioned in healthy subjects, then in a NS mouse model.

The current view of signaling pathways involving PTPN11/ Shp2 downstream of GH receptor in healthy subjects
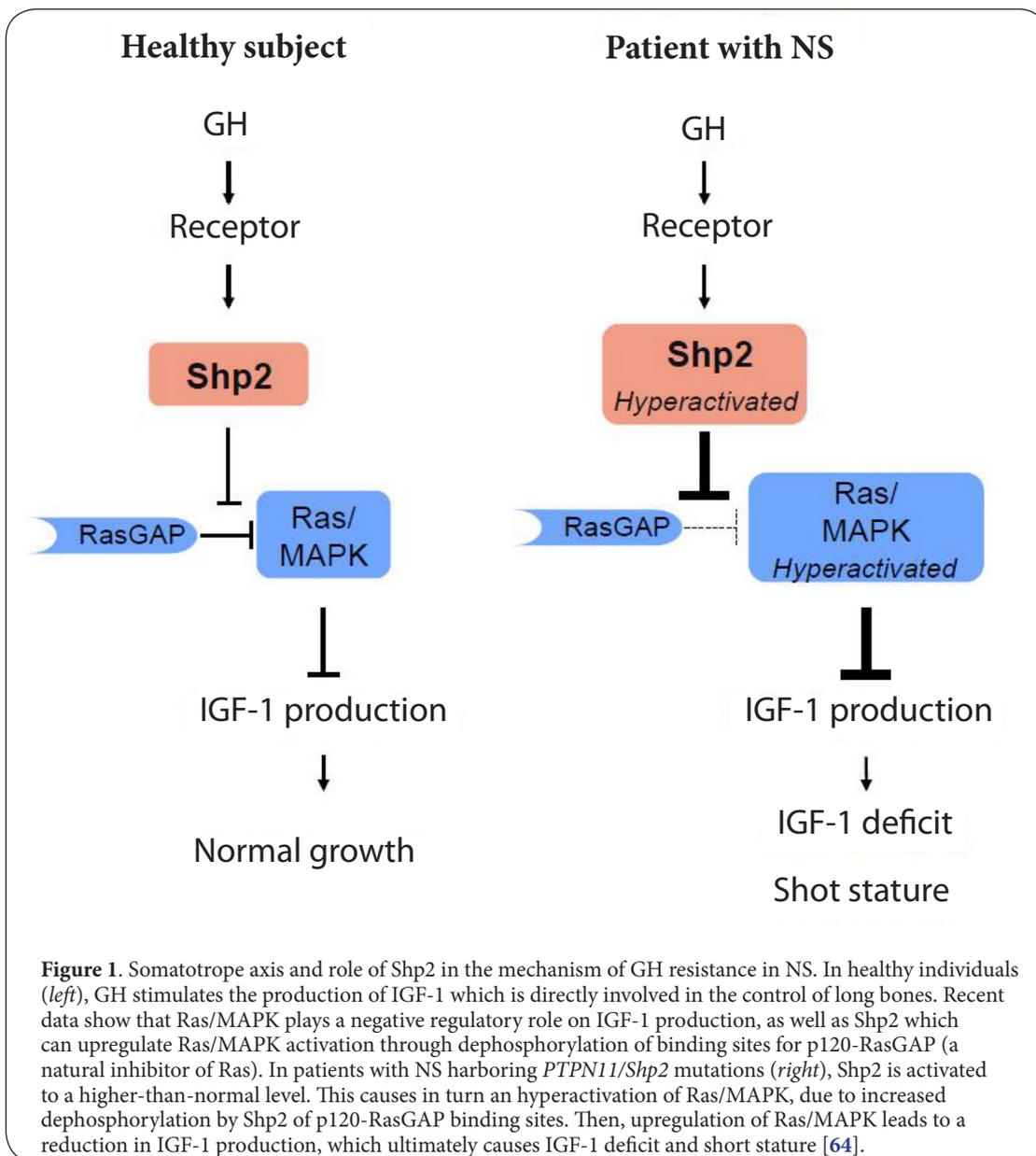When considering as a whole the molecular mechanisms resulting from GH binding to its membrane receptor, it begins with activation of the GH receptor-associated cytoplasmic tyrosine kinase, Janus kinase-2 (JAK2). GH-induced JAK2 stimulation leads to engagement of three major intracellular signaling pathways, namely the signal transducer and activator of transcription-5 (STAT5), the phosphoinositide 3-kinase (PI3K) and the Ras/MAPK pathways. These signaling modules are thought to mediate virtually all of GH biological activities [56].

Regarding the specific involvement of Shp2 in GH signaling, only a few studies have addressed this question, despite its interest from both fundamental and pathophysiological points of view. Two different research groups reported that Shp2 is rapidly recruited during cell stimulation with GH, which suggested that this phosphatase is a significant signaling intermediate downstream of the GH receptor [57,58]. In addition, the adapter protein Gab-1 was found to be significantly phosphorylated in a preadipocyte murine cell line stimulated with GH [59] (our unpublished data). This observation strengthened the idea that Shp2 could participate in GH receptor signaling, since a major general function for phosphorylated Gab-1 consist in mediating Shp2 activation in response to various stimuli [60,61].

Once activated, Shp2 most certainly plays a role in GH receptor signaling but its function downstream of this receptor is unclear. Studies in transfected cells over expressing either wild type Shp2, or Shp2 forms defective for one of its molecular functions, suggested that the phosphatase could act as a negative regulator of GH receptor signaling, possibly by dephosphorylating STAT5A [62,63]. Nevertheless, although these findings have been reported more than ten years ago, they remain to be validated in different cell types and in animal models. Moreover, research presented in the following paragraphs does not argue in favor of a major role of Shp2 in STAT5 regulation.

Role of PTPN11/Shp2 mutant causing NS in Ras/MAPK upregulation and GH resistance in a NS mouse model
The notion that short stature in NS could be linked with GH resistance was recently reinforced by a study taking advantage of a mouse model expressing a Shp2 mutant which corresponds to a mutation causing NS in human (*PTPN11*[D61G/+]) [5]. These mice exhibit a smaller size, which is associated with lower blood concentrations of IGF-1 and IGFBP-3 than in wild

Figure 1. Somatotrope axis and role of Shp2 in the mechanism of GH resistance in NS. In healthy individuals (*left*), GH stimulates the production of IGF-1 which is directly involved in the control of long bones. Recent data show that Ras/MAPK plays a negative regulatory role on IGF-1 production, as well as Shp2 which can upregulate Ras/MAPK activation through dephosphorylation of binding sites for p120-RasGAP (a natural inhibitor of Ras). In patients with NS harboring *PTPN11/Shp2* mutations (*right*), Shp2 is activated to a higher-than-normal level. This causes in turn an hyperactivation of Ras/MAPK, due to increased dephosphorylation by Shp2 of p120-RasGAP binding sites. Then, upregulation of Ras/MAPK leads to a reduction in IGF-1 production, which ultimately causes IGF-1 deficit and short stature [**64**].

type animals [**64**]. Therefore this mouse model appeared to present similar endocrine dysregulations as those observed in children with NS. This led us to explore the impact of this mutant on GH signaling, which was achieved in transfected cells. We thus observed that, in cells stimulated with GH, the mutant produced higher-than-normal activation of Ras/MAPK, whereas STAT5 and PI3K pathways appeared to respond with normal intensity to GH stimulation. The molecular mechanism of this Ras/MAPK upregulation was found to involve increased dephosphorylation by a NS-causing Shp2 mutant of a binding site for p120-RasGAP (GTPase activating protein), a negative regulator of Ras. Therefore, enhanced dephosphorylation of this binding site by the mutant results in downregulation of

p120-RasGAP recruitment in GH-induced signaling complexes, which eventually produces an increased activation of Ras [**64,65**] (see **Figure 1** for schematic representation of this regulation).

Interestingly, this study also showed that treating NS mice with a Mek inhibitor restores IGF-1 level and increases their growth [**64**]. In agreement with this, earlier reports incidentally showed that Mek inhibitors can rescue growth defect in other NS mouse models (*RAF1*[L613V/+] and *SOS1*[E846K/E846K]) [**7,66**]. Altogether, these reports suggest that pharmacological regulation of Ras/MAPK could be an alternative approach to treat short stature in NS patients, even though a lot requires to be accomplished to assess the efficacy and safety of these

future treatments, in comparison with GH therapy.

Finally, the emerging concept that NS patients display GH resistance also suggests that an alternative treatment for short stature could be provided by recombinant human IGF-1 (rhIGF-1). This therapy is currently used to treat patients with severe GH insensitivity (e.g., patients with Laron syndrome, caused by absent or defective GH receptor) [67]. Therefore, even if the efficacy of rhIGF-1 to treat severe GH resistance is currently debated [68], this treatment could be helpful in NS patients, possibly in combination with GH therapy to improve its efficiency.

Conclusions

The future of GH therapy in NS remains difficult to predict, as prospective longer duration studies are still required to determine the effect of GH therapy on height and to establish the links between response to treatment and genotype. One can assume that the entry on the market of GH generics and of IGF-1 will offer more opportunities and perspectives for the clinicians. However, even though recent progress was made in understanding the cause of short stature in NS, further studies are required to decipher the mechanisms of growth retardation in NS, with the aim of improving the therapy outcome. Whereas it is relatively clear that these mechanisms should involve GH resistance due to dysfuntion in postreceptor signaling, the only defect identified thus far is an hyperactivation of Ras/MAPK in response to GH, observed in NS mice. This may thus appear paradoxical with the fact that patients can be treated by increasing their GH level. Indeed it seems difficult to imagine that increasing GH concentration in NS patients leads to a downregulation of Ras/MAPK activation to a normal level, which may thus explain the modest outcomes of GH therapy in NS. Consequently additional work must be performed to address how GH therapy can compensate for Ras/MAPK hyperstimulation in NS.

List of abbreviations
ALS: acid-labile subunit
BRAF: gene encoding the isoform B of rapidly accelerated fibrosarcoma protein
GAP: GTPase-activating protein
GH: growth hormone
IGF-1: insulin-like growth factor-1
IGFBP-3: insulin-like growth factor-binding protein-3
JAK-2: Janus kinase-2
MAPK: mitogen-activated protein kinase
 NS: Noonan syndrome
PI3K: phosphoinositide 3-kinase
PTPN11: protein tyrosine phosphatase non-receptor type 11
RAF1: gene encoding the isoform C of rapidly accelerated fibrosarcoma protein
rhIGF-1: recombinant human IGF-1
SDS: standard deviation score
SHOC2: Soc-2 suppressor of clear homolog (C. elegans)
SHP2: Src-homology type 2 domain-containing protein tyrosine phosphatase-2
SOS1: son of sevenless-1
STAT: signal transducer and activator of transcription

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